OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

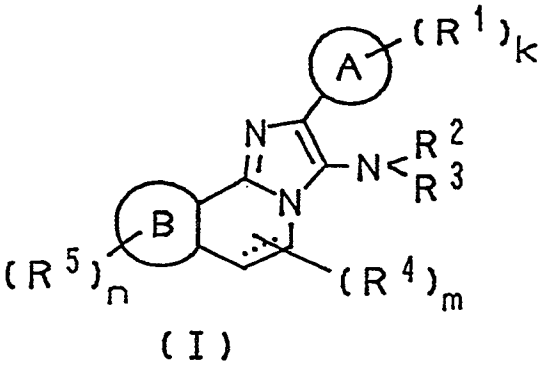
(12) (19) (CA) **Demande-Application**

(21) (A1) **2,218,705**
(86) 1996/04/10
(87) 1996/10/24

(72) TANAKA, Hironori, JP
(72) FUKUZUMI, Kazuyoshi, JP
(72) TOGAWA, Takeshi, JP
(72) BANNO, Kimiko, JP
(72) USHIRO, Toshihisa, JP
(72) MORII, Masaaki, JP
(72) NAKATANI, Takafumi, JP
(71) SHINNIPPON PHARMACEUTICAL INC., JP

(51) Int.Cl.[6] C07D 471/04, C07D 471/14, C07D 491/147, C07D 495/14, A61K 31/495, A61K 31/435, A61K 31/535
(30) 1995/04/21 (097130/1995) JP

(54) **IMIDAZO[1,2-A]PYRIDINES DE FUSION**
(54) **FUSED IMIDAZO[1,2-A]PYRIDINES**



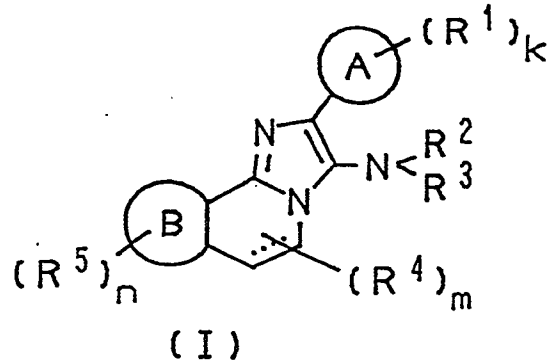
(I)

(57) Composés représentés par la formule générale (I), utiles comme médicaments anti-ulcéreux.

(57) Compounds represented by general formula (I) and useful as an antiulcer drug.

ABSTRACT

Compounds of the formula:



(I)

which are useful as anti-ulcer agent are provided.

DESCRIPTION

FUSED IMIDAZO[1,2-a]PYRIDINES

FIELD OF THE INVENTION

The present invention relates to novel fused imidazo[1,2-a]pyridines and medicaments containing them. More particularly, it relates to fused imidazo[1,2-a]pyridines useful for treatment of peptic ulcers, which are characterized by having a (hetero)aryl group on the 2-position and an amino group on the 3-position, and pharmaceutically acceptable salts or solvates thereof, and pharmaceutical compositions containing them.

BACK GROUND OF THE INVENTION

It has been explained that peptic ulcers like gastric and duodenal ulcers are developed due to collapse of balance between aggressive factors (gastric acid, pepsin, etc.) and defensive factors (blood flow, mucus, mucosal resistance, mucosal protection, etc.). Peptic ulcers are usually subjected to medical treatment, and various medications are applied thereto. The drugs for peptic ulcer therapy may be divided into two types, one being inhibitors of aggressive factors, the other being promoters of defensive factors, and they are used properly according to the type of diseases. Currently, histamine H_2-blockers (e.g. cimetidine, ranitidine, etc.) are generally used in the clinical stage as inhibitors against aggressive factors. However, it has been reported that there are refractory ulcers, and that the H_2-blockers possess adverse side effects, such as antiandrogen action and inhibitory action against liver metabolizing enzymes. Recently, it has been found that H^+/K^+-ATPase is associated with the final step for acid secretion, and it has been suggested that benzimidazoles having inhibitory action on this enzyme, such as omeprazole, are useful as anti-ulcer drugs. However, palindromia of ulcer is a problem remained unsolved. Furthermore, other problems requiring an improvement exist, such as development of carcinoid, and an interaction with other drugs, which decreases liver clearances for diazepam and fenitoin. On the other hand, it is well-known

that the promoters of defensive factors show limited healing rate as compared with the inhibitors of aggressive factors, and that the former provides delayed disappearance of subjective symptom. Thus, anti-ulcer drugs presently available are not satisfactory, and development of promising new anti-ulcer drugs has being desired.

The purpose of the present invention is to find compounds having both inhibitory action against aggressive factors and promoting action on mucosal defensive factors, and to provide more promising anti-ulcer drugs.

European Patent Publication No.0165545 and United States Patent No.4,468,400 disclose tricyclic compounds which have similar structures to the compounds of the present invention. However, they don't disclose compounds which have the same substituents as the substituents on the compounds of the present invention. European Patent Publications No.0033094, No.0068378 and No.0204285 disclose non-fused imidazo[1,2-a]pyridines which, on account of their antisecretory and cytoprotective actions, are intended to use for the treatment of ulcer.

DETAILED DESCRIPTION

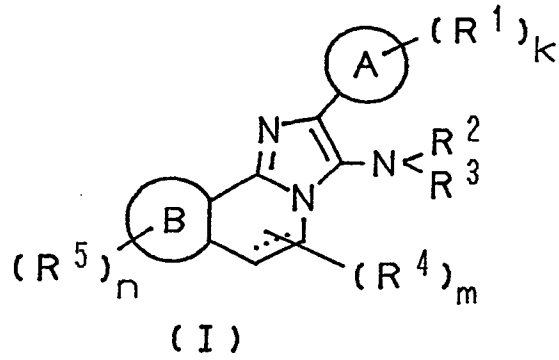
The present inventors have now discovered, after extensive studies, that novel fused imidazo[1,2-a]pyridines bearing a (hetero)aryl group on the 2-position and an amino group on the 3-position, and pharmaceutically acceptable salts or solvates thereof have noteworthy pharmacological properties and they are advantageously different from known imidazo[1,2-a]pyridines above-noted in their-pharmacological activities. The present invention is based on such findings.

Accordingly, one object of the present invention is to provide novel fused imidazo[1,2-a]pyridines and pharmaceutically acceptable salts or solvates thereof, which show an inhibitory action on gastric acid secretion and a protective action of gastric mucosa.

Another object of the invention is to provide pharmaceutical compositions comprising, as an active ingredient, said fused imidazo[1,2-a]pyridine, or a pharmaceutically acceptable salt or solvate thereof.

The compound of the invention is represented by the following general

formula (I):



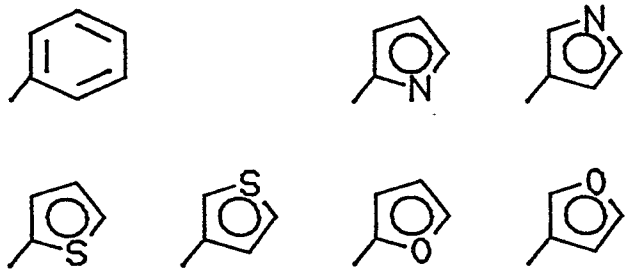
(I)

wherein ring A and ring B each independently represent an aromatic ring selected from benzene, thiophene, furan or pyrrole ring; R^1 is hydroxyl group, halogen atom, lower alkyl group which may be halogenated, lower alkoxy group or acyloxy group, k represents 0, 1, 2 or 3; R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group, acyl group, alkoxycarbonyl group or lower alkyl group which may have substituent(s) selected from the group consisting of 1) halogen atom, 2) hydroxyl group, 3) lower alkoxy group, 4) lower alkylthio group, 5) alkylsulfinyl group, 6) alkoxycarbonyl group, 7) carbamoyl group, 8) alkylamino group and 9) aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form an alkylideneamino group or arylalkylideneamino group; R^4 and R^5 each independently represent halogen atom, cyano group, hydroxyl group, carboxyl group, alkoxycarbonyl group, acyl group, alkylamino group, aryl group, acyloxy group, carbamoyloxy group, lower alkyl group which may have substituent(s) selected from the group consisting of 1) hydroxyl group, 2) lower alkoxy group, 3) aryl group and 4) aryloxy group, lower alkoxy group which may have substituent(s) selected from the group consisting of 1) hydroxyl group, 2) lower alkoxy group, 3) lower alkoxycarbonyl group and 4) aryl group, or lower alkylthio group which may be substituted with aryl group; m represents 0, 1 or

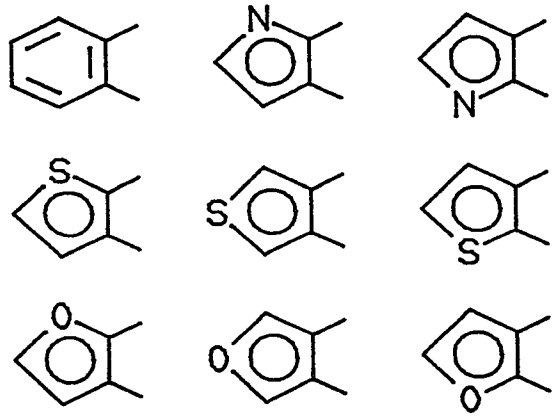
2; n represents 0, 1 or 2; the dotted line, together with the solid line, represents a single or double bond, provided that plural R^4s may be attached to the same carbon atom.

The terms used herein are defined below. Substituents on the compounds(I) of the present invention have the following significances, whether the substituents exist alone or constitute part of other group.

"Benzene, thiophene, furan or pyrrole ring represented by ring A" are shown below.



"Benzene, thiophene, furan or pyrrole ring represented by ring B" are shown below.



"Halogen atom" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom.

"Lower alkyl group" means straight, branched or cyclic alkyl group having 1 to 6 carbon atoms, and may include, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl

group, tert-butyl group, pentyl group, isopentyl group, neopentyl group, tert-pentyl group, 1-methylbutyl group, 2-methylbutyl group, 1,2-dimethylpropyl group, hexyl group, isohexyl group, 1-methylpentyl group, 2-methylpentyl group, 3-methylpentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethylbutyl group, 1,3-dimethylbutyl group, 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 1-ethylbutyl group, 2-ethylbutyl group, 1,2,2-trimethylpropyl group, 1-ethyl-1-methylpropyl group, 1-ethyl-2-methylpropyl group, cyclopropyl group, cyclobutyl group, cyclopentyl group, 2-methylcyclopentyl group, cyclohexyl group and the like. Preferable lower alkyl groups include an alkyl group having 1 to 4 carbon atoms, in particular, lower alkyl group having 1 to 3 carbon atoms.

"Acyl group" may include a residue of an organic acid such as aliphatic saturated carboxylic acid, aliphatic unsaturated carboxylic acid and arylcarboxylic acid, and specific examples are lower alkanoyl group carrying, for example, formyl group, acetyl group, propionyl group, butyryl group, isobutyryl group, hexanoyl group, bromoacetyl group, trifluoroacetyl group, methoxyacetyl group, butoxyacetyl group, phenoxyacetyl group, 4-bromomethylphenylacetyl group, 4-methoxyphenylacetyl group, 1-naphthylacetyl group, 3-pyridylacetyl group, 3-chloropropionyl group, 3-bromopropionyl group, 3-(methylthio)propionyl group, 3-ethoxypropionyl group, 3-(3,4-dimethoxyphenyl)propionyl group, 3-carboxypropionyl group, 3-benzoylpropionyl group, 4-chlorobutyryl group, 3-acetylbutyryl group, succinyl group, cyclopentylacetyl group, 6-bromohexanoyl group and the like; lower alkenoyl group carrying, for example, acryloyl group, 2-furylacryloyl group, crotonoyl group, 3-methylcrotonoyl group, cinnamoyl group, 4-methoxycinnamoyl group, methoxymaleoyl group, methoxyfumaroyl group and the like; arylcarbonyl group such as benzoyl group, 4-pentylbenzoyl group, p-anisoyl group, o-anisoyl group, 3,5-bis(trifluoromethyl)benzoyl group, 4-bromobenzoyl group, 4-butoxybenzoyl group, 4-chlorobenzoyl group, 3-chlorobenzoyl group, 4-chloromethylbenzoyl group, 4-cyanobenzoyl group, 3,4-dichlorobenzoyl group, 3,5-dichlorobenzoyl group, 2,4-difluorobenzoyl group, 3,4-dimethoxybenzoyl group, 4-ethoxybenzoyl group, 3-fluorobenzoyl group, 4-isopropylbenzoyl group, 3-(trifluoromethyl)benzoyl group, 3,4,5-

trimethoxybenzoyl group, 3,4-dimethylbenzoyl group, m-toluoyl group, o-toluoyl group, p-toluoyl group, 1-naphthoyl group, 2-naphthoyl group, 1-bromo-2-naphthoyl group and the like; or heteroarylcarbonyl group such as 2-thenoyl group, 3-thenoyl group, 5-methyl-2-thenoyl group, 2-furoyl group, 5-bromo-2-furoyl group, nicotinoyl group, isonicotinoyl group, 6-methylpicolinoyl group, 3-methyl-2-benzo[b]furoyl group, quinoline-2-carbonyl group and the like. Preferable acyl groups are residues of aliphatic carboxylic acids, in particular, residues of aliphatic saturated carboxylic acids.

"Alkenyl group" means straight or branched alkenyl group having 2 to 6 carbon atoms, and may include, for example vinyl group, allyl group, 1-propenyl group, isopropenyl group, 2-methyl-1-propenyl group, 1-butenyl group, 2-butenyl group, 3-butenyl group, 2-ethyl-1-butenyl group, 3-methyl-2-butenyl group, 1,3-butadienyl group, 1-pentenyl group, 2-pentenyl group, 3-pentenyl group, 4-pentenyl group, 4-methyl-3-pentenyl group, 1-hexenyl group, 2-hexenyl group, 3-hexenyl group, 4-hexenyl group, 5-hexenyl group and the like. Preferable alkenyl groups are alkenyl groups having 2 to 3 carbon atoms.

"Lower alkoxy group" means alkoxy group having 1 to 6 carbon atoms, such as methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, tert-pentyloxy group, 1-methylbutoxy group, 2-methylbutoxy group, 1,2-dimethylpropoxy group, hexyloxy group, isohexyloxy group, 1-methylpentyloxy group, 2-methylpentyloxy group, 3-methylpentyloxy group, 1-ethylbutoxy group, 2-ethylbutoxy group, 1,2,2,-trimethylpropoxy group, 1-ethyl-1-methylpropoxy group, 1-ethyl-2-methylpropoxy group and the like. Preferable alkoxy groups are alkoxy groups having 1 to 4 carbon atoms, in particular, alkoxy groups having 1 to 3 carbon atoms.

"Lower alkylthio group" may include methylthio group, ethylthio group, propylthio group, isopropylthio group, butylthio group, isobutylthio group, sec-butylthio group, tert-butylthio group, pentylthio group, isopentylthio group, neopentylthio group, tert-pentylthio group, 1-methylbutylthio group, 2-methylbutylthio group and the like.

"Alkylsulfinyl group" means the above-mentioned "alkyl group" to

which a sulfinyl group is bonded, and it may include, for example, methylsulfinyl group, ethylsulfinyl group, isopropylsulfinyl group, butylsulfinyl group and the like.

"Lower alkoxycarbonyl group" means the above-mentioned "lower alkoxy group" to which a carbonyl group is bonded, and it may include, for example, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, isopropoxycarbonyl group, butoxycarbonyl group, isobutoxycarbonyl group, sec-butoxycarbonyl group, tert-butoxycarbonyl group, pentyloxycarbonyl group, isopentyloxycarbonyl group, 3-methylpentyloxycarbonyl group, 2,3-dimethylbutoxycarbonyl group, 3,3-dimethylbutoxycarbonyl group, 2-ethylbutoxycarbonyl group and the like.

"Carbamoyl group" may include carbamoyl group, dimethylcarbamoyl group, ethylcarbamoyl group, diethylcarbamoyl group, allylcarbamoyl group, cyclopentylcarbamoyl group, hexylcarbamoyl group, N-(4-ethoxycarbonyl oxyphenyl)carbamoyl group, N-(4-trifluoromethylphenyl)carbamoyl group and the like.

"Alkylamino group" may include methylamino group, ethylamino group, dimethylamino group, diethylamino group, dipropylamino group, N-methyl-N-ethylamino group, N-methyl-N-propylamino group, N-ethyl-N-propylamino group and the like.

"Aryl group" may include phenyl group, 2-chlorophenyl group, 3-fluorophenyl group, 4-bromo-3-methylphenyl group, 4-methoxyphenyl group, 2-thienyl group, 2-chloro-5-thienyl group, 3-methyl-2-furyl group, 4-methyl-5-thiazolyl group, 4-chloro-2-methyl-5-oxazolyl group, 1-methyl-2-imidazolyl group, 1-bromo-2-naphthyl group, 6-methyl-2-naphthyl group, 8-methoxy-1-naphthyl group, 3-methyl-2-benzo[b]furyl group, 5-chloro-3-benzo[b]thienyl group and the like.

"5- or 6-membered cyclic ring formed together with the nitrogen atom" may include, for example, pyrrolyl group, 2-pyrrolinyl group, 3-pyrrolinyl group, pyrrolidinyl group, imidazolidinyl group, pyrazolidinyl group, succinimide group, piperidino group, piperazinyl group, morpholino group, glutarimide group and the like.

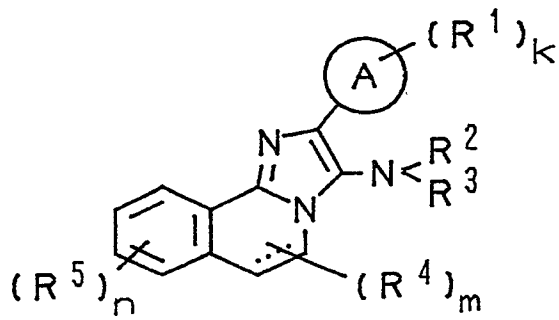
"Alkylideneamino group" may include ethylideneamino group,

propylideneamino group, isopentylideneamino group, 2-methylpentylideneamino group, 3,3-dimethylbutylideneamino group, 2-ethylbutylideneamino group and the like.

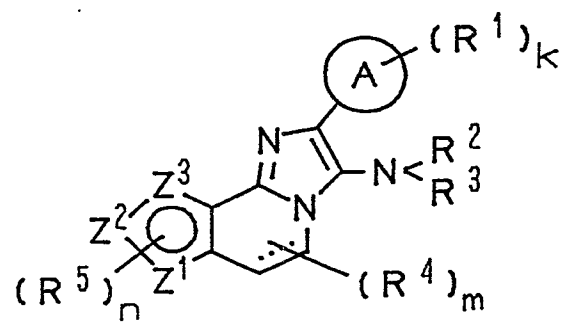
"Arylalkylideneamino group" may include benzylideneamino group, 4-bromobenzylideneamino group, 2-chloro-6-fluorobenzylideneamino group, 2-methylbenzylideneamino group, 4-methylbenzylideneamino group, 2,5-dimethylbenzylideneamino group, 2,4,6-trimethylbenzylideneamino group, 3-methoxybenzylideneamino group, 3,4-dimethoxybenzylideneamino group, 2-phenethylideneamino group, (1-bromo-2-naphthyl)methylideneamino group, cinnamylideneamino group and the like.

"Acyloxy group", "carbamoyloxy group" or "aryloxy group" respectively means the above-mentioned "acyl group", "carbamoyl group" or "aryl group", to which an oxygen atom is bonded.

The novel compounds of the present invention represented by the formula (I) may be classified into the following two-types according to the partial structure of the compounds. Thus, when ring B is benzene ring, the compounds of the invention can be represented by the formula (I-1), and when ring B is thiophene, furan or pyrrole ring, the compounds of the invention can be represented by the formula (I-2).



(I-1)



(I-2)

wherein ring A, R^1, R^2, R^3, R^4, R^5, k, m and n are as defined above, any one of Z^1, Z^2, or Z^3 represents a hetero-atom selected from sulfur, oxygen or nitrogen atom , and the others represent carbon atom.

Preferred compounds of the invention represented by the formula (I) may include the compounds (I-1) wherein ring B is benzene ring, or the compounds (I-2) wherein ring B is thiophene, furan, or pyrrole ring, and either Z^1 or Z^3 represents a hetero atom selected from sulfur, oxygen or nitrogen atom, and the other represents carbon atom. In particular, ring B preferably represents benzene or thiophene ring.

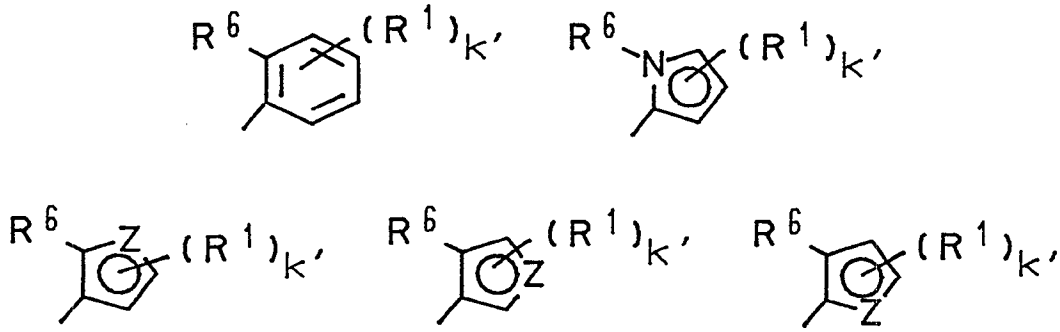
Preferred compounds of the invention represented by the formula (I) may include those wherein R^1 represents halogen atom, lower alkyl group which may be halogenated, or lower alkoxy group. In particular, R^1 preferably represents lower alkyl group having 1 or 2 carbon atoms.

Further preferred compounds of the invention represented by the formula (I) may include those wherein R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring. Additional preferred compounds are those wherein at least one of R^2 and R^3 represents hydrogen atom.

Other preferred compounds of the invention represented by the formula (I) are those wherein ring A is benzene, thiophene, furan or pyrrole ring; ring B is benzene or thiophene ring; one of R^1 is halogen atom, lower alkyl group which may be halogenated, or lower alkoxy group; k is 1 or 2; R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring.

Especially preferable compounds of the invention represented by the formula (I) are those wherein ring A is benzene, thiophene, furan or pyrrole ring; and at least one of the substituent(s) on ring A is located at ortho-position with respect to the binding site where ring A is bound to other part of the molecule

including ring B moiety, as illustrated below:



wherein R^1 and R^6 represent halogen atom, lower alkyl group which may be halogenated, or lower alkoxy group; k' represents 0 or 1; and Z represents a hetero-atom selected from sulfur, oxygen or nitrogen atom; ring B represents benzene or thiophene ring represented by the formula (I-2) in which either Z^1 or Z^3 represents sulfur atom; R^2 is hydrogen atom; R^3 is hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group; and the dotted line, together with the solid line, represents a double bond.

Most preferable compounds of the invention represented by the formula (I) are those wherein ring A is benzene, thiophene, furan or pyrrole ring; the substituent R^6 on the ring A represented by the above-illustrated formulae is lower alkyl group having 1 or 2 carbon atoms; k' is 0 or 1; ring B represents benzene or thiophene ring represented by the formula (I-2) in which Z^1 is sulfur atom; R^2 and R^3 are each a hydrogen atom; R^4 and R^5 are each halogen atom, lower alkyl group, lower alkoxy group or lower alkylthio group; m is 0, 1 or 2; n is 0, 1 or 2; and the dotted line, together with the solid line, represents a double bond.

The following may be mentioned as examples of the compounds according to the invention to be singled out in particular:

3-amino-9-chloro-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,

3-amino-5-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,

3-amino-9-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-5-ethyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-5-isopropyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-5-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-2-(2-methylphenyl)-9-(methylthio)imidazo[2,1-a]isoquinoline,
3-amino-9-fluoro-5-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline,
3-amino-2-(4-fluoro-2-methylphenyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(5-fluoro-2-methylphenyl)-9-methoxyimidazo[2,1-a]isoquinoline,
3-amino-2-(2-methyl-3-thienyl)imidazo[2,1-a]isoquinoline,
3-amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[2,1-a]isoquinoline,
3-amino-2-(2-methyl-3-thienyl)-9-(methylthio)imidazo[2,1-a]isoquinoline,
3-amino-5-methoxy-2-(2-methyl-3-thienyl)imidazo[2,1-a]isoquinoline,
3-amino-9-fluoro-5-methyl-2-(2-methyl-3-thienyl)imidazo[2,1-a]isoquinoline,
3-amino-2-(2-ethyl-3-thienyl)imidazo[2,1-a]isoquinoline,
3-amino-2-(2,5-dimethyl-3-thienyl)-9-fluoroimidazo[2,1-a]isoquinoline,
3-amino-2-(2,5-dimethyl-3-thienyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(2,5-dimethyl-3-thienyl)-9-methoxyimidazo[2,1-a]isoquinoline,
3-amino-2-(5-chloro-2-methyl-3-thienyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(5-ethyl-2-methyl-3-thienyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(2-chloro-3-methyl-4-thienyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(2-methyl-3-furyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-2-(2,5-dimethyl-3-furyl)-5-methylimidazo[2,1-a]isoquinoline,
3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5-ethyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5,8-dimethyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(4-fluoro-2-methylphenyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-8-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5,6-dimethyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(4-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2-ethyl-3-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,

3-amino-2-(2-methoxy-3-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(5-chloro-2-methyl-3-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2,5-dimethyl-3-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2,5-dimethyl-3-thienyl)-5-ethylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(5-ethyl-2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(5-methoxy-2-methyl-3-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2-chloro-3-methyl-4-thienyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5-methyl-2-(2-methyl-3-furyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2-methoxy-3-furyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-5-methyl-2-(1-methyl-2-pyrrolyl)imidazo[1,2-a]thieno[3,2-c]pyridine,
3-amino-2-(2,5-dimethyl-3-thienyl)furo[3,2-c]imidazo[1,2-a]pyridine,
3-amino-7-(4-chlorobenzyl)-2-(2-methylphenyl)imidazo[1,2-a]pyrrolo[3,2-c]pyridine,
3-amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,4-c]pyridine,
3-amino-2-(2-chlorophenyl)imidazo[1,2-a]thieno[2,3-c]pyridine,
3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine,
3-amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[2,3-c]pyridine,
3-amino-2-(2,5-dimethyl-3-thienyl)imidazo[1,2-a]thieno[2,3-c]pyridine,
3-amino-2-(2,5-dimethyl-3-furyl)-5-methylimidazo[1,2-a]thieno[2,3-c]pyridine,
3-amino-2-(1-methyl-2-pyrrolyl)imidazo[1,2-a]thieno[2,3-c]pyridine,

Suitable pharmaceutically acceptable salts of the compound (I) may include conventional salts used for drugs, such as those formed with an alkali metal (e.g. sodium, potassium, etc.) or an alkaline earth metal (e.g. magnesium, calcium, etc.) or an inorganic base(e.g. aluminum, etc.), and those formed with an organic base (e.g. ethylamine, propylamine, diethylamine, triethylamine, morpholine, pyridine, piperidine, N-ethylpiperidine, diethanolamine, cyclohexylamine, etc.), those formed with a basic amino acid (e.g. lysine, ornithine etc.), an ammonium salt, those formed with a mineral acid (e.g. hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid, etc.), those formed with an organic acid (e.g. acetic acid, oxalic acid, succinic acid, citric

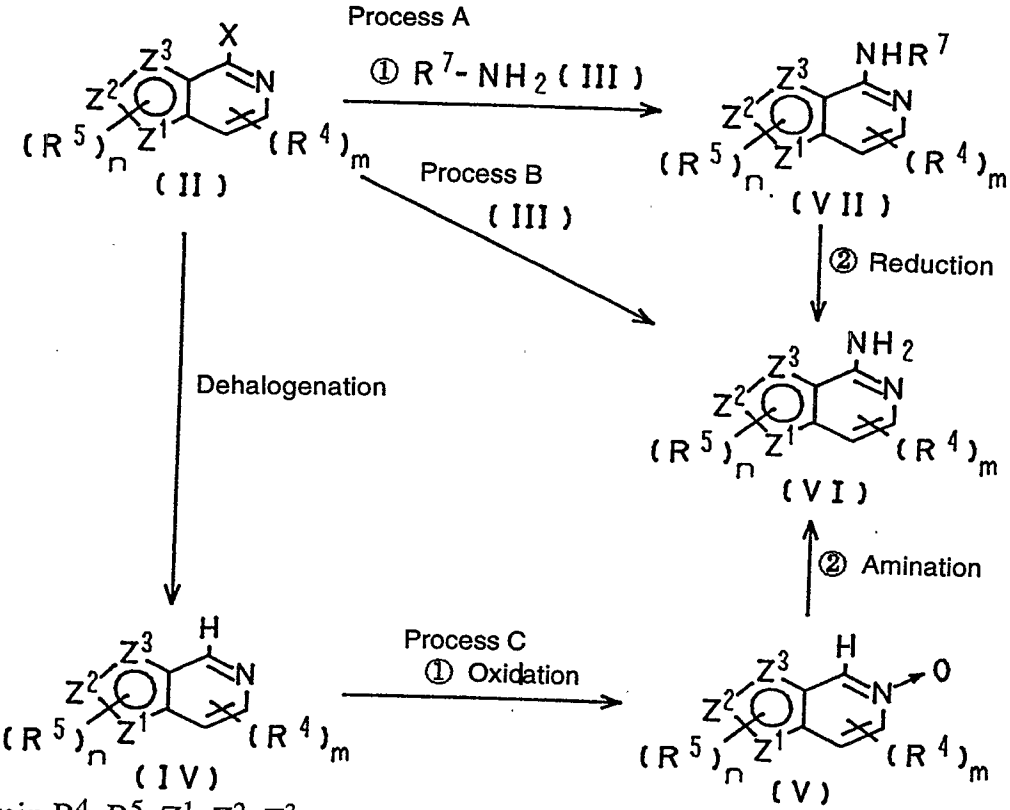
acid, maleic acid, malic acid, fumaric acid, tartaric acid, picric acid, methanesulfonic acid, ethanesulfonic acid, etc.), and those formed with an acidic amino acid (e.g. glutamic acid, aspartic acid, etc.).

The compounds (I) of the present invention and pharmaceutically acceptable salts thereof may include their solvates (e.g. water, ethanol, etc.) and polymorphism, in case that they can be isolated.

The compounds (I) of the invention include stereoisomers, optical isomers or geometrical isomers thereof.

The compounds of the invention may be prepared by various methods. Typical methods are shown below.

(Process 1)



wherein R^4, R^5, Z^1, Z^2, Z^3, m and n are as defined above; X is a leaving group to be replaced by amine, R^7 is hydrogen atom, amino group, arylalkyl group which may have substituent(s), or alkyl group which may have substituent(s).

Among the compounds represented by the formula (II), thienopyridines, in which any one of Z^1, Z^2 or Z^3 is a sulfur atom, can be prepared according to

methods known to those skilled in the art [see, for example, Journal of Chemical Society, Perkin Transactions 1, p1390, (1975)], or analogous methods thereto. Furopyridines, any one of Z^1, Z^2 or Z^3 is an oxygen atom in the formula (II), can also be prepared according to methods known to those skilled in the art [see, for example, Journal of Heterocyclic Chemistry, 19, p1207, (1982)], or analogous methods thereto. Pyrrolopyridines, any one of Z^1, Z^2 or Z^3 is a nitrogen atom in the formula (II), can be prepared according to methods known to those skilled in the art [see, for example, Tetrahedron, 32, p773, (1976)], or analogous methods thereto. The leaving group X to be replaced by amine, may include, for example, alkoxy group, alkylthio group, alkylsulfinyl group, alkylsulfonyl group and halogen atom. Suitable leaving group X is halogen atom, in particular, chlorine atom.

