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(71) **Applicant** *(for JP only):* **PFIZER JAPAN INC.** [JP/JP]; Shinjuku Bunka Quint Bldg., 3-22-7, Yoyogi, Shibuya-ku,, Tokyo 151-8589 (JP).

(71) **Applicant** *(for all designated States except JP, US):* **PFIZER INC.** [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only):* **IWAMURO, Yuko** [JP/JP]; Pfizer Global Research and Development, Nagoya, Pfizer Japan Inc., 2, Aza 5-gochi, Taketoyo-cho, Chita-gun, Aichi-ken 470-2393 (JP). **KOIKE, Hiroki** [JP/JP]; Pfizer Global Research and development, Nagoya, Pfizer Japan Inc., 2, Aza 5-gochi, Taketoyo-cho, Chita-gun, Aichi-ken 470-2393 (JP). **MORITA, Mikio** [JP/JP]; Pfizer Global Research and Development, Nagoya, Pfizer Japan Inc., 2, Aza 5-gochi, Taketoyo-cho, Chita-gun, Aichi-ken 470-2393 **(JP). SAKAKIBARA, Sachiko** [JP/JP]; Pfizer Global Research and Development, Nagoya, Pfizer Japan, Inc., 2, Aza 5-gochi, Taketoyo-cho, Chita-gun, Aichi-ken 470-2393 **(JP).**

(74) **Agent: FULLER, Grover, E, Jr.;** c/o DROUIN, Stephane, Pfizer Global Research and Development, Ramsgate Road, Kent, Sandwich CT13 9NJ (GB).

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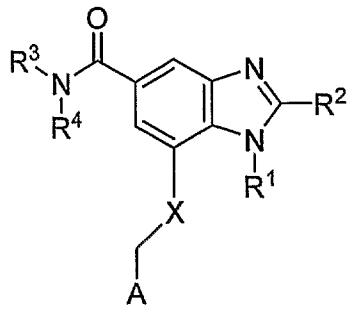
(54) Title: BENZIMIDAZOLE-S-CARBOXAMIDE DERIVATIVES



(I)

(57) Abstract: This invention relates to compounds of the formula (I): or a pharmaceutically acceptable salt thereof, wherein: R^1, R^2, R^3, R^4, A and X are each as described herein or a pharmaceutically acceptable salt, and compositions containing such compounds and the use of such compounds in the treatment of a condition mediated by acid pump antagonistic activity such as, but not limited to, as gastrointestinal disease, gastroesophageal disease, gastroesophageal reflux disease (GERD), peptic ulcer, gastric ulcer, duodenal ulcer, NSAID-induced ulcers, gastritis, infection of Helicobacter pylori, dyspepsia, functional dyspepsia, Zollinger-Ellison syndrome, non-erosive reflux disease (NERD), visceral pain, heartburn, nausea, esophagitis, dysphagia, hypersalivation, airway disorders or asthma.

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Benzimidazole-5-carboxamide Derivatives

Background of the Invention

This invention relates to benzimidazole-5-carboxamide derivatives. These compounds have selective acid pump inhibitory activity. The present invention also relates to a pharmaceutical composition, method of treatment and use, comprising the above derivatives for the treatment of disease conditions mediated by acid pump modulating activity; in particular acid pump inhibitory activity.

It has been well established that proton pump inhibitors (PPIs) are prodrugs that undergo an acid-catalyzed chemical rearrangement that permits them to inhibit H^+/K^+-ATPase by covalently binding to its Cystein residues (Sachs, G. *et.* a/., *Digestive Diseases and Sciences,* 1995, 40, 3S-23S; Sachs *et.* a/., *Annu Rev Pharmacol Toxicol,* 1995, 35, 277-305.). However, unlike PPIs, acid pump antagonists inhibit acid secretion via reversible potassium-competitive inhibition of H^+/K^+-ATPase. SCH28080 is one of such reversible inhibitors and has been studied extensively. Other newer agents (revaprazan, soraprazan, AZD-0865 and CS-526) have entered in clinical trials confirming their efficacy in human (Pope, A.; Parsons, M., *Trends in Pharmacological Sciences,* 1993,14, 323-5; Vakil, N., *Alimentary Pharmacology and Therapeutics,* 2004, 19, 1041-1049.). In general, acid pump antagonists are found to be useful for the treatment of a variety of diseases, including gastrointestinal disease, gastroesophageal disease, gastroesophageal reflux disease (GERD), laryngopharyngeal reflux disease, peptic ulcer, gastric ulcer, duodenal ulcer, non-steroidal anti-inflammatory drug (NSAID)-induced ulcers, gastritis, infection of Helicobacter pyiori, dyspepsia, functional dyspepsia, Zollinger-Ellison syndrome, non-erosive reflux disease (NERD), visceral pain, cancer, heartburn, nausea, esophagitis, dysphagia, hypersalivation, airway disorders or asthma (hereinafter, referred as "APA Diseases"; Kiljander, Toni O, *American Journal of Medicine,* 2003, 115 (Suppl. 3A), 65S-71S; Ki-Baik Hahm etal., *J. Clin. Biochem. Nutr.,* 2006, 38, (1), 1-8 .).

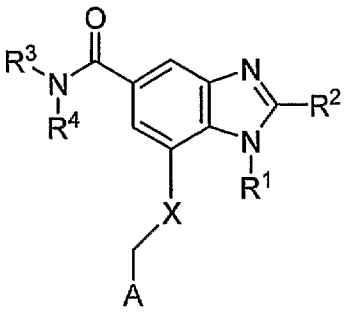
WO05/111000 refers to some compounds, such as 7-substituted benzimidazole-5-carboxyamide derivatives, as acid pump antagonists.

There is a need to provide new acid pump antagonists that are good drug candidates and address unmet needs by PPIs for treating diseases. In particular, preferred compounds should bind potently to the acid pump whilst showing little affinity for other receptors and show functional activity as inhibitors of acid-secretion in stomach. They should be well absorbed from the gastrointestinal tract, be metabolically stable and possess favorable pharmacokinetic properties. They should be non-toxic. Furthermore, the ideal drug candidate will exist in a physical form that is stable, non-hygroscopic and easily formulated.

Summary of the Invention

In this invention, it has now been found out that the new class of benzimidazole compounds having a substituted alkyl group at 1 position show acid pump inhibitory activity and good bioavailability as drug candidates, and thus are useful for the treatment of disease conditions mediated by acid pump inhibitory activity such as APA Diseases.

The present invention provides a compound of the following formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 represents a C_1-C_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a CrC $_6$ alkoxy group, a hydroxy-substituted C_3-C_7 cycloalkyl group, a hydroxy-C_r C_β alkyl-substituted C_3-C_7 cycloalkyl group, an aryl group, a hydroxy-substituted aryl group, a heteroaryl group and a halogen-substituted heteroaryl group;

R^2 represents a hydrogen atom or a C_1-C_6 alkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group;

R^3 and R^4 independently represent a hydrogen atom, or a C_1-C_6 alkyl, C_3-C_7 cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group being unsubstituted or substituted with 1 to 2substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group, and a hydroxy-C_r C_6 alkyl group;

A represents an aryl or heteroaryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-C_r C_6 alkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$;

R^5, R^7 and R^8 independently represent a hydrogen atom or a C_1-C_6 alkyl group;

R^6 represents a C_1-C_6 alkyl group; and

X represents an oxygen atom or NH.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, together with a pharmaceutically acceptable carrier for said compound.

Also, the present invention provides a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, further comprising other pharmacologically active agent(s).

Also, the present invention provides a method of treatment of a condition mediated by acid pump inhibitory activity, in a mammalian subject, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein.

Examples of conditions mediated by acid pump inhibitory activity include, but are not limited to, APA Diseases.

Further, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of a condition mediated by acid pump inhibitory activity.

Preferably, the present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, each as described herein, for the manufacture of a medicament for the treatment of diseases selected from APA Diseases.

The compounds of the present invention may show good bioavailability, less toxicity, good absorption, good distribution, good half life, good solubility, less protein binding affinity other than acid pump, less drug-drug interaction, and good metabolic stability.

Detailed Description of the Invention

In the compounds of the present invention:

Where R^1, R^2, R^3, R^4, R^5, R^6, R^7 or R^8 is a C_1-C_6 alkyl group, the substituents of the 4 to 6 membered heterocyclic group are a C_1-C_6 alkyl group, or the substituents of A are a C_1-C_6 alkyl group, this C_1-C_6 alkyl group may be a straight or branched chain group having one to six carbon atoms, and examples include, but are not limited to, a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, teff-butyl, pentyl, 1-ethylpropyl and hexyl. Of these, C_1-C_3 alkyl is preferred; methyl is more preferred for R^2, R^4 R^5, R^6, R^7 and R^8; C_1-C_3 aikyl is preferred and methyl, ethyl and propyl are more preferred for R^1; methyl and ethyl are more preferred for R^3.

The wording which is 'R^3 and R^4 independently represent a hydrogen atom, or a C_1-C_6 alkyl, C_3-C_7 cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group' stands for 'R^3 and R^4 independently represent a hydrogen atom, a C_1-C_6 alkyl group, a C_3-C_7 cycloalkyl group or a heteroaryl group, said C_1-C_6 alkyl group, said C_3-C_7 cycloalkyl group and said heteroaryl group being substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group'.

Where R^3 or R^4 is a C_3-C_7 cycloalkyl group, or the substituents of R^3 or R^4 are a C_3-C_7 cycloalkyl group, this represents cycloalkyl group having three to seven carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Of these, C_3-C_5 cycloalkyl group is preferred; cyclopropyl is more preferred.

Where the substituents of R^1, R^2, R^3 or R^4 are a C_1-C_6 alkoxy group, this represents the oxygen atom substituted with the C_1-C_6 alkyl group which is aforementioned above, and examples include, but are not limited to, methoxy, ethoxy, propyloxy, isopropyloxy, n-butoxy, isobutoxy, sec-butoxy and terf-butoxy, pentyloxy and hexyloxy. Of these, a C_1-C_3 alkoxy is preferred; methoxy is more preferred.

Where R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group, this 4 to 6 membered heterocyclic group represents a saturated heterocyclic group having three to five ring atoms selected from carbon atom, nitrogen atom, sulfur atom and oxygen atom other than the said nitrogen atom, and examples include, but are not limited to, a azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morphoiino and thiomorpholino. Of these, piperazinyl and morphoiino are preferred.

Where the substituents of the 4 to 6 membered heterocyclic group are a hydroxy-C_r C_6 alkyl group or the substituents of A are a hydroxy-CrC $_6$ alkyl group, this represents a CrC $_6$ alkyl group substituted with a hydroxy group, and examples include, but are not limited to, a hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-hydroxy propyl, 2-hydroxypropyl, 2-hydroxy-1-methylethyl, 4-hydroxybutyl, 3-hydroxybutyl, 2-hydroxybutyl, 3-hydroxy-2-methylpropyl, 3-hydroxy-1-methylpropyl, 5-hydroxypentyl and 6-hydroxyhexyl. Of these, a hydroxy-CrC $_3$ alkyl group is preferred; hydroxymethyl is more preferred.

Where the substituents of the 4 to 6 membered heterocyclic group are a C_1-C_6 acyl group, this represents a carbonyl group substituted with hydrogen atom or the said C_1-C_5 alkyl group, and examples include, but are not limited to, a formyl, acetyl, propionyl, butyryl, pentanoyl and hexanoyl. Of these, C_2-C_6 acyl is preferred and acetyl is more preferred.

The wording which is 'A represents an aryl or heteroaryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-C_r C_6 alkyl group, a Ci-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR ^{5}SO_2R^6 and -CONR ^{7}R$^{8'}$ stands for 'A represents an aryl group or a heteroaryl group, said aryl group and said heteroaryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-C_r C_6 alkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR ^{5}SO_2R^6 and -CONR ^{7}R$^{8'}$.

Where A and the substituents of R^1 are an aryl group, these may be phenyl, naphtyl or anthracenyl. Of these, phenyl is preferred.

Where the substituents of R^3, R^4 and A are a halogen atom, they may be a fluorine, chlorine, bromine or iodine atom. Of these, a fluorine atom and a chlorine atom are preferred.

Where the substituent of R^1 is a hydroxy-substituted aryl group, this hydroxy-substituted aryl group represents an aryl group which is substituted with hydroxy group(s) and the aryl group is aforementioned above. Examples include, but not limited to, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2,3-dihydroxyphenyl, 2,4-dihydroxyphenyl, 3,5-dihydroxyphenyl, 1-hydroxynaphthyl, 2-hydroxynaphthyl, 1-hydroxyanthracenyl. Of these, 3-hydroxyphenyl is preferred.

Where A, R^3, R^4 or the substituents of R^1 are a heteroaryl group, this represents 5 to 6-membered ring containing at least one hetero atom selected from N, O and S, and examples include, but not limited to, 2-thienyl, 2-thiazolyl, 4-thiazolyl, 2-furyl, 2-oxazolyl, 1-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrazinyl and 2-pyrimidinyl. Of these, the heteroaryl group containing at least one nitrogen atom is preferred; 2-thiazolyl, 4-thiazolyl and 1-pyra∑olyl are more preferred for the substituent of R^1; 2-pyridyl, 3-pyridyl and 4-pyridyl are more preferred for A.

Where the substituent of R^1 is a hydroxy-substituted C_3-C_7 cycloalkyl group, this hydroxy-substituted C_3-C_7 cycloalkyl group represents a C_3-C_7 cycloalkyl group which is substituted with hydroxy group(s) and the C_3-C_7 cycloalkyl is aforementioned above. Examples of a hydroxy-substituted C_3-C_7 cycloalkyl group include, but are not limited to, 1-hydroxycyclopropyl, 2-hydroxycyclopropyl, 1-hydroxycyclobutyl, 2-hydroxycyclobutyl, 2,3-dihydroxycyclobutyl 2-hydroxycyclopentyl, 3-hydroxycyclopentyl, 1-hydroxycyclohexyl, 2-hydroxycyclohexyl, 3-hydroxycyclohexyl, 4-hydroxycyclohexyl, 2,4-dihydroxycyclohexyl, 3,5-dihydroxycyclohexyl, 1-hydroxycycloheptyl, 2-hydroxycycloheptyl, 3-hydroxycycloheptyl and 4-hydroxycycloheptyl. Of these, hydroxy-substituted C_3-C_5 cycloaikyl is preferred; 1-hydroxycyclopropyl is more preferred.

Where the substituent of R^1 is a hydroxy-C_1-C_6 alkyl-substituted C_3-C_7 cycloalkyl group, this hydroxy-C_1-C_6 alkyl-substituted C_3-C_7 cycloalkyl group represents a C_3-C_7 cycloalkyl group which is substituted with hydroxy-C_1-C_6 alkyl group(s), and the hydroxy-C_1-C_6 alkyl and the C_3-C_7 cycloalkyl are aforementioned above. Examples of a hydroxy-C_1-C_6 alkyl-substituted C_3-C_7 cycloalkyl group include, but are not limited to, 1-hydroxymethylcyclopropyl, 1-(2-hydroxyethyl)-cyclopropyl, 2-hydroxymethylcyclopropyl, 1-hydroxymethylcyclobutyl, 2-hydroxymethylcyclobutyl, 2,3-bis(hydroxymethyl)cyclobutyl, 1-hydroxymethylcyclopentyl, 2-hydroxymethylcyclopentyl, 3-hydroxymethylcyclopentyl, 1-hydroxmethylcyclohexyl, 2-hydroxymethylcyclohexyl, 3-hydroxymethylcyclohexyl, 4-hydroxymethylcyclohexyl, 1-hydroxymethylcycloheptyl, 2-hydroxymethylcycloheptyl, 3-hydroxymethylcycloheptyl and 4-hydroxymethylcycloheptyl. Of these, hydroxy-C_1-C_3 alkyl-substituted C_3-C_5 cycloalkyl is preferred; 1-hydroxymethylcyclopropyl and 1-(2-hydroxyethyl)-cyclopropyl are more preferred.

Where the substituent of R^1 is a halogen-substituted heteroaryl group, this halogen-substituted heteroaryl group represents a heteroaryl group which is substituted with halogen atom(s), and the halogen atom and the heteroaryl are aforementioned above. Examples of a halogen-substituted heteroaryl group include, but are not limited to, 4-fluoro-2-thienyl, 4-fluoro-2-thiazolyl, 2-fluoro-4-thiazolyl, 4-fluoro-2-furyl, 4-fluoro-2-oxazolyl, 4-fluoro-1-pyrazolyl, 4-fluoro-2-pyridyl, 5-fluoro-3-pyridyl, 3-fluoro-4-pyridyl, 3,4-difluoro-2-pyridyl, 3,5-difluoro-2-pyridyl, 5-fluoro-2-pyrazyl, 5-fluoro-2-pyrimidinyl, 4-chloro-2-thienyl, 4-chloro-2-thiazolyl, 2-chloro-4-thiazolyl, 4-chloro-2-furyl, 4-chloro-2-oxazolyl, 4-chloro-1-pyrazolyl, 4-chloro-2-pyridyl, 5-chloro-3-pyridyl, 3-chloro-4-pyridyl, 3,4-dichloro-2-pyridyl, 3,5-dichloro-2-pyridyl, 5-chloro-2-pyrazyl and 5-chloro-2-pyrimidinyl. Of these, 3,5-difluoro-2-pyridyl is preferred.

Where the substituent of A is a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, this C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group represents a C_1-C_6 alkyl group which is substituted by C_1-C_6 alkoxy group(s) and the C_1-C_6 alkoxy and the C_1-C_6 alkyl are aforementioned above. Examples of a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group include, but are not limited to, methoxy methyl, 2-methoxyethyl, 3-methoxypropyl, 4-methoxybutyl, 5-methoxypentyl, 6-methoxyhexyl, 1-ethoxymethyl, 2-ethoxyethyl, 3-ethoxypropyl, 4-ethoxybutyl, 5-ethoxypentyl. Of these, C_1-C_3 alkoxy-substituted C_1-C_3 alkyl is preferred; methoxymethyl is more preferred.

The term **"treating"** and **"treatment",** as used herein, refers to curative, palliative and prophylactic treatment, including reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition.

Preferred class of compounds of the present invention are those compounds of formula (I) or pharmaceutically acceptable salts thereof, each as described herein, in which:

(a) R^1 is a C_1-C_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a C_1-C_6 alkoxy group, a hydroxy-substituted. C_3-C_7 cycloalkyl group, a hydroxy-C_1-C_6 alkyl-substituted C_3-C_7 cycloalkyl group, an aryl group, a hydroxy-substituted aryl group, a heteroaryl group and a halogen-substituted heteroaryl group;

(b) R^1 is a C_1-C_6 alkyl group being substituted with selected from the group consisting of a C_1-C_6 alkoxy group and a heteroaryl group;

(c) R^1 is a C_1-C_6 alkyl group being substituted with selected from the group consisting of a C_1-C_6 alkoxy

group a thiazolyl group and a pyrazolyl group;

(d) R^1 is a C_2-C_3 alkyl group being substituted with a C_1-C_3 alkoxy group;

(e) R^1 is a 2-methoxyethyl or 3-methoxypropyl group;

(f) R^1 is a 2-methoxyethyl;

(g) R^2 is a hydrogen atom or a CrC $_6$ alkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group and a C_r C_6 alkoxy group;

(h) R^2 is a C_1-C_6 alkyl group;

(i) R^2 is a C_1-C_3 alkyl group;

(j) R^2 is a methyl group;

(k) R^3 is a hydrogen atom, or a C_1-C_6 alkyl, C_3-C_7 cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group;

(l) R^3 is a C_1-C_6 alkyl group being unsubstituted or substituted with one substituent selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group;

(m) R^3 is a C_1-C_3 alkyl group being unsubstituted or substituted with a hydroxy group;

(n) R^3 is a methyl group, an ethyl group, 2-hydroxyethyl group, a 3-hydroxypropyl group or a 2-methoxyethyl group;

(o) R^4 is a hydrogen atom, or a C_1-C_6 alkyl, C_3-C_7 cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group;

(p) R^4 is a hydrogen atom or a C_1-C_6 alkyl group;

(q) R^4 is a C_1-C_3 alkyl group;

(r) R^4 is a methyl group;

(s) R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group, and a hydroxy-C-i-C_6 alkyl group;

(t) R^3 and R^4 taken together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl, piperazinyl or morpholino group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group and a hydroxy-CrCe alkyl group;

(u) R^3 and R^4 taken together with the nitrogen atom to which they are attached form a piperazinyl or morpholino group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group and a hydroxy-C_r C_3 alkyl group;

(v) R^3 and R^4 taken together with the nitrogen atom to which they are attached form a piperazinyl group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group and a hydroxy-C_r C_3 alkyl group;

(w) R^3 and R^4 taken together with the nitrogen atom to which they are attached form a morpholino group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group and a hydroxy-C_r C_3 alkyl group;

(x) R^3 and R^4 taken together with the nitrogen atom to which they are attached form a morpholino group;

(y) A is an aryl or heteroaryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-C_r C_6 alkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$;

(z) A is a phenyl or 2-pyrodinyl group being unsubstituted or substituted with 1 to 5 substituents selected from the group consisting of hydrogen atom, a halogen atom, a C_1-C_6 alkyl group and a hydroxy-CrC_6 alkyl group;

(aa) A is a phenyl or 2-pyrodinyl group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of hydrogen atom, a fluorine atom, a methyl group and a hydroxymethyl group;

(bb) A is a phenyl group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of hydrogen atom, a fluorine atom, a methyl group and a hydroxymethyl group;

(cc) A is a 2-pyrodinyl group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of hydrogen atom, a fluorine atom, a methyl group and a hydroxymethyl group;

(dd) R^5 is a hydrogen atom or a C_1-C_6 alkyl group;

(ee) R^5 is a hydrogen atom or a methyl group;

(ff) R^6 is a C_1-C_6 alkyl group;

(gg) R^6 is a methyl group

(hh) R^7 is a hydrogen atom or a C_1-C_6 alkyl group;

(ii) R^7 is a hydrogen atom or a methyl group;

(jj) R^8 is a hydrogen atom or a C_1-C_6 alkyl group;

(kk) R^8 is a hydrogen atom or a methyl group;

(II) X is an oxygen atom or NH; and

(mm) X is an oxygen atom.