Among the compounds represented by the formula (IV), thienopyridines, in which any one of Z^1, Z^2 or Z^3 is a sulfur atom, can be prepared according to methods known to those skilled in the art [see, for example, Journal of Heterocyclic Chemistry, 9, p843, (1972), Journal of Heterocyclic Chemistry, 30, p289, (1993)], or analogous methods thereto. Furopyridines, any one of Z^1, Z^2 or Z^3 is an oxygen atom in the formula (IV), can be prepared according to methods known to those skilled in the art [see, for example, United States Patent No.4808595, Journal of Heterocyclic Chemistry, 8, p57, (1971), Tetrahedron Letters, p1741, (1977)], or analogous methods thereto. Pyrrolopyridines, any one of Z^1, Z^2 or Z^3 is a nitrogen atom in the formula (IV), can be prepared according to methods known to those skilled in the art [see, for example, Journal of Heterocyclic Chemistry, 29, p359, (1992)], or analogous methods thereto.

Among the compounds represented by the formula (VI), pyrrolo[3,2-c]pyridines, in which Z^1 is a nitrogen atom, can be prepared according to methods known to those skilled in the art [see, for example, Journal of Chemical Research. Synopses, 1, p4, (1986) or literatures mentioned therein], or analogous methods thereto.

Compound (VI) shown in Process 1 can be prepared according to Process A wherein compound (II) is condensed with compound (III) with heating (first

step) and the resultant compound (VII) is reduced (second step), or Process B wherein compound (II) is condensed with compound (III) in which R^7 is a hydrogen atom with heating, or Process C wherein compound (IV)is subjected to oxidation (first step) and then the resultant compound (V) is subjected to amination (second step).

Process A

(1) First step :

Of the compounds represented by the formula (III), suitable R^7 may include amino group, methyl group substituted by phenyl which has 1-3 straight or branched alkyl or alkoxy groups having 1 to 4 carbon atom(s), or benzyl group.

The reaction of compound (II) with compound (III) is conveniently carried out in an organic solvent, if neccessary, such as alcohols [e.g. 2-methoxyethanol,etc.], ethers [e.g. tetrahydrofuran, diethyl ether, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or other solvents which do not adversely affect the reaction. Preferably, this reaction is carried out without a solvent and at high temperature.

(2) Second step :

The reduction in this step may include hydrogenolysis in the presence of catalyst [e.g. acids such as hydrochloric acid, sulfuric acid, Lewis acid and the like, Raney nickel, palladium-carbon, platinum oxide, etc.].

The reaction is carried out in a solvent such as organic nitriles [e.g. acetonitrile, etc.], acids [e.g. acetic acid, trifluoroacetic acid, etc.], alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], organic amides [e.g. N,N-dimethylformamide, etc.], any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 24 hours.

Process B

The reaction is usually carried out in ammonium hydroxide or a solution of ammonia in alcohol [e.g. methanol, ethanol, etc.] in a sealed reaction tube.

The reaction temperature is not critical, and the reaction is carried out with heating at 50 to 200°C.

The reaction is completed in 2 to 72 hours.

Process C

(1) First step :

The oxidation in this step may include oxidation by peroxide [e.g. inorganic peroxides such as hydrogen peroxide and the like, organic peroxides such as 3-chloroperbenzoic acid, alkyl hydroperoxide, peracetic acid and the like].

The reaction is carried out in a solvent such as organic amides [e.g. N,N-dimethylformamide, etc.], alcohols [e.g. methanol, ethanol; etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], organic nitriles [e.g. acetonitrile, etc.], acids [e.g. hydrochloric acid, sulfuric acid, acetic acid, etc.], water, any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 24 hours.

(2) Second step :

The amination applied to this reaction may include the reaction with an aminating agent [e.g. ethanolamine, ammonia, etc.] in the presence of an acylating agent [e.g. p-toluenesulfonyl chloride, methanesulfonyl chloride, acetyl chloride, etc.].

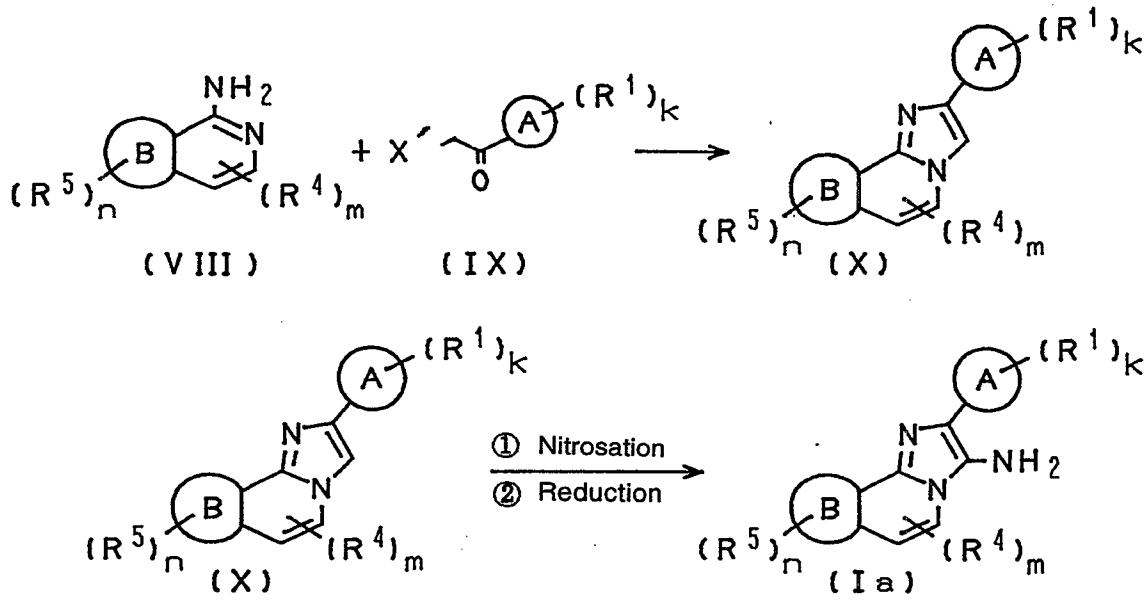
The reaction is carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], halogenated hydrocarbons

[e.g. dichloromethane, chloroform, etc.], cyclic organic bases [e.g. pyridine, picoline, etc.], water, any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 30 minutes to 48 hours.

(Process 2)



wherein ring A, ring B, R^1, R^4, R^5, k, m and n are as defined above; X' is a halogen atom.

Aminoisoquinolines, represented by the formula (VIII) in which ring B is benzene ring, can be prepared according to procedures known to those skilled in the art [e.g. Chemical and Pharmaceutical Bulletin, 5, p606, (1957); Heterocycles, 38, p375, (1994); European Patent Publication No.143001], or analogous methods thereto. Among compounds of the formula (VIII), the compounds wherein ring B is thiophene, furan or pyrrole ring, may be represented by the formula (VI), and processes for preparing the same have been shown in aforementioned Process 1. 2-Halogenoethanones represented by the formula (IX) can be prepared according to procedures known to those skilled in the art [e.g. Japanese Patent Publication (Kokai) No.152677/86; Journal of Medicinal Chemistry, 37, p57, (1994)], or analogous methods thereto.

Compound (X) or a salt thereof can be prepared by reacting Compound (VIII) or a salt thereof with Compound (IX).

The reaction is conveniently carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], halogenated hydrocarbons [e.g. dichloromethane, chloroform, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction may be preferably carried out in the presence of an inorganic base or an organic base, such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate, etc.], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate, etc.], trialkylamine [e.g. trimethylamine, triethylamine, etc.], pyridine or lutidine, or the like.

The reaction temperature is not critical, and the reaction is usually carried out at room temperature or with heating.

The reaction is completed in 30 minutes to 24 hours.

The compounds represented by the formula (X) may also be prepared by change of partial structure of Compound (X) having suitable substituent(s) by means of a suitable means. For example, the aimed compound can be obtained in accordance with the following reactions: by replacing halogen such as chlorine, bromine, and the like with nitrile [see Shin jikken kagaku kouza; Maruzene company: Japan, 14, p1437], or by cross-coupling to convert halogen such as chlorine, bromine and the like into alkyl group such as methyl, ethyl and the like or aryl group such as phenyl, naphthyl, and the like [Synthesis, p317, (1985)], or hydrolysis of nitrile to carboxylic acid and its derivative [Organic Syntheses, 2, p588, (1943)], or conversion of nitrile into acyl group by using an organic metal reagent [Journal of Chemical Society, p4566, (1965)], or protection and deprotection of hydroxy or amino group [W.Greene, "Protective Groups in Organic Synthesis"], or reduction of nitro group into amino group, or reduction of carboxylic acid or its derivative into hydroxymethyl group, or alkylation of hydroxy or amino group, or conversion of amino group into alkylthio or arylthio group via diazonium salt [Journal of the American Chemical

Society, 82, p2872, (1960)].

Compound (Ia) or a salt thereof can be prepared by subjecting compound (X) or a salt thereof to nitrosation (first step) and then subjecting the resultant compound to reduction (second step).

(1) First step :

Suitable nitrosating agents to be used in this reaction may include alkali metal nitrite salt [e.g. sodium nitrite, potassium nitrite, etc.], or nitrite ester [e.g. t-butyl nitrite, pentyl nitrite, isopentyl nitrite, etc.] and the like.

The reaction is carried out in a solvent such as organic amides [e.g. N,N-dimethylformamide, etc.], alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], organic nitriles [e.g. acetonitrile, etc.], acids [e.g. hydrochloric acid, sulfuric acid, acetic acid, etc.], water, any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 6 hours.

(2) Second step :

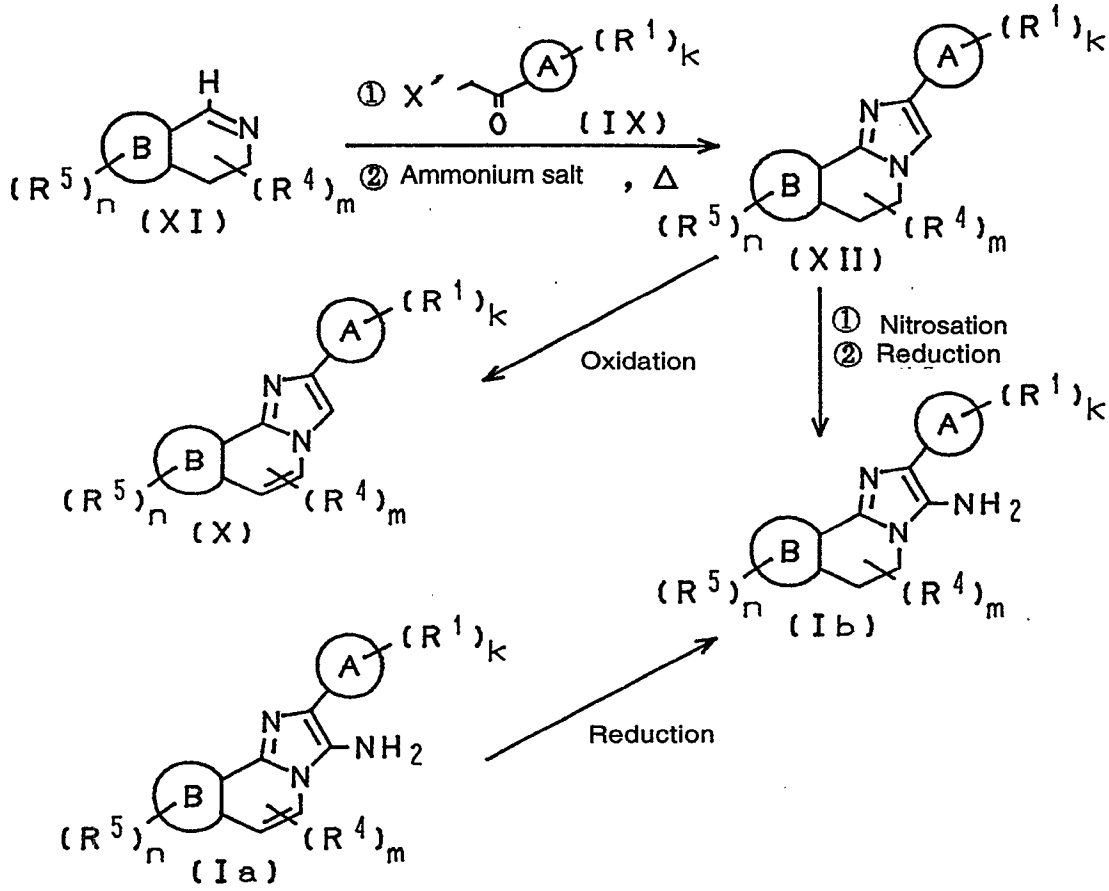
The reduction applied to this reaction may include catalytic reduction in the presence of catalyst [e.g. palladium-carbon, platinum oxide, etc.] or reductions using a combination of a metal [e.g. titanium, iron, zinc, etc.] with an inorganic or organic acid such as hydrochloric acid, acetic acid, propionic acid and the like.

The reaction is carried out in a solvent such as organic amides [e.g. N,N-dimethylformamide, etc.], alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], organic nitriles [e.g. acetonitrile, etc.], acids [e.g. hydrochloric acid, sulfuric acid, acetic acid, etc.], water, any other solvents which do not adversely affect the reaction, or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 24 hours.

(Process 3)



wherein ring A, ring B, R^1, R^4, R^5, k, m and n are as defined above; X' is a halogen atom.

3,4-Dihydroisoquinolines represented by the formula (XI) in which ring B is benzene ring, can be prepared according to procedures known to those skilled in the art [e.g. Japanese Patent Publication (Kokai) No.213870/93 or literatures cited therein], or analogous methods thereto. Compounds represented by the formula (XI) wherein ring B is thiophene, furan or pyrrole ring, can be prepared according to procedures known to those skilled in the art [e.g. Journal of Medicinal Chemistry, 31, p641, (1988); Journal of Chemical Research Synopses, 1, p4, (1986), or literautures cited therein], or analogous methods thereto.

5,6-Dihydroimidazopyridines represented by the formula (XII) can be prepared by reacting compound (XI) with compound (IX) (first step) and then subjecting the resultant compound to react with an ammonium salt (second step).

(1) First step :

The reaction is carried out in a solvent such as ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], halogenated hydrocarbons [e.g. dichloromethane, chloroform, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at room temperature or with heating.

The reaction is completed in 30 minutes to 24 hours.

(2) Second step :

Suitable ammonium salts to be used in this reaction include inorganic ammonium salts [e.g. ammonium carbonate, ammonium sulfate, etc.] or organic ammonium salts [e.g. ammonium formate, ammonium acetate, etc.].

The reaction is carried out in a solvent such as organic amides [e.g. N,N-dimethylformamide, etc.], alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], organic nitriles [e.g. acetonitrile, etc.], acids [e.g. hydrochloric acid, sulfuric acid, acetic acid, etc.], water or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at room temperature or with heating.

The reaction is completed in 30 minutes to 24 hours.

The compounds represented by the formula (XII) can also be prepared by conversion of partial structure of the compounds (XII) having suitable substituent(s) by using the means exemplified above.

Compound (Ib) or a salt thereof in Process 3 can be prepared from compound (XII) in a similar manner to the method the compound (Ia) or a salt

thereof from the compound (X) or a salt thereof aforementioned in Process 2.

The compound (X) or a salt thereof in Process 3 can also be prepared by subjecting compound (XII) or a salt thereof to oxidation.

The oxidation applied to this reaction may include dehydrogenation in the presence of catalyst [e.g. platinum, palladium-carbon, precipitated alumina-chromium oxide, copper, nickel, etc.].

The reaction solvent may include, for example, diphenylether, diphenylmethane, benzene, toluene, naphthalene, tetralin, decalin, and the like. The reaction can also be carried out without solvent.

High reaction temperature is required although it is not critical, and the reaction is usually carried out with heating.

The reaction is completed in 30 minutes to 24 hours.

Compound (Ib) or a salt thereof can also be prepared by subjecting Compound (Ia) or a salt thereof to reduction.

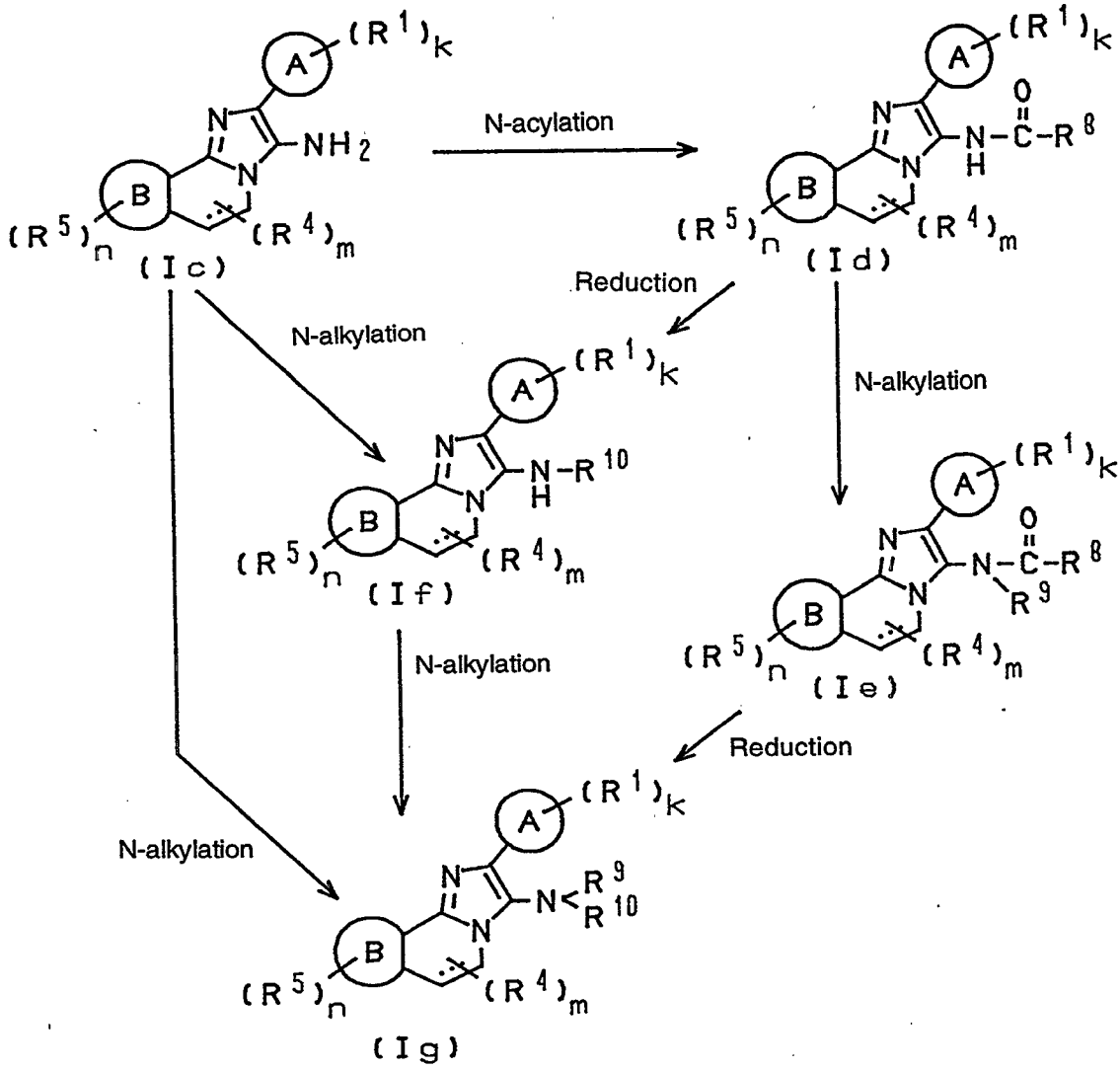
The reduction applied to this reaction may include catalytic reduction in the presence of catalyst [e.g. palladium-carbon, platinum oxide, etc.].

The reaction is carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is preferably carried out at ambient temperature or at the boiling point of the solvent used.

The reaction is completed in 30 minutes to 72 hours.

(Process 4)



wherein ring A, ring B, R^1, R^4, R^5, k, m and n are as defined above; R^8 is hydrogen atom, lower alkoxy group, alkenyl group, or lower alkyl group which may have substituent(s) selected from halogen atom, hydroxy group, lower alkoxy group, alkylthio group, alkylsulfinyl group, alkoxycarbonyl group, carbamoyl group, alkylamino group, or aryl group; R^9 and R^{10} may be same or different and each represent hydrogen atom, lower alkoxy group, alkenyl group or lower alkyl group which may have substituent(s) selected from halogen atom,

alkoxycarbonyl group, carbamoyl group, alkylamino group or aryl group.

Compound (Id) or a salt thereof can be prepared by subjecting compound (Ic) or a salt thereof to acylation.

The acylating agent to be used in this reaction may include desired carboxylic acids, carboxylic anhydrides, halogenated acyls or a combination of any one of those compounds with a suitable condensing agent.

The reaction is carried out in a solvent such as cyclic organic bases [e.g. pyridine, etc.], alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], halogenated hydrocarbons [e.g. dichloromethane, chloroform, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 6 hours.

Compounds (If), (Ig) and (Ie) or salts thereof can be prepared by subjecting the compounds (Ic), (If) and (Id) or salts thereof to alkylation.

The alkylating agent to be used in this reaction may include desired halogenated alkyls, halogenated arylalkyls or halogenated alkenyls and the like.

The reaction is usually carried out in the presence of a base.

Suitable bases may include inorganic bases such as alkali metal hydrides [e.g. sodium hydride, potassium hydride, etc.], alkali metal hydroxides [e.g. sodium hydroxide, potassium hydroxide, etc.], alkaline earth metal hydroxides [e.g. magnesium hydroxide, calcium hydroxide, etc.], alkali metal carbonates [e.g. sodium carbonate, potassium carbonate, etc.], alkaline earth metal carbonates [e.g. magnesium carbonate, calcium carbonate, etc.], alkali metal bicarbonates [e.g. sodium bicarbonate, potassium bicarbonate, etc.], alkaline earth metal phosphates [e.g. magnesium phosphate, calcium phosphate, etc.], alkali metal acetates [e.g. sodium acetate, potassium acetate, etc.], or the like, and organic bases such as trialkylamines [e.g. trimethylamine, triethylamine, etc.], pyridine, picoline, N-methylmorpholine, N-methylpyrrolidine, or the like.

The reaction is carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.],

hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is preferably carried out at ambient temperature or at the boiling point of the solvent used.

The reaction is completed in 5 minutes to 24 hours.

Compounds (If) and (Ig) or salts thereof can also be prepared by subjecting compounds (Id) and (Ie) or salts thereof to reduction.

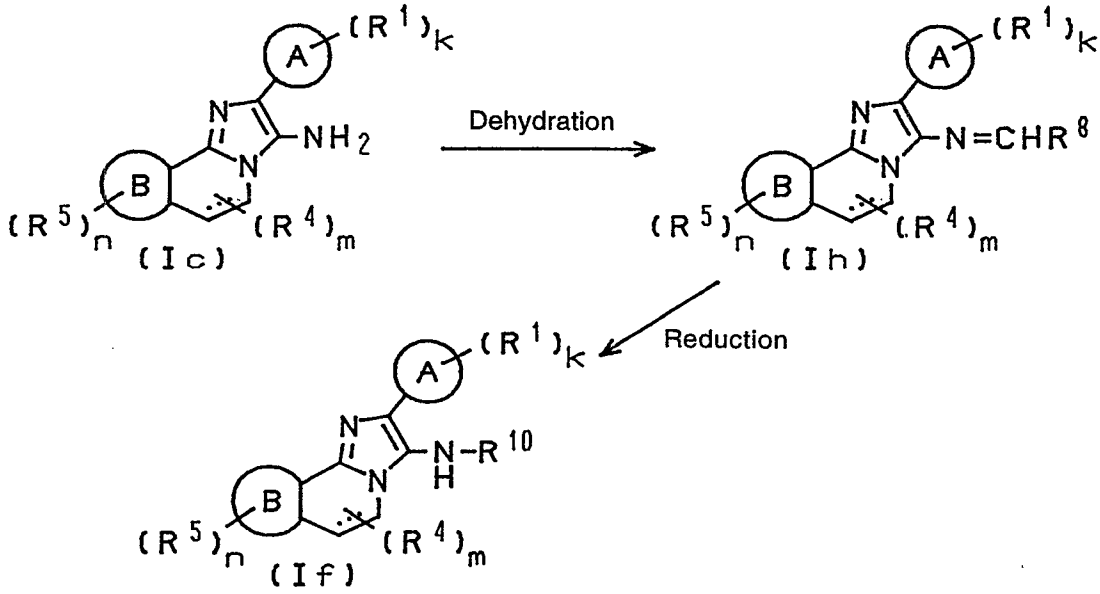
Suitable reducing agent to be used in this reaction may include lithium aluminium hydride and the like.

This reaction is usually carried out in a solvent such as ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], hydrocarbons [e.g. benzene, toluene, xylene, hexane, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 24 hours.

(Process 5)



wherein ring A, ring B, R^1, R^4, R^5, R^8, R^{10}, k, m and n are as defined above.

Compound (Ih) or a salt thereof can be prepared by subjecting

compound (Ic) or a salt thereof and a desired aldehyde to dehydration.

This reaction is usually carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], halogenated hydrocarbons [e.g. dichloromethane, chloroform, etc.] or any other solvents which do not adversely affect the reaction, or without solvent.

As a catalyst, there may be used an inorganic base such as alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide, etc.], an inorganic acid [e.g. hydrochloric acid, sulfuric acid, etc.] or Lewis acid [e.g. toluenesulfonic acid, zinc chloride, boron trifluoride, etc.].

The reaction temperature is not critical, and the reaction is usually carried out with cooling or heating.

The reaction is completed in 5 minutes to 24 hours.

Compound (If) or a salt thereof can also be prepared by subjecting compound (Ih) or a salt thereof to reduction.

Reductions applied to this reaction may include a reduction using metal hydride complex [e.g. sodium borohydride, etc.] and catalytic reduction in the presence of catalyst [e.g. palladium-carbon, platinum oxide, etc.].

This reaction is carried out in a solvent such as alcohols [e.g. methanol, ethanol, etc.], ethers [e.g. tetrahydrofuran, diethyl ether, dioxane, etc.], aromatic hydrocarbons [e.g. benzene, toluene, xylene, etc.], organic amides [e.g. N,N-dimethylformamide, etc.] or any other solvents which do not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is preferably carried out at ambient temperature or at the boiling point of the solvent used.

The reaction is completed in 5 minutes to 24 hours.

Suitable salts of compounds (Ia)-(Ih), (X) and (XII) are acid addition salts as exemplified in compounds (I).

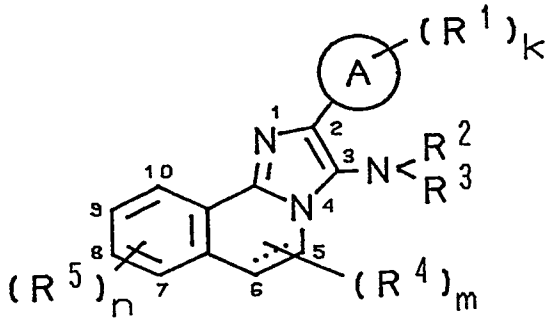
The compounds represented by the formula (I) can also be prepared by conversion of partial structure of compounds (I) having suitable substituent(s) using means as partly exemplified above.

The intermediates and aimed compounds obtained in the above processes can be isolated and purified using purification processes conveniently used in

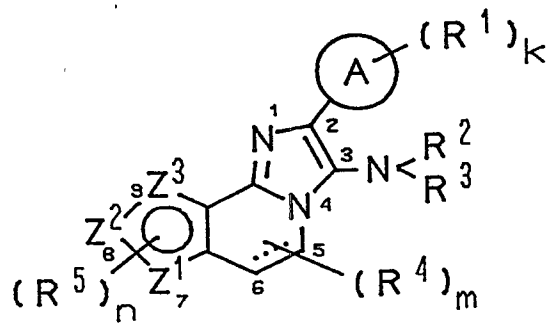
synthetic organic chemistry, for example, filtration, extraction, washing, concentration, drying, recrystallization, various chromatographies and the like. Intermediates can also be used in subsequent reactions without further purification.

When salts of compounds (I) are desirous to obtain and compound (I) is produced in the form of a salt, it may be suitably purified. When compound (I) is produced in the form of a free base, a salt can be obtained by the addition of an acid to a solution or suspension of compound (I) in a suitable organic solvent. Compounds (I) and pharmaceutically acceptable salts thereof can also exist as adducts with water or the solvent used. These adducts are included in this invention.

The compounds of the invention represented by the general formula (I) are shown in Table 1 and Table 2. The compound numbers will be referred to in the description hereinafter. The compounds represented by the formula (I-1) are shown in Table 1 and the compounds represented by the formula (I-2) are shown in Table 2. For reader's convenience, chemical formulae (I-1) and (I-2) in which position numbers are indicated are provided below.



(I-1)



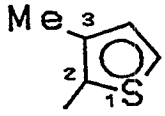
(I-2)

In Table 1 and Table 2, substituents are sometimes indicated using abbreviations, which are as follows:

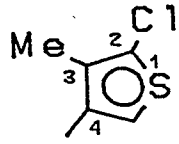
Me	methyl group	Pip	piperidino group
Et	ethyl group	Mor	morpholino group
Pr	n-propyl group	Suc	succinimide group
i-Pr	isopropyl group	Ph	phenyl group

Bu	n-butyl group	Pyr	pyrrolyl group
Pen	n-pentyl group	Fu	furyl group
i-Pen	isopentyl group	Th	thienyl group
c-Pen	cyclopentyl group	Naph	naphthyl group
Hex	n-hexyl group	Bzfu	benzo[b]furyl group
Ac	acetyl group		

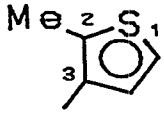
In Table 1 and Table 2, the number in parentheses means the position where ring A binds to the 2-position, and the number and substitution in brackets means where the substituent(s) R^1 locates on ring A. In addition, the number in parentheses indicates the position on the aryl group at which it binds to other group, and the number and substitution in brackets indicates the position and nature of the substitution on the aryl group. Several examples are given below.



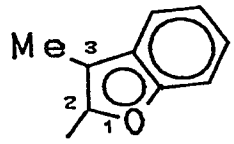
[3-Me]Th(2)



[2-Cl,3-Me]Th(4)

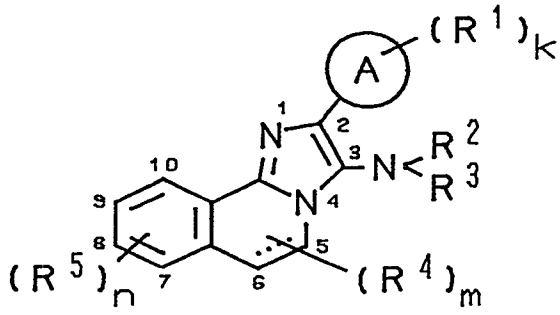


[2-Me]Th(3)



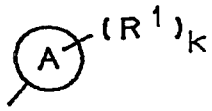
[3-Me]BzFu(2)

In column "5-6" of Table 1 and Table 2, "DB" means that the dotted line, together with the solid line, represents a double bond between the 5- and 6-positions in the the formula (I-1) or (I-2), while "SB" means that the bond represents a single bond.



(I-1)

Table 1 Examples of the compounds according to the invention represented by the formula (I-1).

Compound No		NR^2R^3	R^4, R^5	5-6
1	[2–F]Ph	NH_2	–	DB
2	[2–Cl]Ph	NH_2	–	DB
3	[2–Me]Ph	NH_2	–	DB
4	[2–Me]Ph	NH_2	9–F	DB
5	[2–Me]Ph	NH_2	7–Cl	DB
6	[2–Me]Ph	NH_2	9–Cl	DB
7	[2–Me]Ph	NH_2	10–Cl	DB
8	[2–Me]Ph	NH_2	7–Br	DB
9	[2–Me]Ph	NH_2	5–Me	DB
10	[2–Me]Ph	NH_2	9–Me	DB
11	[2–Me]Ph	NH_2	5–Et	DB
12	[2–Me]Ph	NH_2	5–Pr	DB
13	[2–Me]Ph	NH_2	7–Pr	DB
14	[2–Me]Ph	NH_2	5–i–Pr	DB
15	[2–Me]Ph	NH_2	6–i–Pen	DB
16	[2–Me]Ph	NH_2	6–CH_2OMe	DB
17	[2–Me]Ph	NH_2	6–CH_2OPh	DB
18	[2–Me]Ph	NH_2	7–CH_2OH	DB
19	[2–Me]Ph	NH_2	9–CH(OH)Me	DB
20	[2–Me]Ph	NH_2	9–Ph	DB
21	[2–Me]Ph	NH_2	6–[4–OMe]Ph	DB
22	[2–Me]Ph	NH_2	9–OH	DB
23	[2–Me]Ph	NH_2	5–OMe	DB
24	[2–Me]Ph	NH_2	6–OMe	DB
25	[2–Me]Ph	NH_2	7–OMe	DB
26	[2–Me]Ph	NH_2	9–OMe	DB
27	[2–Me]Ph	NH_2	6–OEt	DB
28	[2–Me]Ph	NH_2	9–OEt	DB

	29	[2–Me]Ph	NH_2	9–OPr	DB
	30	[2–Me]Ph	NH_2	9–O–i–Pr	DB
	31	[2–Me]Ph	NH_2	9–OBu	DB
	32	[2–Me]Ph	NH_2	7,9–$(OMe)_2$	DB
5	33	[2–Me]Ph	NH_2	8,9–$(OMe)_2$	DB
	34	[2–Me]Ph	NH_2	9,10–$(OMe)_2$	DB
	35	[2–Me]Ph	NH_2	9–OCH_2CO_2Et	DB
	36	[2–Me]Ph	NH_2	9–OCH_2CH_2OH	DB
	37	[2–Me]Ph	NH_2	9–OCH_2CH_2OMe	DB
10	38	[2–Me]Ph	NH_2	6–OCH_2Ph	DB
	39	[2–Me]Ph	NH_2	7–OCH_2Ph	DB
	40	[2–Me]Ph	NH_2	9–OCH_2Ph	DB
	41	[2–Me]Ph	NH_2	9–OAc	DB
	42	[2–Me]Ph	NH_2	9–OCOPr	DB
15	43	[2–Me]Ph	NH_2	9–OCO–i–Pr	DB
	44	[2–Me]Ph	NH_2	9–$OCONMe_2$	DB
	45	[2–Me]Ph	NH_2	7–SCH_2Ph	DB
	46	[2–Me]Ph	NH_2	7–SMe	DB
	47	[2–Me]Ph	NH_2	6–Ac	DB
20	48	[2–Me]Ph	NH_2	7–CO–[4–OMe]Ph	DB
	49	[2–Me]Ph	NH_2	7–CO_2H	DB
	50	[2–Me]Ph	NH_2	6–CO_2Me	DB
	51	[2–Me]Ph	NH_2	7–CO_2Me	DB
	52	[2–Me]Ph	NH_2	7–CN	DB
25	53	[2–Me]Ph	NH_2	9–CN	DB
	54	[2–Me]Ph	NH_2	7–$N(Et)_2$	DB
	55	[2–Me]Ph	NH_2	9–OMe, 10–Cl	DB
	56	[2–Me]Ph	NH_2	5–Me, 9–OMe	DB
	57	[3–Me]Ph	NH_2	–	DB
30	58	[4–Me]Ph	NH_2	–	DB
	59	[2–Et]Ph	NH_2	–	DB
	60	[2–CF_3]Ph	NH_2	–	DB
	61	[2–OMe]Ph	NH_2	–	DB

	62	[2,4–Me_2]Ph	NH_2	–	DB
	63	[2–Me, 4–Et]Ph	NH_2	–	DB
	64	[2–Me, 4–F]Ph	NH_2	5–Me	DB
	65	[2–Me, 5–F]Ph	NH_2	6–OMe	DB
5	66	[2–Me, 4–Cl]Ph	NH_2	–	DB
	67	[2–Me, 5–Cl]Ph	NH_2	10–Cl	DB
	68	[2–Me, 4–OH]Ph	NH_2	–	DB
	69	[2–Me, 4–OMe]Ph	NH_2	–	DB
	70	[2–Me, 4–OAc]Ph	NH_2	–	DB
10	71	[2,4,6–Me_3]Ph	NH_2	–	DB
	72	[2–Me, 4–OMe, 5–Br]Ph	NH_2	–	DB
	73	[3–Me]Th(2)	NH_2	–	DB
	74	[3–Me]Th(2)	NH_2	6–OMe	DB
	75	[3–Me]Th(2)	NH_2	9–OMe	DB
15	76	[4–Me]Th(2)	NH_2	–	DB
	77	[3–Et]Th(2)	NH_2	–	DB
	78	[2–Me]Th(3)	NH_2	–	DB
	79	[2–Me]Th(3)	NH_2	5–Me	DB
	80	[2–Me]Th(3)	NH_2	5–OMe	DB
20	81	[4–Me]Th(3)	NH_2	–	DB
	82	[2–Et]Th(3)	NH_2	–	DB
	83	[2,5–Me_2]Th(3)	NH_2	–	DB
	84	[2,5–Cl_2, 4–Me]Th(3)	NH_2	–	DB
	85	[2–Cl, 3–Me]Th(4)	NH_2	–	DB
25	86	[2–Cl, 3–Me]Th(4)	NH_2	7–Br	DB
	87	[2–Cl, 3–Me]Th(4)	NH_2	5–Me	DB
	88	[3–Me]Fu(2)	NH_2	–	DB
	89	[2–Me]Fu(3)	NH_2	–	DB
	90	[2–Me]Fu(3)	NH_2	5–Me	DB
30	91	[2,5–Me_2]Fu(3)	NH_2	–	DB
	92	[2,5–Me_2]Fu(3)	NH_2	5–OMe	DB
	93	[2,5–Me_2]Fu(3)	NH_2	9–OMe	DB
	94	[1–Me]Pyr(2)	NH_2	–	DB

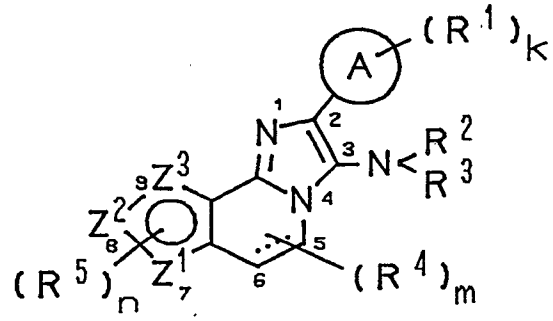
	95	[1–Et]Pyr(2)	NH_2	–	DB
	96	[2–Me]Ph	NH_2	–	SB
	97	[2–Me]Ph	NH_2	9–F	SB
	98	[2–Me]Ph	NH_2	8–Cl	SB
5	99	[2–Me]Ph	NH_2	9–Br	SB
	100	[2–Me]Ph	NH_2	5–Me	SB
	101	[2–Me]Ph	NH_2	7–Me	SB
	102	[2–Me]Ph	NH_2	9–Me	SB
	103	[2–Me]Ph	NH_2	9–OMe	SB
10	104	[2–Me]Ph	NH_2	5,5–Me_2	SB
	105	[2–Me]Ph	NH_2	6,7–Me_2	SB
	106	[2–Me]Ph	NH_2	5–Me, 9–OMe	SB
	107	[2–Me, 4–OH]Ph	NH_2	–	SB
	108	[2–Me, 4–OH, 5–Br]Ph	NH_2	–	SB
15	109	[2–Me]Th(3)	NH_2	–	SB
	110	[2,5–Me_2]Th(3)	NH_2	–	SB
	111	[2–F]Ph	NH(Ac)	–	DB
	112	[2–Me]Ph	NH(Ac)	–	DB
	113	[2–Me]Ph	NH(Ac)	6–i–Pen	DB
20	114	[2–Me]Ph	NH(Ac)	7–Pr	DB
	115	[2–Me]Ph	NH(Ac)	6–OMe	DB
	116	[2–Me]Ph	NH(Ac)	9–OMe	DB
	117	[2–Me]Ph	NH(Ac)	7,9–$(OMe)_2$	DB
	118	[3–Me]Ph	NH(Ac)	–	DB
25	119	[4–Me]Ph	NH(Ac)	–	DB
	120	[2–Et]Ph	NH(Ac)	–	DB
	121	[3–Me]Th(2)	NH(Ac)	–	DB
	122	[3–Et]Th(2)	NH(Ac)	–	DB
	123	[2–Cl, 3–Me]Th(4)	NH(Ac)	–	DB
30	124	[2–Me]Ph	$NH(COCH_2CH_2Cl)$	–	DB
	125	[2–Me]Ph	$NH(COCH_2CH_2SMe)$	–	DB
	126	[2–Me]Ph	$NH(COCH_2CH_2COOH)$	–	DB
	127	[2,4–Me_2]Ph	$NH(COCH_2CH_2COOH)$	–	DB

	128	[2–Me]Ph	NH(COPen)	–	DB
	129	[2–Me]Ph	NH(COCH=CHCO$_2$Me)	–	DB
	130	[2–Me]Ph	NH(CO–[3–CF$_3$]Ph)	–	DB
	131	[2–Me]Ph	NH(CO–[4–OMe]Ph)	–	DB
5	132	[2–Me]Ph	NH(CO–Th(2))	–	DB
	133	[2–Me]Ph	NH(CO–[3–Me]Bzfu(2))	–	DB
	134	[2–Me]Ph	N(Ac)(CH$_2$CO$_2$Et)	–	DB
	135	[3–Et]Th(2)	N(Ac)(CH$_2$CON(Et)$_2$)	–	DB
	136	[2–Me]Ph	N(Ac)(CH$_2$CH$_2$OMe)	–	DB
10	137	[2–F]Ph	N(Ac)(Pr)	–	DB
	138	[2–Me]Ph	N(Ac)(Pr)	–	DB
	139	[2–Me]Ph	N(Ac)(Pr)	6–i–Pen	DB
	140	[2–Me]Ph	N(Ac)(Pr)	6–OMe	DB
	141	[2–Me]Ph	N(Ac)(Pr)	9–OMe	DB
15	142	[2–Me]Ph	N(Ac)(Pr)	8,9–(OMe)$_2$	DB
	143	[3–Me]Ph	N(Ac)(Pr)	–	DB
	144	[3–Me]Th(2)	N(Ac)(Pr)	–	DB
	145	[2–Me]Ph	N(Ac)(i–Pr)	–	DB
	146	[2–Me]Ph	N(Ac)(CH$_2$CH=CH$_2$)	–	DB
20	147	[4–Me]Ph	N(Ac)(i–Pen)	–	DB
	148	[2–Et]Ph	N(Ac)(i–Pen)	–	DB
	149	[2,4–Me$_2$]Ph	N(Ac)(i–Pen)	–	DB
	150	[2–Et]Ph	N(Ac)(CH$_2$–[4–Me]Ph)	–	DB
	151	[2–Me]Ph	N(Ac)(CH$_2$–[4–Me]Ph)	–	DB
25	152	[2–Me]Ph	N(COCH$_2$CH$_2$SMe)(Et)	–	DB
	153	[2–Me]Ph	Suc	–	DB
	154	[2,4–Me$_2$]Ph	Suc	–	DB
	155	[2–Me]Ph	NH(CH$_2$CO$_2$Et)	–	DB
	156	[2–Me]Ph	NH(CH$_2$CO$_2$Pr)	–	DB
30	157	[2–Me]Ph	NH(CH$_2$CON(Et)$_2$)	–	DB
	158	[2–Me]Ph	NH(Et)	–	DB
	159	[2–Me]Ph	NH(Et)	7–Cl	DB
	160	[2–Me]Ph	NH(Et)	9–Cl	DB

161	[2–Me]Ph	NH(Et)	5–Me	DB
162	[2–Me]Ph	NH(Et)	6–i–Pen	DB
163	[2–Me]Ph	NH(Et)	7–Pr	DB
164	[2–Me]Ph	NH(Et)	6–CH_2OMe	DB
165	[2–Me]Ph	NH(Et)	7–OH	DB
166	[2–Me]Ph	NH(Et)	6–OMe	DB
167	[2–Me]Ph	NH(Et)	9–OMe	DB
168	[2–Me]Ph	NH(Et)	6–OCH_2Ph	DB
169	[2–Me]Ph	NH(Et)	7–OCH_2Ph	DB
170	[2–Me]Ph	NH(Et)	7–SMe	DB
171	[2–Me]Ph	NH(Et)	7–OAc	DB
172	[2–Me]Ph	NH(Et)	7–CO_2Me	DB
173	[2–Me]Ph	NH(Et)	7–CO_2Et	DB
174	[2–Me]Ph	NH(Et)	7–$N(Et)_2$	DB
175	[2–CF_3]Ph	NH(Et)	–	DB
176	[3–Me]Th(2)	NH(Et)	6–OMe	DB
177	[3–Me]Th(2)	NH(Et)	9–OMe	DB
178	[3–Et]Th(2)	NH(Et)	–	DB
179	[2–Cl, 3–Me]Th(4)	NH(Et)	–	DB
180	[2–Me]Ph	$NH(CH_2CH_2OMe)$	–	DB
181	[2–Me]Ph	NH(Pr)	6–i–Pen	DB
182	[2–Me]Ph	NH(Pr)	6–OMe	DB
183	[2–Me]Ph	NH(Pr)	9–OMe	DB
184	[2–Me]Ph	NH(i–Pr)	–	DB
185	[2–Me]Ph	$NH(CH_2CH_2CH_2SMe)$	–	DB
186	[2–Me]Ph	$NH(CH_2CH_2CH_2SOMe)$	–	DB
187	[2–Me]Ph	NH(Pen)	–	DB
188	[2–Me]Ph	NH(i–Pen)	–	DB
189	[2,4–Me_2]Ph	NH(i–Pen)	–	DB
190	[2–Me]Ph	NH(c–Pen)	–	DB
191	[2–Me]Ph	NH(Hex)	–	DB
192	[2–Me]Ph	NH(CH(Me)(Ph))	–	DB
193	[2–Me]Ph	$NH(CH_2$–[4–F]Ph)	–	DB

194	[2–Me]Ph	$NH(CH_2$–[4–Me]Ph)	–	DB
195	[2–Me]Ph	$NH(CH_2$–[1–Br]Naph(2))	–	DB
196	[2–Me]Ph	$NH(CH_2$–[3–Me]Bzfu(2))	–	DB
197	[2–Me]Ph	$N(Me)_2$	7–CO_2Me	DB
198	[2–Me]Ph	$N(CH_2CON(Et)_2)_2$	–	DB
199	[2–Me]Ph	$N(Et)_2$	7–Cl	DB
200	[2–Me]Ph	$N(Et)_2$	7–Br	DB
201	[2–Cl, 3–Me]Th(4)	$N(Et)_2$	–	DB
202	[2–Me]Ph	$N(Et)(CH_2CH_2Cl)$	–	DB
203	[3–Et]Th(2)	$N(Et)(CH_2CH_2N(Et)_2)$	–	DB
204	[2–Me]Ph	$N(Et)(CH_2CH_2OH)$	–	DB
205	[2–Me]Ph	$N(Et)(CH_2CH_2OMe)$	–	DB
206	[2–F]Ph	N(Et)(Pr)	–	DB
207	[2–Me]Ph	N(Et)(Pr)	–	DB
208	[2–Me]Ph	N(Et)(Pr)	6–i–Pen	DB
209	[2–Me]Ph	N(Et)(Pr)	9–OMe	DB
210	[2–Me]Ph	N(Et)(Pr)	7,9–$(OMe)_2$	DB
211	[3–Me]Ph	N(Et)(Pr)	–	DB
212	[3–Me]Th(2)	N(Et)(Pr)	–	DB
213	[2–Me]Ph	N(Et)(i–Pr)	–	DB
214	[2–Me]Ph	$N(Et)(CH_2CH_2\ CH_2SMe)$	–	DB
215	[2,5–Me_2]Th(3)	$N(Et)(CH_2CH_2CH_2SMe)$	7–OCH_2Ph	DB
216	[2–Et]Ph	N(Et)(i–Pen)	–	DB
217	[2–Me]Ph	Pip	–	DB
218	[2–Me]Ph	Mor	–	DB
219	[2–Me]Ph	$N(Et)(CH_2$–[4–Me]Ph)	–	DB
220	[2–Et]Ph	$N(Et)(CH_2$–[4–Me]Ph)	–	DB
221	[2–Me]Ph	$NH(CH_2CH{=}CH_2)$	–	DB
222	[2–Me]Ph	$N(Et)(CH_2CH{=}CH_2)$	–	DB
223	[2–Me]Ph	$N(CH_2CH{=}CH_2)_2$	–	DB
224	[2–Me]Ph	$N{=}CHCH_2CH_3$	–	DB
225	[2–Me]Ph	N=CH–[4–Me]Ph	–	DB
226	[2–Et]Ph	N=CH–[4–Me]Ph	–	DB

227	[2–Me]Fu(3)	N=CH–[4–Me]Ph	7–SCH_2Ph	DB
228	[2–Me]Ph	N=CH–[1–Br]NaPh(2)	–	DB



(I-2)

Table 2 Examples of the compounds according to the invention represented by the formula (I-2).

Compound No	Z^1	Z^2	Z^3	A-$(R^1)_k$	NR^2R^3	R^4, R^5	5-6
229	S	C	C	Ph	NH_2	–	DB
230	S	C	C	Ph	NH_2	5–Me	DB
231	S	C	C	[2–OH]Ph	NH_2	5–Me	DB
232	S	C	C	[2–Cl]Ph	NH_2	–	DB
233	S	C	C	[4–Cl]Ph	NH_2	5–Me	DB
234	S	C	C	[2–Me]Ph	NH_2	–	DB
235	S	C	C	[2–Me]Ph	NH_2	8–Br	DB
236	S	C	C	[2–Me]Ph	NH_2	5–Me	DB
237	S	C	C	[2–Me]Ph	NH_2	8–Me	DB
238	S	C	C	[2–Me]Ph	NH_2	5–Et	DB
239	S	C	C	[2–Me]Ph	NH_2	5,6–Me_2	DB
240	S	C	C	[2–Me]Ph	NH_2	5,8–Me_2	DB
241	S	C	C	[2–Me]Ph	NH_2	8–OMe	DB
242	S	C	C	[3–Me]Ph	NH_2	5–Me	DB
243	S	C	C	[2–Et]Ph	NH_2	5–Me	DB
244	S	C	C	[2–CF_3]Ph	NH_2	5–Me	DB

	245	S	C	C	[2–OMe]Ph	NH_2	5–Me	DB
	246	S	C	C	[4–OAc]Ph	NH_2	5–Me	DB
	247	S	C	C	[2–Me, 4–F]Ph	NH_2	5–Me	DB
	248	S	C	C	[2–Me, 4–Cl]Ph	NH_2	5–Me	DB
5	249	S	C	C	Th(2)	NH_2	5–Me	DB
	250	S	C	C	[3–Me]Th(2)	NH_2	–	DB
	251	S	C	C	[3–Me]Th(2)	NH_2	5–Me	DB
	252	S	C	C	[3–Me]Th(2)	NH_2	8–Me	DB
	253	S	C	C	Th(3)	NH_2	5–Me	DB
10	254	S	C	C	[2–Me]Th(3)	NH_2	–	DB
	255	S	C	C	[2–Me]Th(3)	NH_2	5–Me	DB
	256	S	C	C	[2–Me]Th(3)	NH_2	8–Me	DB
	257	S	C	C	[2–Me]Th(3)	NH_2	8–OMe	DB
	258	S	C	C	[2–Me]Th(3)	NH_2	5,6–Me_2	DB
15	259	S	C	C	[4–Me]Th(3)	NH_2	–	DB
	260	S	C	C	[2–Et]Th(3)	NH_2	5–Me	DB
	261	S	C	C	[2–OMe]Th(3)	NH_2	5–Me	DB
	262	S	C	C	[2,5–Cl_2]Th(3)	NH_2	–	DB
	263	S	C	C	[2,5–Cl_2]Th(3)	NH_2	5–Me	DB
20	264	S	C	C	[2,5–Me_2]Th(3)	NH_2	–	DB
	265	S	C	C	[2,5–Me_2]Th(3)	NH_2	5–Me	DB
	266	S	C	C	[2–Cl, 3–Me]Th(4)	NH_2	5–Me	DB
	267	S	C	C	Fu(2)	NH_2	5–Me	DB
	268	S	C	C	Fu(3)	NH_2	5–Me	DB
25	269	S	C	C	[2–Me]Fu(3)	NH_2	–	DB
	270	S	C	C	[2–OMe]Fu(3)	NH_2	–	DB
	271	S	C	C	[2,5–Me_2]Fu(3)	NH_2	–	DB
	272	S	C	C	[2,5–Me_2]Fu(3)	NH_2	8–Br	DB
	273	S	C	C	[2,5–Me_2]Fu(3)	NH_2	5–Me	DB
30	274	S	C	C	[2,5–Me_2]Fu(3)	NH_2	8–Me	DB
	275	S	C	C	[1–Me]Pyr(2)	NH_2	–	DB
	276	O	C	C	[2–Me]Ph	NH_2	–	DB
	277	O	C	C	[2–Me]Ph	NH_2	5–Me	DB

	278	O	C	C	[2–CF_3]Ph	NH_2	–	DB
	279	O	C	C	[2–CF_3]Ph	NH_2	5–Me	DB
	280	O	C	C	[2–Me]Th(3)	NH_2	–	DB
	281	O	C	C	[2–Me]Th(3)	NH_2	5–Me	DB
5	282	O	C	C	[2–Et]Th(3)	NH_2	5–Me	DB
	283	O	C	C	[2–OMe]Th(3)	NH_2	5–Me	DB
	284	O	C	C	[2,5–Cl_2]Th(3)	NH_2	–	DB
	285	O	C	C	[2–Me, 5–Br]Th(3)	NH_2	–	DB
	286	O	C	C	[2,5–Me_2]Th(3)	NH_2	–	DB
10	287	O	C	C	[3–Me]Fu(2)	NH_2	–	DB
	288	O	C	C	[2,5–Me_2]Fu(3)	NH_2	–	DB
	289	O	C	C	[1–Me]Pyr(3)	NH_2	–	DB
	290	N	C	C	[2–Me]Ph	NH_2	–	DB
	291	N	C	C	[2–Me]Ph	NH_2	7–Me	DB
15	292	N	C	C	[2–Me]Ph	NH_2	7–CH_2Ph	DB
	293	N	C	C	[2–Me]Ph	NH_2	7–CH_2–[4–Cl]Ph	DB
	294	N	C	C	[2–Me]Ph	NH_2	7–CH_2–[4–OMe]Ph	DB
	295	N	C	C	[2–Me]Ph	NH_2	5,7–Me_2	DB
	296	N	C	C	[2–Me]Th(3)	NH_2	7–Me	DB
20	297	N	C	C	[2–Et]Th(3)	NH_2	7–CH_2Ph	DB
	298	N	C	C	[2–Me]Th(3)	NH_2	5,7–Me_2	DB
	299	N	C	C	[2–Cl, 3–Me]Th(4)	NH_2	7–Me	DB
	300	N	C	C	[2–Cl]Fu(3)	NH_2	7–CH_2Ph	DB
	301	N	C	C	[2,5–Me_2]Fu(3)	NH_2	7–Me	DB
25	302	N	C	C	[1–Me]Pyr(2)	NH_2	7–Me	DB
	303	C	S	C	[2–Me]Ph	NH_2	5–Me	DB
	304	C	S	C	[3–Me]Th(2)	NH_2	–	DB
	305	C	S	C	[2–Me]Th(3)	NH_2	5–Me	DB
	306	C	S	C	[1–Me]Pyr(2)	NH_2	–	DB
30	307	C	O	C	[2–Me]Ph	NH_2	–	DB
	308	C	O	C	[2–Me]Th(3)	NH_2	–	DB
	309	C	C	S	[2–Cl]Ph	NH_2	5–Me	DB
	310	C	C	S	[2–Me]Ph	NH_2	–	DB

	311	C	C	S	[2–Me]Ph	NH_2	5–Me	DB
	312	C	C	S	[2–Me]Ph	NH_2	8–Me	DB
	313	C	C	S	[2–CF_3]Ph	NH_2	5–Me	DB
	314	C	C	S	[2–Me]Th(3)	NH_2	5–Me	DB
5	315	C	C	S	[4–Me]Th(3)	NH_2	–	DB
	316	C	C	S	[2,5–Me_2]Fu(3)	NH_2	–	DB
	317	C	C	S	[1–Me]Pyr(2)	NH_2	–	DB
	318	C	C	O	[2–Me]Ph	NH_2	–	DB
	319	C	C	O	[2–Me]Th(3)	NH_2	5–Me	DB
10	320	C	C	O	[3–Et, 5–Me]Fu(2)	NH_2	–	DB
	321	C	C	N	[2–Me]Ph	NH_2	9–Me	DB
	322	C	C	N	[2–Me]Th(3)	NH_2	9–Me	DB
	323	C	C	S	[2–Me]Ph	NH_2	–	SB
	324	S	C	C	[2–Me]Ph	NH_2	5,5–Me_2	SB
15	325	S	C	C	[2–Me]Th(3)	NH_2	5,6–Me_2	SB
	326	S	C	C	[2,5–Me_2]Th(3)	NH_2	–	SB
	327	S	C	C	[2–Me]Fu(3)	NH_2	–	SB
	328	S	C	C	[2–Me]Ph	NH(Ac)	–	DB
	329	S	C	C	[2–Me]Ph	NH(Ac)	5–Me	DB
20	330	S	C	C	[2–Me]Th(3)	NH(Ac)	–	DB
	331	S	C	C	[2,5–Me_2]Fu(3)	NH(Ac)	–	DB
	332	N	C	C	[1–Me]Pyr(2)	NH(Ac)	7–Me	DB
	333	C	C	S	[2–Me]Ph	NH(Ac)	–	DB
	334	S	C	C	[2–Me]Ph	NH(COPen)	5–Me	DB
25	335	S	C	C	[2–Me]Ph	N(Ac)(Pr)	5–Me	DB
	336	S	C	C	[2–Me]Th(3)	N(Ac)(Pr)	–	DB
	337	C	C	S	[2–Me]Ph	N(Ac)(Pr)	–	DB
	338	S	C	C	[2–Me]Ph	N(Ac)($CH_2CH{=}CH_2$)	5–Me	DB
	339	S	C	C	[2–Me]Th(3)	N(Ac)($CH_2CH{=}CH_2$)	5–Me	DB
30	340	S	C	C	[2–Me]Ph	NH(Et)	–	DB
	341	S	C	C	[2–Me]Ph	NH(Et)	5–Me	DB
	342	S	C	C	[2–Me]Th(3)	NH(Et)	–	DB
	343	S	C	C	[2,5–Me_2]Fu(3)	NH(Et)	–	DB

344	N	C	C	[2,5–Me_2]Fu(3)	NH(Et)	7–Me	DB
345	C	C	S	[2–Me]Ph	NH(Et)	–	DB
346	C	C	S	[1–Me]Pyr(2)	NH(Et)	–	DB
347	S	C	C	[2–Me]Ph	NH(Hex)	5–Me	DB
348	S	C	C	[2–Me]Ph	NH($CH_2CH=CH_2$)	5–Me	DB
349	S	C	C	[2–Me]Th(3)	NH($CH_2CH=CH_2$)	5–Me	DB
350	S	C	C	[2–Me]Ph	N(Et)(Pr)	5–Me	DB
351	S	C	C	[2–Me]Th(3)	N(Et)(Pr)	–	DB
352	O	C	C	[2–Cl, 3–Me]Th(4)	N(Et)(Pr)	–	DB
353	S	C	C	[2–Me]Ph	N(Et)($CH_2CH=CH_2$)	5–Me	DB
354	S	C	C	[2–Me]Th(3)	N(Et)($CH_2CH=CH_2$)	5–Me	DB
355	S	C	C	[2–Me]Ph	NH(CO_2Et)	–	DB
356	C	C	S	[2–Me]Ph	N(Et)(Pr)	–	DB
357	C	C	S	[3–Et]Th(2)	N(Et)(Pr)	–	DB

INDUSTRIAL APPLICABILITY

For illustrating superior inhibitory action on gastric acid secretion and superior protective action of gastric mucosa of the compounds of the invention, pharmacological and acute toxicity tests are shown below, which were conducted using experimental animal models. In Table 3, Table 4, Table 5, Table 6, and Table 7, the numbers of test compounds correspond to the compound numbers shown in Table 1 and Table 2.

Experiment 1 Inhibitory action on H^+/K^+-ATPase activity

According to the method of Hongo et al. [The Japanese Journal of Pharmacology, 52, p295, (1990)], a microsome fraction prepared from porcine gastric mucosa was used as a standard enzyme. The standard enzyme (10-20μg protein) and the test compound (0.1-100μM) dissolved in dimethylsulfoxide was incubated at 37°C for 30 minutes in the 50mM Tris-acetate buffer (pH7.4, containing 2mM magnesium chloride, 5mM potassium chloride). The enzyme reaction was started by adding adenosinetriphosphate (ATP)•Tris at the final concentration of 2mM, and the reaction was kept at 37°C for 15 minutes. The reaction was stopped by adding chilled 10% trichloroacetic acid. Inorganic phosphate released during the reaction was colorimetrically determined according to the method of Fiske-Subbarow [The Journal of Biological Chemistry, 66, p375, (1925)]. H^+/K^+-ATPase activity was determined by the difference of the enzyme activities under the conditions with or without potassium chloride. The inhibitory activities of test compounds were determined as the 50% inhibitory concentration (IC_{50} value) from reaction-concentration curve, and the results are shown in Table 3.