Of these classes of compounds, any combination among (a) to (mm) is also preferred.

Preferred compounds of the present invention are those compounds of formula (I) or pharmaceutically acceptable salts thereof, each as described herein, in which:

(A) R^1 is a C_1-C_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a Ci-C_6 alkoxy group and a heteroaryl group; R^2 is a C_1-C_6 alkyl group; R^3 and R^4 are independently a hydrogen atom or a C_1-C_6 alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group and a hydroxy-C_r C_6 alkyl group; A is an aryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-Ci-C_6 alkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$; R^5, R^7 and R^8 independently are a hydrogen atom or a C_1-C_6 alkyl group; R^6 is a C_1-C_6 alkyl group; and X is an oxygen atom;

(B) R^1 is a C_1-C_6 alkyl group being substituted with a C_1-C_6 alkoxy group; R^2 is a C_1-C_6 alkyl group; R^3 and R^4 are independently a hydrogen atom or a C_1-C_6 alkyl group being unsubstituted or substituted with a substituent selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group; or R^3 and

R^4 taken together with the nitrogen atom to which they are attached form a morpholino group; A is an aryl group being unsubstituted or substituted with a halogen atom; and X is an oxygen atom;

(C) R^1 is a CrC $_3$ alkyl group being substituted with a substituent independently selected from the group consisting of a C_1-C_3 alkoxy group, a thiazolyl group and pyrazolyl group; R^2 is a C_1-C_3 alkyl group; R^3 and R^4 independently are a hydrogen atom or a C_1-C_3 alkyl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a hydroxy group and a C_1-C_3 alkoxy group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a piperazinyl or morpholino group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_3 alkyl group, and a hydroxy-C-t-C_3 alkyl group; A is an aryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_3 alkyl group, a hydroxy-C_1-C_3 alkyl group, a C_1-C_3 alkoxy-substituted C_1-C_3 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$; R^5, R^7 and R^8 independently are a hydrogen atom or a C_1-C_3 alkyl group; R^6 is a C_1-C_3 alkyl group; and X is an oxygen atom.

One embodiment of the invention provides a compound selected from the group consisting of:

7-t(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)- *N*,*N*,2-trimethyl-1f/-benzimidazole-5-carboxamide;

7-[(4-fluorobenzyl)oxy]- *N*-(2-hydroxyethyl)-1-(2-methoxyethyl)- *N*,2-dimethyl-1H-benzimidazole-5-carboxamide;

7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-5-(morpholin-4-ylcarbonyl)-1H-benzimidazole;

or a pharmaceutical acceptable salt thereof.

Pharmaceutically acceptable salts of a compound of formula (I) include the acid addition salts and base salts (including disalts) thereof.

Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinofoate salts. Also included are acid addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemic, for example, DL-tartrate or DL-arginine.

The base addition salts include alkali metal salts, for example lithium salts, sodium salts and potassium salts; alkaline earth metal salts, for example calcium salts and magnesium salts; ammonium salts; organic base salts, for example triethylamine salts, diisopropylamine salts and cyclohexylamine salts; and the like. Preferred salts are alkali metal salts and more preferred salts are sodium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002). A pharmaceutically acceptable salt of a compound of formula (I) may be readily prepared by mixing together solutions of the compound of formula (I) and the desired acid or base, as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to almost non-ionized.

Pharmaceutically acceptable salts of the compounds of formula (I) thereof include both unsolvated and solvated forms. The term "solvate" is used herein to describe a molecular complex comprising a compound of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Pharmaceutically acceptable solvates in accordance with the invention include hydrates and solvates wherein the solvent of crystallization may be isotopically substituted, e.g. D_2O, d_6-acetone, de-DMSO.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci. 64 (8), 1269-1288 by Haleblian (August 1975).

The compounds of formula (I) may exist in one or more crystalline forms. These polymorphs, including mixtures thereof are also included within the scope of the present invention.

The compounds of formula (I) containing one or more asymmetric carbon atoms can exist as two or more stereoisomers.

Included within the scope of the present invention are all stereoisomers of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof.

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of formula (I) wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature.

Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{38}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labeled compounds of formula (I), for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, i.e. ^{3}H, and carbon-14, i.e. ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, i.e. ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying examples and preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

All of the compounds of the formula (I) can be prepared by the procedures described in the general

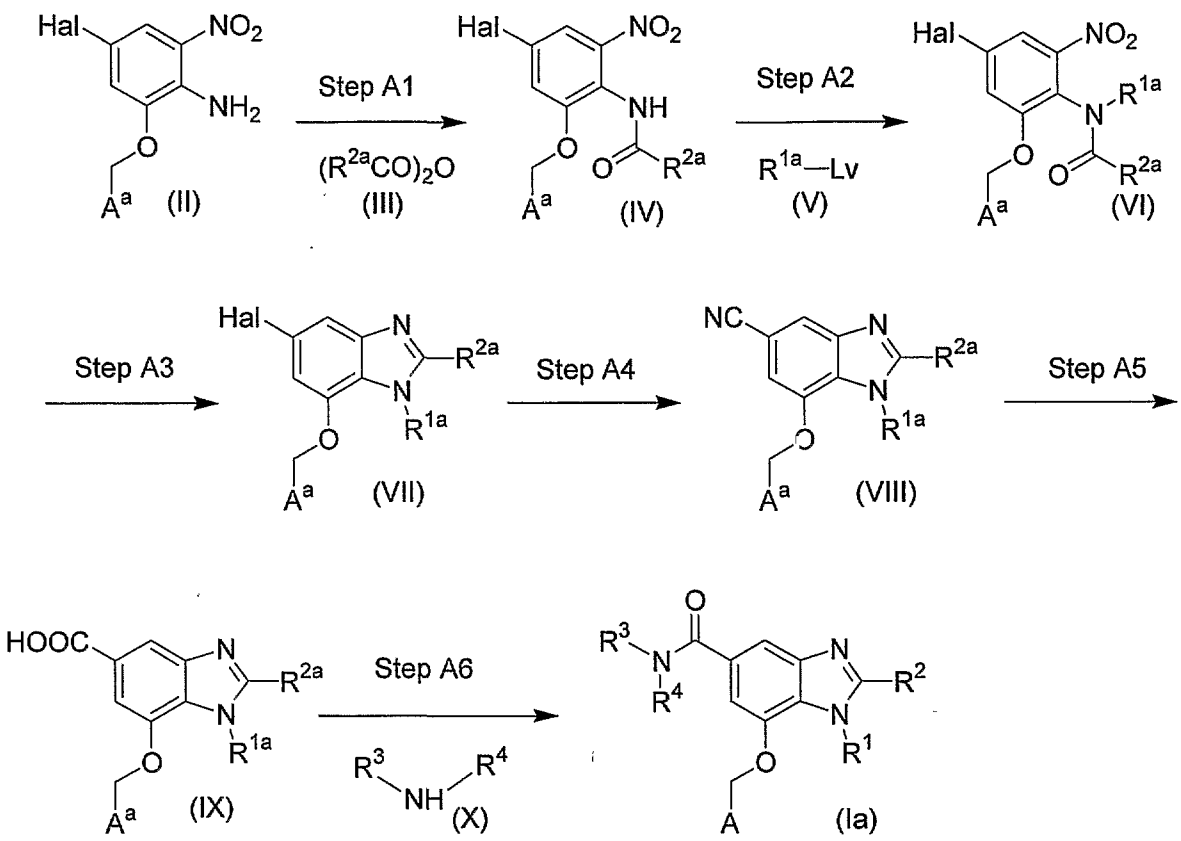
methods presented below or by the specific methods described in the examples section and the preparations section, or by routine modifications thereof. The present invention also encompasses any one or more of these processes for preparing the compounds of formula (I), in addition to any novel intermediates used therein.

General Synthesis

Method A

This illustrates the preparation of compounds of formula (Ia) wherein X is an oxygen atom.

Reaction Scheme A



In Reaction Scheme A, R^1, R^2, R^3, R^4 and A are each as defined above; Hal is a halogen atom, preferably a bromine atom; Lv is a leaving group; R^{1a} is R^1 as defined above or R^1 wherein hydroxy group is protected by a hydroxy-protecting group; R^{2a} is R^2 as defined above or R^2 wherein hydroxy group is protected by a hydroxy-protecting group; R^{3a} is R^3 as defined above or R^3 wherein hydroxy group is protected by a hydroxy-protecting group; R^{4a} is R^4 as defined above or R^4 wherein hydroxy group is protected by a hydroxy-protecting group; A^a is A as defined above or A wherein hydroxy group is protected by a hydroxy-protecting group; and the same shall apply hereinafter.

The term "leaving group", as used herein, signifies a group capable of being substituted by nucleophilic groups, such as a hydroxy group or amines and examples of such leaving groups include a halogen atom, a alkylsulfonyloxy group, a halogenoalkylsulfonyloxy group and a phenylsulfonyloxy group. Of these, a bromine atom, a chlorine atom, a methylsulfonyloxy group, a trifluoromethylsulfonyloxy group and a 4-methylphenylsulfonyloxy group are preferred.

The term "hydroxy-protecting groups", as used herein, signifies a protecting group capable of

being cleaved by various means to yield a hydroxy group, such as hydrogenolysis, hydrolysis, electrolysis or photolysis, and such hydroxy-protecting groups are described in Protective Groups in Organic Synthesis edited by T. W. Greene et al. (John Wiley & Sons, 1999). Such as for example, C_1-C_6 alkoxycarbonyl, C_1-C_6 alkylcarbonyl, W-C_1-C_6 alkylsilyl or W-C_1-C_6 alkylarylsilyl groups, and C_1-C_6 alkoxy-C_1-C_6 alkyl groups. Suitable hydroxy-protecting groups include acetyl and ferf-butyldimethylsilyl.

(StepAI)

In this step, the compound (IV) is prepared by amide formation of the amino group of the compound of formula (II), which is commercially available or may be prepared by the methods described in WO 2004054984, with acid anhydride (III).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; carboxylic acids, such as acetic acid; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and hexamethylphosphoric triamide; Of these solvents, acetic acid is preferred.

The reaction may be carried out in the presence of an acid. There is likewise no particular restriction on the nature of the acids used, and any acid commonly used in reactions of this type may equally be used here. Examples of such acids include: acids, such as hydrochloric acid, sulfuric acid or hydrobromic acid; sulfonic acids, such as methanesulfonic acid or toluenesulfonic acid. Of these, sulfuric acid is preferred.

The reaction may be carried out in the presence or absence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: amines, such as *N*-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, *N*-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N*,*N*-dimethylamino)pyridine, 2,6-di(ferf-butyl)-4-methylpyridine, quinoline, *N*,*N*-dimethylaniline, *N*,*N*-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Of these, the reaction in the absence of base is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours will usually suffice.

(StepA2)

In this step, the compound of formula (VI) is prepared by the nucleophilic substitution of the compound of formula (IV) with the compound of formula (V).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; amides, such as formamide, *N,N*-dimethylformamide, *N,N*-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile and benzonitrile; and sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents, *N,N*-dimethylformamide is preferred.

The reaction is carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydrides, such as lithium hydride, sodium hydride and potassium hydride; and alkali metal amides, such as lithium amide, sodium amide, potassium amide, lithium diisopropyl amide, potassium diisopropyl amide, sodium diisopropyl amide, lithium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide. Of these, sodium hydride is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about -20^{0}C to about 8O^{0}C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 24 hours, will usually suffice.

(Step A3)

In this step, the compound of formula (VII) is prepared by reduction and cyclization of the compound of formula (VI).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; carboxylic acids, such as acetic acid; amides, such as formamide, *N,N*-dimethylformamide, *N,*/v-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; Of these solvents, the reaction in the absence of solvent or acetic acid is preferred.

The reaction is carried out in the presence of a reducing agent. There is likewise no particular restriction on the nature of the reducing agents used, and any reducing agent commonly used in reactions of this type may equally be used here. Examples of such reducing agents include: a combination of metals, such as zinc and iron, and acids, such as hydrochloric acid, acetic acid and acetic acid-ammonium chloride complex; a combination of a hydrogen supplier, such as hydrogen gas and ammonium formate, and a catalyst, such as palladium-carbon, platinum and Raney nickel; Of these, the combination of iron

and acetic acid or a combination of hydrogen gas and palladium carbon is preferred.

The reaction may be carried out in the presence of an acid. There is likewise no particular restriction on the nature of the acids used, and any acid commonly used in reactions of this type may equally be used here. Examples of such acids include: acids, such as hydrochloric acid, sulfuric acid or hydrobromic acid; carboxylic acids, such as acetic acid; sulfonic acids, such as methanesulfonic acid or toluenesulfonic acid. Of these, acetic acid is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction temperature of from about O^{0}C to about 120^{0}C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 24 hours will usually suffice.

(StepA4)

In this step, the compound of formula (VIII) is prepared by substitution of the halogen atom of the compound of formula (VII) with metal cyanide.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, 1-methylpyrrolidin-2-one and hexamethylphosphoric triamide; Of these solvents, *N*,*N*-dimethylformamide is preferred.

The reaction is carried out in the presence of a metal cyanide reagent. There is no particular restriction on the nature of the metal cyanide reagent to be employed, and any metal cyanide reagent commonly used in reactions of this type may equally be used here. Examples of such metal cyanide reagents include: zinc(ll) cyanide, copper(l) cyanide, potassium cyanide and sodium cyanide; Of these, zinc(ll) cyanide is preferred.

The reaction is carried out in the presence or absence of a palladium catalyst. There is no particular restriction on the nature of the palladium catalyst to be employed, and any palladium catalyst commonly used in reactions of this type may equally be used here. Examples of such palladium catalysts include: a palladium metal, palladium chloride, palladium (II) acetate, tris(dibenzylideneacetone)dipalladiumch!oroform, allyl palladium chloride, [1,2-bis(diphenylphosphino)ethane]palladium dichloride, bis(tri-o-tolylphosphine)palladium dichloride, bis(triphenylphosphine)pal!adium dichloride, tetrakis(triphenylphosphine)palladium, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium, or a catalyst produced in solution by adding a ligand into the reaction solution of these. The ligand added into the reaction solution may be a phosphoric

ligand such as triphenylphosphine, 1,1'-bis(diphenylphosphino)ferrocene, bis(2-diphenylphosphinophenyl) ether, 2,2'-bis(diphenylphosphino)-1,1'-binaphthol, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, tri-o-tolylphosphine, 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl or 2,2- bis (diphenylphosphino)-1,1'-binaphthyl. Of these, tetrakis(triphenylphosphine)palladium is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 50°C to about 150°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 24 hours will usually suffice.

In this reaction, microwave can be employed to accelerate the reaction. In the case of employing microwave in sealed tube, the reaction at a temperature may be from about 50°C to about 180°C and the reaction time from about 5 minutes to about 12 hours will usually suffice.

(StepA δ)

In this step, the compound (IX) is prepared by hydrolysis of the nitrile group of the compound of formula (VIII) with a base or an acid.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; alcohols, such as methanol, ethanol, propanol, 2-propanol, butanol and ethylene glycol; sulfoxides, such as dimethyl sulfoxide and sulfolane; water; or mixed solvents thereof. Of these solvents, methanol, ethanol, tetrahydrofuran or ethylene glycol is preferred.

The reaction may be carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide and potassium hydroxide; alkali metal carbonates, such as lithium carbonate, sodium carbonate and potassium carbonate. Of these, potassium hydroxide, lithium hydroxide or sodium hydroxide is preferred.

The reaction may be carried out in the presence of an acid. There is likewise no particular restriction on the nature of the acids used, and any acid commonly used in reactions of this type may equally be used here. Examples of such acids include: carboxylic acids, such as acetic acid or propionic acid; acids, such as hydrochloric acid, sulfuric acid or hydrobromic acid. Of these, hydrochloric acid is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to

carry out the reaction at a temperature of from about O^0C to about 150°C The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 60 minutes to about 24 hours, will usually suffice.

In this reaction, microwave can be employed to accelerate the reaction. In the case of employing microwave in sealed tube, the reaction at a temperature may be from about 50°C to about $18O^0C$ and the reaction time from about 5 minutes to about 12 hours will usually suffice.

(StepA6)

In this step, the compound (Ia) is prepared by amidation of the compound of formula (IX) with the compound of formula $(X)_1$ which is commercially available or described in J. Org. Chem., 5935 (1990) and Canadian Journal of Chemistry, 2028 (1993).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; or mixed solvents thereof. Of these, *N*,*N*-dimethylformamide is preferred.

The reaction is carried out in the presence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: amines, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(*N*,*N*-dimethylamino)pyridine, 2,6-di(terf-butyl)-4-methylpyridine, quinoline, *N*,/V-dimethylaniline, W./V-diethylaniline, DBN, DABCO, and DBU. Of these, triethylamine or diisopropylethylamine is preferred.

The reaction is carried out in the presence of a condensing agent. There is likewise no particular restriction on the nature of the condensing agents used, and any condensing agent commonly used in reactions of this type may equally be used here. Examples of such condensing agents include: 2-halo-1-lower alkyl pyridinium salts, such as 2-chloro-1-methylpyridinium iodide and 2-bromo-1-ethylpyridinium tetrafluoroborate (BEP); diarylphosphoryl azides, such as diphenylphosphoryl azide (DPPA); chloroformates, such as ethyl chloroformate and isobutyl chloroformate; phosphorocyanidates, such as diethyl phosphorocyanidate (DEPC); imidazole derivatives, such as *N*,*N*'-carbonyldiimidazole (CDI); carbodiimide derivatives, such as *N*,*N*'-dicyclohexylcarbodiimide (DCC) and 1-(3-dimethylarninopropyl)-3-ethylcarbodiimide hydrochloride (EDCI); iminium salts, such as 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) and tetramethyl fluoroformamidinium hexafluorophosphate (TFFH); and phosphonium salts, such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP) and bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrop). Of these, EDCI or HBTU is preferred.

Reagents, such as 4-(N,N-dimethylamino)pyridine (DMAP), and 1-hydroxybenztriazole (HOBt), may be employed for this step. Of these, HOBt is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0^0C to about 80^0C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 48 hours, will usually suffice.

Introduction of the hydroxy-protecting group

In the case where R^1, R^2, R^3, R^4 or A has a hydroxy group, if necessary, the reaction may be accomplished by protecting the hydroxy group.

The introduction of the hydroxy-protecting group can be carried out at an appropriate step before the reaction affected by the hydroxy group.

This reaction is described in detail by T. W. Greene et al., Protective Groups in Organic Synthesis, 369-453, (1999), the disclosures of which are incorporated herein by reference. The following exemplifies a typical reaction involving the protecting group terf-butyldimethylsilyl.

For example, when the hydroxy-protecting group is a " terf-butyldimethylsilyl ", this step is conducted by reacting with a desired hydroxy- protecting group halide in an inert solvent in the presence of a base.

Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, N.N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; or mixed solvents thereof. Of these, tetrahydrofuran or N,N-dimethylformamide is preferred.

Examples of the hydroxy-protecting group halide usable in the above reaction include trimethylsilyl chloride, triethylsilyl chloride, terf-butyldimethylsilyl chloride, acetyl chloride are preferred.

Examples of the base include alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate, and organic amines such as triethylamine, tributylamine, N- methylmorpholine, pyridine, imidazole, 4-dimethylaminopyridine, picoline, lutidine, collidine, DBN and DBU. Out of these, triethylamine, imidazole, or pyridine is preferred. Upon use of an organic amine in the liquid form, it also serves as a solvent when used in large excess.

The deprotection reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0^0C to about 100^0C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected

under the preferred conditions outlined above, a period of from about 10 minutes to about 24 hours, will usually suffice.

Deprotecting step

In the case where R^{1a}, R^{2a}, R^{3a}, R^{4a} or A^a has a protected hydroxy group, the deprotection reaction will follow to yield a hydroxy group. This reaction is described in detail by T. W. Greene et al., Protective Groups in Organic Synthesis, 369-453, (1999), the disclosures of which are incorporated herein by reference. The following exemplifies a typical reaction involving the protecting group terf-butyldimethylsilyl.

The deprotection of the hydroxyl groups is carried out with an acid, such as acetic acid, hydrogen fluoride, hydrogen fluoride-pyridine complex, or fluoride ion, such as tetrabutylammonium fluoride (TBAF).