Table 3

The inhibitory action on H^+/K^+-ATPase activity

Test Compound		$IC_{50}(\mu M)$	Test Compound		$IC_{50}(\mu M)$
3		26.0	195		8.8
6		12.0	200	hydrochloride	1.2
7		8.0	202	hydrochloride	9.8
9		34.0	206		2.3
10		20.0	207	hydrochloride	9.3
12		12.5	211	hydrochloride	2.4
15		3.7	212	hydrochloride	1.9
21		7.4	214		7.0
22		1.9	216	hydrochloride	2.5
24		13.5	217	hydrochloride	4.7
26		32.0	219	hydrochloride	3.6
38		4.8	222	hydrochloride	2.0
46		8.4	223	hydrochloride	4.5
54	hydrochloride	1.0	226		1.9
75	hydrochloride	6.4	230		20.0
78		17.0	232		17.0
83	hydrochloride	5.6	234		7.6
91		5.6	236		4.7
94		3.0	238		2.9
96	maleate	17.5	239		26.0
104		12.0	245		9.0
107		33.0	248		4.7
151	hydrochloride	7.8	254		4.5
158	hydrochloride	13.0	255		6.6
163	hydrochloride	4.6	264		1.2
166	hydrochloride	23.0	271	hydrochloride	5.2
169		5.8	275		24.0
176		9.0	291	hydrochloride	4.8
179		4.8	292	hydrochloride	8.8

182		11.0	310		26.0
188		10.5	311		8.0
189	hydrochloride	6.8	340	hydrochloride	33.0
191	hydrochloride	5.2	356	hydrochloride	8.4
192		4.4			

Experiment 2 Inhibition of gastric acid secretion observed under acute fistula method

Male Wistar rats (6-8weeks) fasted for 24 hours (water ad libitum) were used. The rats were anesthetized by intraperitoneal administration of 1.25g/kg of urethane. The abdomen was incised, and acute gastric fistula was connected to the stomach. Two ml of saline was injected into the stomach, and recovered every 20 minutes. The gastric acid secretion was determined by titrating of gastric juice by 150mM sodium hydroxide up to pH7.0 using an autotitrator. Test compounds (30mg/kg) suspended in a 0.5% aqueous sodium carboxymethylcellulose (CMC-Na) solution were administered intraduodenally. After 1 hour, gastric acid secretion was stimulated by subcutaneous administration of histamine dihydrochloride dissolved in saline (10mg/kg). Inhibition (%) of gastric acid secretion was determined by calculating cumulative amount of the acid secretion during two hours after histamine stimulation and then comparing the cumulative amount with that in the control group. In the control group, only 0.5% aqueous CMC-Na solution was administered intraduodenally. The test results are shown in Table 4.

Table 4

Inhibition of gastric acid secretion observed under acute fistula method

Test Compound		Inhibition (%)	Test Compound		Inhibition (%)
3		82.2	179		52.8
6		79.6	182		58.4
7		74.9	188		79.1
9		90.7	205	hydrochloride	86.0
26		90.8	207	hydrochloride	67.4
46		73.8	214		56.0

75	hydrochloride	73.3	221	hydrochloride	66.7
158	hydrochloride	83.6	222	hydrochloride	72.6
166	hydrochloride	54.9	223	hydrochloride	60.1
176		49.9			

Experiment 3 Inhibition of gastric acid secretion observed under stomach perfusion method

Male Sprague Dawrey rats (6-7weeks) fasted for 24 hours were used (water ad libitum). The rats were anesthetized by intraperitoneal administration of 1.25g/kg of urethane. The abdomen was incised, and gastral cavity was perfused with saline during experiment. The perfusate was titrated by 10mM sodium hydroxide up to pH5.5 using an autotitrator in accordance with Stat-method. Gastric acid secretion was stimulated by intravenous administration of histamine dihydrochloride (8mg/kg/hr). Two hours after histamine stimulation, a test compound (1-10mg/kg) was administered intrapenetorially. The test compound was mixed with small amount of polysorbate-80, and the mixture was suspended in saline. The test compound was evaluated using ID_{50} (dose showing 50% inhibition of acid secretion) which was calculated based on inhibition of the acid secretion observed one hour after administration of the compound. The results are shown in Table 5.

Table 5

Inhibition of gastric acid secretion observed under stomach perfusion method

Test Compound		ID_{50} (mg/kg)	Test Compound		ID_{50} (mg/kg)
3		3.4	103		7.4
6		5.0	158	hydrochloride	8.6
9		3.1	230		6.2
10		4.2	232		3.2
12		7.2	234		1.8
24		5.4	236		1.4
26		2.8	254		1.1
43		7.0	255		1.0
56		6.5	271	hydrochloride	2.4

78		1.6	291	hydrochloride	6.4
94		5.8	310		3.0
96	maleate	8.8	340	hydrochloride	4.9

Experiment 4 Inhibition of ethanol-induced gastric lesion (Protection of gastric mucosa)

Male Wister rats (6-7weeks, 5 rats per group) fasted for 24 hours were used (water ad libitum). Test compound (30mg/kg) suspended in 0.5% aqueous CMC-Na solution was orally administered. In the control group, only 0.5% aqueous CMC-Na solution was administered. Thirty minutes after administration, 0.5ml/100g body weight of ethanol was orally administered to cause gastric lesion. After one hour, the rat was killed by excessive amount of ether, and the stomach was removed and fixed with 2% formalin. After fixation, the stomach was dissected along the large curvature. The size of each of mucosal lesions was measured under dissecting microscope, and the total size of the lesions per rat was determined and used as ulcer index (mm). Inhibition of gastric lesion was determined by comparing the ulcer index in the control group and test group. Test results are shown in Table 6.

Table 6 Inhibition of ethanol-induced gastric lesion

Test Compound		Inhibition (%)
3		73.5
158	hydrochloride	92.4
166	hydrochloride	49.7
205	hydrochloride	98.6
216	hydrochloride	81.7
221	hydrochloride	73.7
222	hydrochloride	98.8
236		91.5
254		92.4
271	hydrochloride	99.5

Experiment 5 Acute toxicity

Male ICR mice (6 weeks, 3 mice per group) fasted for 16 hours were used (water ad libitum). A test compound suspended in 5% aqueous gum arabic solution was orally administered. After administration, mortality of the animals was observed during 7 days and approximate lethal dose was determined. The results are shown in Table 7.

Table 7

Acute toxicity

Test Compound		Approximate lethal dose(mg/kg)	Test Compound		Approximate lethal dose(mg/kg)
3		> 2,000	188		> 2,000
6		> 2,000	205	hydrochloride	> 2,000
9		> 2,000	212	hydrochloride	> 2,000
26		> 2,000	216	hydrochloride	> 2,000
91		> 2,000	217	hydrochloride	> 2,000
158	hydrochloride	> 2,000	221	hydrochloride	> 2,000
166	hydrochloride	> 2,000	222	hydrochloride	> 2,000
176		> 2,000	236		> 2,000
179		> 2,000	310		> 2,000
182		> 2,000			

The above experiments revealed that the compounds of the present invention exert inhibitory actions against H^+/K^+-ATPase activity and gastric acid secretion and protection of gastric mucosa. Furthermore, the compounds of the invention have low toxicity.

Accordingly, the present invention provides promised anti-ulcer drugs having inhibitory action on aggressive factors and promoting action on defensive factors. The anti-ulcer drugs of the invention are therefore useful for treating and preventing gastroduodenal ulcers, gastritis, reflex esophagitis, Zollinger-Erison syndrome, and the like.

A pharmaceutical composition containing one or more of the compound(s) (I) of the present invention or pharmaceutically acceptable salts or solvates thereof as an active ingredient may be used as the above-mentioned

drugs. The pharmaceutical composition can be administered orally or parenterally in the form of tablets, powders, granules, capsules, pills, syrups, suppositories, injections, external preparations, drip injections, and the like. The pharmaceutical composition may be produced by conventional methods without difficulty. For instance, solid preparations for oral use may be prepared by a conventional method using vehicles, binders, disintegrators, lubricants, coloring agents, corrigents, and other commonly used additives. Examples of such vehicles may include lactose, corn starch, sucrose, glucose, crystalline cellulose, silica, sorbitol, and the like. Examples of such binders are polyvinylalcohol, polyvinylether, ethylcellulose, gum arabic, tragacanth, gelatin, hydroxypropylcellulose, hydroxypropylstarch, polyvinylpyrrolidone, and the like. Examples of disintegrators may include starch, agar, gelatin, crystalline cellulose, calcium carbonate, sodium bicarbonate, calcium citrate, calcium carboxymethylcellulose, dextran, and the like. Examples of lubricants may include magnesium stearate, talc, polyethyleneglycol, silica, hydrogenated vegetable oil, and the like. The coloring agents may be selected from those which are approved as additives for pharmaceutical preparations. Examples of corrigents are powdered cocoa, mentha oil, powdered cinnamon bark, and the like. Tablets and granules may be coated with sugar, gelatin, and the like. Injections can readily be prepared by a conventional method, using, if necessary, distilled water, pH-regulating agent, buffering agent, stabilizer, solubilizer, and other commonly used additives.

Dosage of the compound of the invention, when used as an anti-ulcer agent, will vary according to environmental conditions, such as symptom, age, body weight of particular patient and administration route. The dosage may be usually 3 to 1,500 mg, preferable 5 to 800 mg per day for adults. Increased or decreased dosage is also acceptable, and it may be administered once a day or after divided into some portions.

The compounds of the invention may conveniently be administered for a continued period of time, for example, for a week or more.

The phamaceutical composition of the invention containing the compound (I), pharmaceutically acceptable salt or solvate thereof useful for the treatment of the above-mentioned diseases may also include one or more

pharmacologically active constituents, such as antacids (magnesium carbonate, magnesium hydroxide, aluminum hydroxide, magnesium aluminate etc.), non-steroidal anti-inflammatory agents (indomethacin, aspirin, naproxen etc.), steroids, nitrite scavengers (ascorbic acid, aminosulphonic acid etc.), antibiotics (penicillins, tetracyclines etc.) and, if appropriate, enzymes, vitamins, or amino acids.

Special attention should be directed to a combination of the compound according to the invention with other agents inhibiting acid secretion, such as H_2 blockers (cimetidine or ranitidine etc.) or with so-called peripheral anticholinergic agents (pirenzepine, telenzepine or zolenzepine etc.) with the aim of reinforcing the principal action in an additive or superadditive sense and/or eliminating or reducing side effects, or with antibacterial substances (cephalosporins, tetracyclines, nalidixic acid etc.) with the aim of eradication of Helicobacter pylori.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention is illustrated in more detail with working examples. However, the present invention is not limited thereto. Starting compounds used in the present invention include novel compounds. Processes for preparing such starting compounds are also described below under preparations. In Preparations and Examples, IR means infrared spectrum, wherein data is given using cm^{-1} unit, and the method used is shown in parentheses, MS means mass spectrum, HRMS means high-resolution mass spectrum wherein the method used is shown in parentheses, and NMR means proton nuclear magnetic resonance spectrum, wherein data is given in ppm and the solvent used is shown in parentheses using following abbreviations.

CDCL	Chloroform-d
DMSO	Dimethylsulfoxide-d_6
ACET	Acetone-d_6
METH	Methanol-d_4

Preparation 1

4-(4-Methoxybenzyl)amino-6-methylthieno[3,2-c]pyridine

To a solution of 5.1g of sodium hydride in oil (prewashed by decantation with hexane.) in 60ml of dry tetrahydrofuran was added dropwise 30g of triethyl 2-phosphonopropionate over a period of 30 minutes under dry argon atmosphere at room temperature. After the mixture was stirred for further 1 hour, a solution of 11.8g of 2-thiophenealdehyde in 30ml of tetrahydrofuran was added dropwise. The mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed successively with water and saturated saline, dried over anhydrous magnesium sulfate. Drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 11.0g of ethyl 2-methyl-3-(2-thienyl)acrylate as a yellow oil. Next, 150ml of ethanol and 60ml of aqueous 2N sodium hydroxide were added to the oil, and the mixture was refluxed for 1 hour. After cooling, ethanol was removed under reduced pressure, and the residue was acidified with dilute hydrochloric acid. Crystalline precipitate was collected by filtration to give 8.2g of 2-methyl-3-(2-thienyl)acrylic acid as a white powder.

To a mixture of 8.2g of 2-methyl-3-(2-thienyl)acrylic acid and 9.5ml of triethylamine in 45ml of acetone was added dropwise 7.2ml of ethyl chlorocarbonate over a period of 30 minutes under ice-cooling with stirring. After being stirred for 1 hour, a solution of 5.1g of sodium azide in 10ml of water was added dropwise over 30 minutes, and then stirred for 1 hour. The reaction mixture was poured into water and extracted with benzene. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. Drying agent was removed by filtration, and the solvent was removed under reduced pressure, and then 15ml of diphenylether was added to the residue. The resultant solution was added dropwise to a mixture of 14ml of tri-n-butylamine and 35ml of diphenylether at 200°C. When addition was complete, the reaction mixture was allowed to cool and the crystalline precipitate was washed with diethyl ether to give 6.2g of 6-methylthieno[3,2-c]pyridin-4(5H)-one as a pale yellow powder.

A solution of 6.2g of 6-methylthieno[3,2-c]pyridin-4(5H)-one in 30ml of phosphoryl chloride was heated under reflux for 1 hour. After being cooled, the excess phosphoryl chloride was removed under reduced pressure, and the residue was poured into ice water, made basic with aqueous 2N sodium hydroxide and extracted with chloroform. The extract was washed successively with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to give 7.0g of 4-chloro-6-methylthieno[3,2-c]pyridine as a brown oily material.

A mixture of 7.0g of 4-chloro-6-methylthieno[3,2-c]pyridine and 28ml of 4-methoxybenzylamine was stirred at 170°C for 4 hours. After being cooled, the reaction mixture was diluted with 400ml of chloroform, washed with water and saturated saline, dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 10g of the title compound as a yellow oily material.

IR(Neat): 3420, 3080, 3000, 2950, 2920, 2840, 1680, 1590, 1544, 1510, 1444, 1400, 1334, 1302, 1248, 1172, 1158, 1108, 1090, 1060, 1030, 888, 810, 690

NMR(CDCL): 7.37(2H,d,J=9.0Hz), 7.18(2H,s), 6.98(1H,s), 6.87(2H,d,J=9.0Hz), 5.10-4.60(1H,br), 4.70(2H,d,J=5.0Hz), 3.79(3H,s), 2.50(3H,s)

Preparation 2

4-Amino-6-methylthieno[3,2-c]pyridine

To a solution of 24g of 4-(4-methoxybenzyl)amino-6-methylthieno[3,2-c]pyridine in 80ml of trifluoroacetic acid was added 15ml of concentrated sulfuric acid, and the mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was poured into ice water, rendered alkaline by the addition of 28% ammonia water and extracted with chloroform. The extract was washed with water and saturated saline, dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel and recrystallized from chloroform/petroleum ether

to give 15g of the title compound as a white powder.

m.p.: 136.0-136.5°C

IR(KBr): 3470, 3300, 3140, 1632, 1584, 1540, 1452, 1420, 1370, 1346, 1270, 1080, 894, 802, 700

NMR(CDCL): 7.20(2H,s), 7.00(1H,s), 5.40-5.00(2H,br), 2.45(3H,s)

Preparation 3

7-Aminothieno[2,3-c]pyridine

To a solution of 18g of thieno[2,3-c]pyridine in 300ml of chloroform was added 33g of 3-chloroperbenzoic acid portionwise with ice-cooling over a period of 1 hour, and the mixture was stirred for further 1 hour under the same conditions. The reaction mixture was diluted with 400ml of chloroform, washed successively with water, a saturated sodium carbonate solution and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to give 16.6g of thieno[2,3-c]pyridine-N-oxide as a white powder.

To a solution of 16.6g of thieno[2,3-c]pyridine-N-oxide in 500ml of chloroform was added 25g of p-toluenesulfonyl chloride portionwise with ice-cooling over a period of 1 hour. After the reaction mixture was stirred for further 30 minutes under the same conditions, 250ml of 10% ammonia water was added, and stirred at ambient temperature for 16 hours. The reaction mixture was diluted with 400ml of chloroform, washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 2.8g of the title compound as a brown oily material.

IR(Neat): 3450, 3320, 3150, 1625, 1580, 1552, 1488, 1459, 1400, 1304, 1245, 1152, 1110, 1035, 1005, 800, 750

NMR(CDCL): 8.00(1H,d,J=6.0Hz), 7.52(1H,d,J=5.0Hz), 7.24(1H,d,J=5.0Hz), 7.11(1H,d,J=6.0Hz), 5.33(2H,brs)

Preparation 4

1-Amino-8-chloro-7-methoxyisoquinoline

To a solution of 1.3g of 8-chloro-7-methoxyisoquinoline-N-oxide in 40ml of pyridine was added 1.4g of p-toluenesulfonyl chloride, and the mixture was stirred at ambient temperature for 2 hours. The solvent was removed under reduced pressure, 20ml of ethanolamine was added to the resultant residue, and then the mixture was stirred for further 3 hours. The reaction mixture was poured into water, and the crystalline precipitate was collected by filtration, washed with water, and dried under reduced pressure to give 0.8g of the title compound as a yellow powder.

IR(KBr): 3540, 3300, 3130, 3050, 2950, 2850, 1633, 1600, 1540, 1518, 1450, 1423, 1370, 1330, 1290, 1265, 1068, 1025, 957, 818

NMR(CDCL): 7.82(1H,d,J=6.0Hz), 7.60(1H,d,J=9.0Hz), 7.32(1H,d,J=9.0Hz), 6.90(1H,d,J=6.0Hz), 6.50-6.02(2H,br), 4.00(3H,s)

Preparation 5

1-Amino-7-methoxyisoquinoline

A solution of 8.0g of 7-methoxyisoquinoline in 45ml of N,N-dimethylaniline was warmed at 60°C, and then 5.9g of sodium amide was added. The reaction mixture was heated at 130°C over a period of 2 hours, and stirred for further 1 hour under the same conditions. After being cooled, the reaction mixture was poured into ice water and extracted with chloroform. The extract was washed with water, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel and recrystallized from benzene to give 5.7g of the title compound as colorless flakes.

m.p.: 137.5-138.0°C

IR(KBr): 3440, 3340, 3150, 3080, 2980, 2850, 1652, 1605, 1569, 1516, 1455, 1428, 1385, 1350, 1298, 1241, 1209, 1190, 1136, 1085, 1032, 915, 890, 853, 830

NMR(CDCL): 7.84(1H,d,J=6.0Hz), 7.59(1H,d,J=9.0Hz), 7.20(1H,dd,J=2.0Hz,9.0Hz), 7.07(1H,d,J=2.0Hz), 6.95(1H,d,J=6.0Hz), 5.33(2H,brs), 3.82(3H,s)

Preparation 6

2'-Methyl-2-bromoacetophenone

To a solution of 3.0g of 2'-methylacetophenone in 60ml of acetic acid was added successively 9.7ml of 47% hydrobromic acid and 8.6g of pyridinium hydrobromide perbromide, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and a saturated sodium carbonate solution, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to give 5.4g of the title compound as a colorless oily material.

IR(Neat): 3075, 3030, 2980, 2940, 1682, 1604, 1573, 1490, 1459, 1435, 1385, 1358, 1295, 1260, 1210, 1189, 1040, 1008, 978, 754, 735

NMR(CDCL): 7.72-7.05(4H,m), 4.36(2H,s), 2.49(3H,s)

Preparation 7

2-(2-Methylphenyl)imidazo[2,1-a]isoquinoline

A mixture of 3.0g of 1-aminoisoquinoline, 6.7g of 2'-methyl-2-bromoacetophenone and 17.5g of sodium bicarbonate in 50ml of ethanol was refluxed for 2 hours. After being cooled, the reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel and recrystallized from dichloromethane/petroleum ether to give 4.4g of the title compound as pale brown prisms.

m.p.: 93.0°C

IR(KBr): 3070-3020, 2960, 1640, 1604, 1538, 1515, 1480, 1458, 1382, 1316, 1208, 1193, 1144, 1120, 1078, 1045, 938, 870, 788, 770, 730, 700

NMR(CDCL): 8.90-8.60(1H,m), 8.15-7.83(1H,m), 7.79(1H,d,J=7.0Hz), 7.70-7.10(7H,m), 6.90(1H,d,J=7.0Hz), 2.54(3H,s)

Preparation 8

9-Methoxy-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline

To a solution of 3.1g of 7-methoxy-3,4-dihydroisoquinoline in 40ml of

methylene chloride was added 7.3g of 2'-methyl-2-bromoacetophenone, and the mixture was stirred at room temperature for 4 hours and evaporated in vacuo. To the resultant residue was added a mixture of 20ml of acetic acid and 10.4g of ammonium acetate, and the mixture was refluxed for 6 hours. After being cooled, the reaction mixture was poured into aqueous 2N sodium hydroxide and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 0.7g of the title compound as a brown viscous material.

IR(Neat): 3070, 3020, 2960, 2910, 2850, 1617, 1578, 1548, 1500, 1482, 1465, 1442, 1380, 1332, 1309, 1280, 1252, 1227, 1212, 1180, 1123, 1078, 1036, 947, 915, 868, 810, 745

NMR(CDCL): 8.09-7.80(1H,m), 7.74(1H,d,J=2.0Hz), 7.38-7.11(4H,m), 7.05(1H,s), 6.85(1H,dd,J=2.0Hz,6.0Hz), 4.17(2H,t,J=7.0Hz), 3.90(3H,s), 3.08(2H,t,J=7.0Hz), 2.53(3H,s)

Preparation 9

9-Methoxy-5-methyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline

To a solution of 12g of 7-methoxy-3-methyl-3,4-dihydroisoquinoline in 120ml of dimethoxyethane was added 16g of 2'-methyl-2-bromoacetophenone, and the mixture was stirred at room temperature for 14 hours. The resulting white powder was collected by filtration to give 13g of 7-methoxy-3-methyl-2-(2-methylphenyl)-3,4-dihydroisoquinolinium bromide. A mixture of this white powder, 80ml of acetic acid and 12.8g of ammonium acetate was then refluxed for 3 hours. After being cooled, the reaction mixture was poured into water, rendered alkaline by the addition of a saturated sodium carbonate solution and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 5.3g of the title compound as a yellow oily material.

IR(Neat): 3060, 3010, 2970, 2940, 2900, 2840, 1612, 1532, 1493, 1482, 1462,

1455, 1440, 1372, 1338, 1287, 1274, 1241, 1220, 1170, 1078, 1032, 945, 870, 742

NMR(CDCL): 8.02-7.78(1H,m), 7.71(1H,d,J=3.0Hz), 7.40-7.08(5H,m), 6.83(1H,dd,J=3.0Hz,9.0Hz), 4.69-4.02(1H,m), 3.88(3H,s), 3.38-2.72(2H,m), 2.52(3H,s), 1.52(3H,d,J=7.0Hz)

Preparation 10

9-Methoxy-5-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline

To a solution of 4.9g of 9-methoxy-5-methyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline in 30ml of decalin was added 0.97g of palladium on activated carbon (Pd 10%) and the mixture was refluxed for 6 hours. After being cooled and an addition of 200ml of chloroform, the mixture was filtered and the filtrate was evaporated in vacuo. The resultant residue was crystallized from a mixture of hexane and ethyl acetate(6:1) to give 3.0g of the title compound.

IR(KBr): 2940, 2830, 1618, 1538, 1520, 1498, 1481, 1460, 1440, 1405, 1345, 1280, 1259, 1247, 1210, 1174, 1130, 1100, 1030, 872, 830, 800, 770, 730

NMR(CDCL): 8.10(1H,d,J=2.0Hz), 8.07-7.81(1H,m), 7.59(1H,s), 7.55(1H,d,J=9.0Hz), 7.40-7.02(4H,m), 6.79(1H,s), 3.98(3H,s), 2.59(6H,s)

Preparation 11

2-(2-Methyl-3-thienyl)furo[3,2-c]imidazo[1,2-a]pyridine

A solution of 6.1g of 2-(5-bromo-2-methyl-3-thienyl)furo[3,2-c]imidazo[1,2-a]pyridine, which was prepared by the reaction of 4-aminofuro[3,2-c]pyridine and 5-bromo-3-bromoacetyl-2-methylthiophene in a similar manner to that of aforementioned Preparation 7, in 50ml of tetrahydrofuran was added dropwise to a solution of 3.5g of lithium aluminum hydride in 50ml of tetrahydrofuran. When addition was complete, the mixture was refluxed for 2 hours. After being cooled, excessive lithium aluminum hydride was decomposed by the addition of hydrous ether, and the mixture was dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure to give 4.5g of the title compound as a white powder.

m.p.: 83.5-85.0°C

IR(KBr): 3370, 3140, 3090, 2910, 1671, 1645, 1574, 1510, 1440, 1402, 1338, 1305, 1270, 1240, 1148, 1136, 1079, 1062, 1038, 890, 855, 768, 738, 712, 682

NMR(CDCL): 7.98(1H,d,J=8.0Hz), 7.71(1H,d,J=2.0Hz), 7.65(1H,s), 7.56(1H,d,J=5.0Hz), 7.31(1H,d,J=2.0Hz), 7.13(1H,d,J=5.0Hz), 7.08(1H,d,J=8.0Hz), 2.69(3H,s)

Example 1

3-Amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 3)

In a mixture of 30ml of acetic acid and 6ml of water was dissolved 2.5g of 2-(2-methylphenyl)imidazo[2,1-a]isoquinoline with ice-cooling and stirring. A solution of 3.4g of sodium nitrite in 12ml of water was added portionwise to this solution and then the mixture was stirred at room temperature for 1 hour. The resulting crude crystals were collected by filtration and washing. The obtained powder was suspended in a mixture of 30ml of acetic acid and 15ml of water. To this suspension was added portionwise 6.3g of zinc powder. After 1 hour, the reaction mixture was filtered, the filtrate was rendered alkaline by the addition of 28% ammonia water, and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel and recrystallized from ethyl acetate/petroleum ether to give 2.1g of the title compound as orange needles.

m.p.: 151.0-153.0°C

Analysis Calcd.for $C_{18}H_{15}N_3$

: C 79.10%, H 5.53%, N 15.37%

Found: C 79.29%, H 5.62%, N 15.18%

IR(KBr): 3370, 3120-3080, 1645, 1612, 1582, 1528, 1490, 1458, 1382, 1277, 1146, 893, 764, 725

NMR(CDCL): 8.76-8.40(1H,m), 7.78(1H,d,J=7.0Hz), 7.69-7.09(7H,m), 6.95(1H,d,J=7.0Hz), 3.28(2H,brs), 2.37(3H,s)

MS(EI)m/z: 273(M^+), 257, 144

Example 2

3-Amino-2-(2,5-dimethyl-3-furyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 271) hydrochloride

To a solution of 4.0g of 2-(2,5-dimethyl-3-furyl)imidazo[1,2-a]thieno[3,2-c]pyridine, which was prepared by the reaction of 4-aminothieno[3,2-c]pyridine and 3-bromoacetyl-2,5-dimethylfuran in a similar manner to that of aforementioned Preparation 7, in 60ml of dioxane was added dropwise 6ml of isopentyl nitrite at 60°C. When addition was complete, the mixture was stirred for further 20 minutes at 70°C. After being cooled, precipitated crystalline was collected by filtration, washed with ether, and added with 9.8g of zinc powder after addition of 40ml of acetic acid and 30ml water under ice-cooling. The mixture was stirred for 16 hours. The solution was filtered, the filtrate was rendered alkaline by the addition of 28% ammonia water, and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 2.3g of 3-Amino-2-(2,5-dimethyl-3-furyl)imidazo[1,2-a]thieno[3,2-c]pyridine(Compound 271) as a pale yellow amorphous solid. To a solution of 2.3g of the product in 100ml of ether was added a saturated solution of hydrogen chloride in ether, precipitated crystalline was collected by filtration, and recrystallized from ethanol to give 2.0g of the title compound as pale yellow plates.

m.p.: 210.0-211.5°C(dec.)

IR(KBr): 3370, 3300, 3140, 3050, 2650, 1665, 1630, 1623, 1580, 1538, 1445, 1420, 1400, 1378, 1265, 1224, 1000, 710

NMR(DMSO): 8.60(1H,d,J=7.5Hz), 8.48(1H,d,J=5.0Hz), 8.18(1H,d,J=5.0Hz), 8.08(1H,d,J=7.5Hz), 6.44(1H,s), 2.42(3H,s), 2.35(3H,s)

Example 3

Compounds obtained in the same manner as in Examples 1 and 2 are collectively shown below.

3-Amino-2-(2-fluorophenyl)imidazo[2,1-a]isoquinoline (Compound 1)

hydrochloride
m.p.: 221.0-229.0°C(dec.)
IR(KBr): 3500, 3130, 3060, 2950, 2760, 2700, 2570, 1670, 1634, 1575, 1550, 1509, 1460, 1430, 1332, 1270, 1214, 1109, 790, 760
NMR(DMSO): 9.23-8.89(1H,m), 8.58(1H,d,J=7.8Hz), 8.19-7.18(8H,m)

3-Amino-2-(2-chlorophenyl)imidazo[2,1-a]isoquinoline (Compound 2)
m.p.: 185.0-187.0°C
IR(KBr): 3360-3150, 1645, 1610, 1580, 1483, 1460, 1433, 1380, 1050, 1030, 895, 785, 760
NMR(CDCL): 8.81-8.46(1H,m), 8.01-7.15(8H,m), 7.01(1H,d,J=7.0Hz), 3.60-3.23(2H,brs)

3-Amino-9-fluoro-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 4)
m.p.: 191.0-192.5°C
IR(KBr): 3390, 3140, 2930, 1615, 1578, 1559, 1523, 1499, 1455, 1419, 1379, 1276, 1248, 1218, 1181, 1140, 1073, 920, 868, 813, 755, 723
NMR(CDCL): 8.22(1H,dd,J=2.0Hz,9.8Hz), 7.84-7.11(6H,m), 7.77(1H,d,J=7.0Hz), 6.98(1H,d,J=7.0Hz), 3.51-3.10(2H,br), 2.42(3H,s)

3-Amino-9-chloro-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 6)
m.p.: 190.0-191.0°C
IR(KBr): 3380, 3320, 1608, 1582, 1518, 1480, 1438, 1408, 1386, 1368, 1104, 826, 726
NMR(DMSO): 8.34(1H,d,J=2.0Hz), 8.16(1H,d,J=7.0Hz), 7.83(1H,d,J=9.0Hz), 7.70-7.10(6H,m), 5.10(2H,brs), 2.46(3H,s)

3-Amino-10-chloro-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 7)
m.p.: 147.0-147.5°C
IR(KBr): 3360, 3100, 1640, 1610, 1575, 1520, 1482, 1451, 1377, 1270, 1140, 759
NMR(CDCL): 8.71-8.44(1H,br), 7.81-6.70(8H,m), 3.30(2H,s), 2.38(3H,s)

3-Amino-5-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 9)
m.p.: 158.0-159.0°C(dec.)
Analysis Calcd.for $C_{19}H_{17}N_3$
: C 79.41%, H 5.96%, N 14.62%
Found: C 79.39%, H 6.07%, N 14.58%
MS(EI)m/z: 287(M^+), 270, 158, 143
HRMS(EI)m/z: 287.14189(Calcd.for: $C_{19}H_{17}N_3$; 287.3634)
IR(KBr): 3410, 3180, 3060, 1647, 1610, 1575, 1533, 1491, 1480, 1456, 1390, 1352, 1289, 1260, 1210, 1160, 1040, 945, 868, 828, 760, 745, 720
NMR(CDCL): 8.75-8.50(1H,m), 7.58-7.12(7H,m), 6.58(1H,brs), 3.32(2H,brs), 2.87(3H,s), 2.35(3H,s)

3-Amino-9-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 10)
m.p.: 172.5-173.0°C
IR(KBr): 3470, 3380, 3300, 3170, 3060, 3030, 2960, 2930, 1624, 1582, 1520, 1490, 1450, 1410, 1378, 1302, 1275, 1182, 1084, 1034, 945, 910, 855, 822, 770, 726
NMR(CDCL): 8.48(1H,brs), 7.75(1H,d,J=7.0Hz), 7.60-7.12(6H,m), 6.96(1H,d,J=7.0Hz), 3.30(2H,brs), 2.50(3H,s), 2.40(3H,s)

3-Amino-2-(2-methylphenyl)-7-propylimidazo[2,1-a]isoquinoline (Compound 13)
m.p.: 137.0-138.0°C
IR(KBr): 3370, 3120, 2950, 2930, 2860, 1640, 1608, 1580, 1520, 1490, 1450, 1382, 1275, 1150, 1080, 763, 720
NMR(CDCL): 8.63(1H,dd,J=2.0Hz,7.6Hz), 7.91(1H,d,J=7.8Hz), 7.70-7.20(7H,m), 3.31(2H,brs), 3.00(2H,t,J=8.0Hz), 2.41(3H,s), 2.10-1.46(2H,m), 1.03(3H,t,J=8.0Hz)

3-Amino-6-isopentyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound

15)

m.p.: 150.5-151.5°C

IR(KBr): 3440, 3110, 3060, 2960, 2930, 2875, 1645, 1622, 1608, 1582, 1520, 1492, 1465, 1455, 1392, 1369, 1230, 860, 840-810, 760, 724, 690

NMR(CDCL): 8.80-8.60(1H,m), 7.95-7.14(8H,m), 3.30(2H,brs), 3.10-2.75(2H,m), 2.40(3H,s), 1.85-1.45(3H,m), 1.06(6H,d,J=6.0Hz)

3-Amino-6-methoxymethyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 16)

m.p.: 102.5-103.5°C

IR(KBr): 3430, 3340, 3070, 2940, 2900, 2860, 2830, 1650, 1610, 1580, 1522, 1488, 1455, 1445, 1398, 1386, 1352, 1295, 1278, 1225, 1200, 1150, 1023, 1096, 1050, 1030, 970, 913, 848, 760, 740, 700

NMR(CDCL): 8.85-8.55(1H,m), 8.10-7.29(8H,m), 4.77(2H,s), 3.48(3H,s), 3.32(2H,brs), 2.41(3H,s)

3-Amino-2-(2-methylphenyl)-6-(phenoxymethyl)imidazo[2,1-a]isoquinoline (Compound 17)

m.p.: 187.0-188.5°C

IR(KBr): 3450, 3330, 3170, 3070, 2930, 2880, 1651, 1615, 1600, 1590, 1528, 1495, 1480, 1458, 1380, 1350, 1330, 1296, 1230, 1175, 1150, 1100, 1080, 1029, 1005, 989, 860, 816, 752, 723, 688

NMR(CDCL): 8.80-8.58(1H,m), 7.91(1H,s), 7.87-6.85(12H,m), 5.25(2H,s), 3.30(2H,brs), 2.38(3H,s)

3-Amino-7-hydroxymethyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 18)

IR(KBr): 3500, 3350, 3230, 3000, 2970, 2900, 1652, 1592, 1525, 1496, 1455, 1390, 1320, 1280, 1254, 1220, 1015, 777

NMR(DMSO): 8.60-8.01(2H,m), 7.81-7.07(7H,m), 5.58-5.22(1H,m), 5.20-4.66(4H,br), 2.48(3H,s)

3-Amino-9-(1-hydroxyethyl)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline

(Compound 19)
m.p.: 227.5-229.0°C
IR(KBr): 3460, 3180, 2980, 2940, 1648, 1624, 1590, 1522, 1490, 1445, 1412, 1378, 1272, 1073, 824, 767, 721
NMR(DMSO): 8.46(1H,brs), 8.12(1H,d,J=7.0Hz), 7.88-7.12(7H,m), 5.40(1H,d,J=4.0Hz), 5.20-4.78(1H,m), 4.98(2H,brs), 2.48(3H,s), 1.44(3H,d,J=6.0Hz)

3-Amino-2-(2-methylphenyl)-9-phenylimidazo[2,1-a]isoquinoline (Compound 20) hydrochloride
m.p.: 229.0°C(dec.)
IR(KBr): 3420, 3100, 3060, 2780, 2600, 1668, 1630, 1604, 1558, 1491, 1462, 1422, 1300, 1278, 1255, 1160, 900, 830, 753, 722, 682
NMR(DMSO): 9.54(1H,s), 8.64(1H,d,J=7.6Hz), 8.20-7.28(12H,m), 2.46(3H,s)

3-Amino-6-(4-methoxyphenyl)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 21)
m.p.: 182.0-183.0°C
IR(KBr): 3400, 1640, 1610, 1574, 1506, 1454, 1394, 1364, 1286, 1246, 1178, 1030, 826, 762
NMR(CDCL): 8.92-8.56(1H,m), 7.78(1H,s), 7.70-6.90(11H,m), 3.90(3H,s), 3.50-3.06(2H,br), 2.42(3H,s)

3-Amino-6-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 24)
m.p.: 162.0-163.0°C
IR(KBr): 3430, 3120, 2960, 2850, 1650, 1630, 1580, 1521, 1491, 1449, 1383, 1338, 1285, 1259, 1235, 1160, 1120, 1098, 1030, 982, 863, 760, 728
NMR(CDCL): 8.72-8.45(1H,m), 8.15-7.85(1H,m), 7.71-7.09(7H,m), 3.87(3H,s), 3.78(2H,brs), 2.38(3H,s)

3-Amino-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 26)

m.p.: 131.0-132.0°C

IR(KBr): 3380, 3125, 3000, 2950, 2840, 1616, 1577, 1546, 1520, 1503, 1458, 1442, 1380, 1292, 1255, 1233, 1205, 1175, 1076, 1033, 870, 803, 752, 720

NMR(CDCL): 8.00(1H,d,J=3.0Hz), 7.68(1H,d,J=7.2Hz), 7.57(1H,d,J=8.0Hz), 7.60-7.00(5H,m), 6.93(1H,d,J=7.2Hz), 3.93(3H,s), 3.28(2H,brs), 2.40(3H,s)

3-Amino-9-isopropoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 30)

m.p.: 127.0-128.0°C

IR(KBr): 3400, 3160, 3000, 2940, 1615, 1578, 1520, 1500, 1459, 1380, 1335, 1290, 1230, 1112, 955, 825

NMR(CDCL): 8.06(1H,d,J=2.0Hz), 7.72(1H,d,J=7.0Hz), 7.60(1H,d,J=8.0Hz), 7.50-7.10(5H,m), 6.98(1H,d,J=7.0Hz), 4.82(1H,qui,J=6.0Hz), 3.29(2H,brs), 2.41(3H,s), 1.40(6H,d,J=6.0Hz)

3-Amino-8,9-dimethoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 33)

m.p.: 189.0-192.0°C(dec.)

IR(KBr): 3400, 3320, 3070, 3020, 2970, 2840, 1620, 1578, 1550, 1520, 1500, 1478, 1443, 1400, 1362, 1279, 1245, 1223, 1198, 1160, 1080, 1011, 860, 765, 725

NMR(CDCL): 8.05(1H,s), 7.76(1H,d,J=7.0Hz), 7.57-7.21(4H,m), 7.05(1H,s), 6.93(1H,d,J=7.0Hz), 4.05(3H,s), 3.98(3H,s), 3.25(2H,brs), 2.41(3H,s)

3-Amino-9-ethoxycarbonylmethoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 35)

IR(KBr): 3400, 3330, 2980, 1750, 1615, 1575, 1520, 1499, 1440, 1380, 1338, 1275, 1195, 1090, 1060, 1015, 910, 855, 820, 750

NMR(CDCL): 7.93(1H,d,J=2.4Hz), 7.67(1H,d,J=7.6Hz), 7.56(1H,d,J=8.4Hz), 7.48-7.05(5H,m), 6.91(1H,d,J=7.6Hz), 4.76(2H,s), 4.25(2H,q,J=7.0Hz), 3.32(2H,brs), 2.40(3H,s), 1.29(3H,t,J=7.0Hz)

3-Amino-9-(2-hydroxyethoxy)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 36)

m.p.: 122.0-124.0°C

IR(KBr): 3420, 3330, 3050, 2950, 2760, 1620, 1583, 1520, 1500, 1458, 1417, 1388, 1340, 1295, 1230, 1080, 1060, 940, 900, 818, 770, 725

NMR(DMSO): 8.00(1H,d,J=7.0Hz), 7.85(1H,d,J=2.0Hz), 7.76(1H,d,J=8.4Hz), 7.68-7.05(7H,m), 4.99(3H,br), 4.19(2H,t,J=4.6Hz), 4.00-3.70(2H,m), 2.43(3H,s)

3-Amino-9-(2-methoxyethoxy)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 37)

m.p.: 151.0-152.0°C

IR(KBr): 3410, 3340, 2925, 1645, 1632, 1617, 1575, 1550, 1500, 1492, 1452, 1378, 1340, 1298, 1275, 1225, 1200, 1122, 1105, 1048, 1023, 935, 858, 820, 764, 720

NMR(CDCL): 7.98(1H,d,J=2.0Hz), 7.65(1H,d,J=7.0Hz), 7.55(1H,d,J=9.0Hz), 7.45-7.00(5H,m), 6.90(1H,d,J=7.0Hz), 4.39-4.15(2H,m), 3.85-3.65(2H,m), 3.45(3H,s), 3.30(2H,brs), 2.40(3H,s)

3-Amino-6-benzyloxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 38)

m.p.: 149.0-150.0°C

IR(KBr): 3470, 3310, 3180, 3090, 2940, 2880, 1651, 1622, 1575, 1520, 1495, 1460, 1395, 1375, 1336, 1300, 1285, 1236, 1160, 1115, 1092, 1030, 982, 912, 880, 760, 730, 692

NMR(CDCL): 8.75-8.50(1H,m), 8.25-8.00(1H,m), 7.70-7.10(12H,m), 5.12(2H,s), 3.25(2H,brs), 2.40(3H,s)

9-Acetoxy-3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 41)

m.p.: 145.0-146.5°C

IR(KBr): 3400, 1762, 1612, 1575, 1520, 1495, 1373, 1300, 1272, 1209, 1180, 930, 902, 822, 770

NMR(CDCL): 8.28(1H,d,J=2.0Hz), 7.60(1H,d,J=7.0Hz), 7.52(1H,d,J=8.0Hz), 7.49-7.08(5H,m), 6.80(1H,d,J=7.0Hz), 4.17(2H,brs), 2.39(3H,s), 2.30(3H,s)

3-Amino-9-isobutyryloxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 43)

m.p.: 138.0-140.0°C

IR(KBr): 3400, 3300, 2960, 2900, 2860, 1737, 1625, 1608, 1550, 1520, 1490, 1470, 1460, 1420, 1385, 1370, 1350, 1300, 1273, 1240, 1207, 1180, 1155, 1137, 929, 909, 880, 806, 765, 745

NMR(CDCL): 8.26(1H,d,J=2.0Hz), 7.64(1H,d,J=7.6Hz), 8.57(1H,d,J=8.4Hz), 8.57-7.05(5H,m), 6.86(1H,d,J=7.6Hz), 3.33(2H,brs), 3.20-2.45(1H,m), 2.40(3H,s), 1.35(6H,d,J=7.0Hz)

3-Amino-9-(N,N-dimethylcarbamoyloxy)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 44)

m.p.: 169.0-171.0°C

IR(KBr): 3420, 3310, 3220, 2990, 2920, 1705, 1642, 1626, 1580, 1568, 1518, 1489, 1440, 1410, 1390, 1325, 1300, 1270, 1237, 1210, 1170, 1065, 1018, 914, 888, 808, 750

NMR(CDCL): 8.18(1H,d,J=2.4Hz), 7.50(1H,d,J=7.0Hz), 7.53-7.03(6H,m), 6.69(1H,d,J=7.0Hz), 3.50(2H,brs), 3.08(6H,brs), 2.42(3H,s)

3-Amino-7-benzylthio-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 45)

m.p.: 188.0-189.5°C

IR(KBr): 3380, 3100, 2940, 1640, 1605, 1578, 1548, 1522, 1482, 1458, 1438, 1400, 1380, 1293, 1274, 1230, 1200, 1180, 1157, 1130, 1068, 1028, 1000, 905, 760, 716, 692,

NMR(CDCL): 8.53(1H,dd,J=2.0Hz,6.0Hz), 7.80(1H,d,J=7.0Hz), 7.63-7.15(12H,m), 4.10(2H,s), 3.30(2H,brs), 2.40(3H,s)

3-Amino-2-(2-methylphenyl)-7-(methylthio)imidazo[2,1-a]isoquinoline (Compound 46)

m.p.: 142.0-144.0°C

IR(KBr): 3430, 3100, 2950, 1642, 1607, 1483, 1458, 1421, 1380, 1344, 1274, 1256, 1203, 1165, 1138, 1048, 962, 898, 777

NMR(CDCL): 8.62(1H,dd,J=3.6Hz,6.0Hz), 7.93-7.07(8H,m), 3.55-3.15(2H,br), 2.93(3H,s), 2.40(3H,s)

6-Acetyl-3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 47)

m.p.: 190.0-191.0°C

IR(KBr): 3410, 3230, 2960, 1672, 1616, 1595, 1490, 1454, 1408, 1368, 1336, 1324, 1289, 1185, 1160, 767

NMR(DMSO): 9.10-8.75(1H,m), 9.04(1H,s), 8.63-8.31(1H,m), 7.90-7.09(6H,m), 5.42(2H,brs), 2.79(3H,s), 2.47(3H,s)

3-Amino-7-(p-anisoyl)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 48)

m.p.: 164.0-165.0°C

IR(KBr): 3400, 3330, 1650, 1600, 1572, 1514, 1422, 1373, 1312, 1278, 1260, 1175, 1142, 1015, 965, 887, 846, 794, 754

NMR(CDCL): 8.93-8.61(1H,m), 8.02-6.75(12H,m), 3.85(3H,s), 3.46(2H,brs), 2.40(3H,s)

3-Amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinolin-7-carboxylic acid (Compound 49) hydrochloride

m.p.: 231.0-233.5°C

IR(KBr): 3450-3340, 2950-2800, 2720, 2680, 2630, 1710, 1670, 1627, 1548, 1496, 1458, 1396, 1270, 1220, 1128, 792

NMR(DMSO): 9.55-9.25(1H,m), 8.95-8.32(3H,m), 7.98(1H,t,J=8.0Hz), 7.50(4H,s), 2.44(3H,s)

3-Amino-6-methoxycarbonyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 50)

m.p.: 185.0-186.0°C

IR(KBr): 3410, 3330, 3180, 2960, 1712, 1633, 1607, 1586, 1485, 1455, 1439, 1401, 1330, 1302, 1282, 1244, 1198, 1156, 1045, 1030, 928, 760

NMR(CDCL): 8.95-8.52(2H,m), 8.64(1H,s), 7.73-7.05(6H,m), 3.93(3H,s),

3.40(2H,brs), 2.37(3H,s)

3-Amino-7-cyano-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 52)

m.p.: 190.0-191.0°C

IR(KBr): 3400, 3140, 2250, 1642, 1600, 1576, 1528, 1492, 1450, 1378, 1325, 1275, 1218, 1150, 928, 768

NMR(CDCL): 8.78(1H,dd,J=2.0Hz,7.0Hz), 7.99(1H,d,J=7.0Hz), 7.90-7.01(7H,m), 3.57(2H,brs), 2.44(3H,s)

3-Amino-7-diethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 54)

IR(KBr): 3430, 3320, 3060, 2980, 2940, 2870, 2830, 1640, 1600, 1556, 1486, 1450, 1380, 1250, 1210, 1135, 1030, 945, 780-750

NMR(CDCL): 8.40(1H,brd,J=7.0Hz), 7.92-7.10(8H,m), 3.52-2.93(2H,br), 3.19(4H,q,J=7.0Hz), 2.43(3H,s), 1.05(6H,t,J=7.0Hz)

(hydrochloride m.p.:211.0-215.0°C)

3-Amino-10-chloro-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 55)

m.p.: 180.5-181.5°C

IR(KBr): 3180, 3010, 2940, 2840, 1648, 1603, 1573, 1538, 1490, 1460, 1440, 1409, 1370, 1280, 1254, 1222, 1180, 1154, 1118, 1067, 1040, 1010, 952, 855, 800, 753, 720

NMR(CDCL): 7.55(1H,d,J=7.0Hz), 7.45(1H,d,J=8.0Hz), 7.40-7.12(4H,m), 7.04(1H,d,J=8.0Hz), 6.78(1H,d,J=7.0Hz), 3.95(3H,s), 3.40(2H,brs), 2.50(3H,s)

3-Amino-9-methoxy-5-methyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 56)

m.p.: 165.0-166.0°C

IR(KBr): 3400, 3280, 3160, 1675, 1613, 1524, 1495, 1455, 1436, 1390, 1355, 1296, 1240, 1180, 1150, 1098, 1032, 890, 850, 765, 728

NMR(CDCL): 8.01(1H,d,J=2.6Hz), 7.62-7.25(5H,m),

7.09(1H,dd,J=2.6Hz,9.0Hz), 6.61(1H,s), 3.94(3H,s), 3.32(2H,brs), 2.94(3H,s), 2.40(3H,s)

3-Amino-2-(3-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 57) hydrochloride

m.p.: 192.0°C(dec.)

IR(KBr): 3320, 3170, 3060, 2940, 2720, 1662, 1615, 1549, 1496, 1460, 1425, 1335, 794, 685

NMR(DMSO): 9.42-9.08(1H,m), 8.58(1H,d,J=7.0Hz), 8.20-7.00(8H,m), 2.38(3H,s)

3-Amino-2-(2-ethylphenyl)imidazo[2,1-a]isoquinoline (Compound 59) hydrochloride

m.p.: 215.0-216.0°C

IR(KBr): 3450, 3120, 2980, 2940, 2890, 2600, 1668, 1630, 1550, 1498, 1460, 1426, 1330, 1281, 1250, 1168, 868, 794, 770, 680

NMR(DMSO): 9.15-8.88(1H,m), 8.65(1H,d,J=7.0Hz), 8.29-7.70(4H,m), 7.50(4H,s), 2.78(2H,q,J=7.0Hz), 1.11(3H,t,J=7.0Hz)

3-Amino-2-(2-trifluoromethylphenyl)imidazo[2,1-a]isoquinoline (Compound 60) hydrochloride

m.p.: 189.0-194.0°C(dec.)

IR(KBr): 3470, 3270, 3150, 3050, 2920, 2800, 2730, 2680, 1668, 1632, 1608, 1582, 1550, 1500, 1460, 1439, 1425, 1318, 1270, 1241, 1171, 1120, 1059, 1033, 970, 798, 778, 675

NMR(DMSO): 8.92-8.70(1H,m), 8.55(1H,d,J=7.4Hz), 8.30-7.60(8H,m)

3-Amino-2-(2,4-dimethylphenyl)imidazo[2,1-a]isoquinoline (Compound 62)

m.p.: 191.0-192.5°C

IR(KBr): 3100, 2920, 1645, 1615, 1583, 1529, 1505, 1490, 1458, 1380, 1275, 1145, 825, 770

NMR(CDCL): 8.72-8.50(1H,m), 7.90-6.89(8H,m), 3.28(2H,brs), 2.34(6H,s)

3-Amino-2-(4-chloro-2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 66)

m.p.: 223.0-224.0°C

IR(KBr): 3390, 3250, 3120, 3070, 3040, 2930, 1645, 1615, 1580, 1525, 1487, 1459, 1437, 1415, 1380, 1315, 1284, 1204, 1173, 1145, 1100, 1029, 985, 893, 866, 824, 770, 680

NMR(DMSO): 8.43-8.19(1H,m), 8.03(1H,d,J=7.0Hz), 7.87-7.23(6H,m), 7.10(1H,d,J=7.0Hz), 5.04(2H,brs), 2.41(3H,s)

3-Amino-2-(4-hydroxy-2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 68)

m.p.: 273.0-276.0°C(dec.)

IR(KBr): 3400, 3330, 3050, 3000, 2910, 2770, 2670, 2600, 1638, 1608, 1510, 1500, 1453, 1380, 1300, 1245, 1165, 948, 899, 860, 810, 785, 740

NMR(DMSO): 9.35(1H,s), 8.50-8.28(1H,m), 8.09(1H,d,J=7.0Hz), 7.92-7.02(5H,m), 6.82-6.58(2H,m), 4.82(2H,brs), 2.33(3H,s)

3-Amino-2-(4-methoxy-2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 69) hydrochloride

m.p.: 215.5-217.5°C

IR(KBr): 3380, 3090, 2920, 2830, 2750, 2680, 2600, 1665, 1610, 1567, 1545, 1510, 1460, 1420, 1292, 1245, 1162, 1068, 1038, 790

NMR(DMSO): 9.28-8.94(1H,m), 8.65(1H,d,J=7.0Hz), 8.29-7.70(4H,m), 7.48(1H,d,J=9.0Hz), 7.09-6.80(2H,m), 5.60-4.55(2H,br), 3.85(3H,s), 2.83(3H,s)

2-(4-Acetoxy-2-methylphenyl)-3-aminoimidazo[2,1-a]isoquinoline (Compound 70) hydrochloride

m.p.: 201.0-205.0°C

IR(KBr): 3600, 3450, 3350, 3150, 2910, 2640, 1750, 1662, 1625, 1547, 1500, 1453, 1420, 1370, 1203, 1158, 1013, 950, 904, 788

NMR(DMSO): 9.13-8.90(1H,m), 8.61(1H,d,J=7.0Hz), 8.28-7.50(5H,m), 7.31-7.08(2H,m), 2.40(3H,s), 2.31(3H,s)

3-Amino-2-(2,4,6-trimethylphenyl)imidazo[2,1-a]isoquinoline (Compound 71)
m.p.: 103.0-105.0°C
IR(KBr): 3420, 3320, 3150, 3070, 3020, 2970, 2930, 2860, 1645, 1615, 1585, 1520, 1485, 1450, 1375, 1311, 1275, 1210, 1139, 1085, 1025, 983, 891, 850, 784, 745, 685
NMR(CDCL): 8.75-8.52(1H,m), 7.83(1H,d,J=7.0Hz), 7.74-7.32(3H,m), 7.02(1H,d,J=7.0Hz), 6.95(2H,s), 3.33-2.95(2H,br), 2.31(3H,s), 2.12(6H,s)

3-Amino-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 73)
m.p.: 174.0-175.0°C
IR(KBr): 3400, 3340, 3100, 3060, 2920, 1640, 1605, 1519, 1482, 1458, 1371, 935, 890, 833, 785, 732, 712, 673
NMR(CDCL): 8.78-8.52(1H,m), 7.84-7.41(4H,m), 7.29(1H,d,J=5.0Hz), 6.99(1H,d,J=7.4Hz), 6.98(1H,d,J=5.0Hz), 3.41(2H,brs), 2.44(3H,s)

3-Amino-6-methoxy-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 74)
m.p.: 143.0-146.0°C
IR(KBr): 3440, 3110, 2950, 1652, 1627, 1590, 1521, 1470, 1450, 1381, 1330, 1298, 1257, 1235, 1161, 1125, 1099, 1028, 995, 960, 924, 861, 762
NMR(CDCL): 8.70-8.46(1H,m), 8.13-7.91(1H,m), 7.78-7.42(2H,m), 7.27(1H,s), 7.22(1H,d,J=5.0Hz), 6.93(1H,d,J=5.0Hz), 3.92(3H,s), 3.62-3.08(2H,br), 2.45(3H,s)

3-Amino-9-methoxy-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 75)
IR(KBr): 3420, 2930, 1616, 1518, 1500, 1439, 1370, 1337, 1297, 1275, 1229, 1180, 1139, 1026, 905, 854, 820
NMR(CDCL): 7.99(1H,d,J=2.4Hz), 7.64(1H,d,J=7.6Hz), 7.53(1H,d,J=8.2Hz), 7.35-7.10(2H,m), 6.96(1H,d,J=8.2Hz), 6.94(1H,d,J=6.4Hz), 3.96(3H,s), 3.55-3.30(2H,br), 2.42(3H,s)
(hydrochloride m.p.: 195.0°C(dec.))

3-Amino-2-(4-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 76)
m.p.: 152.0-155.0°C
IR(KBr): 3460, 3310, 3175, 3070, 2930, 1645, 1623, 1584, 1552, 1520, 1488, 1459, 1375, 1265, 1212, 1182, 1155, 922, 890, 848, 788, 720
NMR(CDCL): 8.75-8.45(1H,m), 7.69(1H,d,J=7.0Hz), 7.69-7.47(3H,m), 7.33(1H,d,J=1.0Hz), 6.89(1H,d,J=7.0Hz), 6.84(1H,d,J=1.0Hz), 3.53-3.08(2H,br), 2.30(3H,s)

3-Amino-2-(3-ethyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 77)
IR(KBr): 3410, 3300, 2970, 2930, 2870, 1642, 1610, 1588, 1519, 1483, 1457, 1370, 1324, 1272, 1210, 1175, 1138, 888, 780
NMR(CDCL): 8.68-8.39(1H,m), 7.66(1H,d,J=7.0Hz), 7.58-7.30(3H,m), 7.22(1H,d,J=5.0Hz), 6.98(1H,d,J=5.0Hz), 6.86(1H,d,J=7.0Hz), 3.38(2H,brs), 2.83(2H,q,J=7.0Hz), 1.22(3H,t,J=7.0Hz)

3-Amino-2-(2-methyl-3-thienyl)imidazo[2,1-a]isoquinoline (Compound 78)
m.p.: 124.0-124.5°C
IR(KBr): 3400, 3330, 3090, 2910, 1638, 1606, 1518, 1482, 1455, 1440, 1373, 1230, 1209, 1170, 1139, 1084, 890, 858, 784, 732, 690
NMR(CDCL): 8.75-8.45(1H,m), 7.78(1H,d,J=7.0Hz), 7.70-7.40(3H,m), 7.23(1H,d,J=5.0Hz), 7.10(1H,d,J=5.0Hz), 6.98(1H,d,J=7.0Hz), 3.30(2H,brs), 2.62(3H,s)

3-Amino-2-(4-methyl-3-thienyl)imidazo[2,1-a]isoquinoline (Compound 81)
m.p.: 155.5-156.0°C
IR(KBr): 3440, 3300, 3150, 3050, 1640, 1620, 1580, 1548, 1518, 1485, 1455, 1370, 1360, 1262, 1210, 1180, 1154, 890, 848, 790, 720
NMR(CDCL): 8.72-8.48(1H,m), 7.67-7.44(4H,m), 7.28(1H,brs), 6.86-6.73(2H,m), 3.30(2H,brs), 2.27(3H,s)

3-Amino-2-(2,5-dimethyl-3-thienyl)imidazo[2,1-a]isoquinoline (Compound 83) hydrochloride
m.p.: 233.0°C(dec.)

IR(KBr): 3350, 3140, 3050, 2910, 2850, 2750, 2660, 1665, 1625, 1545, 1440, 1420, 1380, 1328, 1305, 1246, 1110, 790

NMR(DMSO): 9.20-8.97(1H,m), 8.62(1H,d,J=7.0Hz), 8.26-7.68(4H,m), 7.01(1H,s), 2.48(6H,s)

3-Amino-2-(2-chloro-3-methyl-4-thienyl)imidazo[2,1-a]isoquinoline (Compound 85)

m.p.: 167.0-170.0°C(dec.)

IR(KBr): 3400, 3150, 3100, 1640, 1613, 1595, 1520, 1477, 1455, 1369, 1352, 1138, 1005, 763, 680

NMR(CDCL): 8.71-8.42(1H,m), 7.71(1H,d,J=7.0Hz), 7.70-7.38(3H,m), 7.13(1H,s), 6.99(1H,d,J=7.0Hz), 3.42(2H,br), 2.35(3H,s)

3-Amino-7-bromo-2-(2-chloro-3-methyl-4-thienyl)imidazo[2,1-a]isoquinoline (Compound 86)

IR(KBr): 3420, 3100, 2930, 1638, 1615, 1596, 1513, 1478, 1435, 1400, 1370, 1342, 1257, 1211, 1102, 1030, 961, 895, 858, 776, 740

NMR(CDCL): 8.55(1H,brd,J=7.4Hz), 7.93-7.62(2H,m), 7.55-7.19(2H,m), 7.15(1H,s), 3.62-3.23(2H,br), 2.29(3H,s)

3-Amino-2-(3-methyl-2-furyl)imidazo[2,1-a]isoquinoline (Compound 88)

m.p.: 183.0-185.0°C(dec.)

IR(KBr): 3420, 3325, 2925, 1640, 1600, 1545, 1521, 1481, 1458, 1367, 1168, 1078, 885, 795, 746, 725

NMR(DMSO): 8.53-8.30(1H,m), 8.10(1H,d,J=7.0Hz), 7.95-7.48(4H,m), 7.18(1H,d,J=7.0Hz), 6.47(1H,d,J=2.0Hz), 5.42(2H,brs), 2.46(3H,s)

3-Amino-2-(2,5-dimethyl-3-furyl)imidazo[2,1-a]isoquinoline (Compound 91)

m.p.: 135.0-136.0°C(dec.)

IR(KBr): 3410, 3310, 2920, 1640, 1594, 1520, 1482, 1452, 1374, 1268, 1212, 1186, 1080, 994, 922, 890, 784, 740

NMR(CDCL): 8.80-8.54(1H,m), 7.77(1H,d,J=7.0Hz), 7.70-7.40(3H,m), 6.95(1H,d,J=7.0Hz), 6.28(1H,s), 3.22(2H,brs), 2.54(3H,s), 2.29(3H,s)

3-Amino-2-(1-methyl-2-pyrrolyl)imidazo[2,1-a]isoquinoline (Compound 94)
m.p.: 134.0-136.0°C(dec.)
IR(KBr): 3400, 3320, 3090, 1638, 1607, 1585, 1532, 1515, 1492, 1453, 1374, 1313, 1289, 1262, 1177, 1086, 1053, 970, 892, 780, 718, 700
NMR(CDCL): 8.70-8.35(1H,m), 7.61(1H,d,J=7.0Hz), 7.58-7.33(3H,m), 6.88(1H,d,J=7.0Hz), 6.70(1H,t,J=2.0Hz), 6.34-6.12(2H,m), 3.87(3H,s), 3.44(2H,brs)

3-Amino-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 96) maleate
m.p.: 157.0-158.0°C
IR(KBr): 3350, 3210, 3060, 2960, 2920, 2840, 2800, 2740, 1655, 1585, 1480, 1360, 1210, 1192, 1010-988, 868, 760, 700
NMR(DMSO): 8.10-7.72(1H,m), 7.67-7.27(7H,m), 6.05(2H,s), 4.23(2H,t,J=7.0Hz), 3.28(2H,t,J=7.0Hz), 2.35(3H,s)

3-Amino-9-fluoro-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 97)
m.p.: 157.5-158.0°C
IR(KBr): 3410, 3150, 2920, 1620, 1575, 1538, 1496, 1456, 1356, 1315, 1270, 1258, 1202, 1174, 1070, 911, 876, 862, 799, 766, 722
NMR(CDCL): 7.75(1H,dd,J=2.0Hz,10.0Hz), 7.50-6.70(6H,m), 3.98(2H,t,J=7.0Hz), 3.50-2.90(2H,br), 3.09(2H,t,J=7.0Hz), 2.40(3H,s)

3-Amino-8-chloro-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 98) hydrochloride
m.p.: 199.0-201.0°C(dec.)
IR(KBr): 3425, 3320, 3130, 2930, 2850, 2760, 2700, 2660, 2620, 1640, 1560, 1504, 1480, 1453, 1314, 1290, 1193, 1110, 1084, 850, 823, 764
NMR(DMSO): 8.42(1H,d,J=8.0Hz), 7.82-7.27(6H,m), 4.31(2H,t,J=7.0Hz), 3.31(2H,t,J=7.0Hz), 2.39(3H,s)

3-Amino-9-bromo-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 99)

m.p.: 167.0-170.0°C

IR(KBr): 3450, 3370, 2960, 2930, 1610, 1588, 1530, 1490, 1460, 1431, 1387, 1347, 1317, 1250, 1224, 1203, 1150, 1100, 1068, 1040, 885, 812, 792, 765, 725

NMR(CDCL): 8.18(1H,d,J=2.0Hz), 7.50-6.90(6H,m), 3.98(2H,t,J=7.0Hz), 3.48-2.88(2H,br), 3.07(2H,t,J=7.0Hz), 2.40(3H,s)

3-Amino-5-methyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 100)

IR(KBr): 3400, 3300, 3120, 3050, 2960, 2920, 1605, 1572, 1530, 1485, 1475, 1450, 1412, 1377, 1353, 1265, 1250, 1200, 1150, 1083, 1030, 978, 940, 755, 720

NMR(CDCL): 8.17-7.88(1H,m), 7.50-7.05(7H,m), 4.80-4.20(1H,m), 3.42(1H,dd,J=6.0Hz,16.0Hz), 3.20(2H,br), 2.78(1H,dd,J=1.6Hz,16.0Hz), 2.39(3H,s), 1.24(3H,d,J=7.0Hz)

3-Amino-9-methyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 102)

m.p.: 141.5-143.0°C

IR(KBr): 3420, 3300, 3150, 3050, 2900, 1632, 1615, 1602, 1570, 1532, 1490, 1450, 1378, 1350, 1338, 1315, 1270, 1218, 1186, 1095, 1036, 943, 916, 865, 810, 762, 720

NMR(CDCL): 7.87(1H,brs), 7.50-6.95(6H,m), 3.93(2H,t,J=7.0Hz), 3.17(2H,brs), 3.04(2H,t,J=7.0Hz), 2.39(3H,s), 2.32(3H,s)

3-Amino-5,5-dimethyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 104)

m.p.: 151.0-152.0°C(dec.)