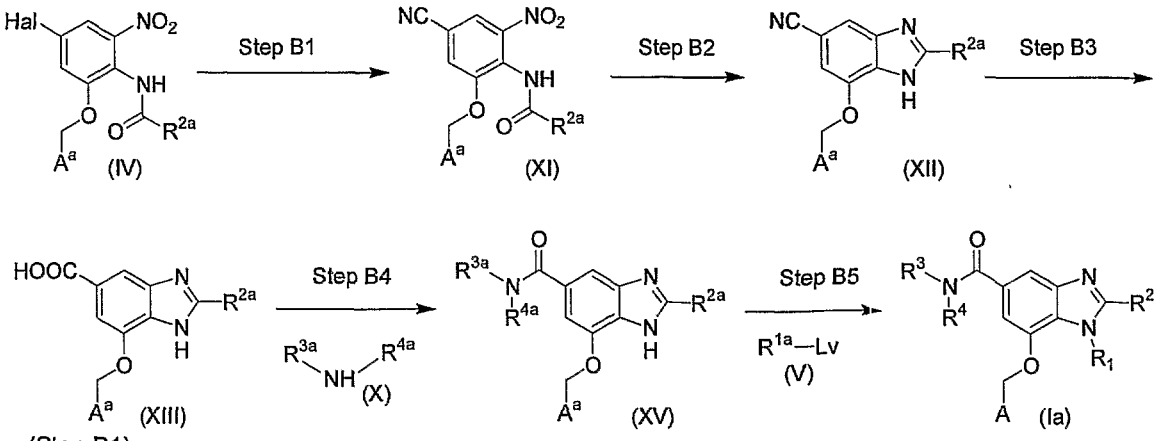
The deprotection reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include, but are not limited to: alcohol, such as methanol, ethanol or mixed solvents thereof.

The deprotection reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0^0C to about 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 10 minutes to about 24 hours, will usually suffice.

Method B

This illustrates the preparation of compounds of formula (Ia) wherein X is an oxygen atom.

Reaction Scheme B



(Step B1)

In this step, the compound of formula (XI) is prepared by substitution of the halogen atom of the compound of formula (IV), which is commercially available or may be prepared by the Step A2 of the Method A, with metal cyanide. The reaction may be carried out under the same condition as described in

Step A4 of Method A.

(Step B2)

In this step, the compound (XII) is prepared is prepared by reduction and cyclization of the compound of formula (XI). The reaction may be carried out under the same condition as described in Step A3 of Method A.

(Step B3)

In this step, the compound (XIII) is prepared by hydrolysis of the nitrile group of the compound of formula (XII) with a base or an acid. The reaction may be carried out under the same condition as described in Step A5 of Method A.

(Step B4)

In this step, the compound (XV) is prepared by amidation of the compound of formula (XIII) with the compound of formula (X), which is commercially available or described in J. Org. Chem., 5935 (1990) and Canadian Journal of Chemistry, 2028 (1993). The reaction may be carried out under the same condition as described in Step A6 of Method A.

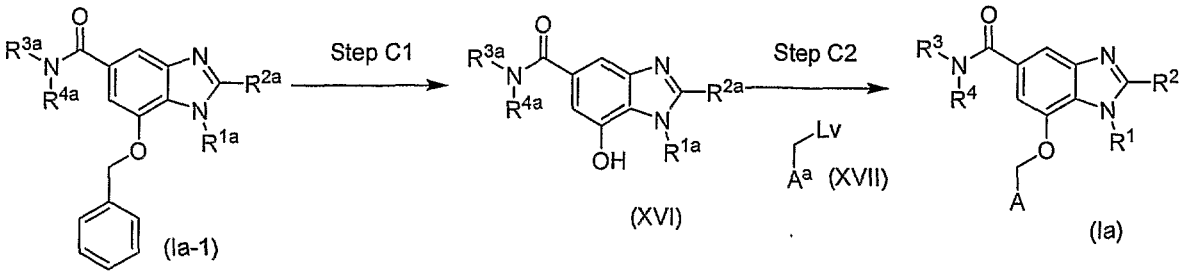
(Step B5)

In this step, the compound of formula (Ia) is prepared by the nucleophilic substitution of the compound of formula (XV) with the compound of formula (V). The reaction may be carried out under the same condition as described in StepA2 of Method A.

Method C

This illustrates the preparation of compounds of formula (Ia) wherein X is an oxygen atom.

Reaction Scheme C



(Step C1)

In this step, the compound of formula (XVI) is prepared by catalytic hydrogenation of the compound of formula (Ia-1), which is commercially available or may be prepared by the method described in the following Method A under the hydrogen gas.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; ethers,

such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; amides, such as formamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; sulfoxides, such as dimethyl sulfoxide and sulfolane; Of these solvents, methanol or ethanol is preferred.

The reaction is carried out in the presence of a palladium catalyst. There is no particular restriction on the nature of the palladium catalyst to be employed, and any palladium catalyst commonly used in reactions of this type may equally be used here. Examples of such palladium catalysts include: palladium metal, palladium-carbon, palladium hydroxide, palladium chloride, palladium (II) acetate, tris(dibenzylideneacetone)dipalladiurnchloroform, **ally!** palladium chloride, [1,2-bis(diphenylphosphino)ethane]palladium dichloride, bis(tri-o-tolylphosphine)palladium dichloride, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium, or **a** catalyst produced in solution by adding **a** ligand into the reaction solution of these. The ligand added into the reaction solution may be a phosphoric ligand such as 1,1'-bis(diphenylphosphino)ferrocene, bis(2- diphenylphosphinophenyl) ether, 2,2'-bis(diphenylphosphino)-1,1'-binaphthol, 1,3- bis(diphenylphosphino)propane, 1,4rbis(diphenylphosphino)butane, tri-o-tolylphosphine, 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl or 2,2-bis(diphenylphosphino)-1,1 '-binaphthyl. The above palladium catalyst is preferably palladium acetate, tris(dibenzylideneacetone)dipalladium-chloroform, a combination of palladium acetate and the ligand bis(2-diphenylphosphinophenyl)ether, or a combination of tris(dibenylideneacetone)dipalladium-chlorof orm and the ligand 1,1'- bis(diphenylphosphino)ferrocene, more preferably a combination of palladium acetate and the ligand bis(2-diphenylphosphinophenyl) ether, or a combination of tris(dibenzylideneacetone)dipalladium-chloroform and the ligand 1,1'-bis(diphenylphosphino)ferrocene. Of these, palladium-carbon or palladium hydroxide is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about O^0C to about 100^0C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 10 minutes to about 24 hours, will usually suffice.

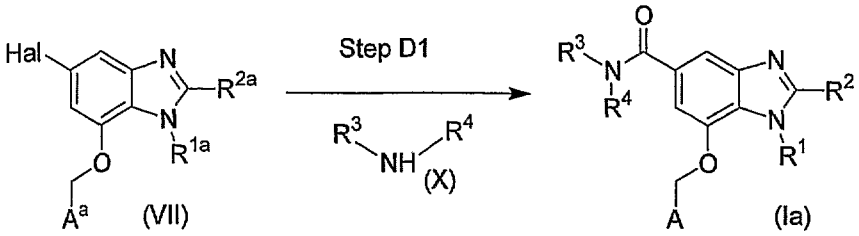
(Step C2)

In this step, the compound of formula (Ia) is prepared by the nucleophilic substitution of the compound of formula (XVI) with the compound of formula (XVII). The reaction may be carried out under the same condition as described in Step A2 of Method A.

Method D

This illustrates the preparation of compounds of formula (Ia) wherein X is an oxygen atom.

Reaction Scheme D



(Step D1)

In the Step D1, the compound of formula (Ia) is prepared by direct amidation of the compound of formula (VII), which is prepared by the Step A3 of Method A, with the compound of formula (X) in the presence of a palladium catalyst and carbon monoxide.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide and hexamethylphosphoric triamide; sulfoxides, such as dimethyl sulfoxide and sulfolane; ketones, such as acetone and diethylketone. Of these solvents, tetrahydrofuran or *N*,*N*-dimethylformamide is preferred.

The reaction is carried out in the presence of carbon monoxide and a palladium catalyst. There is no particular restriction on the nature of the palladium catalyst to be employed, and any palladium catalyst commonly used in reactions of this type may equally be used here. Examples of such palladium catalysts include: palladium metal, palladium-carbon, palladium hydroxide, palladium chloride, palladium (II) acetate, tris(dibenzylideneacetone)dipalladiumchloroform, allyl palladium chloride, [1,2-bis(diphenylphosphino)ethane]palladium dichloride, bis(tri-o-tolylphosphine)palladium dichloride, bis(triphenylphosphine)palladium dichloride, tetrakis(triphenylphosphine)palladium, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium, or a catalyst produced in solution by adding a ligand into the reaction solution of these. The ligand added into the reaction solution may be a phosphoric ligand such as 1,1'-bis(diphenylphosphino)ferrocene, bis(2- diphenylphosphinophenyl) ether, 2,2'-bis(diphenylphosphino)-1 ,1'-binaphthol, 1,3- bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, triphenylphosphine, tri-o-tolylphosphine, 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl or 2,2- bis (diphenylphosphino)-1,1'-binaphthyl. The above palladium catalyst is preferably palladium acetate, tris(dibenzylideneacetone)dipalladium-chloroform, a combination of palladium acetate and the ligand bis(2- diphenylphosphinophenyl) ether, or a combination of tris(dibenzylideneacetone)dipalladium-chloroform and the ligand 1,1'-bis(diphenylphosphino)ferrocene, more preferably a combination of palladium acetate and the ligand bis(2-diphenylphosphinophenyl) ether, or a combination of tris(dibenzylideneacetone)dipalladium-chloroform and the ligand 1,1'-bis(diphenylphosphino)ferrocene. Of these, tetrakis(triphenylphosphine)pal!adium or a combination of palladium acetate and the ligand triphenylphosphine is preferred.

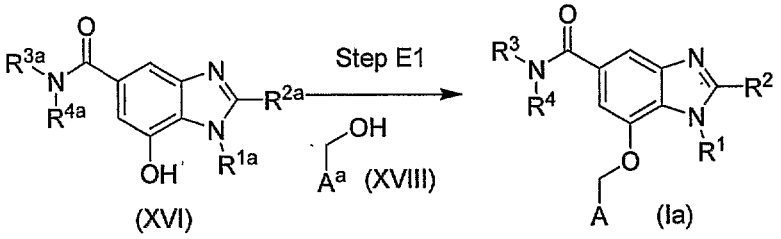
The reaction can take place over a wide range of temperatures, and the precise reaction

temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about O^0C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 48 hours, will usually suffice.

Method E

This illustrates the preparation of compounds of formula (Ia) wherein X is an oxygen atom.

Reaction Scheme E



(Step EI)

In this step, the compound (Ia) is prepared by ether formation reaction of the compound of formula (XVI), which is prepared by the Step C1 of Method C, with the compound (XVIII), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, *N*,/V-dimethylformamide, *N*,*N*-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile and benzonitrile; or mixed solvents thereof. Of these, toluene is preferred.

The reaction is carried out in the presence of a condensing agent. There is likewise no particular restriction on the nature of the condensing agents used, and any condensing agent commonly used in reactions of this type may equally be used here. Examples of such condensing agents include: azodicarboxylic acid di-lower alkyl esters, such as diethyl azodicarboxylate (DEAD), diisopropyl azodicarboxylate (DIAD) and di-ferf-butyl azodicarboxylate (DTAD); azodicarboxamides, such as *N*,*N*,*N*',*N*'-tetraisopropyiazodicarboxamide $(TIPA)_1$ 1,1'-(azodicarbonyl)dipiperidine (ADDP) and *N*,*N*,*N*',*N*'-tetramethylazodicarboxamide (TMAD); phosphoranes, such as (cyanomethylene)tributylphosphorane (CMBP) and (cyanomethylene)trimethylphosphorane (CMMP). Of these, DIAD is preferred.

Phosphine reagents, such as triphenylphosphine, trimethylphosphine and tributylphosphine, may be employed for this step. Of these, triphenylphosphine is preferred.

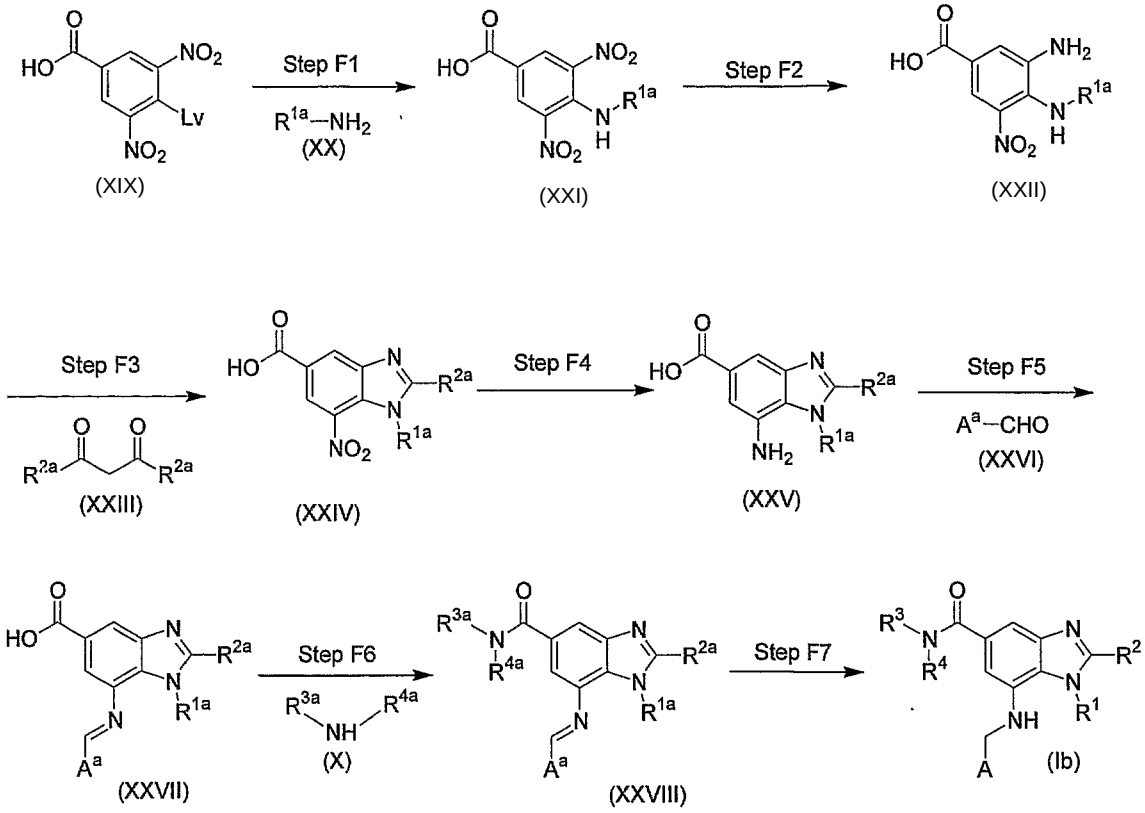
The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such

factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0^0C to about 120^0C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 60 minutes to about 48 hours, will usually suffice.

Method F

This illustrates the preparation of compounds of formula (Ib) wherein X is **NH.**

Reaction Scheme F



(Step F1)

In this step, the compound (XXI) is prepared by substitution of the leaving group of the compound of formula (XIX), which is commercially available, with the compound (XX), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: water; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; amines, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine,

N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, N,N-dimethylaniline and N,N- diethylamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; ketones, such as acetone and diethylketone; or mixed solvents thereof. Of these solvents, tetrahydrofuran, water or ethanol is preferred.

The reaction is carried out in the presence or absence of a base. There is likewise no particular restriction on the nature of the bases used, and any base commonly used in reactions of this type may equally be used here. Examples of such bases include: alkali metal hydrogencarbonates, such as lithium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; amines, such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(terf-butyl)-4-methylpyridine, quinoline, N.N-dimethylaniline, N,N-diethylaniline, DBN, DABCO and DBU. Of these, the reaction in the absence of base is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 120°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 48 hours, will usually suffice.

(Step F2)

In this step, the compound (XXII) is prepared by reduction of the compound of formula (XXI).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; sulfoxides, such as dimethyl sulfoxide and sulfolane; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; or mixed solvents thereof. Of these, ethanol or tetrahydrofuran is preferred.

The reaction is carried out in the presence of a reducing agent. There is likewise no particular restriction on the nature of the reducing agents used, and any reducing agent commonly used in reactions of this type may equally be used here. Examples of such reducing agents include: a combination of a hydrogen supplier, such as hydrogen gas and ammonium formate, and a catalyst, such as palladium-carbon, platinum and Raney nickel; a combination of metals, such as zinc, iron and tin chloride, and acids, such as hydrochloric acid, acetic acid and acetic acid-ammonium chloride complex; sulfides such as ammonium polysulfide, ammonium sulfide, sodium sulfide, hydrogen sulfide and sodium disulfide. Of these, ammonium polysulfide or ammonium sulfide is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such

factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 80°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 10 minutes to about 8 hours will usually suffice.

(Step F3)

In this step, the compound (XXIV) is prepared by formation of a benzimidazole ring from the compound of formula (XXII) and the compound of formula (XXIII), which is commercially available, according to a method described in Synthesis, 1283-1286 (1992).

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: aliphatic hydrocarbons, such as hexane, heptane and petroleum ether; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride and 1,2-dichloroethane; ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; Of these solvents, ethanol is preferred.

The reaction is carried out in the presence of an acid. There is likewise no particular restriction on the nature of the acids used, and any acid commonly used in reactions of this type may equally be used here. Examples of such acids include: acids, such as hydrochloric acid, sulfuric acid or hydrobromic acid; sulfonic acids, such as methanesulfonic acid or toluenesulfonic acid. Of these, hydrochloric acid is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 30 minutes to about 24 hours will usually suffice.

(Step F4)

In this step, the compound (XXV) is prepared by reduction of the compound of formula (XXIV). The reaction may be carried out under the same condition as described in Step A3 of Method A.

(Step F5)

In this step, the compound (XXVII) is prepared by imine formation of the compound of formula (XXV) with the compound of formula (XXVI), which is commercially available.

The reaction is normally and preferably effected in the presence of solvent. There is no particular restriction on the nature of the solvent to be employed, provided that it has no adverse effect on the

reaction or the reagents involved and that it can dissolve reagents, at least to some extent. Examples of suitable solvents include: ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran and dioxane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; nitrites, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; or mixed solvents thereof. Of these, methanol is preferred.

The reaction may be carried out in the presence of an acid. There is likewise no particular restriction on the nature of the acids used, and any acid commonly used in reactions of this type may equally be used here. Examples of such acids include: acids, such as hydrochloric acid, sulfuric acid or hydrobromic acid; sulfonic acids, such as methanesulfonic acid or toluenesulfonic acid; carboxylic acids, such as acetic acid. Of these, acetic acid is preferred.

The reaction can take place over a wide range of temperatures, and the precise reaction temperature is not critical to the invention. The preferred reaction temperature will depend upon such factors as the nature of the solvent, and the starting materials. However, in general, it is convenient to carry out the reaction at a temperature of from about 0°C to about 100°C. The time required for the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the starting materials and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period of from about 5 minutes to about 24 hours, will usually suffice.

(Step F6)

In this step, the compound (XXVIII) is prepared by amidation of the compound of formula (XXVII) with the compound of formula (X), which is commercially available. The reaction may be carried out under the same condition as described in Step A6 of Method A.

(Step F7)

In this step, the compound (Ib) is prepared by reduction of the compound of formula (XXVIII). The reaction may be carried out under the same condition as described in Step A3 of Method A.

The compounds of formula (I), and the intermediates in the above-mentioned preparation methods can be isolated and purified by conventional procedures, such as distillation, recrystallization or chromatographic purification.

Compounds of the invention intended for pharmaceutical use may be administered as crystalline or amorphous products. They may be obtained, for example, as solid plugs, powders, or films by methods such as precipitation, crystallization, freeze-drying, spray drying, or evaporative drying. Microwave or radio frequency drying may be used for this purpose.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC).

Alternatively, a method of optical resolution of a racemate (or a racemic precursor) can be

appropriately selected from conventional procedures, for example, preferential crystallization, or resolution of diastereomeric salts between a basic moiety of the compound of formula (I) and a suitable optically active acid such as tartaric acid.

They may be administered alone or in combination with one or more other compounds of the invention or in combination with one or more other drugs (or as any combination thereof). Generally, they will be administered as a pharmaceutical composition or formulation in association with one or more pharmaceutically acceptable carriers or excipients. The term "carrier" or "excipient" is used herein to describe any ingredient other than the compound(s) of the invention. The choice of carrier or excipient will to a large extent depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form.

Pharmaceutical compositions suitable for the delivery of compounds of the present invention and methods for their preparation will be readily apparent to those skilled in the art. Such compositions and methods for their preparation may be found, for example, in 'Remington's Pharmaceutical Sciences', 19th Edition (Mack Publishing Company, 1995).

ORALADMINISTRATION

The compounds of the invention may be administered orally. Oral administration may involve swallowing, so that the compound enters the gastrointestinal tract, or buccal or sublingual administration may be employed by which the compound enters the blood stream directly from the mouth.

Formulations suitable for oral administration include solid formulations such as, for example, tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid-filled), chews, multi- and nano-particulates, gels, solid solution, liposome, films (including muco-adhesive), ovules, sprays and liquid formulations.

Liquid formulations include, for example, suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

The compounds of the invention may also be used in fast-dissolving, fast-disintegrating dosage forms such as those described in Expert Opinion in Therapeutic Patents, H (6), 981-986 by Liang and Chen (2001).