IR(KBr): 3440, 3280, 3060, 2960, 2925, 2760, 1680, 1602, 1570, 1488, 1470, 1460, 1435, 1370, 1341, 1300, 1282, 1262, 1239, 1189, 1162, 1120, 1100, 983, 955, 815, 760, 723

NMR(CDCL): 8.20-8.00(1H,m), 8.10-7.80(2H,br), 7.55-7.00(7H,m), 2.93(1H,d,J=16.0Hz), 2.59(1H,d,J=16.0Hz), 2.35(3H,s), 1.70(3H,s), 1.65(3H,s)

3-Amino-6,7-dimethyl-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 105)
m.p.: 107.0-110.0°C(dec.)
IR(KBr): 3420, 3300, 3050, 2970, 2940, 2880, 1675, 1617, 1602, 1580, 1490, 1458, 1418, 1380, 1325, 1150, 753
NMR(CDCL): 8.07-7.72(1H,m), 7.57-6.91(6H,m), 4.05-2.90(5H,m), 2.41(3H,s), 2.35(3H,s), 1.20(3H,d,J=7.0Hz)

3-Amino-2-(4-hydroxy-2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 107)
m.p.: 262.0-265.0°C(dec.)
IR(KBr): 3410, 3330, 3050, 2960, 2760, 2650, 2580, 1605, 1500, 1456, 1419, 1380, 1350, 1300, 1245, 1200, 1188, 1168, 910, 864, 764
NMR(DMSO): 9.22(1H,s), 7.88-7.62(1H,m), 7.40-7.03(4H,m), 6.80-6.50(2H,m), 4.50(2H,brs), 4.00(2H,t,J=7.0Hz), 3.09(2H,t,J=7.0Hz), 2.30(3H,s)

3-Amino-2-(5-bromo-4-hydroxy-2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 108)
m.p.: 285.0°C(dec.)
IR(KBr): 3360, 3140, 2920, 1654, 1610, 1560, 1503, 1480, 1455, 1421, 1357, 1298, 1248, 1220, 864, 815, 772
NMR(DMSO): 9.73(1H,s), 8.11-7.82(1H,m), 7.65-7.10(3H,m), 6.98-6.64(2H,m), 5.88-5.40(2H,br), 4.28(2H,t,J=7.0Hz), 3.29(2H,t,J=7.0Hz), 2.22(3H,s)

3-Amino-5-methyl-2-phenylimidazo[1,2-a]thieno[3,2-c]pyridine (Compound 230)
m.p.: 193.0-194.0°C
IR(KBr): 3370, 3280, 3090, 1620, 1596, 1580, 1560, 1530, 1485, 1442, 1380, 1360, 1285, 1230, 1195, 990, 915, 878, 818, 792, 770, 730, 710, 685
NMR(DMSO): 8.35-8.00(2H,m), 7.86-7.63(2H,m), 7.62-7.20(3H,m), 7.06(1H,s), 4.58(2H,brs), 3.02(3H,s)

3-Amino-2-(2-hydroxyphenyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine (Compound 231)

m.p.: 199.5-201.0°C

IR(KBr): 3400, 3320, 1630, 1570, 1538, 1490, 1455, 1410, 1373, 1290, 1250, 1013, 818, 754, 710

NMR(DMSO): 8.38-8.20(1H,m), 7.78(2H,s), 7.37-6.72(4H,m), 4.83(2H,brs), 3.60-2.92(1H,br), 3.05(3H,s)

3-Amino-2-(2-chlorophenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 232)

m.p.: 180.0-181.0°C

IR(KBr): 3330, 3170, 3080, 1626, 1578, 1482, 1432, 1409, 1402, 1352, 1294, 1252, 1268, 1188, 1168, 1150, 1046, 1030, 954, 900, 756, 702

NMR(CDCL): 7.97(1H,d,J=5.0Hz), 7.96(1H,d,J=7.0Hz), 7.87-7.60(1H,m), 7.53(1H,d,J=5.0Hz), 7.50-7.21(3H,m), 7.21(1H,d,J=7.0Hz), 3.42(2H,brs)

3-Amino-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 234)

m.p.: 136.0-137.0°C

Analysis Calcd.for $C_{16}H_{13}N_3S$

: C 68.79%, H 4.69%, N 15.04%

Found: C 68.53%, H 4.82%, N 14.75%

MS(EI)m/z: 279(M^+), 263, 150, 135, 83

HRMS(EI)m/z: 279.08338(Calcd.for: $C_{16}H_{13}N_3S$; 279.3588)

IR(KBr): 3350-3200, 3090, 2910, 1628, 1580, 1513, 1490, 1478, 1450, 1410, 1400, 1351, 1294, 1265, 1185, 1168, 1080, 1010, 953, 765, 743, 700

NMR(CDCL): 7.95(1H,d,J=5.8Hz), 7.85(1H,d,J=7.0Hz), 7.49(1H,d,J=5.8Hz), 7.50-7.10(5H,m), 3.30(2H,brs), 2.39(3H,s)

3-Amino-8-bromo-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 235)

m.p.: 221.5-222.0°C

IR(KBr): 3360, 3080, 1627, 1605, 1580, 1480, 1450, 1400, 1350, 1290, 1270, 1200, 1170, 1152, 980, 923, 826, 763, 726

NMR(CDCL): 7.95(1H,s), 7.91(1H,d,J=7.5Hz), 7.50-7.23(4H,m), 7.10(1H,d,J=7.5Hz), 3.28(2H,brs), 2.40(3H,s)

3-Amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236)

m.p.: 185.0-185.5°C

Analysis Calcd.for $C_{17}H_{15}N_3S$

: C 69.60%, H 5.15%, N 14.32%

Found: C 69.34%, H 5.20%, N 14.11%

MS(EI)m/z: 293(M^+), 277, 164, 149, 83

HRMS(EI)m/z: 293.09827(Calcd.for: $C_{17}H_{15}N_3S$; 293.3856)

IR(KBr): 3390, 3280, 3170, 3070, 1632, 1574, 1530, 1488, 1440, 1376, 1286, 1250, 1170, 1012, 882, 810, 760, 718, 700

NMR(CDCL): 7.70(1H,d,J=5.0Hz), 7.40-7.00(5H,m), 6.62(1H,s), 3.22(2H,brs), 2.87(3H,s), 2.28(3H,s)

3-Amino-5-ethyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 238)

m.p.: 178.0-179.0°C

IR(KBr): 3390, 3330, 3090, 2960, 2940, 2910, 2870, 1630, 1580, 1564, 1534, 1485, 1460, 1434, 1402, 1375, 1289, 1275, 1245, 1176, 1153, 1076, 1000, 870, 830, 772, 705

NMR(CDCL): 7.80(1H,d,J=5.0Hz), 7.44-7.03(5H,m), 6.80(1H,s), 3.40(2H,q,J=7.0Hz), 3.38-3.13(2H,br), 2.32(3H,s), 1.37(3H,t,J=7.0Hz)

3-Amino-5,6-dimethyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 239)

m.p.: 173.5-175.0°C

IR(KBr): 3390, 3200, 3060, 2920, 2850, 1625, 1578, 1555, 1519, 1509, 1489, 1465, 1452, 1435, 1395, 1358, 1282, 1255, 1192, 1085, 1006, 880, 832, 762, 712

NMR(CDCL): 7.90(1H,d,J=5.5Hz), 7.60-7.15(4H,m), 7.40(1H,d,J=5.5Hz), 3.45-3.15(2H,br), 3.00(3H,s), 2.44(3H,s), 2.38(3H,s)

3-Amino-5-methyl-2-(3-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 242)

m.p.: 165.0-166.0°C

IR(KBr): 3420, 3340, 3080, 2910, 1630, 1606, 1530, 1488, 1446, 1410, 1372, 1290, 1254, 1210, 1170, 1096, 1040, 892, 790, 710

NMR(CDCL): 7.93(1H,d,J=5.0Hz), 7.80-7.00(5H,m), 6.72(1H,s), 3.46(2H,brs), 2.93(3H,s), 2.41(3H,s)

3-Amino-5-methyl-2-(2-trifluoromethylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 244)

m.p.: 194.0-195.0°C

IR(KBr): 3380, 3320, 3070, 1630, 1580, 1536, 1490, 1473, 1450, 1440, 1405, 1378, 1312, 1295, 1268, 1240, 1190, 1163, 1140, 1100, 1050, 1030, 1010, 990, 968, 880, 818, 770, 700

NMR(CDCL): 8.10-7.90(1H,m), 7.98(1H,d,J=5.8Hz), 7.90-7.50(3H,m), 7.48(1H,d,J=5.8Hz), 7.08(1H,s), 2.68(3H,s)

3-Amino-2-(2-methoxyphenyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine (Compound 245)

m.p.: 135.0-136.0°C

IR(KBr): 3410, 3100, 2930, 2830, 1630, 1568, 1532, 1492, 1463, 1456, 1434, 1386, 1372, 1280, 1240, 1178, 1120, 1068, 1016, 884, 810, 752, 708

NMR(CDCL): 7.85(1H,d,J=5.0Hz), 7.74(1H,dd,J=2.0Hz,7.0Hz), 7.40-6.83(4H,m), 6.70(1H,s), 3.84(3H,s), 3.52(2H,br), 2.96(3H,s)

3-Amino-2-(4-chloro-2-methylphenyl)-5-methylimidazo[1,2-a]thieno[3,2-c]pyridine (Compound 248)

m.p.: 206.0-207.0°C

IR(KBr): 3370, 3150, 1630, 1579, 1530, 1480, 1410, 1385, 1370, 1245, 1205, 1173, 1090, 1070, 1010, 862, 810, 700

NMR(CDCL+DMSO): 7.75(1H,d,J=6.0Hz), 7.42(1H,d,J=6.0Hz), 7.40(1H,d,J=8.0Hz), 7.40-7.10(2H,m), 6.85(3H,s), 3.90(2H,brs), 3.05(3H,s), 2.39(3H,s)

3-Amino-5-methyl-2-(2-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 249)

m.p.: 185.0-186.0°C

IR(KBr): 3400, 3050, 1630, 1580, 1528, 1468, 1434, 1402, 1372, 1300, 1256, 1200, 1172, 1080, 1034, 876, 830, 780, 708, 680

NMR(DMSO): 7.73(1H,d,J=5.0Hz), 7.58(1H,d,J=4.0Hz), 7.48(1H,d,J=5.0Hz), 7.29(1H,d,J=5.0Hz), 7.03(1H,dd,J=4.0Hz,5.0Hz), 6.81(1H,s), 3.40(2H,brs), 2.95(3H,s)

3-Amino-2-(3-methyl-2-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 250)

m.p.: 164.5-165.5°C

IR(KBr): 3400, 3280, 3060, 1626, 1510, 1472, 1402, 1384, 1342, 1276, 1252, 1190, 1168, 1148, 1012, 980, 948, 830, 790, 716

NMR(CDCL): 7.90(1H,d,J=5.0Hz), 7.78(1H,d,J=7.0Hz), 7.44(1H,d,J=5.0Hz), 7.24(1H,d,J=5.0Hz), 7.10(1H,d,J=7.0Hz), 6.89(1H,d,J=5.0Hz), 3.42(2H,brs), 2.38(3H,s)

3-Amino-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 254)

m.p.: 161.0-162.0°C

IR(KBr): 3430, 3270, 3100, 1638, 1622, 1604, 1544, 1516, 1492, 1478, 1448, 1410, 1330, 1268, 1198, 1152, 1080, 952, 860, 814, 768, 702

NMR(CDCL): 7.91(1H,d,J=5.0Hz), 7.81(1H,d,J=7.0Hz), 7.47(1H,d,J=5.0Hz), 7.30-7.05(3H,m), 3.30(2H,brs), 2.58(3H,s)

3-Amino-5-methyl-2-(2-methyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 255)

m.p.: 139.0-140.0°C

IR(KBr): 3375, 3250, 3160, 3080, 2910, 1630, 1594, 1532, 1510, 1472, 1450, 1438, 1408, 1382, 1308, 1250, 1212, 1158, 1000, 880, 816, 696, 675

NMR(CDCL): 7.88(1H,d,J=5.5Hz), 7.38(1H,d,J=5.5Hz), 7.15(2H,s), 6.78(1H,brs), 3.35(2H,brs), 2.97(3H,s), 2.55(3H,s)

3-Amino-2-(2,5-dimethyl-3-thienyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 264)

m.p.: 142.0-143.0°C

IR(KBr): 3375, 3260, 3175, 3075, 2900, 1625, 1540, 1515, 1475, 1435, 1404, 1391, 1375, 1338, 1322, 1246, 1192, 1165, 1149, 1135, 1085, 950, 818, 765, 703

NMR(CDCL): 7.95(1H,d,J=5.5Hz), 7.84(1H,d,J=7.0Hz), 7.50(1H,d,J=5.5Hz), 7.15(1H,d,J=7.0Hz), 6.89(1H,brs), 3.35(2H,brs), 2.53(3H,s), 2.47(3H,s)

3-Amino-2-(1-methyl-2-pyrrolyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 275)

m.p.: 140.0-141.0°C

IR(KBr): 3380, 3070, 1622, 1490, 1470, 1404, 1342, 1300, 1170, 1148, 1090, 1052, 984, 952, 796, 710

NMR(CDCL): 7.84(1H,d,J=5.0Hz), 7.68(1H,d,J=7.0Hz), 7.41(1H,d,J=5.0Hz), 7.02(1H,d,J=7.0Hz), 6.70(1H,t,J=2.0Hz), 6.37-6.10(2H,m), 3.80(3H,s), 3.49(2H,brs)

3-Amino-2-(2-methylphenyl)furo[3,2-c]imidazo[1,2-a]pyridine (Compound 276)

m.p.: 151.0-152.0°C(dec.)

IR(KBr): 3400, 3270, 3100, 1638, 1592, 1504, 1490, 1398, 1360, 1268, 1248, 1176, 1130, 1058, 1030, 990, 890, 730

NMR(CDCL): 7.89(1H,d,J=7.0Hz), 7.67(1H,d,J=2.0Hz), 7.56-7.20(5H,m), 7.10(1H,d,J=7.0Hz), 3.28(2H,brs), 2.40(3H,s)

3-Amino-2-(2-methyl-3-thienyl)furo[3,2-c]imidazo[1,2-a]pyridine (Compound 280)

m.p.: 146.5-147.0°C

IR(KBr): 3400, 3300, 3190, 3140, 2920, 1640, 1618, 1532, 1507, 1440, 1402, 1332, 1275, 1250, 1193, 1165, 1130, 1059, 892, 859, 730

NMR(CDCL): 7.90(1H,d,J=7.0Hz), 7.70(1H,d,J=2.0Hz), 7.32-7.03(4H,m), 3.26(2H,brs), 2.60(3H,s)

3-Amino-2-(2,5-dimethyl-3-furyl)furo[3,2-c]imidazo[1,2-a]pyridine (Compound 288)

m.p.: 145.5-146.0°C

IR(KBr): 3450, 3420, 3110, 3075, 2920, 1650, 1638, 1597, 1568, 1510, 1445, 1404, 1332, 1279, 1258, 1222, 1210, 1180, 1138, 1118, 1064, 995, 980, 924, 892, 800, 752, 730

NMR(CDCL): 7.80(1H,d,J=7.0Hz), 7.60(1H,d,J=2.0Hz), 7.28-7.14(1H,m), 6.99(1H,d,J=7.0Hz), 6.25(1H,brs), 3.21(2H,brs), 2.52(3H,s), 2.30(3H,s)

3-Amino-7-methyl-2-(2-methylphenyl)imidazo[1,2-a]pyrrolo[3,2-c]pyridine (Compound 291) hydrochloride

m.p.: 219.0°C(sublimation)

IR(KBr): 3360, 3260, 3110, 3070, 2950, 2860, 2770, 2700, 1665, 1560, 1538, 1495, 1460, 1425, 1380, 1290, 1252, 1212, 1090, 1040, 750

NMR(DMSO): 8.42(1H,d,J=7.0Hz), 7.73(1H,d,J=7.0Hz), 7.95-7.30(4H,m), 7.58(1H,d,J=3.0Hz), 7.26(1H,d,J=3.0Hz), 3.98(3H,s), 2.41(3H,s)

3-Amino-7-benzyl-2-(2-methylphenyl)imidazo[1,2-a]pyrrolo[3,2-c]pyridine (Compound 292) hydrochloride

m.p.: 225.0°C(dec.)

IR(KBr): 3360, 3120, 3060, 2650, 1660, 1630, 1490, 1445, 1378, 1340, 1300, 1259, 1210, 815, 760, 740, 695

NMR(DMSO): 8.42(1H,d,J=7.6Hz), 7.79(1H,d,J=7.6Hz), 7.76(1H,d,J=3.0Hz), 7.60-7.10(10H,m), 5.63(2H,s), 2.40(3H,s)

3-Amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,4-c]pyridine (Compound 303)

m.p.: 154.0-154.5°C

IR(KBr): 3390, 3170, 3100, 3050, 3010, 2960, 2920, 1645, 1610, 1580, 1530, 1488, 1455, 1430, 1403, 1382, 1366, 1310, 1292, 1270, 1220, 1190, 1095, 1038, 960, 858, 835, 825, 770, 750, 730

NMR(CDCL): 7.98(1H,d,J=3.0Hz), 7.40-7.00(5H,m), 6.36(1H,s), 3.29(2H,brs), 2.70(3H,s), 2.32(3H,s)

3-Amino-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine (Compound 310)

m.p.: 133.5-134.0°C

Analysis Calcd.for $C_{16}H_{13}N_3S$

: C 68.79%, H 4.69%, N 15.04%

Found: C 68.74%, H 4.87%, N 14.79%

MS(EI)m/z: 279(M^+), 263, 150, 135, 83

HRMS(EI)m/z: 279.08233(Calcd.for: $C_{16}H_{13}N_3S$; 279.3588)

IR(KBr): 3350, 3150, 2920, 1630, 1575, 1510, 1490, 1450, 1412, 1373, 1306, 1262, 940, 850, 762, 726

NMR(CDCL): 7.78(1H,d,J=7.0Hz), 7.50-7.00(7H,m), 3.28(2H,brs), 2.37(3H,s)

3-Amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine (Compound 311)

m.p.: 179.5-180.0°C

IR(KBr): 3380, 3270, 3180, 1632, 1572, 1532, 1490, 1443, 1427, 1385, 1360, 1338, 1298, 1278, 1247, 1200, 1032, 930, 820, 764

NMR(CDCL): 7.33-7.03(6H,m), 6.66(1H,s), 3.25(2H,brs), 2.90(3H,s), 2.30(3H,s)

3-Amino-8-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine (Compound 312)

m.p.: 153.0-153.5°C

IR(KBr): 3330, 3250, 3160, 2900, 1626, 1570, 1516, 1490, 1448, 1422, 1373, 1298, 1262, 1198, 1170, 1038, 912, 822, 760, 720

NMR(CDCL): 7.83(1H,d,J=7.0Hz), 7.63-7.20(4H,m), 7.00(1H,d,J=7.0Hz),

6.96(1H,s), 3.36(2H,brs), 2.60(3H,s), 2.38(3H,s)

3-Amino-2-(2-methylphenyl)furo[2,3-c]imidazo[1,2-a]pyridine (Compound 318)
m.p.: 65.5-67.0°C
IR(KBr): 3400, 3300, 3120, 1620, 1584, 1532, 1490, 1438, 1388, 1363, 1270, 1250, 1159, 1118, 1002, 888, 766, 720
NMR(CDCL): 7.86(1H,d,J=7.0Hz), 7.70(1H,d,J=2.0Hz), 7.55-7.20(4H,m), 6.97(1H,d,J=7.0Hz), 6.80(1H,d,J=2.0Hz), 3.46(2H,brs), 2.40(3H,s)

3-Amino-2-(2-methylphenyl)-5,6-dihydroimidazo[1,2-a]thieno[2,3-c]pyridine (Compound 323)
IR(KBr): 3400, 3300, 3050, 2920, 1665, 1625, 1560, 1480, 1432, 1380, 1340, 1220, 1178, 1134, 1090, 1040, 945, 870, 750, 720
NMR(CDCL): 7.40-7.10(5H,m), 6.89(1H,d,J=5.0Hz), 4.02(2H,t,J=7.0Hz), 3.30-3.00(2H,br), 3.10(2H,t,J=7.0Hz), 2.39(3H,s)

Example 4

3-Acetylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 112)

To a solution of 1.5g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 3) in 20ml of ethanol was added 3.0ml of acetic anhydride. After 1 hour, precipitated crude crystalline was collected by filtration and recrystallized from ethanol to give 1.5g of the title compound as a white powder.

m.p.: >270.0°C
IR(KBr): 3090, 2940, 2800, 1690, 1645, 1619, 1598, 1515, 1460, 1405, 1384, 1284, 782
NMR(DMSO): 8.28-8.08(1H,m), 7.81-7.05(9H,m), 2.47(3H,s), 2.20(3H,s)

Example 5

Compounds obtained in the same manner as in Example 4 are collectively shown below.

3-Acetylamino-2-(2-fluorophenyl)imidazo[2,1-a]isoquinoline (Compound 111)
IR(KBr): 3160, 3090, 2950, 2800, 1695, 1645, 1629, 1603, 1580, 1515, 1490,

1459, 1410, 1382, 1370, 1319, 1285, 1272, 1224, 1130, 1095, 1034, 1007, 954, 932, 900, 850, 810, 785, 748, 700

NMR(DMSO): 8.70-8.45(1H,m), 8.20-7.05(10H,m), 2.19(3H,s)

3-(3-Chloropropionylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 124)

m.p.: 223.0°C(sublimation)

IR(KBr): 3150, 3070, 3020, 2940, 2870, 2760, 1690, 1645, 1617, 1596, 1517, 1458, 1438, 1421, 1403, 1380, 1300, 1252, 1215, 980, 928, 900, 770, 718

NMR(DMSO): 10.25(1H,brs), 8.69-8.42(1H,m), 8.04-7.20(9H,m), 4.00(2H,t,J=7.0Hz), 3.00(2H,t,J=7.0Hz), 2.46(3H,s)

2-(2-Methylphenyl)-3-[3-(methylthio)propionylamino]imidazo[2,1-a]isoquinoline (Compound 125)

m.p.: 219.0-220.0°C

IR(KBr): 3090, 2940, 1699, 1643, 1619, 1595, 1515, 1490, 1459, 1425, 1400, 1381, 1286, 1244, 1230, 1140, 900, 775, 726

NMR(DMSO): 10.2(1H,brs), 8.69-8.40(1H,m), 8.14-7.11(9H,m), 2.80(4H,s), 2.43(3H,s), 2.12(3H,s)

3-[(3-Carboxypropionyl)amino]-2-(2,4-dimethylphenyl)imidazo[2,1-a]isoquinoline (Compound 127)

IR(KBr): 3210, 2940, 1750, 1660, 1602, 1516, 1459, 1382, 1260, 1240, 1165, 990, 955, 900, 817, 780

NMR(DMSO): 12.9-11.7(1H,br), 10.1(1H,brs), 8.65-8.33(1H,m), 8.04-6.90(8H,m), 2.65(4H,s), 2.38(3H,s), 2.32(3H,s)

3-Hexanoylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 128)

IR(KBr): 3150, 3080, 2940, 2870, 1698, 1643, 1618, 1597, 1514, 1490, 1458, 1402, 1380, 1312, 1288, 1247, 1180, 1105, 960, 898, 773, 722

NMR(DMSO): 9.90(1H,s), 8.70-8.43(1H,m), 8.05-7.15(9H,m), 2.40(3H,s), 1.95-0.70(11H,m)

3-(Methoxyfumaroylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 129)

m.p.: 254.0-256.0°C(dec.)

IR(KBr): 3140, 3080, 2960, 2800, 1735, 1691, 1640, 1617, 1598, 1515, 1458, 1400, 1380, 1328, 1310, 1202-1185, 1163, 990, 778, 755

NMR(DMSO): 10.65(1H,s), 8.61-8.39(1H,m), 8.00-7.15(10H,m), 6.77(1H,d,J=16.0Hz), 3.77(3H,s), 2.39(3H,s)

3-(p-Anisoylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 131)

m.p.: >270.0°C

IR(KBr): 3075, 2950, 2860, 1664, 1610, 1590, 1520, 1498, 1460, 1382, 1318, 1287, 1257, 1180, 1030, 845, 780, 725

NMR(DMSO): 10.37(1H,brs), 8.66-8.37(1H,m), 8.17-6.90(13H,m), 3.85(3H,s), 2.44(3H,s)

2-(2-Methylphenyl)-3-(2-thenoylamino)imidazo[2,1-a]isoquinoline (Compound 132)

m.p.: >270.0°C

IR(KBr): 3080, 2925, 1660, 1615, 1592, 1525, 1490, 1460, 1422, 1400, 1383, 1359, 1290, 1100, 788, 720

NMR(DMSO): 10.6(1H,brs), 8.70-8.40(1H,m), 8.16-7.10(12H,m), 2.46(3H,s)

3-[(3-Methyl-2-benz[b]furoyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 133)

m.p.: >280.0°C

IR(KBr): 3230, 3150, 3070, 2940, 1673, 1609, 1590, 1500, 1453, 1420, 1400, 1380, 1315, 1294, 1268, 1190, 1145, 1095, 910, 833, 768

NMR(DMSO): 10.73(1H,brs), 8.36-8.10(1H,m), 7.91-7.08(13H,m), 2.67(3H,s), 2.54(3H,s)

3-Ethoxycarbonylamino-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine

(Compound 355)

m.p.: 204.0°C(sublimation)

IR(KBr): 3080, 2970, 2900, 1722, 1629, 1618, 1594, 1475, 1409, 1390, 1349, 1299, 1241, 1210, 1182, 1095, 1060, 1010, 957, 760, 708

NMR(CDCL): 7.92(1H,d,J=5.4Hz), 7.68(1H,d,J=6.6Hz), 7.50(1H,d,J=5.4Hz), 7.40-7.00(6H,m), 4.18(2H,q,J=7.0Hz), 2.30(3H,s), 1.21(3H,t,J=7.0Hz)

Example 6

3-(N-Acetyl-N-propylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 138) hydrochloride

A solution of 6.0g of 3-acetylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 112) in 250ml of dry N,N-dimethylformamide was added dropwise to a solution of 0.9g of sodium hydride in oil (prewashed with hexane) in 50ml of dry N,N-dimethylformamide over 30 minutes under dry argon atmosphere at room temperature. After the mixture was stirred for further 1 hour, 2.2ml of propyl bromide was added dropwise. When addition was complete, the mixture was stirred at room temperature for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 11.0g of 3-(N-acetyl-N-propylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 138) as a brown viscous material. To a solution of 3.0g of the product in 100ml of ether was added a saturated solution of hydrogen chloride in ether, and precipitated crystalline was collected by filtration. Recrystallization from ether/chloroform gave 2.7g of the title compound as a white powder.

m.p.: 174.5-177.0°C

Analysis Calcd.for $C_{23}H_{23}N_3 \cdot HCl \cdot 0.3H_2O$

: C 69.18%, H 6.21%, N 10.52%

Found: C 69.30%, H 6.08%, N 10.54%

IR(KBr): 3075, 3040, 2980, 2940, 2890, 2500, 2260, 1683, 1630, 1543, 1498, 1460, 1430, 1397, 1332, 1300, 1243, 1148, 810, 750

NMR(DMSO): 9.48-9.10(1H,m), 8.50(1H,d,J=8.0Hz), 8.36-7.78(4H,m), 7.60-7.30(4H,m), 3.80-3.10(2H,m), 2.45(3H,s), 2.38,2.00(3H,each s), 1.62-1.02(2H,m), 0.65(3H,t,J=7.0Hz)

MS(EI)m/z: 357$(M-HCl)^+$, 314, 272, 245, 128

Example 7

Compounds obtained in the same manner as in Example 6 are collectively shown below.

3-[N-Acetyl-N-(ethoxycarbonylmethyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 134)

m.p.: 127.0-128.0°C

IR(KBr): 3070, 3000, 2950, 2875, 1752, 1692, 1640, 1610, 1585, 1565, 1520, 1490, 1458, 1401, 1379, 1335, 1269, 1238, 1205, 1165, 1140, 1094, 1030, 980, 895, 800, 769, 729, 705

NMR(CDCL): 8.80-8.60(1H,m), 8.41(1H,d,J=7.0Hz), 7.80-7.50(3H,m), 7.40-7.10(5H,m), 4.81(1H,d,J=17.0Hz), 4.19(2H,q,J=7.0Hz), 3.52(1H,d,J=17.0Hz), 2.40(3H,s),1.95(3H,s), 1.25(3H,t,J=7.0Hz)

3-[N-Acetyl-N-(N,N-diethylcarbamoylmethyl)amino]-2-(3-ethyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 135)

IR(Neat): 3080, 2980, 2940, 2880, 1690, 1656, 1610, 1582, 1520, 1480, 1452, 1371, 1330, 1260, 1238, 1215, 1144, 1072, 1031, 980, 950, 908, 800-780, 740

NMR(CDCL): 8.92(1H,d,J=7.0Hz), 8.86-8.60(1H,m), 7.87-7.51(3H,m), 7.33-7.00(3H,m), 5.21(1H,d,J=16.0Hz), 3.58(1H,d,J=16.0Hz), 3.57-3.00(6H,m), 1.93(3H,s), 1.48-0.98(9H,m)

3-[N-Acetyl-N-(2-methoxyethyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 136) hydrochloride

m.p.: 104.0-107.0°C

IR(KBr): 3100-3000, 2950-2800, 2750-2300, 1684, 1665, 1629, 1545, 1498, 1455, 1429, 1400, 1385, 1338, 1272, 1245, 1235, 1196, 1120, 1100, 1008, 805-740

NMR(CDCL): 10.00-9.65(1H,m), 8.25-7.60(5H,m), 7.50-7.20(4H,m), 4.60-2.80(4H,m), 3.11(3H,s), 2.55, 2.40(3H,each s), 2.48, 2.00(3H,each s)

3-(N-Acetyl-N-propylamino)-2-(2-fluorophenyl)imidazo[2,1-a]isoquinoline (Compound 137)

IR(KBr): 3080, 2960, 2870, 1680, 1636, 1610, 1570, 1523, 1452, 1380, 1348, 1300, 1254, 1220, 1150, 800, 760, 740

NMR(CDCL): 8.90-8.60(1H,m), 8.10-6.90(9H,m), 4.20-2.85(2H,m), 1.98(3H,s), 1.80-1.10(2H,m), 0.78(3H,t,J=7.0Hz)

3-(N-Acetyl-N-propylamino)-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 141)

IR(KBr): 3070, 2960, 2940, 2880, 1680, 1635, 1618, 1518, 1500, 1440, 1380, 1340, 1290, 1230, 1140, 1028, 824

NMR(CDCL): 8.13(1H,d,J=3.0Hz), 7.70(1H,d,J=8.0Hz), 7.63(1H,d,J=7.0Hz), 7.43-7.07(6H,m), 4.11-2.90(2H,m), 4.00(3H,s), 2.46(3H,s), 1.98(3H,s), 1.78-1.10(2H,m), 0.78(3H,t,J=7.0Hz)

3-(N-Acetyl-N-propylamino)-2-(3-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 143)

IR(KBr): 3070, 2980, 2930, 2880, 1670, 1640, 1612, 1570, 1522, 1486, 1458, 1420, 1396, 1375, 1349, 1295, 1256, 1240, 1215, 1155, 1072, 1035, 977, 798, 749, 728, 702

NMR(CDCL): 8.92-8.67(1H,m), 8.00-7.00(9H,m), 4.25-3.18(2H,m), 2.42(3H,s), 1.90-1.22(2H,m), 1.89(3H,s), 0.83(3H,t,J=7.0Hz)

3-(N-Acetyl-N-propylamino)-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 144)

IR(Neat): 3070, 3010, 2960, 2940, 2880, 1678, 1640, 1610, 1584, 1520, 1482, 1456, 1441, 1370, 1335, 1298, 1260, 1240, 1218, 1150, 1070, 1030, 960, 934, 890, 832, 790, 748

NMR(CDCL): 8.90-8.60(1H,m), 7.84-7.54(4H,m), 7.35-7.19(2H,m), 7.00(1H,d,J=5.0Hz), 4.29-3.79(1H,m), 3.59-3.09(1H,m), 2.71(3H,s), 1.90(3H,s),

1.78-1.10(2H,m), 0.83(3H,t,J=7.0Hz)

3-(N-Acetyl-N-isopropylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 145)

IR(KBr): 3080, 2990, 2950, 2890, 1670, 1640, 1612, 1588, 1568, 1518, 1485, 1456, 1370, 1330, 1310, 1238, 1212, 1176, 1132, 1118, 1102, 1088, 1040, 956, 925, 892, 796, 782, 740

NMR(CDCL): 8.92-8.58(1H,m), 7.88-7.02(9H,m), 5.10-4.56(1H,m), 2.52(3H,s), 2.00(3H,s), 0.93(3H,d,J=7.0Hz), 0.69(3H,d,J=7.0Hz)

3-(N-Acetyl-N-allylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 146)

IR(Neat): 3080, 3030, 2950, 1675, 1640, 1612, 1590, 1570, 1520, 1485, 1456, 1372, 1326, 1240, 1142, 1100, 1046, 980, 928, 896, 740

NMR(CDCL): 8.83-8.53(1H,m), 7.88-7.46(4H,m), 7.39-7.02(5H,m), 6.10-5.40(1H,m), 5.20-4.74(2H,m), 4.74-4.40(1H,m), 3.93-3.55(1H,m), 2.45(3H,s), 1.94(3H,s)

3-(N-Acetyl-N-isopentylamino)-2-(2-ethylphenyl)imidazo[2,1-a]isoquinoline (Compound 148)

IR(Neat): 3090, 2980, 2950, 2890, 1680, 1641, 1612, 1588 ,1568 ,1520, 1490, 1458, 1378, 1345, 1295, 1270, 1250, 1233, 1210, 1155, 1100, 1070, 1031, 981, 893, 790, 750, 700

NMR(CDCL): 8.88-8.62(1H,m), 7.88-7.50(4H,m), 7.40-7.13(5H,m), 4.19-3.70(1H,m), 3.48-2.68(3H,m), 2.00(3H,s), 1.60-1.00(3H,m), 1.26(3H,t,J=7.0Hz), 0.80(3H,d,J=6.0Hz), 0.72(3H,d,J=6.0Hz)

3-[N-Acetyl-N-(4-methylbenzyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 151)

IR(KBr): 3070, 3030, 2940, 1680, 1640, 1612, 1587, 1565, 1519, 1486, 1458, 1376, 1333, 1318, 1290, 1250, 1230, 1190, 1100, 1035, 970, 892, 790, 730

NMR(CDCL): 8.90-8.60(1H,m), 7.85-7.55(3H,m), 7.45-6.80(10H,m), 5.32(1H,d,J=13.0Hz), 4.10(1H,d,J=13.0Hz), 2.34(3H,s), 2.22(3H,s), 1.95(3H,s)

(hydrochloride m.p.: 126.0-128.0°C)

3-[N-Ethyl-N-[3-(methylthio)propionyl]amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 152)

IR(Neat): 3080, 2990, 2940, 1678, 1640, 1612, 1588, 1568, 1520, 1488, 1458, 1377, 1350, 1258, 1217, 1150, 1128, 1000, 1045, 1022, 980, 930, 893, 790, 750-730, 700

NMR(CDCL): 8.87-8.55(1H,m), 7.89-7.49(4H,m), 7.37-7.02(5H,m), 4.23-3.18(2H,m), 2.98-2.62(2H,m), 2.57-2.17(2H,m), 2.48(3H,s), 1.94(3H,s), 1.05(3H,t,J=7.0Hz)

2-(2,4-Dimethylphenyl)-3-succinylaminoimidazo[2,1-a]isoquinoline (Compound 154)

m.p.: 233.0-233.5°C

IR(KBr): 2940, 1728, 1645, 1623, 1600, 1520, 1460, 1427, 1380, 1330, 1169, 780

NMR(CDCL): 8.83-8.53(1H,m), 7.72-6.84(8H,m), 2.81(4H,s), 2.36(3H,s), 2.32(3H,s)

Example 8

3-(N-Ethyl-N-propylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 207) hydrochloride

A solution of 4.0g of 3-(N-acetyl-N-propylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 138) in 30ml of dry tetrahydrofuran was added dropwise to a solution of 0.7g of lithium aluminum hydride in 20ml of dry tetrahydrofuran over a period of 30 minutes. The mixture was stirred at room temperature for 4 hours. After excessive lithium aluminum hydride was decomposed by the addition of hydrous ether, the mixture was dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 3.5g of 3-(N-ethyl-N-propylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 207) as a yellow oily material. To a solution of 3.5g of the product in 100ml of ether was

added a saturated solution of hydrogen chloride in ether, and precipitated crystalline was collected by filtration. Recrystallization from ether/chloroform gave 3.0g of the title compound as a white powder.

m.p.: 168.5-172.5°C

Analysis Calcd.for $C_{23}H_{25}N_3 \cdot HCl \cdot 0.2H_2O$

: C 72.03%, H 6.94%, N 10.96%

Found: C 72.04%, H 6.88%, N 10.93%

IR(KBr): 3050, 2980, 2950, 2880, 2540, 1655, 1620, 1545, 1500, 1460, 1420, 1388, 1328, 1283, 1236, 1096, 808, 750

NMR(DMSO): 9.55-9.22(1H,m), 8.70-7.85(5H,m), 7.70-7.37(4H,m), 3.09(2H,q,J=7.0Hz), 2.92(2H,t,J=7.0Hz), 2.43(3H,s), 1.68-0.93(2H,m), 1.10(3H,t,J=7.0Hz), 0.80(3H,t,J=7.0Hz)

MS(EI)m/z: 343$(M-HCl)^+$, 314, 300, 245, 128

Example 9

2-(2-Methylphenyl)-3-[(1-phenylethyl)amino]imidazo[2,1-a]isoquinoline (Compound 192)

A solution of 5.0g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 3) in 30ml of dry N,N-dimethylformamide was added dropwise to a solution of 1.2g of sodium hydride in oil (prewashed with hexane) in 10ml of dry N,N-dimethylformamide over 30 minutes under dry argon atmosphere at room temperature. After the mixture was stirred for further 1 hour, a solution of 4.1g of (1-bromoethyl)benzene in 30ml of dry N,N-dimethylformamide was added dropwise. When addition was complete, the mixture was stirred at room temperature for 1 hour. The solution was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, and recrystallized from benzene/hexane to give 5.3g of the title compound as colorless needles.

m.p.: 160.5-161.5°C

IR(KBr): 3350, 3060, 3020, 2960, 2920, 1608, 1580, 1558, 1517, 1480, 1455, 1390, 1368, 1264, 1230, 1210, 1183, 1156, 1125, 1090, 1078, 1008, 800, 748, 720, 690

NMR(CDCL): 8.76-8.55(1H,m), 7.95(1H,d,J=7.5Hz), 7.67-7.09(12H,m), 6.99(1H,d,J=7.5Hz), 4.30-3.85(1H,m), 3.48-3.15(1H,m), 2.28(3H,s), 1.28(3H,d,J=6.5Hz)

Example 10

A solution of 3.0g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 3) in 30ml of dry N,N-dimethylformamide was added dropwise to a solution of 0.9g of sodium hydride in oil (prewashed with hexane) in 50ml of dry N,N-dimethylformamide over 30 minutes under dry argon atmosphere at room temperature. After the mixture was stirred for further 1 hour, 1.0ml of allyl bromide was added dropwise. The mixture was stirred at room temperature for 2 hours, and then at 50°C for 16 hours. The solution was poured into water, and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 1.5g of 3-diallylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 223) as a brown oily material. The chromatography successively gave 0.5g of 3-allylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 221) as a brown oily material.

Physico-chemical data of 3-diallylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 223) is shown below.

IR(Neat): 3090, 3030, 3000, 2940, 2850, 1645, 1611, 1583, 1560, 1520, 1482, 1458, 1420, 1375, 1342, 1230, 1189, 1158, 1091, 990, 921, 790, 750-730, 700

NMR(CDCL): 8.84-8.55(1H,m), 8.00(1H,d,J=7.0Hz), 7.83-7.20(7H,m), 7.02(1H,d,J=7.0Hz), 6.20-5.44(2H,m), 5.27-4.83(4H,m), 3.55(4H,d,J=5.0Hz), 2.33(3H,s)

(hydrochloride m.p.: 167.0-168.0°C)

Physico-chemical data of 3-allylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 221) is shown below.

IR(Neat): 3250, 3075, 2990, 2940, 2860, 1643, 1610, 1585, 1519, 1482, 1458, 1419, 1373, 1330, 1244, 1186, 1140, 1093, 1045, 990, 920, 896, 789, 750-730

NMR(CDCL): 8.75-8.46(1H,m), 7.86(1H,d,J=7.0Hz), 7.68-7.13(7H,m), 6.97(1H,d,J=7.0Hz), 6.17-5.39(1H,m), 5.28-4.83(2H,m), 3.48(2H,d,J=5.0Hz), 3.43-2.98(1H,brs), 2.40(3H,s)

(hydrochloride m.p.: 195.0-198.0°C(dec.))

Example 11

Example 10 was repeated except that N,N-diethylchloroacetamide was used in place of allyl bromide, which gave 3-(N,N-diethylcarbamoyl methyl)amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 157) as a brown oily material and 3-[bis(N,N-diethylcarbamoylmethyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 198) as a brown oily material. To a solution of 1.6g of the former compound in 50ml of ether was added a saturated solution of hydrogen chloride in ether, and precipitated crystalline was collected by filtration. Recrystallization from ethyl acetate/chloroform gave 1.0g of 3-(N,N-diethylcarbamoylmethyl)amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 157) hydrochloride as a yellow ocher powder.

Physico-chemical data of 3-(N,N-diethylcarbamoylmethyl)amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 157) hydrochloride is shown below.

m.p.: 187.0-190.0°C

IR(KBr): 3240, 2990, 2950, 2550, 1659, 1570, 1550, 1490, 1462, 1388, 1340, 1310, 1270, 1223, 1138, 1100, 895, 800, 754

NMR(DMSO): 9.20-8.85(1H,m), 8.78(1H,d,J=7.0Hz), 8.22-7.63(4H,m), 7.55-7.18(4H,m), 3.70(2H,s), 3.32-2.67(4H,m), 2.32(3H,s), 0.91(3H,t,J=7.0Hz), 0.73(3H,t,J=7.0Hz)

Physico-chemical data of 3-[bis(N,N-diethylcarbamoylmethyl)amino]-2-

(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 198) is shown below.

IR(Neat): 3080, 2990, 2950, 1658, 1640, 1565, 1519, 1456, 1380, 1310, 1262, 1220, 1190, 1132, 1098, 1048, 980, 945, 897, 740

NMR(CDCL): 8.72-8.51(1H,m), 8.66(1H,d,J=7.0Hz), 7.82-7.17(7H,m), 7.06(1H,d,J=7.0Hz), 3.93(4H,s), 3.52-2.94(8H,m), 2.32(3H,s), 1.06(12H,t,J=7.0Hz)

Example 12

Example 10 was repeated except that 3-amino-7-chloro-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 5) and ethyl iodide were used in place of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline and allyl bromide, which gave 7-chloro-3-ethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 159) as yellow needles and 7-chloro-3-diethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 199) as colorless needles.

Physico-chemical data of 7-chloro-3-diethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 199) is shown below.

m.p.: 102.0-102.5°C

IR(KBr): 2980, 2860, 1600, 1558, 1512, 1490, 1474, 1450, 1370, 1342, 1218, 1088, 900, 788

NMR(CDCL): 8.64(1H,dd,J=3.0Hz,7.0Hz), 8.19(1H,d,J=7.0Hz), 7.72-7.18(7H,m), 2.97(4H,q,J=7.0Hz),2.32(3H,s), 1.00(6H,t,J=7.0Hz)

Physico-chemical data of 7-chloro-3-ethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 159) is shown below.

m.p.: 157.0-158.0°C

IR(KBr): 3270, 2980, 2940, 1638, 1600, 1578, 1505, 1472, 1440, 1405, 1370, 1353, 1300, 1260, 1210, 1190, 1160, 1120, 1083, 996, 900, 820, 772, 740, 720

NMR(CDCL): 8.60(1H,dd,J=2.0Hz,7.0Hz), 8.00(1H,d,J=7.0Hz), 7.67-7.19(7H,m), 3.27-2.98(1H,br), 2.98(2H,q,J=7.0Hz), 2.40(3H,s), 1.07(3H,t,J=7.0Hz)

Example 13

Example 10 was repeated except that 3-amino-7-methoxycarbonyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 51) and methyl iodide were used in place of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline and allyl bromide, which gave 3-dimethylamino-7-methoxycarbonyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 197) as a pale yellow powder.

m.p.: 130.0-130.5°C

IR(KBr): 2950, 2880, 2800, 1713, 1636, 1600, 1560, 1492, 1428, 1370, 1307, 1259, 1200, 1110, 1012, 970, 926, 800

NMR(CDCL): 8.92(1H,dd,J=2.0Hz,7.0Hz), 8.30(1H,d,J=8.0Hz), 8.20(1H,dd,J=2.0Hz,8.0Hz), 7.98(1H,d,J=8.0Hz), 7.57(1H,t,J=8.0Hz), 7.30(4H,s), 4.00(3H,s), 2.72(6H,s), 2.37(3H,s)

Example 14

2-(2-Methylphenyl)-3-piperidinoimidazo[2,1-a]isoquinoline (Compound 217) hydrochloride

To a solution of 3.0g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 3) in 50ml of dry N,N-dimethylformamide was added successively 4.6g of potassium carbonate and 1.6ml of 1,5-dibromopentane, and the mixture was stirred at 140°C for 3 hours. After being cooled, the mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 3.7g of 2-(2-methylphenyl)-3-piperidinoimidazo[2,1-a]isoquinoline (Compound 217) as a brown oily material. To a solution of 2.0g of the product in 80ml of ether was added a saturated solution of hydrogen chloride in ether, and precipitated crystalline was collected by filtration. Recrystallization from ethyl acetate/petroleum ether gave 1.4g of the title compound as a white powder.

m.p.: 212.0-215.0°C

Analysis Calcd.for $C_{23}H_{23}N_3 \cdot HCl \cdot 0.5H_2O$

: C 71.40%, H 6.51%, N 10.86%

Found: C 71.44%, H 6.45%, N 10.94%

IR(KBr): 2950, 2850, 2620, 1660, 1622, 1548, 1498, 1450, 1382, 1283, 1130, 905, 800, 752

NMR(DMSO): 9.40-9.07(1H,m), 8.45(1H,d,J=7.0Hz), 8.35-7.83(4H,m), 7.70-7.37(4H,m), 3.15-2.70(4H,m), 2.40(3H,s), 1.98-1.30(6H,m)

MS(EI)m/z: 341$(M-HCl)^+$, 284, 257, 245, 128

Example 15

2-(2-Methylphenyl)-3-morpholinoimidazo[2,1-a]isoquinoline (Compound 218) hydrochloride

A solution of 5.5g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 3) in 50ml of dry N,N-dimethylformamide was added dropwise to a solution of 1.8g of sodium hydride in oil (prewashed with hexane) in 150ml of dry N,N-dimethylformamide over 30 minutes under dry argon atmosphere at room temperature. After the mixture was stirred for further 1 hour, 3.2g of bis(2-chloroethyl)ether was added dropwise. The mixture was stirred at room temperature for 2 hours, and then at 60°C for 2 hours. The reaction mixture was poured into ice water, and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel to give 2.0g of 2-(2-methylphenyl)-3-morpholinoimidazo[2,1-a]isoquinoline (Compound 218) as a yellow oily material. To a solution of 2.0g of the product in 80ml of ether was added a saturated solution of hydrogen chloride in ether. Precipitated crystalline was collected by filtration, and washed with ethanol to give 1.1g of the title compound as a yellowish white powder.

m.p.: 212.0-217.0°C

Analysis Calcd.for $C_{22}H_{21}N_3O \cdot HCl \cdot 0.2H_2O$

: C 68.90%, H 5.89%, N 10.96%

Found: C 68.87%, H 5.94%, N 10.92%

IR(KBr): 3040, 2980, 2860, 2740, 2600, 1660, 1625, 1542, 1498, 1459, 1304, 1262, 1239, 1202, 1112, 919, 800, 750

NMR(DMSO): 9.38-9.02(1H,m), 8.56(1H,d,J=7.0Hz), 8.41-7.70(4H,m), 7.68-7.38(4H,m), 3.90-3.55(4H,m), 3.10-2.77(4H,m), 2.37(3H,s)

MS(EI)m/z: 343$(M-HCl)^+$, 284, 270, 257, 245, 128

Example 16

3-(4-Methylbenzylideneamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 225)

To a solution of 5.0g of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 3) in 50ml of methanol was added 2.2g of p-tolualdehyde. After the mixture was stirred at room temperature for 22 hours, it was poured into water and extracted with ethyl acetate. The extract was washed with water and saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel, and recrystallization from ethyl acetate/petroleum ether gave 5.4g of the title compound as yellow crystals.

m.p.: 159.5-160.0°C

IR(KBr): 3050, 2930, 1603, 1572, 1515, 1480, 1458, 1378, 1228, 1173, 1088, 900, 791, 755, 690

NMR(CDCL): 8.81-8.58(1H,m), 8.38(1H,d,J=7.0Hz), 8.22(1H,s), 7.84-7.01(12H,m), 2.37(3H,s), 2.27(3H,s)

Example 17

3-[(1-Bromo-2-naphthyl)methylideneamino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 228)

Example 16 was repeated except that 1-bromo-2-naphtoaldehyde was used in place of p-tolualdehyde, which gave the title compound as a yellow powder.

m.p.: 250.0-252.0°C

IR(KBr): 3060, 3020, 2920, 1578, 1515, 1476, 1458, 1380, 1328, 1300, 1260, 1230, 1190, 1160, 972, 940, 893, 860, 810, 786, 760, 730, 688

NMR(CDCL): 8.94(1H,s), 8.82-8.60(1H,m), 8.40(1H,d,J=8.0Hz), 8.36-8.10(2H,m), 7.87-7.30(11H,m), 7.10(1H,d,J=8.0Hz), 2.30(3H,s)

Example 18

2-(2-Methylphenyl)-3-propylideneaminoimidazo[2,1-a]isoquinoline (Compound 224)

Example 16 was repeated except that propylaldehyde was used in place of p-tolualdehyde, which gave the title compound as a brown oily material.

IR(Neat): 3070, 2980, 1642, 1611, 1516, 1480, 1458, 1380, 1218, 1183, 1138, 1090, 1030, 985, 893, 790, 745, 693

NMR(CDCL): 8.84-8.55(1H,m), 8.18(1H,d,J=7.0Hz), 7.78(1H,t,J=4.0Hz), 7.78-7.19(7H,m), 7.02(1H,d,J=7.0Hz), 2.60-2.08(2H,m), 2.27(3H,s), 1.08(3H,t,J=7.0Hz)

Example 19

2-(2-Ethylphenyl)-3-(4-methylbenzylideneamino)imidazo[2,1-a]isoquinoline (Compound 226)

Example 16 was repeated except that 3-amino-2-(2-ethylphenyl)imidazo[2,1-a]isoquinoline (Compound 59) was used in place of 3-amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline, which gave the title compound as a yellow powder.

m.p.: 158.5-159.5°C

IR(KBr): 2970, 2940, 2880, 1600, 1570, 1515, 1476, 1460, 1420, 1380, 1230, 1175, 1088, 970, 900, 812, 790, 765, 742, 690

NMR(CDCL): 8.97-8.67(1H,m), 8.46(1H,d,J=7.4Hz), 8.30(1H,s), 7.91-7.09(12H,m), 2.68(2H,q,J=7.0Hz), 2.39(3H,s), 1.10(3H,t,J=7.0Hz)

Example 20

3-(4-Methylbenzylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 194)

To a solution of 4.3g of 3-(4-methylbenzylideneamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 225) in 50ml of ethanol was added 0.9g of sodium borohydride. After the mixture was refluxed for 2 hours, it was poured into water, and extracted with chloroform. The extract was

washed with saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The crude crystals were recrystallized from petroleum ether/chloroform to give 3.7g of the title compound as pale yellow needles.

m.p.: 139.0-139.5°C

IR(KBr): 3360, 3050, 2940, 2860, 1613, 1571, 1518, 1459, 1374, 1185, 898, 798, 750, 730

NMR(CDCL): 8.87-8.60(1H,m), 7.95(1H,d,J=7.0Hz), 7.75-6.94(12H,m), 4.13-3.89(2H,m), 3.71-3.44(1H,m), 2.37(3H,s), 2.30(3H,s)

Example 21

3-Ethylamino-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 167)

To a solution of 5.0g of 3-amino-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 26) in 100ml of ethanol was added 3.0ml of acetaldehyde, and the mixture was stirred at room temperature for 3 hours. After 3.3g of sodium borohydride was added to the mixture and refluxed for 2 hours, the reaction mixture was poured into water, and extracted with ethyl acetate. The extract was washed with saturated saline, and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration, and the solvent was removed under reduced pressure. The crude crystal was recrystallized from petroleum ether/ethyl acetate to give 5.0g of the title compound as colorless needles.

m.p.: 153.0-154.0°C

IR(KBr): 3240, 3070, 3040, 2960, 2930, 2900, 2850, 1618, 1585, 1568, 1520, 1506, 1473, 1436, 1396, 1379, 1340, 1300, 1270, 1223, 1190, 1140, 1050, 1030, 912, 850, 822, 752, 718

NMR(CDCL): 8.10(1H,d,J=2.0Hz), 7.84(1H,d,J=7.0Hz), 7.63(1H,d,J=8.0Hz), 7.49-6.90(6H,m), 3.97(3H,s),3.28-2.84(1H,br), 2.97(2H,q,J=7.0Hz), 2.40(3H,s), 1.05(3H,t,J=7.0Hz)

Example 22

Compounds obtained in the same manner as in Examples 8, 9, 10 and 21

are collectively shown below.

2-(2-Methylphenyl)-3-(propoxycarbonylmethyl)aminoimidazo[2,1-a]isoquinoline (Compound 156)

IR(Neat): 3450-3150, 3070, 2480, 2440, 1748, 1672, 1640, 1610, 1598-1550, 1520, 1459, 1398, 1378, 1195, 890, 745

NMR(CDCL): 8.75-8.54(1H,m), 8.00(1H,d,J=8.0Hz), 7.75-7.20(7H,m), 7.01(1H,d,J=8.0Hz), 4.00(2H,t,J=6.0Hz), 3.64(2H,s), 2.40(3H,s), 1.80-1.27(2H,m), 0.85(3H,t,J=7.0Hz)

3-Ethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 158) hydrochloride

m.p.: 236.5-239.5°C(dec.)

IR(KBr): 3160, 3050, 3000, 2940, 2890, 2560, 1660, 1625, 1603, 1567, 1550, 1492, 1460, 1424, 1385, 1327, 1305, 1237, 1152, 796, 755, 720

NMR(DMSO): 8.94-8.70(1H,m), 8.50(1H,d,J=6.0Hz), 8.14-7.28(8H,m), 2.94(2H,q,J=7.0Hz), 2.45(3H,s), 1.01(3H,t,J=7.0Hz)

3-Ethylamino-2-(2-methylphenyl)-7-propylimidazo[2,1-a]isoquinoline (Compound 163) hydrochloride

m.p.: 185.0°C(dec.)

IR(KBr): 3170, 3030, 2970, 2940, 2870, 2625, 1658, 1618, 1570, 1542, 1486, 1428, 1380, 1343, 1300, 1282, 1240, 1220, 1154, 1086, 792, 750

NMR(DMSO): 8.97(1H,dd,J=3.0Hz,6.0Hz), 8.78(1H,d,J=8.0Hz), 8.03-7.17(7H,m), 3.10(2H,brt,J=7.0Hz), 2.87(2H,q,J=7.0Hz), 2.41(3H,s), 1.98-1.38(2H,m), 1.02(6H,t,J=7.0Hz)

3-Ethylamino-6-methoxymethyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 164)

m.p.: 115.0-116.5°C

IR(KBr): 3330, 3080, 2980, 2930, 2900, 2860, 2830, 1644, 1610, 1580, 1559, 1523, 1482, 1450, 1395, 1375, 1339, 1278, 1240, 1215, 1195, 1155, 1120, 1090, 1060, 1030, 982, 948, 872, 860, 845, 825, 755, 715, 700

NMR(CDCL): 8.72-8.50(1H,m), 7.98-7.10(8H,m), 4.75(2H,s), 3.47(3H,s), 3.20-

2.75(3H,m), 2.40(3H,s), 1.25-0.90(3H,m)

3-Ethylamino-7-hydroxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 165)

m.p.: 247.0-251.0°C(dec.)

IR(KBr): 3480-3400, 3390, 3100, 2980, 2940, 2875, 2375, 1611, 1588, 1565, 1508, 1448, 1381, 1355, 1280, 1252, 1208, 1186, 1146, 1015, 949, 785, 741

NMR(DMSO): 10.30(1H,s), 8.10(1H,d,J=7.0Hz), 7.90(1H,brd,J=8.0Hz), 7.69-7.20(6H,m), 7.00(1H,dd,J=2.0Hz,8.0Hz), 4.79(1H,brt,J=6.0Hz), 3.05-2.70(2H,m), 2.40(3H,s), 0.96(3H,t,J=7.0Hz)

3-Ethylamino-6-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 166)

IR(Neat): 3260, 3070, 2970, 2950, 2880, 1648, 1610, 1568, 1519, 1485, 1455, 1372, 1338, 1286, 1228, 1158, 1125, 1100, 1044, 1030, 984, 860

NMR(CDCL): 8.79-8.50(1H,m), 8.15-7.88(1H,m), 7.68-7.08(7H,m), 3.90(3H,s), 3.20-2.62(3H,m), 2.39(3H,s), 1.00(3H,t,J=7.0Hz)

(hydrochloride m.p.: 202.0°C(dec.))

7-Benzyloxy-3-ethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 169)

m.p.: 128.0-129.0°C

IR(KBr): 3225, 3050, 2950, 2900, 2850, 1610, 1585, 1565, 1555, 1520, 1500, 1489, 1450, 1395, 1378, 1332, 1305, 1260, 1189, 1176, 1145, 1080, 1060, 1050, 1024, 935, 775, 735, 715

NMR(CDCL): 8.30(1H,brd,J=8.0Hz), 7.90(1H,d,J=7.0Hz), 7.65-7.20(11H,m), 7.00(1H,brd,J=8.0Hz), 5.25(2H,s), 3.20-2.75(3H,m), 2.40(3H,s), 1.07(3H,m)

7-Ethoxycarbonyl-3-ethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 173)

IR(KBr): 3380, 3070, 2980, 2940, 2880, 1718, 1637, 1600, 1557, 1515, 1482, 1450, 1370, 1310, 1260, 1210, 1195, 1119, 1022, 925, 790

NMR(CDCL): 8.96(1H,dd,J=2.0Hz,8.0Hz), 8.32(1H,d,J=8.0Hz),

8.23(1H,dd,J=2.0Hz,8.0Hz), 8.02(1H,d,J=8.0Hz), 7.62(1H,t,J=8.0Hz), 7.58-7.22(4H,m), 4.50(2H,q,J=7.0Hz), 3.13-2.70(1H,br), 2.98(2H,q,J=7.0Hz), 2.42(3H,s), 1.47(3H,t,J=7.0Hz), 1.07(3H,t,J=7.0Hz)

3-Ethylamino-2-(2-trifluoromethylphenyl)imidazo[2,1-a]isoquinoline (Compound 175)

m.p.: 100.5-101.5°C

IR(KBr): 3230, 3060, 2980, 2940, 2910, 2860, 1639, 1610, 1590, 1570, 1520, 1505, 1483, 1457, 1420, 1390, 1373, 1349, 1320, 1275, 1260, 1190, 1168, 1156, 1125, 1115, 1100, 1053, 1032, 980, 950, 900, 845, 792, 754, 697

NMR(CDCL): 8.79-8.45(1H,m), 8.10-7.30(7H,m), 7.88(1H,d,J=7.6Hz), 7.01(1H,d,J=7.6Hz), 3.20-2.63(3H,m), 1.02(3H,t,J=7.0Hz)

3-Ethylamino-6-methoxy-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 176)

m.p.: 142.0-143.0°C

IR(KBr): 3330, 3090, 3040, 2980, 2950, 2925, 2880, 1648, 1590, 1520, 1481, 1471, 1441, 1378, 1341, 1323, 1289, 1230, 1214, 1186, 1160, 1135, 1100, 1074, 1020, 990, 968, 861, 830, 773, 732, 699

NMR(CDCL): 8.83-8.52(1H,m), 8.20-7.89(1H,m), 7.79-7.48(2H,m), 7.41(1H,s), 7.24(1H,d,J=5.0Hz), 6.96(1H,d,J=5.0Hz), 3.96(3H,s), 3.32-2.76(3H,m), 2.51(3H,s), 1.17(3H,t,J=7.0Hz)

2-(2-Chloro-3-methyl-4-thienyl)-3-ethylaminoimidazo[2,1-a]isoquinoline (Compound 179)

m.p.: 80.5-81.0°C

IR(KBr): 3250, 3060, 2960, 2850, 1635, 1608, 1581, 1516, 1486, 1443, 1375, 1340, 1230, 1188, 1136, 1004, 960, 892, 776, 732, 688

NMR(CDCL): 8.85-8.51(1H,m), 7.92(1H,d,J=7.0Hz), 7.82-7.35(3H,m), 7.21(1H,s), 7.06(1H,d,J=7.0Hz), 3.31-2.78(3H,m), 2.38(3H,s), 1.14(3H,t,J=7.0Hz)

3-(2-Methoxyethyl)amino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 180) hydrochloride

m.p.: 206.0-208.0°C(dec.)