For tablet dosage forms, depending on dose, the drug may make up from about 1 wt% to about 80 wt% of the dosage form, more typically from about 5 wt% to about 60 wt% of the dosage form. In addition to the drug, tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, the disintegrant will comprise from about 1 wt% to about 25 wt%, preferably from about 5 wt% to about 20 wt% of the dosage form.

Binders are generally used to impart cohesive qualities to a tablet formulation. Suitable binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums,

polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate.

Tablets may also optionally comprise surface-active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2 wt% to about 5 wt% of the tablet, and glidants may comprise from about 0.2 wt% to about 1 wt% of the tablet.

Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulphate. Lubricants generally comprise from about 0.25 wt% to about 10 wt%, preferably from about 0.5 wt% to about 3 wt% of the tablet.

Other possible ingredients include anti-oxidants, colourants, flavouring agents, preservatives and taste-masking agents.

Exemplary tablets contain up to about 80% drug, from about 10 wt% to about 90 wt% binder, from about 0 wt% to about 85 wt% diluent, from about 2 wt% to about 10 wt% disintegrant, and from about 0.25 wt% to about 10 wt% lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends or portions of blends may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tabletting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.

The formulation of tablets is discussed in *"Pharmaceutical Dosage Forms: Tablets, Vol. 1",* by H. Lieberman and L. Lachman, Marcel Dekker, N.Y., N.Y., 1980 (ISBN 0-8247-691 8-X).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

Suitable modified release formulations for the purposes of the invention are described in US Patent No. 6,1 06,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma *et* a/, Pharmaceutical Technology On-line. 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO 00/35298.

PARENTERALADMINISTRATION

The compounds of the invention may also be administered directly into the blood stream, into muscle, or into an internal organ. Suitable means for parenteral administration include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous. Suitable devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques.

Parenteral formulations are typically aqueous solutions which may contain excipients such as salts, carbohydrates and buffering agents (preferably to a pH of from about 3 to about 9), but, for some applications, they may be more suitably formulated as a sterile non-aqueous solution or as a dried form to be used in conjunction with a suitable vehicle such as sterile, pyrogen-free water.

The preparation of parenteral formulations under sterile conditions, for example, by lyophilisation, may readily be accomplished using standard pharmaceutical techniques well known to those skilled in the art.

The solubility of compounds of formula (I) used in the preparation of parenteral solutions may be increased by the use of appropriate formulation techniques, such as the incorporation of solubility-enhancing agents.

Formulations for parenteral administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release. Thus compounds of the invention may be formulated as a solid, semi-solid, or thixotropic liquid for administration as an implanted depot providing modified release of the active compound. Examples of such formulations include drug-coated stents and PGLA microspheres.

TOPICALADMINISTRATION

The compounds of the invention may also be administered topically to the skin or mucosa, that is, dermally or transdermally.. Typical formulations for this purpose include gels, hydrogels, lotions, solutions, ,creams, ointments, dusting powders, dressings, foams, films, skin patches, wafers, implants, sponges, fibres, bandages and microemulsions. Liposomes may also be used. Typical carriers include alcohol, water, mineral oil, liquid petrolatum, white petrolatum, glycerin, polyethylene glycol and propylene glycol. Penetration enhancers may be incorporated - see, for example, *J Pharm Sci,* 88 (10), 955-958 by Finnin and Morgan (October 1999).

Other means of topical administration include delivery by electroporation, iontophoresis, phonophoresis, sonophoresis and microneedle or needle-free *(e.g.* Powderject™, Bioject™, *etc.)* injection.

Formulations for topical administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

INHALED/INTRANASAL ADMINISTRATION

The compounds of the invention can also be administered intranasally or by inhalation, typically in the form of a dry powder (either alone, as a mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler or as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebuliser, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin.

The pressurized container, pump, spray, atomizer, or nebuliser contains a solution or suspension of the compound(s) of the invention comprising, for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilising, or extending release of the active, a propellant(s) as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid.

Prior to use in a dry powder or suspension formulation, the drug product is micronised to a size suitable for delivery by inhalation (typically less than 5 microns). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form

nanoparticles, high pressure homog'enization, or spray drying.

Capsules (made, for example, from gelatin or HPMC), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound of the invention, a suitable powder base such as lactose or starch and a performance modifier such as /-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose.

A suitable solution formulation for use in an atomizer using electrohydrodynamics to produce a fine mist may contain from about 1µg to about 20mg of the compound of the invention per actuation and the actuation volume may vary from about 1µl to about 100µ. A typical formulation may comprise a compound of formula (I), propylene glycol, sterile water, ethanol and sodium chloride. Alternative solvents which may be used instead of propylene glycol include glycerol and polyethylene glycol.

Suitable flavours, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added to those formulations of the invention intended for inhaled/intranasal administration. Formulations for inhaled/intranasal administration may be formulated to be immediate and/or modified release using, for example, poly(DL-lactic-coglycolic acid (PGLA). Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

In the case of dry powder inhalers and aerosols, the dosage unit is determined by means of a valve which delivers a metered amount. Units in accordance with the invention are typically arranged to administer a metered dose or "puff' containing from about 1 to about 100 µg of the compound of formula (I). The overall daily dose will typically be in the range about 50 µg to about 20 mg which may be administered in a single dose or, more usually, as divided doses throughout the day.

RECTAUINTRAVAGINALADMINISTRATION

The compounds of the invention may be administered rectally or vaginally, for example, in the form of a suppository, pessary, or enema. Cocoa butter is a traditional suppository base, but various alternatives may be used as appropriate.

Formulations for rectal/vaginal administration may be formulated to be immediate and/or modified release. Modified release formulations include delayed-, sustained-, pulsed-, controlled-, targeted and programmed release.

OTHER TECHNOLOGIES

The compounds of the invention may be combined with soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to improve their solubility, dissolution rate, taste-masking, bioavailability and/or stability for use in any of the aforementioned modes of administration.

Drug-cyclodextrin complexes, for example, are found to be generally useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, *i.e.* as a carrier, diluent, or solubiliser. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in. WO 91/11172, WO 94/02518 and WO

98/55148.

KIT-OF-PARTS

Inasmuch as it may be desirable to administer a combination of active compounds, for example, for the purpose of treating a particular disease or condition, it is within the scope of the present invention that two or more pharmaceutical compositions, at least one of which contains a compound in accordance with the invention, may conveniently be combined in the form of a kit suitable for coadministration of the compositions.

Thus the kit of the invention comprises two or more separate pharmaceutical compositions, at least one of which contains a compound of formula (I) in accordance with the invention, and means for separately retaining said compositions, such as a container, divided bottle, or divided foil packet. An example of such a kit is the familiar blister pack used for the packaging of tablets, capsules and the like.

The kit of the invention is particularly suitable for administering different dosage forms, for example, oral and parenteral, for administering the separate compositions at different dosage intervals, or for titrating the separate compositions against one another. To assist compliance, the kit typically comprises directions for administration and may be provided with a so-called memory aid.

DOSAGE

For administration to human patients, the total daily dose of the compounds of the invention is typically in the range of about 0.5 mg to about 300 mg depending, of course, on the mode of administration, preferred in the range of about 1 mg to about 100 mg and more preferred in the range of about 1 mg to about 20 mg. For example, oral administration may require a total daily dose of from about 1 mg to about 20 mg, while an intravenous dose may only require from about 0.5 mg to about 10 mg. The total daily dose may be administered in single or divided doses.

These dosages are based on an average human subject having a weight of about 65kg to about 70kg. The physician will readily be able to determine doses for subjects whose weight falls outside this range, such as infants and the elderly.

COMBINATIONS

As discussed above, a compound of the invention exhibits acid pump inhibitory activity. An acid pump antagonist of the present invention may be usefully combined with another pharmacologically active compound, or with two or more other pharmacologically active compounds, particularly in the treatment of gastroesophageal reflux disease. For example, an acid pump antagonist, particularly a compound of the formula (I), a prodrug thereof or a pharmaceutically acceptable salt of said compound or said prodrug, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

(i) histamine H_2 receptor antagonists, e.g. ranitidine, lafutidine, nizatidine, cimetidine, famotidine and roxatidine;

(ii) proton pump inhibitors, e.g. omeprazole, esomeprazole, pantoprazole, rabeprazole, tenatoprazole, ilaprazole and lansoprazole;

(iii) oral antacid mixtures, e.g. Maalox®, Aludrox® and Gaviscon®;

(iv) mucosal protective agents, e.g. polaprezinc, ecabet sodium, rebamipide, teprenone, cetraxate, sucralfate, chloropylline-copper and plaunotol;

(v) anti-gastric agents, e.g. Anti-gastrin vaccine, itriglumide and Z-360;

(vi) 5-HT_3 antagonists, e.g. dolasetron, palonosetron, alosetron, azasetron, ramosetron, mitrazapine, granisetron, tropisetron, E-3620, ondansetron and indisetron;

(vii) 5-HT_4 agonists, e.g. tegaserod, mosapride, cinitapride and oxtriptane;

(viii) laxatives, e.g. Trifyba®, Fybogel®, Konsyl®, Isogel®, Regulan®, Celevac® and Normacof;

(ix) GABAB agonists, e.g. baclofen and AZD-3355;

(x) $GABA_B$ antagonists, e.g. GAS-360 and SGS-742;

(xi) calcium channel blockers, e.g. aranidipine, lacidipine, falodipine, azelnidipine, clinidipine, lomerizine, diltiazem, gallopamil, efonidipine, nisoldipine, amlodipine, lercanidipine, bevantolol, nicardipine, isradipine, benidipine, verapamil, nitrendipine, barnidipine, propafenone, manidipine, bepridil, nifedipine, nilvadipine, nimodipine and fasudil;

(xii) dopamine antagonists, e.g. metoclopramide, domperidone and levosulpiride;

(xiii) Tachykinin (NK) antagonists, particularly NK-3, NK-2 and NK-1 antagonists, e.g. nepadutant, saredutant, talnetant, (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3 H-1 ,2,4-triazol-3-one (MK-869), lanepitant, dapitant and 3-[[2-methoxy-5-(trifluoromethoxy)phenyl] methylamino]-2-phenyl-piperidine (2S.3S);

(xiv) Helicobacter pylori infection agents, e.g. clarithromicyn, roxithromycin, rokitamycin, flurithromycin, telithromycin, amoxicillin, ampicillin, temocillin, bacampicillin, aspoxicillin, sultamicillin, piperacillin, lenampicillin, tetracycline, metronidazole, bithmuth citrate and bithmuth subsalicylate;

(xv) nitric oxide synthase inhibitors, e.g. GW-274150, tilarginine, P54, guanidioethyldisulfide and nitroflurbiprofen;

(xvi) vanilloid receptor 1 antagonists, e.g. AMG-517 and GW-705498;

(xvii) muscarinic receptor antagonists, e.g. trospium, solifenacin, tolterodine, tiotropium, cimetropium, oxitropium, ipratropium, tiqui∑um, dalifenacin and imidafenacin;

(xviii) calmodulin antagonists, e.g. squalamine and DY-9760;

(xix) potassium channel agonists, e.g. pinacidil, tilisolol, nicorandil, NS-8 and retigabine;

(xx) beta-1 agonists, e.g. dobutamine, denopamine, xamoterol, denopamine, docarpamine and xamoterol;

(xxi) beta-2 agonists, e.g. salbutamol; terbutaline, arformoterol, meluadrine, mabuterol, ritodrine, fenoterol, clenbuterol, formoterol, procaterol, tulobuterol, pirbuterol, bambuterol, tulobuterol, dopexamine and levosalbutamol;

(xxii) beta agonists, e.g. isoproterenol and terbutaline;

(xxiii) alpha 2 agonists, e.g. clonidine, medetomidine, lofexidine, moxonidine, tizanidine, guanfacine, guanabenz, talipexole and dexmedetomidine;

(xxiv) endthelin A antagonists, e.g. bonsetan, atrasentan, ambrisentan, clazosentan, sitaxsentan, fandosentan and darusentan;

(xxv) opioid μ agonists, e.g. morphine, fentanyl and loperamide;

(xxvi) opioid μ antagonists, e.g. naloxone, buprenorphine and alvimopan;

(xxvii) motilin agonists, e.g. erythromycin, mitemcinal, SLV-305 and atilmotin;

(xxviii) ghreiin agonists, e.g. capromorelin and TZP-101;

(xxix) AchE release stimulants, e.g. Z-338 and KW-5092;

(xxx) CCK-B antagonists, e.g. itriglumide, YF-476 and S-0509;

(xxxi) glucagon antagonists, e.g. NN-2501 and A-770077;

(xxxii) piperacillin, lenampicillin, tetracycline, metronidazole, bithmuth citrate and bithmuth subsalicylate;

(xxxiii) Glucagon-like peptide-1 (GLP-1) antagonists, e.g. PNU-126814;

(xxxiv) small conductance calcium-activated potassium channel 3 (SK-3) antagonists, e.g. apamin, dequalinium, atracurium, pancuronium and tubocurarine.

(XXXV) mGluR δ anatagonists, e.g. ADX-10059 and AFQ-056;

(xxxvi) 5-HT3 agonists, *e.g.* pumosetrag(DDP733);

(xxxvii) mGluR δ agonists, *e.g.* (S)-3,4-DCPG and mGluR8-A.

Method for assessing biological activities:

The acid pump inhibitory activity and other biological activities of the compounds of this invention were determined by the following procedures. Symbols have their usual meanings in the specification: mL (milliliter(s)), μl (microlitter(s)), Kg (kirogram(s)), g (gram(s)), mg (milligram(s)), μg (microgram(s)), pmol (pico molar(s)), mmol (milli molar(s)), M (molar mass (m^3/mol)), mM (milli molar mass), μM (micro molar mass), atm (standard atmospheric pressure), r.p.m. (revolutions pre minute), quant, (quantitative yield), nm (nanometer(s)), min (minute(s)) Cat# (catalog number).

Preparation of gastric vesicles from fresh porcine stomachs

The porcine gastric vesicles for Porcine gastric H^+/K^+-ATPaSe inhibition assays were prepared from mucous membrane in fresh porcine stomachs by homogenization with a tight-fitted polytetrafluoroethylene (Teflone®) homogenizer in 0.25 M sucrose at 4^0C. The crude pellet was removed with centrifugation at 20,000 g for 30 min. Then supernatant was centrifuged at 100,000 g for 30 min. The resulting pellet was re-suspended in 0.25 M sucrose, and then subjected to density gradient centrifugation at 132,000 g for 90 min. The gastric vesicles were collected from interface on 0.25 M sucrose layer containing 7% Ficoll™ PM400(Amersham Biosciences). This procedure was performed in a cold room.

Ion-leaky Porcine gastric H+/K+-ATPase inhibition

Ion-leaky porcine gastric H^+/K^+-ATPase inhibition was measured according to the modified method described in *Biochemical Pharmacology,* 1988, 37, 2231-2236.

The isolated vesicles were lyophilized, and then kept in deep-freezer until use. For enzyme assay, lyophilized vesicles were reconstituted with 3 mM $MgSO_4$ containing 40 mM Bis-tris (pH 6.4 at 37^0C).

Enzyme reaction was performed incubating 5 mM KCl, 3 mM Na_2ATP, 3 mM $MgSO_4$ and 1.0 μg of reconstituted vesicles for 30 minutes at 37^0C in a final 60 μl of reaction mixture (40 mM Bis-tris, pH 6.4) with or without the test compound. Enzyme reaction was stopped by adding 10% sodium dodecyl sulphate (SDS). Released inorganic phosphate from ATP was detected by incubation with mixture of 1 part of 35

mM ammonium molybdate tetrahydrate in 15 mM Zinc acetate hydrate and 4 parts of 10% ascorbic acid (pH 5.0), resulting in phosphomolybdate, which has optical density at 750 nm.

Ion-tight porcine gastric H+/K+-ATPase inhibition

Ion-tight porcine gastric H^+/K^+-ATPase inhibition was measured according to the modified method described in *Biochemical Pharmacology,* 1988, 37, 2231-2236.

The isolated vesicles were kept in deep-freezer until use. For enzyme assay, vesicles were diluted with 3 mM $MgSO_4$ containing 5 mM Tris (pH 7.4 at 37°C).

Enzyme reaction was performed incubating 150 mM KCl, 3 mM Na_2ATP, 3 mM $MgSO_4$, 15 µM valinomycin and 3.0 µg of vesicles for 30 minutes at 37°C in a final 60 µl of reaction mixture (5mM Tris, pH 7.4) with or without the test compound. Enzyme reaction was stopped by adding 10% SDS. Released inorganic phosphate from ATP was detected by incubating with mixture of 1 part of 35 mM ammonium molybdate tetrahydrate in 15 mM Zinc acetate hydrate and 4 parts of 10% ascorbic acid (pH 5.0), resulting in phosphomolybdate, which has optical density at 750 nm. The results of IC_{50} values of the inhibition activity for the compounds of Examples are shown in Table 1.

Table 1.

Example No.	IC_{50} (µM)
1	0.084
2	0.20
3	0.084
4	0.11
5	0.27
6	0.32
7	0.21
8	0.34
9	0.12
10	0.54
11	0.13
12	0.35
13	0.081
14	0.52
15	0.095
16	0.15
17	0.16
18	0.044
19	0.50
20	0.16
21	0.11
22	0.14
23	0.060
24	0.13
25	0.33

Canine kidney Na*/K*-ATPase inhibition

The powdered canine kidney Na^+/K^+-ATPase (Sigma) was reconstituted with 3 mM $MgSO_4$ containing 40 mM Tris (pH 7.4 at 37°C). Enzyme reaction was performed incubating 100 mM NaCl, 2 mM KCl, 3 mM Na_2ATP, 3 mM $MgSO_4$ and 12 µg of enzyme for 30 minutes at 37°C in a final 60 µl of reaction mixture (40 mM Tris, pH 7.4) with or without the test compound. Enzyme reaction was stopped by adding

10% SDS. Released inorganic phosphate from ATP was detected by incubating with mixture of 1 part of 35 mM ammonium molybdate tetrahydrate in 15 mM Zinc acetate hydrate and 4 parts of 10% ascorbic acid (pH 5.0), resulting in phosphomolybdate, which has optical density at 750 nm.

Inhibition of acid secretion in the gastric lumen-perfused rat

Acid secretion in the gastric lumen-perfused rat was measured according to Watanabe et al. [Watanabe K et al., *J. Physiol.* (Paris) 2000; 94: 111-116].

Male Sprague-Dawley rats, 8 weeks old, deprived of food for 18 hours before the experiment with free access to water, were anesthetized with urethane (1.4 g/kg, i.p.) and tracheotomized. After a middle abdominal incision, a dual polyethylene cannula was inserted into the forestomach and the stomach was perfused with saline (37 ^{0}C, pH 5.0) at a rate of 1 ml/min. The acid output in the perfusate was determined at 5 minutes interval by titration with 0.02 M NaOH to pH 5.0. After the determination of basal acid secretion for 30 min, the acid secretion was stimulated by a continuous intravenous infusion of pentagastrin (16 µg/kg/h). The test compounds were administered by an intravenous bolus injection or intraduodenal administration after the stimulated acid secretion reached a plateau phase. The acid secretion was monitored after the administration.

The activity was evaluated either inhibition of total acid secretion from 0 hours to 1.5 or 3.5 hours after administration or the maximum inhibition after administration.

Inhibition of gastric acid secretion in the Heidenhain pouch dog

Male Beagle dogs weighing 7 - 15 kg with Heidenhain pouch [Heidenhain R: *Arch Ges Physiol.* 1879; 19: 148-167] were used. The animals were allowed to recover from surgery for at least three weeks before the experiments. The animals were kept at a 12 hour light-dark rhythm, housed singly. They received standard food once daily at 11:00 a.m. and tap water ad libitum, and were fasted overnight prior to the experiment, with free access to water. Gastric juice samples were collected throughout the experiment by gravity drainage every 15 min. Acidity in the gastric juice was measured by titration to the end point of pH 7.0. Acid secretion was stimulated by a continuous intravenous infusion of histamine (80 µg/kg/h). Oral or intravenous bolus administration of the test compounds was done 90 minutes after commencement of the histamine infusion. The acid secretion was monitored after the administration. The activity was evaluated by the maximum inhibition relative to the corresponding control value.

The compound of Example 3 showed a good inhibitory activity.

Human dofetilide binding

Human ether a-go-go related gene (HERG) transfected HEK293S cells were prepared and grown in-house. Cell paste of HEK-293 cells expressing the HERG product can be suspended in 10-fold volume of 50 mM Tris buffer adjusted at pH 7.5 at 25 ^{0}C with 2 M HCI containing 1 mM $MgCl_2$, 10 mM KCI. The cells were homogenized using a Polytron homogenizer (at the maximum power for 20 seconds) and centrifuged at 48,000 g for 20 minutes at 4°C. The pellet was resuspended, homogenized and centrifuged once more in the same manner. The resultant supernatant was discarded and the final pellet was resuspended (10-fold volume of 50 mM Tris buffer) and homogenized at the maximum power for 20 seconds. The membrane homogenate was aliquoted and stored at -8O^{0}C until use. An aliquot was used for protein concentration determination using a Protein Assay Rapid Kit (wako) and Spectra max plate reader

(Wallac). All the manipulation, stock solution and equipment were kept on ice at all times. For saturation assays, experiments were conducted in a total volume of 200 µl. Saturation was determined by incubating 36 µl of [^{3}H]-dofetilide, and 160 µl of membrane homogenates (20-30 µg protein per well) for 60 minutes at room temperature in the absence or presence of 10 µM dofetilide at final concentrations (4 µl) for total or nonspecific binding, respectively. All incubations were terminated by rapid vacuum filtration over PEI soaked glass fiber filter papers using Skatron cell harvester followed by two washes with 50 mM Tris buffer (pH 7.4 at 25 ^{0}C). Receptor-bound radioactivity was quantified by liquid scintillation counting using Packard LS counter.