IR(KBr): 3160, 3050, 2940, 2610, 1662, 1625, 1605, 1570, 1550, 1470-1435, 1430, 1330, 1310, 1241, 1200, 1145, 1120, 958, 789, 752

NMR(CDCL): 16.10-15.60(1H,br), 9.60-9.38(1H,m), 8.55(1H,d,J=8.0Hz), 7.91-7.62(3H,m), 7.58-7.30(1H,m), 7.42(1H,d,J=8.0Hz), 7.10-6.85(3H,m), 3.48-2.85(4H,m), 3.10(3H,s), 2.40(3H,s)

6-Isopentyl-2-(2-methylphenyl)-3-propylaminoimidazo[2,1-a]isoquinoline (Compound 181)

m.p.: 126.5-127.5°C

IR(KBr): 3210, 3070, 3025, 2960, 2940, 2875, 1640, 1610, 1575, 1520, 1495, 1480, 1465, 1455, 1390, 1368, 1360, 1340, 1240, 1154, 760

NMR(CDCL): 8.85-8.55(1H,m), 7.90-7.10(8H,m), 3.20-2.70(5H,m), 2.40(3H,s), 1.86-1.25(5H,m), 1.05(6H,d,J=6.0Hz), 0.85(3H,t,J=7.0Hz)

6-Methoxy-2-(2-methylphenyl)-3-propylaminoimidazo[2,1-a]isoquinoline (Compound 182)

m.p.: 106.0°C

IR(KBr): 3250, 3070, 3030, 2970, 2930, 2840, 1650, 1610, 1589, 1572, 1522, 1482, 1471, 1452, 1412, 1378, 1338, 1308, 1279, 1226, 1192, 1152, 1128, 1100, 1068, 990, 863, 790, 758, 715, 702

NMR(CDCL): 8.71-8.45(1H,m), 8.19-7.91(1H,m), 7.71-7.05(7H,m), 3.98(3H,s), 3.29-2.59(3H,m), 2.38(3H,s), 1.69-1.10(2H,m), 0.86(3H,t,J=7.0Hz)

3-Isopropylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 184) hydrochloride

m.p.: 210.0-214.5°C

IR(KBr): 3450, 3220, 3050, 2990, 2940, 2800, 2725, 1663, 1625, 1606, 1570, 1549, 1498, 1460, 1428, 1385, 1370, 1332, 1238, 1175, 962, 899, 792, 750

NMR(METH): 8.79-8.37(2H,m), 8.37-7.30(8H,m), 3.41-2.94(1H,m), 2.42(3H,s), 1.07(6H,d,J=7.0Hz)

2-(2-Methylphenyl)-3-[(3-methylthiopropyl)amino]imidazo[2,1-a]isoquinoline

(Compound 185)

IR(Neat): 3270, 3070, 2960, 2925, 2860, 1640, 1610, 1568, 1518, 1480, 1455, 1374, 1260, 1183, 1135, 1092, 1042, 950, 893, 787, 745, 690

NMR(CDCL): 8.78-8.52(1H,m), 7.92(1H,d,J=7.0Hz), 7.80-7.40(3H,m), 7.28(4H,s), 7.02(1H,d,J=7.0Hz), 3.31-2.79(3H,m), 2.42(2H,t,J=7.0Hz), 2.38(3H,s), 1.98(3H,s), 1.92-1.50(2H,m)

2-(2-Methylphenyl)-3-[3-(methylsulfinyl)propylamino]imidazo[2,1-a]isoquinoline (Compound 186)

IR(Neat): 3300, 3070, 2960, 2860, 1640, 1610, 1580, 1520, 1480, 1458, 1373, 1260, 1216, 1185, 1095, 1020, 940, 890, 790, 745

NMR(CDCL): 8.78-8.52(1H,m), 7.92(1H,d,J=7.0Hz), 7.84-7.20(7H,m), 7.08(1H,d,J=7.0Hz), 3.50-2.80(3H,m), 2.70-2.35(2H,m), 2.40(6H,s), 2.10-1.15(2H,m)

3-Isopentylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 188)

m.p.: 93.0-93.5°C

IR(KBr): 3300, 3080, 3040, 2960, 2940, 2880, 1638, 1615, 1590, 1576, 1515, 1476, 1460, 1375, 1190, 1092, 900, 795, 772, 738

NMR(CDCL): 8.80-8.52(1H,m), 7.90(1H,d,J=7.0Hz), 7.72-7.19(7H,m), 7.00(1H,d,J=7.0Hz), 3.12-2.73(3H,m), 2.40(3H,s), 1.73-1.05(3H,m), 0.80(6H,d,J=6.0Hz)

3-Isopentylamino-2-(2,4-dimethylphenyl)imidazo[2,1-a]isoquinoline (Compound 189)

IR(Neat): 3250, 3070, 2970, 2940, 2870, 1640, 1612, 1582, 1505, 1485, 1456, 1372, 1265, 1237, 1185, 1140, 1094, 894, 786, 745

NMR(CDCL): 8.86-8.50(1H,m), 7.88(1H,d,J=7.0Hz), 7.80-6.82(7H,m), 3.10-2.64(3H,m), 2.37(6H,s), 1.55-1.05(3H,m), 0.80(6H,d,J=6.0Hz)

(hydrochloride m.p.: 215.0-217.5°C)

3-Cyclopentylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound

190)

IR(KBr): 3300, 3080, 2975, 2890, 1640, 1613, 1569, 1521, 1484, 1460, 1377, 1186, 1090, 898, 790, 741

NMR(CDCL): 8.78-8.50(1H,m), 7.93(1H,d,J=7.0Hz), 7.70-7.16(7H,m), 6.98(1H,d,J=7.0Hz), 3.60-3.22(1H,m), 3.11-2.73(1H,br), 2.40(3H,s), 1.80-1.11(8H,m)

3-Hexylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 191)

IR(Neat): 3240, 3060, 2960, 2930, 2860, 1635, 1608, 1582-1565, 1518, 1480, 1456, 1372, 1260, 1219-1210, 1181, 893, 788, 748

NMR(CDCL): 8.82-8.60(1H,m), 7.92(1H,d,J=7.0Hz), 7.75-7.25(7H,m), 7.06(1H,d,J=7.0Hz), 3.30-2.75(3H,m), 2.40(3H,s), 1.60-0.60(11H,m)

(hydrochloride m.p.: 172.0-175.0°C(dec.))

3-[(1-Bromo-2-naphthyl)methylamino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 195)

m.p.: 129.0-130.0°C

IR(KBr): 3250, 3050, 2940, 2830, 1639, 1610, 1570, 1520, 1498, 1483, 1455, 1375, 1325, 1260, 1230, 1213, 1183, 1135, 1097, 1026, 965, 896, 865, 815, 783, 760, 715

NMR(CDCL): 8.80-8.50(1H,m), 8.33-8.03(1H,m), 7.93(1H,d,J=7.0Hz), 7.81-7.34(7H,m), 7.12-6.87(6H,m), 4.44-4.23(2H,m), 4.18-3.90(1H,m), 2.17(3H,s)

3-[(3-Methyl-2-benz[b]furyl)methylamino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 196)

IR(KBr): 3390, 3060, 2940, 2860, 1610, 1520, 1480, 1458, 1374, 1328, 1265, 1230, 1178, 1117, 790, 740

NMR(CDCL): 8.78-8.54(1H,m), 7.90(1H,d,J=8.0Hz), 7.70-7.03(11H,m), 6.98(1H,d,J=8.0Hz), 4.12(2H,brd,J=5.0Hz), 3.90-3.57(1H,br), 2.26(3H,s), 1.83(3H,s)

7-Bromo-3-diethylamino-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 200)

IR(Neat): 3080, 2980, 2940, 2860, 1635, 1597, 1556, 1515, 1490, 1473, 1436, 1371, 1348, 1218, 1104, 897, 780

NMR(CDCL): 8.82-8.45(1H,m), 8.30-7.10(8H,m), 2.95(4H,q,J=7.0Hz), 2.35(3H,s), 0.98(6H,t,J=7.0Hz)

(hydrochloride m.p.: 186.0-187.5°C)

3-[N-(2-Chloroethyl)-N-ethylamino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 202) hydrochloride

m.p.: 169.0-169.5°C

IR(KBr): 3050, 2980, 2920, 2850, 2570, 2350, 1740, 1651, 1618, 1540, 1493, 1456, 1419, 1380, 1315, 1280, 1240, 1159, 1099, 1030, 894, 804, 747

NMR(DMSO): 9.50-9.19(1H,m), 8.59(1H,d,J=7.0Hz), 8.39-7.75(4H,m), 7.72-7.21(4H,m), 3.70(2H,t,J=5.0Hz), 3.50-2.90(4H,m), 2.40(3H,s), 1.09(3H,t,J=7.0Hz)

3-[N-Ethyl-N-[2-(N,N-diethylamino)ethyl]amino]-2-(3-ethyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 203)

IR(Neat): 3070, 2980, 2940, 2870, 2810, 1638, 1610, 1580, 1520, 1482, 1458, 1372, 1345, 1202, 1155, 1068, 905, 890, 788, 735, 698

NMR(CDCL): 8.83-8.58(1H,m), 8.12(1H,d,J=7.0Hz), 7.81-7.44(3H,m), 7.31-6.95(3H,m), 3.36-2.29(12H,m), 1.25(3H,t,J=7.0Hz), 1.02(3H,t,J=7.0Hz), 0.92(6H,t,J=7.0Hz)

3-[N-Ethyl-N-(2-methoxyethyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 205) hydrochloride

m.p.: 156.5-159.0°C

IR(KBr): 3040, 2990, 2940, 2850, 2575, 2400, 2320, 1783-1769, 1655, 1620, 1605, 1541, 1499, 1455, 1420, 1388, 1375, 1350, 1330, 1300, 1288, 1238, 1198, 1115, 1110, 1072, 1015, 920-855, 808, 765, 751, 725, 695

NMR(CDCL): 10.00-9.72(1H,m), 8.50(1H,d,J=8.0Hz), 8.05-7.78(3H,m), 7.60(1H,d,J=8.0Hz), 7.50-7.25(4H,m), 3.55-2.85(6H,m), 3.25(3H,s), 2.50(3H,s), 1.05(3H,t,J=7.0Hz)

3-(N-Ethyl-N-propylamino)-2-(2-fluorophenyl)imidazo[2,1-a]isoquinoline

(Compound 206)

IR(Neat): 3060, 2960, 2940, 2875, 1625, 1610, 1565, 1520, 1495, 1480, 1456, 1418, 1378, 1260, 1220, 1175, 1150, 1115, 1090, 1030, 891, 820, 790, 750, 696

NMR(CDCL): 8.82-8.10(1H,m), 8.03(1H,d,J=7.2Hz), 7.90-7.20(7H,m), 7.07(1H,d,J=7.2Hz), 3.28-2.75(4H,m), 1.65-1.10(2H,m), 1.04(3H,t,J=7.0Hz), 0.81(3H,t,J=7.0Hz)

3-(N-Ethyl-N-propylamino)-6-isopentyl-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 208) hydrochloride

m.p.: 149.0-151.5°C

IR(KBr): 3060, 3020, 2960, 2940, 2875, 2550, 2275, 1780-1770, 1651, 1615, 1605, 1539, 1495, 1465, 1455, 1422, 1384, 1370, 1330, 1275, 1230, 1170, 1120-1060, 1040, 850, 825, 775, 723

NMR(CDCL): 9.95-9.70(1H,m), 8.20-7.78(4H,m), 7.50-7.25(4H,m), 3.30-2.75(6H,m), 2.50(3H,s), 2.00-1.30(5H,m), 1.10(3H,t,J=8.0Hz), 1.10(6H,d,J=6.0Hz), 0.90(3H,t,J=7.0Hz)

3-(N-Ethyl-N-propylamino)-2-(3-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 211) hydrochloride

m.p.: 152.5-156.0°C

IR(KBr): 3060, 2980, 2940, 2860, 2600, 1656, 1621, 1605, 1543, 1497, 1458, 1420, 1385, 1335, 1238, 1172, 1110-1088, 890, 800, 750, 692

NMR(DMSO): 9.70-9.37(1H,m), 8.53(1H,d,J=7.0Hz), 8.40-7.24(8H,m), 3.25(4H,m), 2.46(3H,s), 1.70-1.10(2H,m), 1.10(3H,t,J=7.0Hz), 0.79(3H,t,J=7.0Hz)

3-(N-Ethyl-N-propylamino)-2-(3-methyl-2-thienyl)imidazo[2,1-a]isoquinoline (Compound 212) hydrochloride

m.p.: 146.0-148.5°C

IR(KBr): 3050, 2970, 2930, 2870, 2660-2590, 2330, 1790, 1655, 1620, 1545, 1459, 1425, 1389, 1320, 1236, 1180, 1065, 890, 800, 750

NMR(DMSO): 9.38-9.11(1H,m), 8.49(1H,d,J=7.0Hz), 8.32-7.74(5H,m), 7.18(1H,d,J=5.0Hz), 3.17(2H,q,J=7.0Hz), 3.00(2H,t,J=7.0Hz), 2.38(3H,s), 1.73-1.03(2H,m), 1.09(3H,t,J=7.0Hz), 0.80(3H,t,J=7.0Hz)

3-[N-Ethyl-N-(3-methylthiopropyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 214)

IR(Neat): 3070, 2980, 2940, 2860, 1639, 1612, 1559, 1520, 1482, 1457, 1376, 1234, 1156, 1045, 954, 895, 792, 750, 700

NMR(CDCL): 8.82-8.55(1H,m), 8.02(1H,d,J=7.0Hz), 7.75-7.21(7H,m), 7.06(1H,d,J=7.0Hz), 3.03(2H,q,J=7.0Hz), 2.99(2H,t,J=7.0Hz), 2.45(2H,t,J=7.0Hz), 2.35(3H,s), 1.98(3H,s), 1.98-1.47(2H,m), 1.06(3H,t,J=7.0Hz)

3-(N-Ethyl-N-isopentylamino)-2-(2-ethylphenyl)imidazo[2,1-a]isoquinoline (Compound 216) hydrochloride

m.p.: 159.5-161.0°C

IR(KBr): 3060, 2970, 2940, 2880, 2600, 1660, 1621, 1550, 1494, 1465, 1424, 1390, 1339, 1290, 1250, 1229, 1165, 1100, 890, 800, 750

NMR(DMSO): 9.20-8.98(1H,m), 8.49(1H,d,J=7.0Hz), 8.33-7.74(4H,m), 7.64-7.38(4H,m), 3.25-2.76(6H,m), 1.52-0.96(9H,m), 0.80(6H,d,J=6.0Hz)

3-[N-Ethyl-N-(4-methylbenzyl)amino]-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 219)

IR(Neat): 3080, 3040, 2990, 2940, 2860, 1645, 1612, 1560, 1519, 1482, 1458, 1380, 792, 750

NMR(CDCL): 8.80-8.50(1H,m), 8.05(1H,d,J=7.0Hz), 7.80-7.20(7H,m), 7.20-6.89(5H,m), 4.05(2H,s), 2.98(2H,q,J=7.0Hz), 2.26(6H,s), 1.00(3H,s)

(hydrochloride m.p.: 116.0-119.0°C)

3-[N-Ethyl-N-(4-methylbenzyl)amino]-2-(2-ethylphenyl)imidazo[2,1-a]isoquinoline (Compound 220)

IR(Neat): 3070, 3040, 2990, 2940, 2890, 1639, 1610, 1558, 1519, 1482, 1455, 1420, 1372, 1270, 1230, 1160, 1020, 896, 840, 790, 700

NMR(CDCL): 8.82-8.50(1H,m), 8.00(1H,d,J=7.4Hz), 7.78-6.88(12H,m), 4.02(2H,s), 2.98(2H,q,J=7.0Hz), 2.62(2H,q,J=7.0Hz), 2.26(3H,s), 1.22(3H,t,J=7.0Hz), 1.00(3H,t,J=7.0Hz)

3-(N-Allyl-N-ethylamino)-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 222) hydrochloride

m.p.: 175.0-178.0°C

IR(KBr): 3100, 2990, 2580, 2400-2310, 1750, 1655, 1620, 1542, 1498, 1420, 1233, 1100, 1082, 1010, 928, 891, 803, 750, 692

NMR(DMSO): 9.34-8.93(1H,m), 8.53(1H,d,J=7.0Hz), 8.40-7.78(4H,m), 7.49(4H,s), 6.18-5.52(1H,m), 5.38-4.88(2H,m), 3.68(2H,d,J=6.0Hz), 3.00(2H,q,J=7.0Hz), 2.40(3H,s), 1.00(3H,t,J=7.0Hz),

3-Ethylamino-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 340) hydrochloride

m.p.: 192.0°C(sublimation)

IR(KBr): 3150, 3060, 3030, 2970, 2910, 2870, 2770, 2710, 2650, 2600, 1650, 1620, 1600, 1533, 1495, 1422, 1379, 1315, 1290, 1243, 1215, 1162, 1086, 1008, 959, 763, 721

NMR(DMSO): 8.41(1H,d,J=5.8Hz), 8.25(1H,d,J=4.0Hz), 8.08-7.86(2H,m), 7.63-7.20(4H,m), 2.97(2H,q,J=7.8Hz), 2.48(3H,s), 1.01(3H,t,J=7.8Hz)

3-Ethylamino-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine (Compound 345) hydrochloride

m.p.: 237.0°C(dec.)

IR(KBr): 3140, 3050, 2960, 2910, 2860, 2780, 2700, 2650, 2550, 1653, 1624, 1600, 1545, 1525, 1500, 1442, 1414, 1385, 1353, 1323, 1280, 1248, 1205, 1150, 1095, 1057, 1040, 920, 840, 792, 750, 733, 715

NMR(DMSO): 8.82(1H,d,J=7.0Hz), 8.32(1H,d,J=5.0Hz), 7.94(1H,d,J=7.0Hz), 7.80(1H,d,J=5.0Hz), 7.66-7.33(4H,m), 2.88(2H,q,J=7.0Hz), 2.40(3H,s), 0.98(3H,t,J=7.0Hz)

3-(N-Ethyl-N-propylamino)-2-(2-methylphenyl)imidazo[1,2-a]thieno[2,3-c]pyridine (Compound 356) hydrochloride

m.p.: 185.0-188.5°C

IR(KBr): 3040, 2960, 2930, 2860, 2530, 2250, 1650, 1613, 1570, 1538, 1490, 1457, 1410, 1386, 1350, 1320, 1278, 1242, 1213, 1173, 1080, 1038, 803, 762, 730

NMR(DMSO): 8.70(1H,d,J=7.0Hz), 8.48(1H,d,J=5.0Hz), 8.10(1H,d,J=7.0Hz), 7.93(1H,d,J=5.0Hz), 7.55(4H,s), 3.10(2H,q,J=7.0Hz), 2.93(2H,t,J=7.0Hz), 2.44(3H,s), 1.78-1.02(2H,m), 1.08(3H,t,J=7.0Hz), 0.78(3H,t,J=7.0Hz)

Example 23

3-Amino-9-methoxy-2-(2-methylphenyl)-5,6-dihydroimidazo[2,1-a]isoquinoline (Compound 103)

To a solution of 8.4g of 3-amino-9-methoxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline(Compound 26) in 100ml of ethanol was added 1.0g of palladium on activated carbon (Pd 10%). After introduction of hydrogen, the mixture was stirred at room temperature for 48 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. Resultant residue was purified by column chromatography on silica gel and recrystallized from ethyl acetate/isopropyl ether to give 1.5g of the title compound as a pale yellow powder.

m.p.: 159.5-160.0°C

IR(KBr): 3460, 3340, 3200, 3070, 3020, 2930, 2900, 2850, 1628, 1618, 1572, 1540, 1498, 1470, 1458, 1440, 1358, 1322, 1283, 1230, 1180, 1035, 820, 770

NMR(CDCL): 7.58(1H,d,J=3.0Hz), 7.46-7.20(4H,m), 7.13(1H,d,J=9.0Hz), 6.77(1H,dd,J=3.0Hz,9.0Hz), 3.96(2H,t,J=7.0Hz), 3.84(3H,s), 3.20(2H,brs), 3.04(2H,t,J=7.0Hz), 2.40(3H,s)

Example 24

3-Amino-9-hydroxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 22).

To a solution of 5.0g of 3-amino-9-benzyloxy-2-(2-methylphenyl)imidazo[2,1-a]isoquinoline (Compound 40) in 100ml of ethanol was added 0.5g of palladium on activated carbon (Pd 10%). After introduction of hydrogen, the mixture was stirred at room temperature for 24 hours. The reaction mixture was filtered, and the filtrate was evaporated in vacuo. Resultant residue was purified by column chromatography on silica gel and recrystallized from water/methanol to give 3.2g of the title compound as pale yellow needles.

m.p.: 240.0-243.0°C(dec.)

IR(KBr): 3400, 3320, 3000-2450, 1610, 1490, 1455, 1420, 1395, 1325, 1255, 1232, 1200, 1130, 1080, 1030, 920, 865, 815, 758, 720

NMR(DMSO): 10.00(1H,brs), 7.92(1H,d,J=7.0Hz), 7.77(1H,d,J=2.0Hz), 7.68(1H,d,J=8.4Hz), 7.65-6.90(5H,m), 7.09(1H,d,J=7.0Hz), 4.92(2H,brs), 2.45(3H,s)

Pharmaceutical formulation 1: Powders containing 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) as an active ingredient

Five grams of 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) and 95g of lactose were admixed uniformly to give the powders.

Pharmaceutical formulation 2: Granules containing 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) as an active ingredient

Five grams of 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236), 36g of lactose, 31g of corn starch, and 22g of crystalline cellulose were admixed, and then the resultant powder was granulated by kneading it with 4g of hydroxypropylcellulose in 100ml of water, and the resultant grains were dried for 4 hours at 50°C. The dried grains were sifted through a 12 mesh sieve, and mixed with 2g of magnesium stearate to obtain granules.

Pharmaceutical formulation 3: Tablets containing 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) as an active ingredient

Five grams of 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236), 35g of lactose, 32g of corn starch, and 24g of crystalline cellulose were admixed, and then the resultant powder was granulated by kneading it with an aqueous solution containing 2g of hydroxypropylcellulose, and then the granules were dried for 4 hours at 50°C.

After mixing with 2g of magnesium stearate, the granules were compressed into tablets, each weighing 200mg, using a tablet machine.

Pharmaceutical formulation 4: Capsules containing 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) as an active ingredient

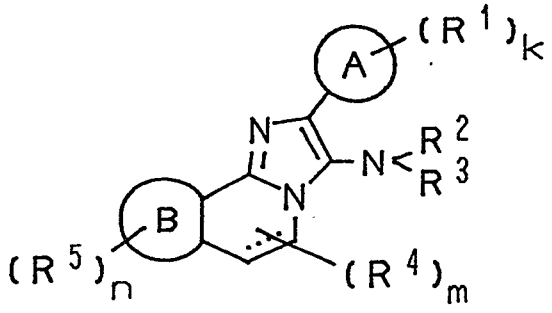
Five grams of 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236), 38g of lactose, 33g of corn starch, 22g of crystalline cellulose, and 2g of magnesium stearate were admixed. The mixture was filled into hard gelatin capsules, each weighing 200mg, using a capsule filler.

Pharmaceutical formulation 5: Syrups containing 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236) as an active ingredient

One gram of 3-amino-5-methyl-2-(2-methylphenyl)imidazo[1,2-a]thieno[3,2-c]pyridine (Compound 236), 30g of sucrose, 25g of D-sorbitol(70w/v%), 30mg of ethyl p-hydroxybenzoate, and 15mg of propyl p-hydroxybenzoate were dissolved in 60g of warm water. After cooling, a flavouring dissolved in 150mg of glycerin and 500mg of ethanol(96%) was added thereto. Water was added to the mixture to give 100ml of syrups.

CLAIMS

1. Fused imidazo[1,2-a]pyridines represented by the following general formula (I) :



(I)

wherein ring A and ring B each independently represent an aromatic ring selected from benzene, thiophene, furan or pyrrole ring; R^1 is hydroxyl group, halogen atom, lower alkyl group which may be halogenated, lower alkoxy group or acyloxy group; k represents 0, 1, 2 or 3; R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group, acyl group, alkoxycarbonyl group or lower alkyl group which may have substituent(s) selected from the group consisting of 1) halogen atom, 2) hydroxyl group, 3) lower alkoxy group, 4) lower alkylthio group, 5) alkylsulfinyl group, 6) alkoxycarbonyl group, 7) carbamoyl group, 8) alkylamino group and 9) aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form an alkylideneamino group or arylalkylideneamino group; R^4 and R^5 each independently represent halogen atom, cyano group, hydroxyl group, carboxyl group, alkoxycarbonyl group, acyl group, alkylamino group, aryl group, acyloxy group, carbamoyloxy group, lower alkyl group which may have substituent(s) selected from the group consisting of 1) hydroxyl group, 2) lower alkoxy group, 3) aryl group and 4) aryloxy group, lower alkoxy group which may have

substituent(s) selected from the group consisting of 1) hydroxyl group, 2) lower alkoxy group, 3) lower alkoxycarbonyl group and 4) aryl group, or lower alkylthio group which may be substituted with aryl group; m represents 0, 1 or 2; n represents 0, 1 or 2; the dotted line, together with the solid line, represents a single or double bond, provided that plural R^4s may be attached to the same carbon atom, or a pharmaceutically acceptable salt or solvate thereof.

2. The compounds of claim 1 wherein ring B is benzene ring, k is 1, 2 or 3.

3. The compounds of claim 2 wherein R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring.

4. The compounds of claim 1 wherein ring B is thiophene, furan or pyrrole ring.

5. The compounds of claim 4 wherein R^2 and R^3 may be the same or different and each represent hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group, or R^2 and R^3, together with the nitrogen atom to which they are attached, may form a 5- or 6-membered monocyclic heterocyclic ring.

6. The compounds of claim 5 wherein ring B is thiophene or pyrrole ring.

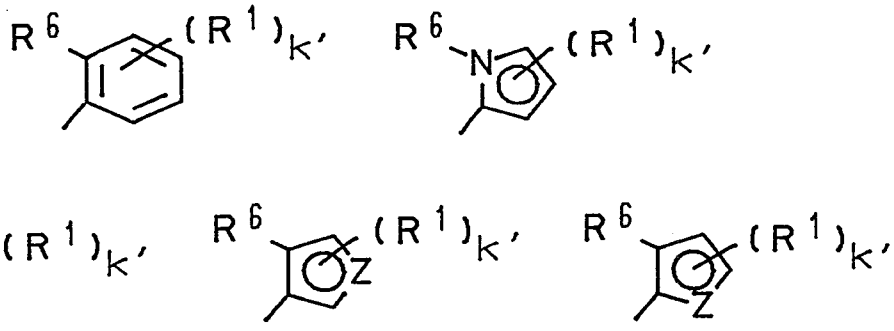
7. The compounds of claim 6 wherein ring B is thiophene ring.

8. The compounds of claim 7 wherein k is 1, 2 or 3.

9. The compounds of claim 1 wherein ring A is an aromatic ring selected from benzene, thiophene, furan or pyrrole ring; ring B is benzene or thiophene ring; R^1 is halogen atom or lower alkyl group which may be halogenated or lower alkoxy group; k is 1 or 2; R^2 is hydrogen atom; R^3 is hydrogen atom, alkenyl group or lower alkyl group which may have substituent(s) selected from the group consisting of halogen atom, lower alkoxy group, lower alkylthio group and aryl group.

10. The compounds of claim 9 wherein the dotted line, together with the solid line, represents a double bond.

11. The compounds of claim 10 wherein ring A and substituent(s) on the ring represent the following formula:



wherein R^1 and R^6 are each independently halogen atom, lower alkyl group which may be halogenated or lower alkoxy group; k' is 0 or 1; Z is a hetero atom selected from sulfur, oxygen or nitrogen atom.

12. The compounds of claim 11 wherein at least one of R^1 and R^6 is lower alkyl group.

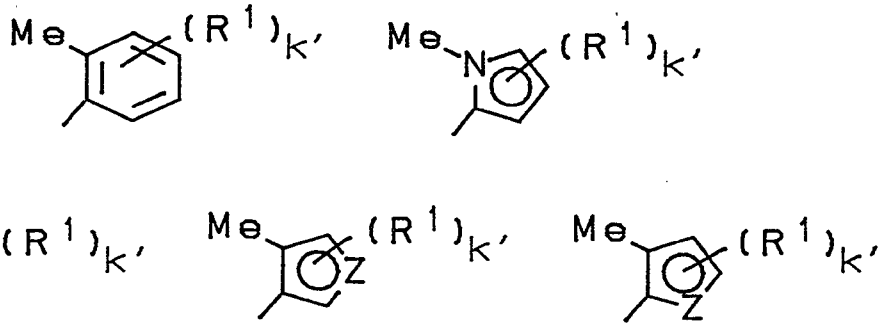
13. The compounds of claim 12 wherein at least one of R^1 and R^6 is lower alkyl group having 1 or 2 carbon atoms.

14. The compounds of claim 13 wherein R^6 is lower alkyl group having 1 or 2 carbon atoms; R^4 and R^5 are each independently a substituent selected from halogen atom, lower alkyl group, lower alkoxy group or lower alkylthio group.

15. The compounds of claim 14 wherein ring B is benzene or thiophene ring represented by the following formula:

R^2 and R^3 are hydrogen atom; k' is 0 or 1.

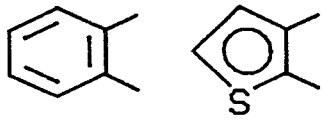
16. The compounds of claim 1 wherein ring A is an aromatic ring selected from benzene, thiophene, furan or pyrrole ring represented by the following formula:



(I-A)

wherein k' and Z are as defined above;

the substituent R^1 on the ring is halogen atom, lower alkyl group which may be halogenated, or lower alkoxy group; ring B is benzene or thiophene ring represented by the following formula:



(I-B)

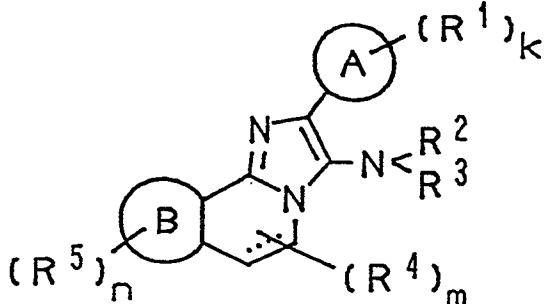
R^2 and R^3 are hydrogen atom; R^4 and R^5 are independently a substituent selected from halogen atom, lower alkyl group, lower alkoxy group or lower alkylthio group; m is 0, 1 or 2; n is 0, 1 or 2; the dotted line, together with the solid line, represents a double bond.

17. Pharmaceutical compositions containing the compound defined in claim 1, in association with a pharmaceutically acceptable carrier.

18. Pharmaceutical compositions according to claim 17 useful for the treatment of gastrointestinal diseases.

19. Pharmaceutical compositions according to claim 17 useful as anti-ulcer agents.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents



(I)