For the competition assay, compounds were diluted in 96 well polypropylene plates as 4-point dilutions in semi-log format. All dilutions were performed in DMSO first and then transferred into 50 mM Tris buffer (pH 7.4 at 25 ^{0}C) containing 1 mM $MgCl_2$, 10 mM KCl so that the final DMSO concentration became equal to 1%. Compounds were dispensed in triplicate in assay plates (4 µl). Total binding and nonspecific binding wells were set up in 6 wells as vehicle and 10 µM dofetilide at final concentration, respectively. The radioligand was prepared at 5.6x final concentration and this solution was added to each well (36 µl). The assay was initiated by addition of YSi poly-L-lysine SPA beads (50 µl, 1 mg/well) and membranes (110 µl, 20 µg/well). Incubation was continued for 60 minutes at room temperature. Plates were incubated for a further 3 hours at room temperature for beads to settle. Receptor-bound radioactivity was quantified by counting Wallac MicroBeta plate counter.

Caco-2 permeability

Caco-2 permeability was measured according to the method described in Shiyin Yee, *Pharmaceutical Research,* 763 (1997).

Caco-2 cells were grown on filter supports (Falcon HTS multiwell insert system) for 14 days. Culture medium was removed from both the apical and basolateral compartments and the monolayers were preincubated with pre-warmed 0.3 ml apical buffer and 1.0 ml basolateral buffer for 0.5 hour at 37^{0}C in a shaker water bath at 50 cycles/min. The apical buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM 2-morpholinoethanesulphonic acid (MES) Biological Buffer, 1.25 mM $CaCl_2$ and 0.5 mM $MgCl_2$ (pH 6.5). The basolateral buffer consisted of Hanks Balanced Salt Solution, 25 mM D-glucose monohydrate, 20 mM 2-[4-(2-hydroxyethyl)-1-piperazinyl]ethanesulfonic acid (HEPES) Biological Buffer, 1.25 mM $CaCl_2$ and 0.5 mM $MgCl_2$ (pH 7.4). At the end of the preincubation, the media was removed and test compound solution (10 µM) in buffer was added to the apical compartment. The inserts were moved to wells containing fresh basolateral buffer at 1 hour. Drug concentration in the buffer was measured by LC/MS analysis.

Flux rate (F, mass/time) was calculated from the slope of cumulative appearance of substrate on the receiver side and apparent permeability coefficient (P_{app}) was calculated from the following equation.

P_{app} (cm/sec) = (F x VD) / (SA x MD)

where SA is surface area for transport (0.3 cm^2), VD is the donor volume (0.3ml), MD is the total amount of drug on the donor side at t = 0. All data represent the mean of 2 inserts. Monolayer integrity was determined by Lucifer Yellow transport.

Half-life in human liver microsomes (HLM)

Test compounds (1 µM) were incubated with 3.3 mM $MgCl_2$ and 0.78 mg/mL HLM (HL101) in 100

mM potassium phosphate buffer (pH 7.4) at 37°C on the 96-deep well plate. The reaction mixture was split into two groups, a non-P450 and a P450 group. NADPH was only added to the reaction mixture of the P450 group. An aliquot of samples of P450 group was collected at 0, 10, 30, and 60 minutes time point, where 0 minutes time point indicated the time when NADPH was added into the reaction mixture of P450 group. An aliquot of samples of non-P450 group was collected at -10 and 65 minutes time point. Collected aliquots were extracted with acetonitrile solution containing an internal standard. The precipitated protein was spun down in centrifuge (2000 rpm, 15 min). The compound concentration in supernatant was measured by LC/MS/MS system.

The half-life value was obtained by plotting the natural logarithm of the peak area ratio of compounds/ internal standard versus time. The slope of the line of best fit through the points yields the rate of metabolism (k). This was converted to a half-life value using following equations:

Half-life = In 2 / k

In vitro drug-drug interaction studies for five major CYPs ffDDh

CYP1A2 Test compounds (3 µM) were pre-incubated with recombinant CYP1A2 (Baculosome lot#21198 Invitrogen, 50 pmol P450/ml) in 100 mM K^+Phosphate Buffer (pH 7.4) and 10 µM Vivid blue 1A2 probe (Invitrogen) as a substrate for 5 minutes at 30^{0}C. Reaction was initiated by adding a solution of a warmed NADPH-regenerating system A, which consists of 0.50 mM NADP and 10 mM $MgCl_2$, 6.2 mM DL-Isocitric acid and 0.5U/ml Isocitric Dehydrogenase (ICD). Plates were placed in the plate reader at 30^{0}C and were taken readings every 1.5 minutes, with a 10 second shake in between each reading for 15 cycles. Wavelengths of excitation/emission were 408/465 nm, respectively.

CYP2C9 Test compounds (3 µM) were pre-incubated with recombinant CYP2C9 (Baculosome lot#20967 Invitrogen, 50 pmol P450/ml) in 100 mM K^+Phosphate Buffer (pH 7.4) and 30 µM MFC probe (Gentest) as a substrate for 5 minutes at 37^{0}C. Reaction was initiated by adding a solution of the warmed NADPH-regenerating system A. Plates were placed in the plate reader at 37°C and were taken readings every 2.0 minutes, with a 10 second shake in between each reading for 15 cycles. Wavelengths of excitation /emission were 408 /535 nm, respectively.

CYP2C19 Test compounds (3 µM) were pre-incubated with recombinant CYP2C19 (Baculosome lot#20795 Invitrogen, 5 pmol P450/ml) in 100 mM K^+Phosphate Buffer (pH 7.4) and 10 µM Vivid blue 2C19 probe (Invitrogen) as a substrate for 5 minutes at 37°C. Reaction was initiated by adding a solution of the warmed NADPH-regenerating system A. Plates were placed in the plate reader at 37°C and were taken readings every 1.5 minutes with a 10 second shake in between each reading for 15 cycles. Wavelengths of excitation /emission were 408 /465 nm, respectively.

CYP2D6 Test compounds (3 µM) were pre-incubated with recombinant CYP2D6 (Baculosome lot#21248 invitrogen, 20 pmol P450/ml) in 100 mM K^+Phosphate Buffer (pH 7.4) and 1 µM 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin (AMMC) probe (Gentest) as a substrate for 5 minutes at 37^{0}C. Reaction was initiated by adding a solution of a warmed NADPH-regenerating system B, which consists of 0.03 mM NADP and 10 mM $MgCl_2$, 6.2 mM DL-Isocitric acid and 0.5 U/ml ICD. Plates were placed in the plate reader at 37°C and were taken readings every 2.0 minutes with a 10 second shake in between each reading for 15 cycles. Wavelengths of excitation /emission were 400 /465 nm, respectively.

CYP3A4 Test compounds (3 µM) were pre-incubated with recombinant CYP3A4 (Baculosome

lot#20814 Invitrogen, 5 pmoi P450/ml) in 100 mM K^+Phosphate Buffer (pH 7.4) and 2 µM Vivid Red probe (Invitrogen) as a substrate for 5 minutes at 30°C. Reaction was initiated by adding a solution of the warmed NADPH-regenerating system A. Plates were placed in the plate reader at 30°C and were taken readings minimum intervals with a 10 second shake in between each reading for 15 cycles. Wavelengths of excitation /emission were 530 /595 nm, respectively.

Drug-drug interaction was. evaluated by the rate of metabolite formation calculated with a slope (Time vs. Fluorescence units) in the linear region .or the percentage of inhibition by test compounds calculated by the following equation.

Inhibition % = $\{(v_0 - Vi)/v_0\}$x100, wherein V_0 is a rate of control reaction (no test compounds) and v_I is a rate of reaction in the presence of test compound.

I_{hERG} assay

Human ether a-go-go related gene (HERG) transfected HEK293 cells are prepared and cultured in-house. The methodology for stable transfection of this channel in HEK cells can be found elsewhere (Z.Zhou et al., 1998, *Biophysical journal,* 74, 230-241). On the day of experimentation, the cells are harvested from culture flasks and stored as cell suspension in a standard external solution (see below of its composition), in the room atmosphere of 23°C. Cells are studied between 0.5-5 hours after harvest.

HERG currents are studied using a standard patch clamp technique of the whole-cell mode. During the experiment, the cells are superfused with a standard external solution of the following composition;(mM) NaCl, 130; KCl, 4; $CaCl_2$, 2; $MgCl_2$, 1; Glucose, 10; HEPES, 5; pH 7.4 with NaOH. Whole-cell recordings is made using a patch clamp amplifier and patch pipettes which have a resistance of 1-3M0hm when filled with the standard internal solution of the following composition; (mM); KCI, 130; MgATP, 5; $MgCl_2$, 1; HEPES, 10; EGTA 5, pH 7.2 with KOH. Only those cells with access resistances below 10 MOhm and seal resistances over 1GOhm are accepted for further experimentation. Series resistance compensation is applied up to a maximum of 80% without any leak subtraction. Following the achievement of whole cell configuration and sufficient time for cell dialysis with pipette solution (>5 min), the membrane Is depolarized from a holding potential of - 80 mV to + 3OmV for 1000 ms followed by a descending voltage ramp (rate 0.5 mV $msec^{-1}$) back to the holding potential. This depolarization and ramp is applied to the cells continuously every 4 seconds (0.25 Hz). The amplitude of the peak current elicited around -40 mV during the ramp is measured. Once stable evoked current responses of minimal changes in the amplitude are obtained in the external solution, the test compound is applied for 10-20 minutes with multiple dosing in a single cell. The cells are also exposed to high dose of dofetilide (5 µM), a specific IKr blocker, to evaluate the insensitive endogenous current.

All experiments are performed at 23+/-1°C. Evoked membrane currents are recorded online on a computer, filtered at 500-1000 Hz (Bessei -3dB) and sampled at 1-2 KHz. Osmolarity and pH change induced by the test compound in external solution will be examined at the highest concentration.

The arithmetic mean of these ten values of peak current is calculated under control conditions and in the presence of drug. Percent decrease of I_N in each experiment is obtained by the normalized current value using the following formula: $I_N = (I_C - I_D)/(I_C - I_{dof})$x100, where I_c is the mean current value under control conditions, I_D is the mean current value in the presence of test compound and I_{dof} is the mean current value in dofetilide application. Separate experiments are performed and pooled data of

arithmetic mean from each experiment is defined as the result of the study.

Bioavailability in rat

Adult rats of the Sprague-Dawley strain were used. One to two days prior to the experiments all rats were prepared by cannulation of the right jugular vein under anesthesia. The cannula was exteriorized at the nape of the neck. Blood samples (0.2-0.3 mL) were drawn from the jugular vein at intervals up to 24 hours after intravenous or oral administrations of the test compound. The samples were frozen until analysis. Bioavailability was assessed by calculating the quotient between the area under plasma concentration curve (AUC) following oral administration or intravenous administration.

Bioavailability in dog

Adult Beagle dogs were used. Blood samples (0.2-0.5 mL) were drawn from the cephalic vein at intervals up to 24 hours after intravenous or oral administrations of the test compound. The samples were frozen until analysis. Bioavailability was assessed by calculating the quotient between the area under plasma concentration curve (AUC) following oral administration or intravenous administration.

Plasma protein binding

Plasma protein binding of the test compound (1 μM) was measured by the method of equilibrium dialysis using 96-well plate type equipment. Spectra-Por®, regenerated cellulose membranes (molecular weight cut-off 12,000-14,000, 22 mm x 120 mm) were soaked for over night in distilled water, then for 20 minutes in 30% ethanol, and finally for 15 minutes in dialysis buffer (Dulbecco's phosphate buffered saline, pH7.4). Frozen plasma of human, Sprague-Dawley rats, and Beagle dogs were used. The dialysis equipment was assembled and added 150 μL of compound-fortified plasma to one side of each well and 150 μL of dialysis buffer to the other side of each well. After 4 hours incubation at 37^0C for 150 r.p.m, aliquots of plasma and buffer were sampled. The compound in plasma and buffer were extracted with 300 μL of acetonitrile containing internal standard compounds for analysis. The concentration of the compound was determined with LC/MS/MS analysis.

The fraction of the compound unbound was calculated by the following equation:

$fu = H\ ([plasma]_{eq} - [buffer]_{eq}) / ([plasma]_{eq})\}$

wherein $[plasma]_{eq}$ and $[buffer]_{eq}$ are the concentrations of the compound in plasma and buffer, respectively.

Aqueous solubility

Aqueous solubility in the mediums (a)-(c) was determined by following method:

Whatman mini-UniPrep chambers (Clifton, NJ, USA) containing more than 0.5 mg of compound and 0.5 mL of each medium were shaken overnight (over 8 hours) at room temperature. All samples were filtered through a 0.45 μm Polyvinylidene Difluoride (PVDF) membrane into the Whatman mini-UniPrep plunger before analysis. The filtrates were assayed by HPLC.

<medium>(a) Simulated gastric fluid with no enzyme (SGN) at pH 1.2: Dissolve 2.0 g of NaCl in 7.0 mL of 10 M HCl and sufficient water to make 1000 mL; (b) Phosphate buffer saline (PBS) at pH 6.5: Dissolve 6.35 g of KH_2PO_4, 2.84 g of Na_2HPO_4 and 5.50 g of NaCl in sufficient water to make 1000 mL, adjusting

the pH to 6.5; (c) 3.94 mg of sodium taurocholate (NaTC) and 1.06 mg of i-palmitoyl-2-oleyl-L-phosphatidylcholine (POPC) in 1 **mL** of PBS (pH 6.5).

Estimation of hepatic clearance using the metabolic stability in human hepatocytes

Tested compounds (1 µM) were incubated statically with hepatocytes from human at 37 °C in a 95 % air/ 5 % CO_2 with target cell density of 0.5 x 10^6 cells/ml and a total volume of 50 µl. Incubation was stopped at each time point by the addition of ice-cold acetonitrile (ACN). Aliquots of samples were mixed with 10 % ACN containing an internal standard for LC/MS/MS analysis. After samples were sonicated for 10 minutes, samples were centrifuged at 2,000 rpm for 15 minutes, and then the supernatant was transferred to the other plates for analysis. The compound concentrations in supernatant were measured by LC/MS/MS system.

The disappearance rates of tested compounds were obtained by plotting the common logarithm of the peak area ratio of compounds / internal standard versus time. The slope of the line of best fit through the points yielded the rate of metabolism (k_β). This value was scaled to take hepatocellularity, liver and body weight into-account to give an intrinsic clearance value (CLi_nO in ml/min/kg as illustrated in Equation 1. Hepatic clearance (CL_h) was predicted from this intrinsic clearance value using the parallel tube model as shown in Equation 2. The predicted clearance divided by the hepatic blood flow (Q_h) afforded the extraction ratio (E_h) (Equation 3).

Equation 1: k_ε x (g liver/kg body weight)x(ml incubation/ number of cells in incubation)x(cells/g liver)

Equation 2: $CL_h = Q_h \times \{ 1 - \exp(-CL_{int} / Q_h) \}$

Equation 3: $E_h = CL_h / Q_h$

Wherein, "gliver weight /kg body weight" is 21, "Cells / g liver" is 1.2 x 10^8, "ml incubation/ number of cells in incubation" is 2.0 x 10^{-6}, and Q_h is 20 ml/min/kg.

Supposing that hepatic metabolism is the main route of drug elimination, systemic exposure ($AUCp_0$) after oral administration is calculated using Equation 4.

Equation 4 $AUC_{po} = \text{Dose} \times (1-E_h) / CL_h$

Method for assaying the compounds phototoxic potential:

The phototoxic potential was measured in the strict accordance with method described in the OECD Guidelines for the Testing of Chemicals 432 (2002). Chlorpromazine (CPZ) and Sodium n-Dodecyl Sulfate (SDS) were used as positive and negative controls, respectively.

Balb/3T3, clone 31 'cells (ATCC, CCL-163) were seeded into 96-wells plates (Nunc, 167008) at a density of 1x104 cells/well. Cells were incubated under a standard condition (37°C, a humidified atmosphere of 95% air and 5% CO2) within the culture medium-DMEM (GIBCO; cat#11885-084) for 24 hour. Following the incubation, the culture medium-DMEM was discarded and the cells were washed carefully with 150 µl of Earle's Balanced Salt Solution (EBSS; Sigma, Cat#E3024), then added 100 µl solution of the test compound in EBSS or solvent control (EBSS contained 1% dimethylsulphoxide or 1% ethanol). The plate was prepared in duplicate. All the plates were incubated under the standard condition

for 60 min in the dark. One of the duplicated plates was used for determination of cytotoxicity (-Irr) and kept at room temperature in the dark for 50 min. For the determination of photocytotoxicity (+Irr), another one was exposed to the sun simulator (UVA irradiance: 1.7mW/cm2; SOL500, Dr. Honle UV Technology, Germany) for 50 min (UVA dose = 5 joules / cm2). Then the solutions were discarded from the two plates and immediately washed with 150 µl of EBSS with care. The cells were further incubated with 150 µl / well of DMED medium for 18 - 22 hr.

After the incubation, the culture medium was discarded, the cells were washed carefully with 150 µl of EBSS and then immediately incubated with 100 µl/well of a 50 µg/ml of neutral red (NR) (3-amino-7-dimethylamino-2-methylphenazine hydrochloride, Kanto Chemical Co., Inc., Japan) in DMEM without serum for 3 hour under the standard condition. After incorporation of neutral red into the cell lysosomes, the NR-DMED medium was discarded and the cells were washed carefully with 150 µl of EBSS. The exact 150 µl of ethanol/acetic acid/water (50:1:49) was added to each well of plate and the extraction was performed for 10 minutes by gently shaking at room temperature. Then optical density (OD) of the NR extract was measured at 540 nm using a spectrophotometer (Plate-reader, POLARstar OPTIMA; BMG Labtechnologies, Germany). The OD values were used to calculate the mean photo effect (MPE) value using OECD provided software "3T3 NRU Phototox". (Version 2.0, Federal Institute for Risk Assessment, Germany). The results for the control (CPZ and SDS) were used for the quality assurance of the assay.

MPE value < 0.1 was evaluated as "no-phototoxicity"; MPE value ≥ 0.1 and < 0.15 was evaluated as "probable phototoxicity" and MPE value ≥ 0.15 was evaluated as "phototoxicity".

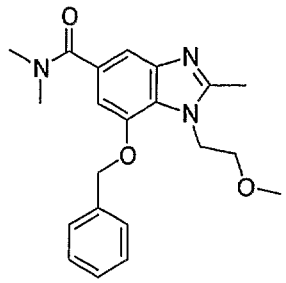
Examples

The following examples are provided for the purpose of further illustration only and are not intended to be limitations on the disclosed invention. Unless stated on otherwise in the following examples, general experimental conditions are as follows: all operations were carried out at room or ambient temperature, that is, in the range of 18-25 ^{0}C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60 ^{0}C; reactions were monitored by thin layer chromatography (TLC) and reaction times are given for illustration only; melting points (mp) given are uncorrected (polymorphism may result in different melting points); the structure and purity of all isolated compounds were assured by at least one of the following techniques: TLC (Merck silica gel 60 F254 precoated TLC plates or Merck NH_2 gel (an amine coated silica gel) F_{254S} precoated TLC plates), mass spectrometry, nuclear magnetic resonance spectra (NMR), infrared absorption spectra (IR) or microanalysis. Yields are given for illustrative purposes only. Flash column chromatography was carried out using Biotage KP-SIL (40-63 µm), Biotage KP-NH (an amine coated silica gel) (40-75 µM) or Wako silica gel 300HG (40-60 µM). Microwave reactions were carried out using Personal Chemistry Emrys™ Optimizer or Biotage Initiator™. Preparative TLC was carried out using Merck silica gel 60 F_{254} precoated TLC plates (0.5 or 1.0 mm thickness). All Mass data was obtained in Low-resolution mass spectral data (ESI) using ZMD™ or ZQ™ (Waters) and mass spectrometer. NMR data were determined at 270 MHz (JEOL JNM-LA 270 spectrometer) or 300 MHz (JEOL JNM-LA300 spectrometer) using deuterated chloroform (99.8%) or dimethyl sulfoxide (99.9%) as solvent unless indicated otherwise, relative to tetramethyisilane (TMS) as internal standard in parts per million (ppm); conventional

abbreviations used are: s = singlet, d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, br. s = broad singlet, etc. IR spectra were measured by a Fourier transform infrared spectrophotometer (Shimazu FTIR-8300).

Example 1

7-(Benzyloxy)-1-[2-methoxyethyl]-N,2-dimethyl-1H-benzimidazole-5-carboxamide



STEP 1: N-[2-(Benzyloxy)-4-bromo-6-nitrophenyl]acetamide

To a solution of 2-(benzyloxy)-4-bromo-6-nitroaniline (33.0 g, 102 mmol, WO 2004054984) and acetic anhydride (14.5 mL, 153 mmol) in acetic acid (90 mL) was added concentrated sulfuric acid (2 drops) at 70°C. The mixture was stirred at 70°C for 20 minutes. After cooling to room temperature, water (800 mL) was added, and the formed precipitate was collected by filtration, and washed with diisopropyl ether to afford the title compound as a brown solid (30.9 g, 83%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.69 (d, J = 2.0 Hz, 1H), 7.56 (br.s, 1H), 7.47-7.38 (m, 5H), 7.34 (d, J = 2.0 Hz, 1H), 5.14 (s, 2H), 2.16 (s, 3H) ppm.

MS (ESI) m/z: 365 $(M+H)^+$.

STEP 2: N-[2-(Benzyloxy)-4-bromo-6-nitrophenyl]-N-(2-methoxyethyl)acetamide

To a suspension of sodium hydride (60% dispersion in mineral oil, 1.78 g, 44.5 mmol) in N,N-dimethylformamide (100 mL) was added dropwise a solution of N-[2-(benzyloxy)-4-bromo-6-nitrophenyl]acetamide (13.5 g, 37.1 mmol, Step 1) in N,N-dimethylformamide at 0°C over 10 minutes. After stirring at 0°C for 20 minutes, 1-bromo-2-methoxyethane (7.21 g, 51.9 mmol) was added, and the mixture was stirred at 50°C for 2 hours. After cooling to room temperature, the mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate/toluene (3:1). The combined organic layer was dried over magnesium sulfate and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (3:1) to afford the title compound as a gray solid (12.1 g, 77%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.70 (d, J = 2.6 Hz, 1H), 7.45-7.32 (m, 6H), 5.22-5.10 (m, 2H), 4.23-4.13 (m, 1H), 3.51-3.34 (m, 2H), 3.24-3.13 (m, 1H), 3.09 (s, 3H), 1.89 (s, 3H) ppm. (Signals of other rotamers were also observed)

MS (ESI) m/z: 423 $(M+H)^+$.

STEP 3: 7-(Benzyloxy)-5-bromo-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole

A mixture of N-[2-(benzyloxy)-4-bromo-6-nitrophenyl]-N-(2-methoxyethyl)acetamide (11.7 g, 27.7 mmol, Step 2) and iron powder (7.74 g, 139 mmol) in acetic acid (150 mL) was refluxed with stirring for 5 hours. After cooling to room temperature, the mixture was filtered through a pad of Celite, and the filtrate

was concentrated *in vacuo.* The residue was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 2:1 to 1:1) to afford the title compound as a pale green solid (9.74 g, 93%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.47-7.37 (m, 6H), 6.89 (d, J = 1.3 Hz, 1H), 5.14 (s, 2H), 4.39 (t, J = 5.3 Hz, 2H), 3.57 (t, J = 5.3 Hz, 2H), 3.16 (s, 3H), 2.57 (s, 3H) ppm.

STEP4: 7-(Benzyloxy)-1-(2-methoxyethyl)-2-methyl-W-benzimidazole-5-carbonitrile

A mixture of 7-(benzyloxy)-5-bromo-1 -(2-methoxyethyl)-2-methyl-1 H-benzimidazole (1.0O g, 2.66 mmol, Step 3), zinc cyanide (376 mg, 3.20 mmol), and tetrakis(triphenylphosphine)palladium (154 mg, 0.13 mmol) in *Λ,Λ*-dimethylformamide (15 ml_) was stirred at 90°C for 3 hours under nitrogen gas. After cooling to room temperature, the mixture was poured onto saturated potassium carbonate aqueous solution (100 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, and concentrated *in vacuo.* The residual solid was washed with ethyl acetate/diisopropyl ether (1:2) to afford the title compound as a white solid (648 mg, 76%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.67 (br.s, 1H), 7.45-7.38 (m, 5H), 6.96 (br.s, 1H), 5.19 (s, 2H), 4.45 (t, J = 5.3 Hz, 2H), 3.60 (t, J = 4.6 Hz, 2H), 3.19 (s, 3H), 2.61 (s, 3H) ppm.

MS (ESI) m/z: 322 $(M+H)^+$.

STEP 5: 7-(Benzyloxy)-1-(2-methoxyethyl)-2-methyl-1/-/-benzimidazole-5-carboxylic acid

A solution of 7-(benzyloxy)-1-(2-methoxyethyl)-2-methyl-1W-benzimidazole-5-carbonitrile (549 mg, 1.71 mmol, Step 4) and potassium hydroxide (85%, 564 mg, 8.54 mmol) in ethylene glycol (10 mL) was stirred at 135°C for 5 hours. After cooling to room temperature, 2 mol/L hydrochloric acid was added until pH of the solution became about 3. The formed precipitate was collected by filtration to afford the title compound as a gray solid (530 mg, 91%).

^{1}H NMR (DMSO-Qf_6, 270 MHz) δ: 7.77 (br.s, 1H), 7.56-7.49 (m, 2H) $_1$7.47-7.33 (m, 4H), 5.30 (s, 2H), 4.47 (t, J = 5.3 Hz, 2H), 3.60 (t, J = 5.3 Hz, 2H), 3.17 (s, 3H), 2.52 (s, 3H) ppm. (COOH was not observed)

MS (ESI) m/z: 341 $(M+H)^+$, 339 $(M-H)^-$.

STEP 6: 7-(Benzyloxy)-1-(2-methoxyethyl)- *Λ,Λ*,2-trimethyl-W-benzimidazole-5-carboxamide

A mixture of 7-(benzyloxy)-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carboxylic acid (520 mg, 1.53 mmol, Step 5), dimethylamine hydrochloride (374 mg, 4.58 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (498 mg, 2.60 mmol), 1-hydroxybenzotriazoie hydrate (413 mg, 3.06 mmol), and triethylamine (0.64 mL, 4.58 mmol) in *Λ,Λ*-dimethylformamide (10 mL) was stirred at room temperature for 1 day. The mixture was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol (10:1) to afford the title compound as a white solid (524 mg, 93%).

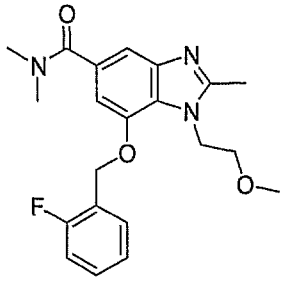
^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46-7.33 (m, 6H), 6.94 (br.s, 1H), 5.20 (s, 2H), 4.44 (t, J = 5.3 Hz, 2H), 3.61

(t, J = 5.3 **Hz, 2H),** 3.17 **(s, 3H),** 3.09 (br.s, **6H),** 2.59 **(s, 3H)** ppm.

MS (ESI) m/z: 368 **$(M+H)^+$.**

Example 2

7-r(2-Fluorobenzvπoxy1-1-(2-methoxyethyl)-W.A/.2-trimethyl-1/y-benzimidazole-5-carboxamide



Step 1: 7-Hvdroxy-1 -(2-methoxyethyl)- *Ν,Ν*,2-trimethyl-1 /-/-benzimidazole-5-carboxamide

A mixture of 7-(benzyloxy)-1-(2-methoxyethyl)- *Ν,Ν*,2-trimethyl-1H-benzimidazole-5-carboxamide (483 mg, 1.31 mmol, Step 6 of Example 1) and 10% palladium-carbon (50 mg) in ethanol (30 mL) was stirred under hydrogen gas for 19 hours. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford the title compound as a white solid (347 mg, 95%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.57 (br.s, 1H), 7.14 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 4.43 (t, J = 5.1 $Hz_1$2H), 3.64 (t, J = 5.1 Hz, 2H), 3.20 (s, 3H), 3.15 (bts, 3H), 3.05 (br.s, 3H), 2.53 (s, 3H) ppm.

MS (ESI) m/z: 278 $(M+H)^+$.

STEP 2: 7-r(2-Fluorobenzyl)oxyl-1-(2-methoxyethyl)- *Ν,Ν*,2-trimethyl-1H-benzimidazole-5-carboxamide

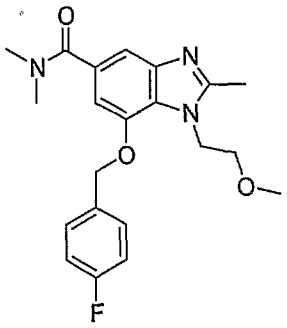
To a solution of 7-hydroxy-1-(2-methoxyethyl)- *Ν,Ν*,2-trimethyl-1H-benzimidazole-5-carboxamide (50 mg, 0.18 mmol, Step 1) in *Ν,Ν*-dimethylformamide (1 mL) was added sodium hydride (60% dispersion in mineral oil, 11 mg, 0.27 mmol) at 0°C. After stirring for 10 minutes at 0°C, 1-(bromomethyl)-2-fluorobenzene (57 mg, 0.36 mmol) was added, and the mixture was stirred at 0°C for 1 hour. Then, the mixture was poured onto brine, and the aqueous layer was extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol (10:1) to afford the title compound as a white solid (53 mg, 76%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.50-7.35 (m, 2H)$_1$7.35 (br.s, 1H)$_1$7.25-7.07 (m, 2H), 6.97 (br.s, 1H), 5.26 (s, 2H), 4.41 (t, J = 5.1 Hz, 2H), 3.60 (t, J = 5.1 Hz, 2H), 3.17 (s, 3H), 3.10 (br.s, 6H), 2.59 (s, 3H) ppm.

MS (ESI) m/z: 386 $(M+H)^+$.

Example 3

7-r(4-Fluorobenzyl)oxy1-1-(2-methoxyethvπ-Ν,/V,2-trimethyl-1H-benzimidazole-5-carboxamide



STEP 1: 4-Bromo-2-r(4-fluorobenzyl)oxy1-6-nitroaniline

A mixture of 2-amino-3-nitrophenol (25.4 g, 165 mmol), 1-(chloromethyl)-4-fluorobenzene (28.6 g, 198 mmol), potassium carbonate (27.3 g, 198 mmol), and sodium iodide (987 mg, 6.59 mmol) in ethanol (250 ml.) was stirred at 80^{0}C for 3 hours. After cooling to room temperature, the solvent was removed *in vacuo.* The residue was poured onto water, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over magnesium sulfate, and concentrated *in vacuo.* The residue was dissolved in acetonitrile, and *N*-bromosuccinimide (32.3 g, 182 mmol) was added to the solution. This solution was refluxed with stirring for 1.5 hours. After cooling to room temperature, silica gel was added to the reaction mixture, and the solvent was removed *in vacuo.* The residue was purified by column chromatography on silica gel eluting hexane/ethyl acetate (4:1) to afford the title compound as a orange solid (39.4 g, 70%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.94 (d, J = 2.0 Hz, 1H), 7.41 (dd, J = 8.6, 5.3 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 7.04 (d, J = 2.0 Hz, 1H), 6.44 (br.s, 2H), 5.07 (s, 2H) ppm.

MS (ESI) m/z: 339 $(M-H)^-$.

STEP 2: *N*-(4-Bromo-2-f(4-fluorobenzyl)oxy1-6-nitrophenyl)acetamide

The title compound was prepared as a white solid in 94% yield from 4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitroaniline (39.4 g, Step 1) by the same manner in Step 1 of Example 1.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.71 (d, J = 2.2 Hz, IH), 7.59 (br.s, 1H), 7.43-7.38 (m, 2H), 7.34 (d, 2.2 Hz, 1H), 7.12 (t, J = 8.8 Hz, 1H), 5.10 (s, 2H), 2.16 (s, 3H) ppm. (NH was not observed)

STEP 3: *N*-{4-Bromo-2-r(4-fluorobenzyl)oxy1-6-nitrophenyl>- *N*-(2-methoxyethyl)acetamide

The title compound was prepared as a brown oil in 86% yield (5.97 g) from *N*-{4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}acetamide (6.00 g, Step 2) and by the same manner in Step 2 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.73 (d, J = 2.0 Hz_1 1H), 7.39 (d, J = 2.6 Hz, 1H), 7.34 (dd, J = 8.6, 5.3 Hz, 2H), 7.11 (t, J = 8.6 Hz, 2H), 5.14 (d, J = 11.9 Hz, 1H), 5.08 (d, J = 12.5 Hz, 1H), 4.23-4.07 (m, 2H), 3.50-3.32 (m, 2H), 3.09 (s, 3H), 1.88 (s, 3H) ppm. (Signals of other rotamers were also observed)

MS (ESI) m/z: 441 $(M+H)^+$.

STEP 4: 5-Bromo-7-f(4-fluorobenzyl)oxyl-1-(2-methoxyethyl)-2-methyl-1 /-/-benzimidazole

The title compound was prepared as a white solid in 88% yield (4.70 g) from *N*-{4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}- *N*-(2-methoxyethyl)acetamide (5.97 g, Step 3) by the same manner in Step 3 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46 (d, J = 1.3 Hz, 1H), 7.41 (dd, J = 8.6, 5.3 Hz, 2H), 7.12 (t, J = 9.2 Hz, 2H), 6.87 (d, J = 2.0 Hz, 1H), 5.10 (s, 2H), 4.37 (t, J = 5.3 Hz, 2H), 3.55 (t, J = 5.3 Hz, 2H), 3.17 (s, 3H), 2.56 (s, 3H) ppm.

MS (ESI) m/z: 393 $(M+H)^+$.

STEP 5: 7-f(4-Fluorobenzyl)oxy 'l-1 -(2-methoxyethyl)-2-methyl-1 H-benzimidazole-5-carbonitrile

The title compound was prepared as a white solid in 81% yield (2.54 g) from 5-bromo-7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1W-benzimidazole (3.64 g, Step 4) by the same manner in Step 4 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.68 (d, J = 1.3 Hz, 1H), 7.42 (dd, J = 9.2, 5.3 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 6.95 (d, J=1.3 Hz, 1H), 5.15 (s, 2H), 4.43 (t, J = 5.3 Hz, 2H), 3.57 (t, J=5.3 Hz, 2H), 3.19 (s, 3H), 2.61 (s, 3H) ppm.

MS (ESI) m/z: 340 $(M+H)^+$.

STEP 6: 7-f(4-Fluorobenzyl)oxy1-1-(2-methoxyethyl)-2-methyl-1H-benzirnidazole-5-carboxylic acid

The title compound was prepared as a white solid in 97% yield (2.59 g) from 7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carbonitrile (2.53 g, Step 5) by the same manner in Step 5 of Example 1.

^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.78 (s, 1H), 7.60 (dd, J = 9.3, 4.7 Hz, 2H), 7.42 (s, 1H), 7.27 (t, J = 9.3 Hz, 2H), 5.28 (s, 2H), 4.45 (t, J = 4.1 Hz, 2H), 3.9 (dd, J = 3.5 Hz, 2H), 3.14 (s, 3H), 2.52 (s, 3H) ppm. (COOH was not observed)

MS (ESI) m/z: 359 $(M+H)^+$, 357 $(M-H)^-$.

STEP 7: 7-f(4-Fluorobenzyl)oxyl-1 -(2-methoxyethyl)-*N*,*N*,2-trimethyl-1 f/-benzimidazole-5-carboxamide

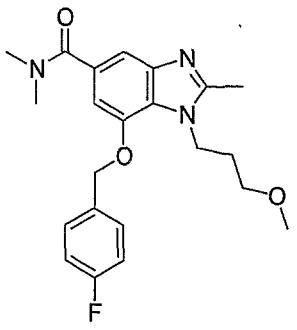
The title compound was prepared as a white solid in 72% yield (1.00 g) from 7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1H-benzimidazoIe-5-carboxylic acid (1.30 g, Step 6) by the same manner in Step 6 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.45-7.33 (m, 2H), 7.35 (s, 1H), 7.16-7.06 (m, 2H), 6.93 (s, 1H), 5.16 (s, 2H), 4.42 (t, J = 5.3 Hz, 2H), 3.58 (t, J = 5.3 Hz, 2H), 3.18 (s, 3H), 3.10 (br.s, 6H), 2.59 (s, 3H) ppm.

MS (ESI) m/z: 386 $(M+H)^+$.

Example 4

7-r(4-FluorobenzvHoxv1-1-(3-methoxvpropvl)-MAf,2-trimethvl-1A/-benzimidazole-5-carboxamide



STEP 1: *N*-(4-Bromo-2-r(4-fluorobenzyl)oxy1-6-nitrophenyl>- *N*-f3-methoxypropy l)acetamide

The title compound was prepared as an orange oil in 84% yield (2.00 g) from *N*-{4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}acetamide (2.00 g, Step 2 of Example 3) and 1-bromo-3-methoxypropane (1.68 g, *HeIv. Chim. Acta,* **1980,** *63,* 2152-2158.) by the same manner in Step 2 of Example 1.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.64 (d, J = 2.2 Hz, 1H), 7.42 (d, J = 2.2 Hz, 1H), 7.35 (dd, J = 8.8, 5.9 Hz, 2H), 7.11 (t, J = 8.8 Hz, 2H), 5.15-5.08 (m, 2H), 3.66-3.46 (m, 2H), 3.33-3.26 (m, 2H), 3.22 (s, 3H), 1.85 (s, 3H), 1.72-1.62 (m, 2H) ppm. (Signals of other rotamers were also observed)

STEP 2: 5-Bromo-7-r(4-fluorobenzyl)oxy1-1 -(3-methoxyproPVI)-2-methyl-1 rt-benzimidazole

The title compound was prepared as a white solid in 81% yield (1.44 g) from *N*-{4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}- *N*-(3-methoxypropyl)acetamide (1.82 g, Step 1) by the same manner in Step 3 of Example 1.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.45 (d, J = 1.5 Hz, 1H), 7.46-7.41 (m, 2H), 7.12 (t, J = 8.8 Hz, 2H), 6.87 (d, J = 1.5 Hz, 1H), 5.10 (s, 2H>, 4.28 (t, J = 6.6 Hz, 2H), 3.24 (s, 3H), 3.11 (t, J = 5.1 Hz, 2H), 2.54 (s, 3H), 1.97-1.89 (m, 2H) ppm.

STEP 3: 7-r(4-Fluorobenzyl)oxy1-1-(3-methoxypropylV *N*.*N*.2-trimethyl-1/-/-benzimidazole-5-carboxamide

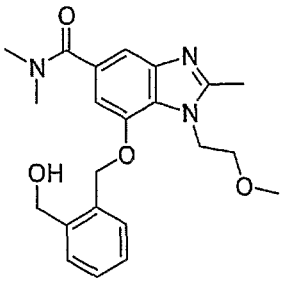
A mixture of 5-bromo-7-[(4-fluorobenzyl)oxy]-1-(3-methoxypropyl)-2-methyl-1H-benzimidazole (804 mg, 1.97 mmol, Step 2), palladium acetate (133 mg, 0.59 mmol), and triphenylphosphine (518 mg, 1.97 mmol) in dimethylamine tetrahydrofuran solution (2 mol/L, 20 mL) was stirred at 85°C for 12 hours under carbon monoxide gas (1 atm). After cooling to room temperature, the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol (gradient elution from dichloromethane only to 50:1) to afford a partially purified fraction, which was purified by column chromatography on silica gel eluting with ethyl acetate to give the title compound (122 mg, 16%) as a white solid.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.44 (dd, J = 8.6, 5.3 Hz, 2H), 7.34 (s, 1H), 7.11 (t, J = 8.6 Hz, 2H), 6.92 (s, 1H), 5.15 (s, 2H), 4.32 (t, J = 6.6 Hz, 2H), 3.24 (s, 3H), 3.17-3.05 (m, 8H), 2.57 (s, 3H), 2.01-1.91 (m, 2H) ppm.

MS (ESI) m/z: 400 $(M+H)^+$.

Example 5

7-fr2-(Hvdroxymethyl)benzvnoxy>-1-(2-methoxyethv π-*N*,*N*.2-tritnethyl-1H-benzimidazole-5-carboxamide



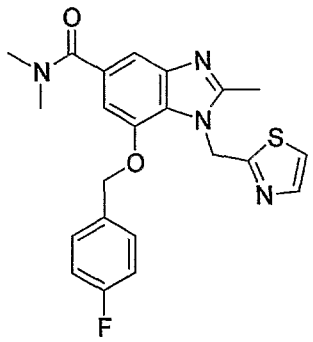
The title compound was prepared as a white solid in 44% yield (63 mg) from 7-hydroxy-1-(2-methoxyethyl)- *N,N*,2-trimethyl-1H-benzimidazole-5-carboxamide (100 mg, Step 1 of Example 2) and [2-(bromomethyl)phenyl]methanol (94 mg, *Synthesis,* **1982,** 1014.) by the same manner in Step 2 of Example 2.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.52-7.33 (m, 4H), 7.31 (br.s, 1H), 6.96 (br.s, 1H) 5.30 (s, 2H), 4.82 (s, 2H), 4.36 (t, J = 5.3 Hz, 2H), 3.52 (t, J = 5.3 Hz, 2H), 3.12 (s, 3H), 3.10 (br.s, 6H), 2.56 (s, 3H) ppm. (OH was not observed)

MS (ESI) m/z: 398 $(M+H)^+$.

Example 6

y-^-Fluorobenzv l)oxvi-JV.*N*.2-trimethvl-i-d.S-thiazol- 2-vlmethvD-lH-benzimidazole- β-carboxamide



STEP 1: N-(4-Cvano-2-K4-fluorobenzyl)oxy1-6-nitrophenyl}acetamide

A mixture of *N*-{4-bromo-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}acetamide (15.0 g, 39.2 mmol, Step 2 of Example 3), zinc cyanide (5.52 g, 47.0 mmol), and tetrakis(triphenylphosphine)palladium (4.52 mg, 1.96 mmol) in *N,N*-dimethylformamide (90 mL) was stirred at 17O^{0}C for 20 minutes under microwave irradiation. After cooling to room temperature, the mixture was poured onto saturated aqueous potassium carbonate solution (150 mL), and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, and concentrated *in vacuo.* To the residual solid was added toluene and the mixture was concentrated. The residue was suspended in diisopropyl ether and the precipitate was collected by filtration to afford the title compound (12.8 g, quant.).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.87 (d, J = 2.0 Hz, 1H), 7.43-7.38 (m, 2H), 7.38 (s, 1H), 7.14 (t, J = 8.6 Hz, 2H), 5.17 (S, 2H), 2.20 (s, 3H) ppm. (NH was not observed)

STEP 2: 7-IT4-Fluorobenzyl)oxyl-2-methyl-1rt-benzimidazole-5-carbonitrile

The title compound was prepared as a gray solid in quantitative yield (11.0 g) from *N*-{4-cyano-2-[(4-fluorobenzyl)oxy]-6-nitrophenyl}acetamide (12.8 g, Step 1) by the same manner in Step 3

of Example 1.

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.60 (s, 1H), 7.44 (dd, J = 8.8, 5.9 Hz, 2H), 7.09 (t, J = 8.8 Hz, 2H), 6.95 (s, 1H)$_1$5.19 (s, 2H), 2.64 (s, 3H) ppm. (NH was not observed)

STEP 3: 7-f(4-Fluorobenzv πoxy1-2-methyl-1H-benzinnidazole-5-carboxylic acid

The title compound was prepared as a gray solid in 86% yield (10.1 g) from 7-[(4-fluorobenzyl)oxy]-2-methyl-1H-ben ∑midazole-5-carbonitrile (11.0 g, Step 2) by the same manner in Step 5 of Example 1.

^{1}H NMR (DMSO-d_6, 300 MHz) δ: 7.79 (s, 1H), 7.62 (dd, J = 8.8, 5.9 Hz, 2H)$_1$7.44 (s, 1H), 7.26 (t, J = 8.8 Hz$_1$2H), 5.34 (s, 2H), 2.57 (s, 3H) ppm. (COOH and NH were not observed)

STEP 4: 7-r(4-Fluorobenzv πoxy1-*N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide

A mixture of 7-[(4-fluorobenzyl)oxy]-2-methyl-1H-benzimidazole-5-carboxylic acid (10.1 g, 33.6 mmol, Step 3), dimethylamine hydrochloride (13.8 g, 168 mmol), O-benzotriazol-1-y!- *N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (19.2 g, 50.4 mmol), and triethylamine (47.0 mL, 336 mmol) in *N*,*N*-dimethylformamide (200 mL) was stirred at room temperature for 1 hour. The mixture was poured onto aqueous ammonium chloride solution, and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over magnesium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with dichloromethane/methanol (gradient elution from 50:1 to 20:1) to afford the title compound as a white solid (8.80 g, 80%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.39 (dd, J = 8.8, 5.9 Hz, 2H)$_1$7.19 (s, 1H), 7.01 (t, J = 8.8 Hz, 2H), 6.76 (s, 1H), 5.15 (s, 2H), 3.20-2.85 (m, 6H)$_1$2.51 (s, 3H) ppm. (NH was not observed)

MS (ESI) m/z: 328 $(M+H)^+$.

STEP 5': 7-r(4-Fluorobenzyl)oxyl- *N*,*N*,2-trimethyl-1-(1,3-thiazol-2-ylmethyl)-1 H-benzimidazole- 5-carboxamide

STEP 5-1: 2-(Bromomethyl)-1,3-thiazole

To a solution of 2-methy 1-1,3-thiazole (151.2 mg, 1.53 mmol) and *N*-bromosuccinimide (285.0 mg, 1.60 mmol) in tetrachloromethane (6 mL) was added 2,2'-azobisisobutyronitrile (25.0 mg, 0.153 mmol) at room temperature, and the mixture was stirred at 100^{0}C for 2 hours. After cooling to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* with *N*,*N*-dimethylformamide (2 mL) to afford a solution of the title compound in *N*,*N*-dimethylformamide, which was used for the next step without purification.

STEP 5-2: 7-[(4-Fluorobenzyl)oxy1-*N*,*N*.2-trimethyl-1-(1,3-thiazol-2-ylmethyl)-1H-benzimidazole-5-carboxamide

To a solution of 7-[(4-fluorobenzyl)oxy]- *N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide (100 mg, 0.31 mmol, Step 4) in *N*,*N*-dimethylformamide (2 mL), was added sodium hydride (60% dispersion in mineral oil, 18 mg, 0.46 mmol) at 0^{0}C. After stirring at O^{0}C for 30 minutes, a solution of 2-(bromomethyl)-1,3-thiazole in *N*,*N*-dimethylformamide (about 2 mL, Step 5-1) was added, and the

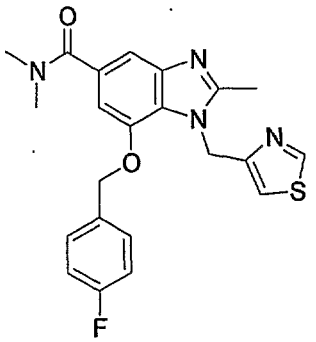
mixture was stirred at room temperature for 1.5 hours, and then at 60°C for 8 hours. After cooling to room temperature, the reaction was quenched by saturated ammonium chloride aqueous solution, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by preparative TLC eluting with dichloromethane/methanol (96:4 and then 95:5) to afford the title compound as a white solid (19 mg, 15%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.73 (d, J = 3.3 Hz, 1H), 7.38 (d, J = 1.3 Hz, 1H), 7.32-7.22 (m, 3H), 7.03 (t, J = 8.9 Hz, 2H), 6.95 (s, 1H), 5.83 (s, 2H), 5.15 (s, 2H), 3.18-3.00 (m, 6H), 2.65 (s, 3H) ppm.

MS (ESI) m/z: 425 $(M+H)^+$.

Example 7

T-^-FluorobenzvHoxyi-W.JV.a-trimethyl-i-fi.S-thiazoM-ylmethvn-IH-benzimidazole-S-carboxainide



4-(Bromomethyl)-1 ,3-thiazole was prepared as a solution in *N*,*N*-dimethylformamide (about 2mL, crude) from 4-methyl-1 ,3-thiazole (151 mg) by the same manner in Step 5-1 of Example 6.

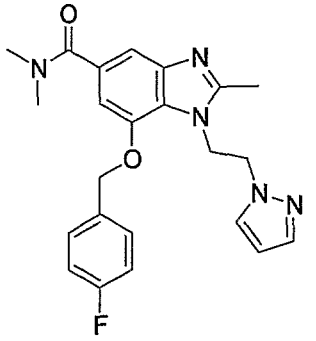
The title compound was prepared as a white solid in 21% yield (27 mg) from 7-[(4-fluorobenzyl)oxy]- *N*,*N*,2-trimethyl-1W-benzimidazole-5-carboxamide (100 mg, Step 4 of Example 6) and a solution of 4-(bromomethyl)-1 ,3-thiazole in *N*,*N*-dimethylformamide (about 2 mL) by the same manner in Step 5-2 of Example 6.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 8.74 (s, 1H), 7.37 (d, J = 1.3 Hz, 1H), 7.28-7.19 (m, 2H), 7.04 (t, J = 8.9 Hz, 2H), 6.92 (d, J = 1.3 Hz, 1H), 6.61 (s, 1H), 5.68 (s, 2H), 5.09 (s, 2H), 3.20-3.00 (m, 6H), 2.66 (s, 3H) ppm.

MS (ESI) m/z: 425 $(M+H)^+$.

Example 8

7-r(4-Fluorobenzv πoxyl- *N*,*N*.2-trimethyl-1-f2-(1H-Dyrazol-1-yl)etr ιvn-1H-benzimidazole-5-carboxam i de



STEP 1: 1-(2-(rterf-Butyl(dimethvnsilv πoxy)ethvn-7-f(4-fluorobenzyl)oxy1- *N*.*N*.2-trimethyl-1H-

benzimidazole-5-carboxamide

To a solution of 7-[(4-fluorobenzyl)oxy]- *N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide (200 mg, 0.61 mmol, Step 4 of Example 6) in *N*,*N*-dimethylformamide (3 mL) was added sodium hydride (60% dispersion in mineral oil, 29 mg, 0.73 mmol) at 0°C. After stirring at 0°C for 30 minutes, (2-bromoethoxy)(tert-butyl)dimethylsilane (0.2 mL, 0.92 mmol) was added, and the mixture was stirred at room temperature for 5 hours. The reaction was quenched with saturated ammonium chloride aqueous solution, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with hexane/ethyl acetate (gradient elution from 1:1 to ethyl acetate only), then with ethyl acetate/methanol (9:1) to afford the title compound as a white solid (142 mg, 32%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.40 (dd, J = 8.6, 5.3 Hz, 2H), 7.36-7.34 (m, 1H), 7.10 (t, J = 8.6 Hz, 2H), 6.92 (s, 1H), 5.16 (s, 2H), 4.36 (t, J = 4.9 Hz, 2H), 3.82 (t, J = 4.9 Hz, 2H), 3.17-3.00 (m, 6H), 2.60 (s, 3H), 0.76 (S, 9H), -0.21 (s, 6H) ppm.

MS (ESI) m/z: 486 $(M+H)^+$.

STEP 2: 7-f(4-Fluorobenzyl)oxy1-1-(2-hvdroxyethyl)- *N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide

To a solution of 1-(2-{[ferf-butyl(dimethyl)silyl]oxy}ethyl)-7-[(4-fluorobenzyl)oxy]- *N*,/V,2-trimethyl-1H-benzimidazole-5-carboxamide (142 mg, 0.29 mmol, Step 1) in tetrahydrofuran (3 mL) was added a solution of tetrabutylammonium fluoride in tetrahydrofuran (1 mol/L, 0.44 mL) at room temperature. After stirring at room temperature for 2 hours, the reaction was quenched by saturated ammonium chloride aqueous solution, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (95:5) to afford the title compound as a white solid (71 mg, 65%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.41 (dd, J = 8.6, 5.3 Hz, 2H), 7.36-7.32 (m, 1H), 7.11 (t, J = 8.6 Hz, 2H), 6.92 (s, 1H), 5.15 (s, 2H), 4.39 (t, J = 5.3 Hz, 2H), 3.88 (t, J = 5.3 Hz, 2H), 3.17-3.00 (m, 6H), 2.60 (s, 3H) ppm. (OH was not observed)

MS (ESI) m/z: 372 $(M+H)^+$.

STEP 3: 2-f5-f(Dimethylamino)carbonvn-7-f(4-fluorobenzyl)oxyl-2-methyl-1 H-benzimidazol-1 -vDethyl methanesulfonate

To a solution of 7-[(4-fluorobenzyl)oxy]-1-(2-hydroxyethyl)- *N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide (60 mg, 0.16 mmol, Step 2) in dichloromethane (2 mL), were added triethylamine (0.045 mL, 0.32 mmol) and methanesulfonyl chloride (0.015 mL, 0.19 mmol) at 0°C. After stirring at 0°C for 2.5 hours, the reaction was quenched by water, and extracted with ethyl acetate. The combined organic layer was washed with saturated sodium hydrogencarbonate aqueous solution, dried over sodium sulfate, and concentrated *in vacuo* to afford the title compound as a white solid (71 mg, 97%), which was used for the next step without purification.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.45-7.35 (m, 3H), 7.13 (t, J = 8.6 Hz, 2H), 6.98-6.95 (m, 1H), 5.16 (s,

2H), 4.57 (t, J = 5.3 Hz, 2H), 4.41 (t, J = 5.3 Hz, 2H), 3.20-2.98 (m, 6H), 2.74 (s, 3H), 2.61 (s, 3H) ppm.

STEP 4: 7-r(4-FluQrob6nzyl)oxy1-*N*,*N*.2-trimethyl-1-f2-(1H-pyrazol-1-vhethyli-i H-benzimidazole-5-carboxamide

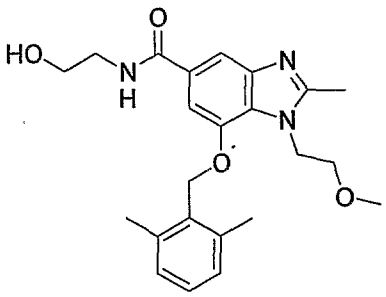
To a solution of pyrazole (17 mg, 0.24 mmol) in *N*,*N*-dimethylformamide (1 mL) was added sodium hydride (60% dispersion in mineral oil, 8 mg, 0.21 mmol) at 0°C. After stirring at O°C for 30 minutes, a solution of 2-{5-[(dimethylamino)carbonyi]-7-[(4-fluorobenzyl)oxy]-2-methyl-1H-benzimidazol-1-yl}ethyl methanesulfonate (71 mg, 0.16 mmol, Step 3) in *N*.W-dimethylformamide (1 mL) was added, and the mixture was stirred at 0°C for 1 hour, and then at room temperature for 1 hour. To the mixture was added a solution of sodium pyrazol-1-ide in *N*,*N*-dimethylformamide (1 mL), which was prepared from pyrazole (33 mg, 0.48 mmol) and sodium hydride (60% dispersion in mineral oil, 17 mg, 0.42 mmol) by the same procedure. After stirring at 60°C for 2 hours, the reaction was quenched by saturated ammonium chloride aqueous solution, and extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by preparative TLC eluting with ethyl acetate/methanol (95:5, 95:5, and then 93:7) to afford the title compound as a white solid (5 mg, 5%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.53 (s, 1H), 7.46 (dd, J = 8.1, 5.1 Hz, 2H), 7.35 (s, 1H), 7.14 (t, J = 7.1 Hz, 2H), 7.00 (s, 1H), 6.57 (d, J = 2.2 Hz, 1H), 6.10 (dd, J = 2.2, 2.2 Hz, 1H), 5.21 (s, 2H), 4.59 (t, J = 4.6 Hz, 2H), 4.38 (t, J = 5.1 $Hz_1$2H), 3.26-3.00 (m, 6H), 1.94 (s, 3H) ppm.

MS **(ESI)** m/z: 422 $(M+H)^+$.

Example 9

7-rf2,6-Dimethylbenzyl)oxy1-Af-(2-hvdroxyethvn-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carboxamide



STEP 1: 4-Bromo-2-f(2.6-dimethylbenzyl)oxyl-6-nitroaniline

The title compound was prepared as an orange solid in 85% yield (4.88 g) from 2-amino-3-nitrophenol (2.50 g) and 2-(chloromethyl)-1,3-dimethylbenzene (2.68 g) by the same manner in Step 1 of Example 3.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.95 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.15 (s, 1H), 7.13 (d, J = 8.1 Hz, 2H), 6.41 (br.s, 2H), 5.10 (s, 2H), 2.39 (s, 6H) ppm.

MS (ESI) m/z: 351 $(M+H)^+$, 349 $(M-H)^-$.

STEP 2: *N*-{4-Bromo-2-r(2,6-dimethvbenzyl)oxy1-6-nitrophenyllacetamide

To a solution of 4-bromo-2-[(2,6-dimethylbenzyl)oxy]-6-nitroaniline (5.70 g, 16.2 mmol, Step 1) in acetic anhydride (90.OmL, 949 mmol) was added concentrated sulfuric acid (2 drops) at 7O^{0}C. The mixture was stirred at 7O^{0}C for 5 minutes. After cooling to room temperature, water (500 ml_) was added, and the formed precipitate was collected by filtration, and washed with diisopropyl ether to afford the title compound as a white solid (3.7 g, 58%).

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.70 (s, 1H), 7.47 (s, 1H), 7.38 (br.s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 2H), 5.13 (s, 2H), 2.38 (s, 6H) 2.08 (s, 3H) ppm.

MS (ESI) m/z: 393 $(M+H)^+$.

STEP 3: *N*-{4-Bromo-2-r(2.6-dimethylbenzyl)oxyl-6-nitrophenyl>- *N*-(2-methoxyethyl)acetamide

The title compound was prepared as a white solid in 84% yield (2.05 g) from *N*-{4-bromo-2-[(2,6-dimethybenzyl)oxy]-6-nitrophenyl}acetamide (2.1 g, Step 2) by the same manner in Step 2 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.73 (s, 1H), 7.55 (s, 1H), 7.24-7.16 (m, 1H), 7.10-7.05 (m, 2H), 5.10 (s, 2H), 4.15-4.01 (m, 1H), 3.46-3.24 (m, 2H), 3.07 (s, 3H), 3.03-2.92 (m, 1H), 2.34 (s, 6H), 1.83 (s, 3H) ppm.

MS (ESI) m/z: 451 $(M+H)^+$.

STEP 4: 5-Bromo-7-r(2.6-dimethylbenzyl)oxyl-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole

The title compound was prepared as a white solid in 93% yield (1.71 g) from *N*-{4-bromo-2-[(2,6-dimethylbenzyl)oxy]-6-nitrophenyl}-/V-(2-methoxyethyl)acetamide (2.04 g, Step 3) by the same manner in Step 3 of Example 1.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.49 (s, 1H), 7.24-7.16 (m, 1H), 7.10 (d, J = 8.1 Hz, 2H), 6.99 (s, 1H), 5.15 (s, 2H), 4.20 (t, J = 5.4 Hz, 2H), 3.38 (t, J = 5.4 Hz, 2H), 3.04 (s, 3H), 2.54 (s, 3H), 2.40 (s, 6H) ppm.

MS (ESI) m/z: 403 $(M+H)^+$.

STEP 5: 7-r(2,6-Dimethylbenzyl)oxy1-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carbonitrile

The title compound was prepared as a white solid in 79% yield (1.03 g) from 5-bromo-7-[(2,6-dimethylbenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1/-/-benzimidazole (1.50 g, Step 4) by the same manner in Step 1 of Example 6.

^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.69 (s, 1H), 7.21 (d, J = 5.4 Hz, 1H), 7.13 (s, 1H), 7.09 (d, J = 5.4 Hz, 2H), 5.19 (s, 2H), 4.26 (t, J = 5.4 Hz, 2H), 3.40 (t, J = 5.4 Hz, 2H), 3.07 (s, 3H), 2.58 (s, 3H), 2.41 (s, 6H) ppm.

MS (ESI) m/z: 350 (M+H)\

STEP6: 7-r(2,6-Dimethylbenzyl)oxy1-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carboxylic acid

A solution of 7-[(2,6-dimethylbenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carbonitrile (1.03 g, 2.95 mmol, Step 5) and potassium hydroxide (85%, 2.87 g, 40.9 mmol) in ethylene glycol (12 mL) was stirred at 170^{0}C for 1.5 hours under microwave irradiation. After cooling to room temperature, 2 mol/L hydrochloric acid was added until pH of the solution became about 3. The aqueous layer was extracted with ethyl acetate/methanol (20:1) and the combined organic layer was washed with water, dried over magnesium

sulfate and concentrated *in vacuo* to afford the title compound as a white solid (780 mg, 72 %).

^{1}H NMR (DMSO-Of$_6$, 270 MHz) δ: 7.83 (br.s, 1H), 7.50-7.74 (m, 2H), 6.99-7.27 (m, 2H)$_1$ 5.29 (s, 2H), 4.20-4.35 (m, 2H), 3.31-3.50 (m, 2H), 3.02 (s, 3H), 2.50 (s, 3H) 2.41 (s, 6H) ppm (COOH was not observed).

MS (ESI) m/z: 369 (M+H)\ 367 (M-H)$^-$.

STEP 7: 7-r(2,6-dimethylbenzyl)oxy1- *N*-(2-hvdroxyethylV1-(2-methoxyethyl)-2-methyl-1/-V-benzimidazole-5-carboxamide

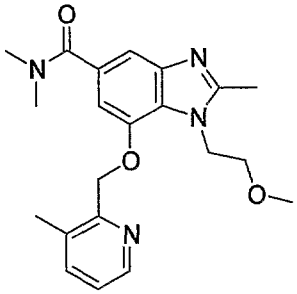
The title compound was prepared as a white solid in 41% yield (68 mg) from 7-[(2,6-dimethylbenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole-5-carboxylic acid (150 mg, Step 6) and 2-aminoethanol (124 mg) by the same manner in Step 4 of Example 6.

^{1}H NMR (CDCl$_3$, 270 MHz) δ: 7.64 (s, 1H), 7.52 (s, 1H), 7.23-7.15 (m, 1H), 7.11-7.05 (m, 2H), 6.93-6.81 (m, 1H), 5.24 (s, 2H), 4.25 (t, *J* = 5.3 Hz, 2H), 3.91-3.86 (m, 2H), 3.73-3.67 (m, 2H), 3.41 (t, J = 5.3 Hz, 2H), 3.05 (s, 3H), 2.56 (s, 3H), 2.40 (s, 6H) ppm. (OH was not observed)

MS (ESI) m/z: 412 (M+H)$^+$.

Example 10

1-f2-Methoxyethv l)-*N*f.Af,2-trimethyl-7-r(3-methylpyridin-2-vHmethoxy1-1H-benzimidazole-5-carboxamide



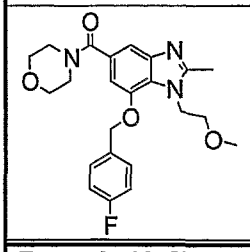
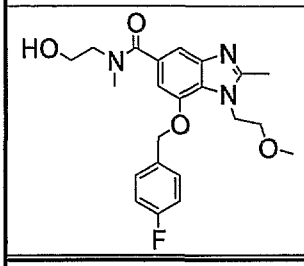
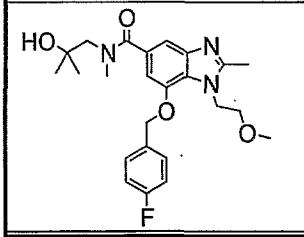
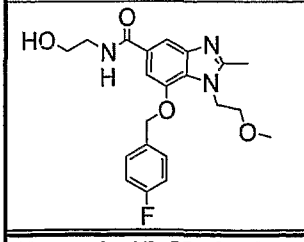
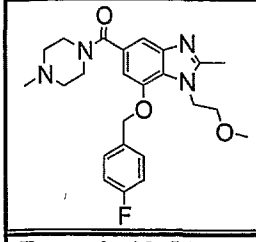
To a solution of 7-hydroxy-1-(2-methoxyethyl)- *N*,*N*,2-trimethyl-1H-benzimidazole-5-carboxamide (64 mg, 0.23 mmol, Step 1 of Example 2), (3-methylpyridin-2-yl)methanol (57 mg, 0.46 mmol, *J. Med. Chern.,* **1998,** *41,* 1827-1837.), and triphenylphosphine (121 mg, 0.46 mmol) in toluene (3 mL) was added diisopropyl azodicarboxylate (0.091 mL, 0.46 mmol) at O°C. After stirring for 30 minutes at 0°C, the mixture was stirred at room temperature overnight. The reaction was quenched by saturated sodium hydrogencarbonate aqueous solution, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over sodium sulfate, and concentrated *in vacuo.* The residue was purified by column chromatography on silica gel eluting with ethyl acetate/methanol (gradient elution from 9:1 to 5.7:1) to afford the title compound as a white solid (39 mg, 44%).

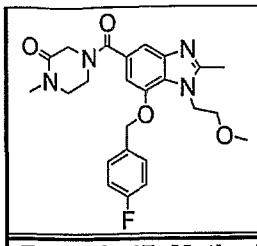
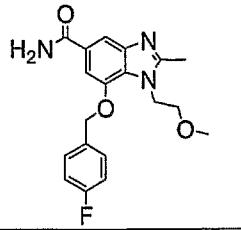
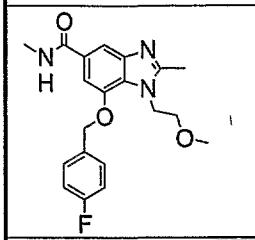
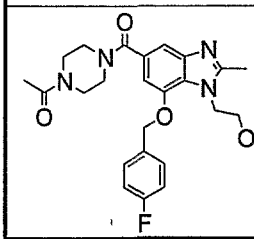
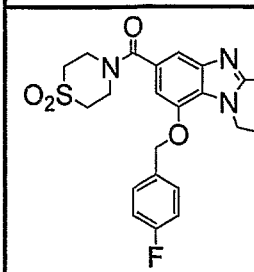
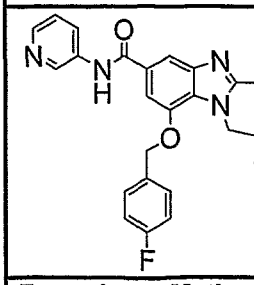
^{1}H NMR (CDCl$_3$, 270 MHz) δ: 8.48 (d, J = 4.0 Hz, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.35 (s, 1H), 7.31-7.20 (m, 1H), 7.01 (s, 1H), 5.32 (s, 2H), 4.38 (t, J = 5.3 Hz, 2H), 3.54 (t, J = 5.3 Hz, 2H), 3.23-3.00 (m, 9H), 2.58 (s, 3H) ppm, 2.44 (s, 3H).

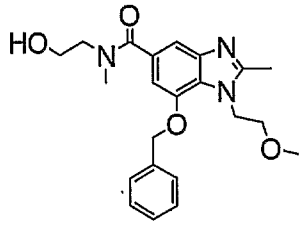
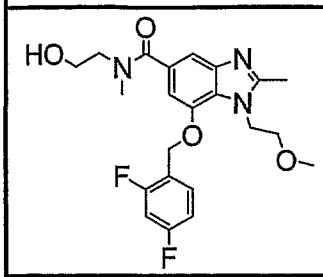
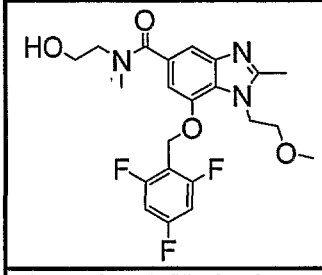
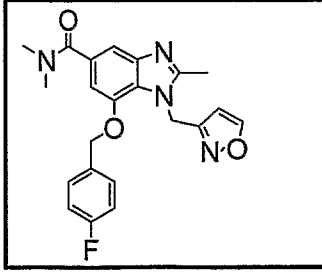
MS (ESI) m/z: 383 (M+H)$^+$.

Following Examples 11 to 21 were prepared from 7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)

-2-methyl-IH-benzimidazole-S-carboxylic acid (Step 6 of Example 3) and corresponding various amines according to the procedure described in Step 6 of Example 1 (Method a) or Step 4 of Example 6 (Method b). Adding to this, **Examples 22 to 25** were prepared by the appropriate carboxylic acid with the amide according to the procedure described in Step 4 of Example 6(Method b) or by the appropriate bromide with the imidazole according to the procedure described in Example 7 (Method c).

Example 11: Method a	**7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-5-(morpholin-4-ylcarbonyl)-1*H*-benzimidazole**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46-7.37 (m, 2H), 7.32 (s, 1H), 7.17-7.05 (m, 2H), 6.91 (s, 1H), 5.17 (s, 2H), 4.47-4.36 (m, 2H), 3.78-3.64 (m, 8H), 3.60-3.56 (m, 2H), 3.16 (s, 3H), 2.59 (s, 3H) ppm. MS (ESI) m/z: 428 $(M+H)^+$, 426 $(M-H)^-$.
Example 12: Method b	**7-[(4-Fluorobenzyl)oxy]-*N*-(2-hydroxyethyl)-1-(2-methoxyethyl)-*N*,2-dimethyl-1*H*-benzimidazole-5-carboxamide**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46-7.36 (m, 3H), 7.16-7.06 (m, 2H), 6.96 (s, 1H), 5.16 (s, 2H), 4.46-4.37 (m, 2H), 4.00-3.81 (m, 2H), 3.80-3.66 (m, 2H), 3.61-3.54 (m, 2H), 3.18 (s, 3H), 3.13 (s, 3H), 2.59 (s, 3H) ppm. (-OH was not observed) MS (ESI) m/z: 398 $(M+H)^+$, 396 $(M-H)^-$.
Example 13: Method a	**7-[(4-Fluorobenzyl)oxy]-*N*-(2-hydroxy-2-methylpropyl)-1-(2-methoxyethyl)-*N*,2-dimethyl-1*H*-benzimidazole-5-carboxamide**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.46-7.33 (m, 3H), 7.18-7.08 (m, 2H), 6.94 (s, 1H), 5.17 (s, 2H), 4.60 (br.s, 1H), 4.48-4.37 (m, 2H), 3.70-3.55 (m, 4H), 3.19 (s, 3H), 3.17 (s, 3H), 2.60 (s, 3H), 1.33 (s, 6H) ppm. MS (ESI) m/z: 444 $(M+H)^+$.
Example 14: Method a	**7-[(4-Fluorobenzyl)oxy]-*N*-(2-hydroxyethyl)-1-(2-methoxyethyl)-2-methyl-1*H*-benzimidazole-5-carboxamide**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.61 (s, 1H), 7.47-7.37 (m, 3H), 7.17-7.05 (m, 2H), 6.89-6.77 (m, 1H), 5.18 (s, 2H), 4.41 (t, 2H, J = 5.14 Hz), 3.88 (m, 2H), 3.73-3.65 (m, 2H), 3.58 (t, 2H, J = 5.14 Hz), 3.43 (br.s, 1H), 3.18 (s, 3H), 2.39 (s, 3H) ppm. MS (ESI) m/z: 402 $(M+H)^+$, 400 $(M-H)^-$.
Example 15: Method a	**7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-5-[(4-methylpiperazin-1-yl)carbonyl]-1*H*-benzimidazole**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.48-7.37 (m, 2H), 7.33 (s, 1H), 7.17-7.06 (m, 2H), 6.90 (s, 1H), 5.16 (s, 2H), 4.42 (t, J = 5.3 Hz, 2H), 3.87-3.57 (m, 4H), 3.58 (t, J = 5.3 Hz, 2H), 3.18 (s, 3H), 2.59 (s, 3H), 2.52-2.36 (m, 4H), 2.32 (s, 3H) ppm. MS (ESI) m/z: 441 $(M+H)^+$.
Example 16: Method b	**4-{[7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1*H*-benzimidazol-5-yl]carbonyl}-1-methylpiperazin-2-one**

	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.47-7.38 (m, 2H), 7.36 (s, 1H), 7.16-7.08 (m, 2H), 6.91 (s, 1H), 5.16 (s, 2H), 4.42 (t, J = 5.3 Hz, 2H), 4.35-4.28 (m, 2H), 4.00-3.86 (m, 2H), 3.58 (t, J = 5.3 Hz, 2H), 3.49-3.37 (m, 2H), 3.19 (s, 3H), 3.01 (s, 3H), 2.60 (s, 3H) ppm. MS (ESI) m/z: 455 $(M+H)^+$.
Example 17: Method a	**7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1*H*-benzimidazole-5-carboxamide**
	white solid ^{1}H NMR (DMSO-d_6, 270 MHz) δ: 7.96 (br.s, 2H), 7.77 (s, 1H), 7.63-7.55 (m, 2H), 7.43 (s, 1H), 7.39-7.29 (s, 2H), 5.27 (s, 2H), 4.43 (t, J = 5.3 Hz, 2H), 3.57 (t, J = 5.3 Hz, 2H), 3.14 (s, 3H), 2.50 (s, 3H) ppm. MS (ESI) m/z: 358 $(M+H)^+$.
Example 18: Method a	**7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-*N*,2-dimethyl-1*H*-benzimidazole-5-carboxamide**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.58 (s, 1H), 7.47-7.37 (m, 3H), 7.16-7.08 (m, 2H), 6.46-6.36 (m, 1H), 5.19 (s, 2H), 4.46-4.38 (m, 2H), 3.58 (t, **J** = 5.3 Hz, 2H), 3.18 (s, 3H), 3.04 (d, J = 4.6 Hz, 3H), 2.59 (s, 3H) ppm. MS (ESI) m/z: 372 $(M+H)^+$, 370 $(M-H)^-$.
Example 19: Method b	**5-[(4-Acetylpiperazin-1-yl)carbonyl]-7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1*H*-benzimidazole**
	white solid ^{1}H NMR ($CDCl_3$, 270 MHz) δ: 7.41(dd, J = 8.6, 5.3 Hz, 2H), 7.33 (s, 1H), 7.11(t, J = 8.6 Hz, 2H), 6.91 (s, 1H), 5.16 (s, 2H), 4.42 (t, J = 5.3, 2H), 3.78-3.45 (m, 10H), 3.19 (s, 3H), 2.60 (s, 3H), 2.13 (s, 3H). MS (ESI) m/z: 469 $(M+H)^+$.
Example 20: Method b	**5-[(1,1-Dioxidothiomorpholin-4-yl)carbonyl]-7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-1H-benzimidazole**
	white solid 1H NMR (CDCl3, 300 MHz) □: 7.43-7.39 (m, 2H), 7.39 (s, 1H), 7.15-7.09 (m, 2H), 6.89 (s, 1H), 5.16 (s, 2H), 4.43 (t, J = 5.1 Hz, 2H), 4.25^.08 (m, 4H), 3.58 (t, J = 5.1 Hz, 2H), 3.19 (s, 3H), 3.07 (m, 4H), 2.60 (s, 3H) ppm. MS (ESI) m/z: 476 (M+H)+.
Example 21: Method b	**7-[(4-Fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-N-pyridin-3-yl-1H-benzimidazole-5-carboxamide**
	brown solid 1H NMR (CDCl3, 270 MHz) □: 8.76 (d, J = 2.0 Hz, 1H), 8.40 (dd, J = 4.6, 1.3 Hz, 1H), 8.34-8.27 (m, 1H), 8.25-8.12 (br, 1H), 7.79 (s, 1H), 7.49-7.40 (m, 3H), 7.35 (dd, J = 8.0, 4.9 Hz, 1H), 7.13 (t, J = 8.9 Hz, 2H), 5.23 (s, 2H), 4.45 (t, J = 5.3 Hz, 2H), 3.60 (t, J = 5.3 Hz, 2H), 3.20 (s, 3H), 2.60 (s, 3H) ppm. MS (ESI) m/z: 435 (M+H)+, 433 (M-H)-.
Example 22: Method b	**7-(Benzyloxy)-N-(2-hydroxyethyl)-1-(2-methoxyethyl)-N,2-dimethyl-1**

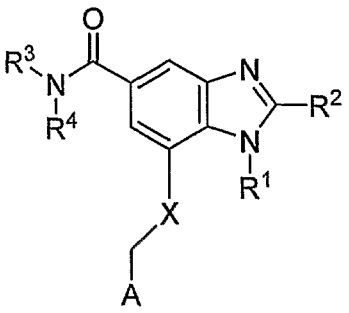
	H-benzimidazole-5-carboxamide
	white solid 1H NMR (CDCl3, 300 MHz) □: 7.43-7.39 (m, 6H), 6.97 (bs, 1H), 5.20 (s, 2H), 4.45 (t, J = 5.1 Hz, 2H), 3.98-3.81 (m, 2H), 3.81-3.75 (m, 2H), 3.61 (t, J = 5.1 Hz, 2H), 3.18 (s, 3H), 3.12 (s, 3H), 2.60 (s, 3H) ppm. (-OH was not observed) MS (ESI) m/z: 398 (M+H)+.
Example 23: Method b	**7-[(2,4-Difluorobenzyl)oxy]-N-(2-hydroxyethyl)-1-(2-methoxyethyl)-N,2-dimethyl-1H-benzimidazole-5-carboxamide**
	white solid 1H NMR (CDCl3, 270 MHz) □: 7.52-7.38 (m, 2H), 7.06-6.85 (m, 3H), 5.20 (s, 2H), 4.39 (t, J = 5.3 Hz, 2H), 4.04-3.85 (m, 2H), 3.84-3.67 (m, 2H), 3.58 (t, J = 5.3 Hz, 2H), 3.19 (s, 3H), 3.15 (s, 3H), 2.59 (s, 3H) ppm. (-OH was not observed) MS (ESI) m/z: 434 (M+H)+.
Example 24: Method b	**N-(2-Hydroxyethyl)-1-(2-methoxyethyl)-N,2-dimethyl-7-[(2,4,6-trifluorobenzyl)oxy]-1H-benzimidazole-5-carboxamide**
	white solid 1H NMR (CDCl3, 300 MHz) □: 7.40 (s, 1H), 7.03 (s, 1H), 6.79-6.73 (m, 2H), 5.22 (s, 2H), 4.33 (t, J = 5.3 Hz, 2H), 4.00-3.61 (m, 4H), 3.54 (t, J = 5.3 Hz, 2H), 3.19 (s, 3H), 3.15 (s, 3H), 2.58 (s, 3H) ppm. (-OH was not observed) MS (ESI) m/z: 452 (M+H)+.
Example 25: Method c	**7-[(4-Fluorobenzyl)oxy]-1-(isoxazol-3-ylmethyl)-N,N,2-trimethyl-1H-benzimidazole-5-carboxamide**
	white solid 1H NMR (CDCl3, 270 MHz) □: 8.31 (s, 1H), 7.37 (d, J = 1.3 Hz, 1H), 7.36-7.29 (m, 2H), 7.06 (t, J = 8.9 Hz, 2H), 6.97 (s, 1H), 6.01 (d, J = 2.0 Hz, 1H), 5.63 (s, 2H), 5.17 (s, 2H), 3.19-3.00 (br, 6H), 2.59 (s, 3H) ppm. MS (ESI) m/z: 409 (M+H)+.

All publications, including but not limited to, issued patents, patent applications, and journal articles, cited in this application are each herein incorporated by reference in their entirety.

Although the invention has been described above with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention.

CLAIMS

1, A compound of the formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 represents a C_1-C_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a C_1-C_6 alkoxy group, a hydroxy-substituted C_3-C_7 cycloalkyl group, a hydroxy-CrC $_6$ alkyl-substituted C_3-C_7 cycloalkyl group, an aryl group, a hydroxy-substituted aryl group, a heteroaryl group and a halogen-substituted heteroaryl group;

R^2 represents a hydrogen atom or a C_1-C_6 alkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group;

R^3 and R^4 independently represent a hydrogen atom, or a C_1-C_6 alkyl, C_3-C_7 cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a halogen atom, a hydroxy group, a C_1-C_6 alkoxy group and a C_3-C_7 cycloalkyl group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group being unsubstituted or substituted with 1 to 2 substituents selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group, and a hydroxy-CrC $_6$ alkyl group;

A represents an aryl or heteroaryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-CrC βalkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$;

R^5, R^7 and R^8 independently represent a hydrogen atom or a C_1-C_6 alkyl group;

R^6 represents a C_1-C_6 alkyl group; and

X represents an oxygen atom or NH.

2. The compound or the pharmaceutically acceptable salt, as claimed in claim 1, wherein

R^1 is a C_1-C_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a C_1-C_6 alkoxy group and a heteroaryl group;

R^2 is a C_1-C_6 alkyl group;

R^3 and R^4 are independently a hydrogen atom or a C_1-C_6 alkyl being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a 4 to 6 membered heterocyclic group being unsubstituted or substituted with 1 to 2 substituent selected from the group consisting of a hydroxy group, an oxo group, a C_1-C_6 alkyl group, a C_1-C_6 acyl group and a hydroxy-CrC $_6$ alkyl group;

A is an aryl group being unsubstituted or substituted with 1 to 5 substituents independently selected from the group consisting of a halogen atom, a C_1-C_6 alkyl group, a hydroxy-CrC βalkyl group, a C_1-C_6 alkoxy-substituted C_1-C_6 alkyl group, -NR $^5SO_2R^6$ and -CONR $^7R^8$;

R^5, R^7 and R^8 are independently a hydrogen atom or a C_1-C_6 alkyl group; and

R^6 is a C_1-C_6 alkyl group; and

X is an oxygen atom.

3. The compound or the pharmaceutically acceptable salt, as claimed in claim 1, wherein

R^1 is a C_1-C_6 alkyl group being substituted with a C_1-C_6 alkoxy group;

R^2 is a C_1-C_6 alkyl group;

R^3 and R^4 are independently a hydrogen atom or a C_1-C_6 alkyl group being unsubstituted or substituted with a substituent selected from the group consisting of a hydroxy group and a C_1-C_6 alkoxy group; or R^3 and R^4 taken together with the nitrogen atom to which they are attached form a morpholino group;

A is an aryl group being unsubstituted or substituted with a halogen atom; and

X is an oxygen atom.

4. The compound of claim 1, which is selected from:

7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)- *N*,*N*,2-trimethyl-1/-/-benzimidazole-5-carboxamide;

7-[(4-fluorobenzyl)oxy]- *N*-(2-hydroxyethyl)-1-(2-methoxyethyl)- *N*,2-dimethyl-1H-benzimidazole-5-carboxamide;

7-[(4-fluorobenzyl)oxy]-1-(2-methoxyethyl)-2-methyl-5-(morpholin-4-ylcarbonyl)-1/-/-benzimidazole;

or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising the compound or the pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, and a pharmaceutically acceptable carrier.

6. The pharmaceutical composition as claimed in claim 5 further comprising other pharmacologically active agent(s).

7. A method for the treatment of a condition mediated by acid pump inhibitory activity in a mammalian subject including a human, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound or the pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4.

8. The method as claimed in claim 7, wherein said condition is gastrointestinal disease, gastroesophageal disease, gastroesophageal reflux disease (GERD), laryngopharyngeal reflux disease, peptic ulcer, gastric ulcer, duodenal ulcer, NSAID-induced ulcers, gastritis, infection of Helicobacter pylori, dyspepsia, functional dyspepsia, Zollinger-Ellison syndrome, non-erosive reflux disease (NERD), visceral pain, cancer, heartburn, nausea, esophagitis, dysphagia, hypersalivation, airway disorders or asthma.

9. A use of the compound of formula (I) or the pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 4, for the manufacture of a medicament for the treatment of a condition mediated by acid pump inhibitory activity,

10. The use as claimed in claim 9, wherein said condition is gastrointestinal disease, gastroesophageal disease, gastroesophageal reflux disease (GERD), laryngopharyngeal reflux disease, peptic ulcer, gastric ulcer, duodenal ulcer, NSAID-induced ulcers, gastritis, infection of Helicobacter pylori, dyspepsia, functional dyspepsia, Zollinger-Ellison syndrome, non-erosive reflux disease (NERD), visceral pain, cancer, heartburn, nausea, esophagitis, dysphagia, hypersalivation, airway disorders or asthma.