Title: SPIRO BENZIMIDAZOLE DERIVATIVES AS ACID PUMP INHIBITORS

Abstract: This invention relates to compounds of the formula (I): (I) or a pharmaceutically acceptable salt thereof, wherein: R1, R2, R3, R4, R5, R6, R7, R8 and A are each as described herein or a pharmaceutically acceptable salt, and compositions containing such compounds and the method of treatment and the use, comprising such compounds for the treatment of a condition mediated by acid pump antagonistic activity such as, but not limited to, 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,
Background of the Invention

This invention relates to spiro 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 $\text{H}^+\text{K}^+\text{ATPase}$ by covalently binding to its Cystein residues (Sachs, G. et. al., Digestive Diseases and Sciences, 1995, 40, 3S-23S; Sachs et. al., Annu Rev Pharmacol Toxicol, 1995, 35, 277-305.). However, unlike PPIs, acid pump antagonists inhibit acid secretion via reversible potassium-competitive inhibition of $\text{H}^+\text{K}^+\text{ATPase}$. SCH28080 is one of such reversible inhibitors and has been studied extensively. Other newer agents (revaprazan, soraprazan, AZD0865 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, 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 (hereinafter, referred as "APA Diseases", Kiljander, Toni O., American Journal of Medicine, 2003, 115 (Suppl. 3A), 65S-71S.).

WO06/134111 refers to some compounds, such as 6,7,8,9-tetrahydro-1H-imidazo[4,5-\text{h}]quinoline 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 compounds having 1,6,7,8-tetrahydrochromeno[8,7-c]imidazole structure showed acid pump inhibitory activity and favorable properties 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):

![Chemical structure](image)

or a pharmaceutically acceptable salt thereof, wherein;

- **R¹** represents a hydrogen atom, a CrC₆ alkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC₆ alkoxy group, a hydroxy-substituted C₃-C₇ cycloalkyl group, a hydroxy-CrC₆ alkyl-substituted C₃-C₇ cycloalkyl group, an aryl group, a hydroxy-substituted aryl group, a heteroaryl group and a halogen-substituted heteroaryl group;
- **R²** represents a hydrogen atom or a CrC₆ alkyl group being unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group and a CrC₆ alkoxy group;
- **R³** and **R⁴** independently represent a hydrogen atom, or a C₁₋₆ alkyl, C₃₋₇ cycloalkyl or heteroaryl group being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a deuterium, a halogen atom, a hydroxy group, a CrC₆ alkoxy group and a C₃₋₇ cycloalkyl group; or **R³** and **R⁴** 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, a halogen atom, an oxo group, a CrC₆ alkoxy group and a C₃₋₇ cycloalkyl group; or **R³** and **R⁴** 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, a halogen atom, an oxo group, a CrC₆ alkoxy group and a C₃₋₇ cycloalkyl group;
alkyl group, a CrC₆ acyl group, and a hydroxy-CrC₆ alkyl group; R⁵, R⁶, R⁷ and R⁸ independently represent a hydrogen atom, a halogen atom or a CrC₆ alkyl group; 

-A- represents -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂O-, -0-CH₂-, -0-CH₂CH₂-, 

-CH₂-O-CH₂-, -CH₂-CH₂O-, -CH₂-S-, -S-CH₂-, -S-CH₂CH₂-, -CH₂-S-CH₂- or  

-CH₂CH₂-S-. 

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 for the treatment of a condition mediated by acid pump modulating activity in a mammalian subject including a human, 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 modulating 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. 

Further, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use in medicine. 

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 acid pump inhibitory activity, less toxicity, good absorption, good distribution, 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 R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈ and the substituent of R³ and R⁴ are the d-C₆ alkyl group, this CrC₆ alkyl group may be a straight or branched chain group having one to six carbon atoms, and examples include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, te/t-butyl, pentyl, 1-ethylpropyl and hexyl. Of these, C₁-C₂ alkyl is preferred; methyl is more preferred.

Where the substituent of R¹, R², R³ and R⁴ are the CrC₆ alkoxy group, this CrC₆ alkoxy group represents the oxygen atom substituted with the said CrC₆ alkyl group, and examples include, but are not limited to, methoxy, ethoxy, propoxy, isoproxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentyloxy and hexyloxy. Of these, a CrC₄ alkoxy is preferred; a C₁-C₂ alkoxy is preferred; methoxy is more preferred.

Where R³, R⁴ and the substituent of R³ and R⁴ are the C₃-C₇ cycloalkyl group, this C₃-C₇ cycloalkyl group represents cycloalkyl group having three to seven carbon atoms, and examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. Of these, C₃-C₅ cycloalkyl group is preferred; cyclopropyl is more preferred.

Where R³ and R⁴, taken together with the nitrogen atom to which they are attached form the 4 to 6 membered heterocyclic group, this 4 to 6 membered heterocyclic group represents a saturated heterocyclic group having three to six ring atoms selected from carbon atom, nitrogen atom, sulfur atom and oxygen atom other than said nitrogen atom, and examples include, but are not limited to, azetidinyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, hexahydroazepinyl, hexahydrodiazepinyl, morpholino, thiomorpholino and homomorpholino. Of these, azetidinyl, pyrrolidinyl and morpholino are preferred; pyrrolidinyl is more preferred.

Where R⁵, R⁶, R⁷, R⁸ and the substituent of R³ and R⁴ are the halogen atom, it may be a fluorine, chlorine, bromine or iodine atom. Of these, a fluorine atom and a chlorine atom are preferred.

Where the substituent of the 4 to 6 membered heterocyclic group is the hydroxy-CrC₆ alkyl group, this hydroxy-CrC₆ alkyl represents said CrC₆ alkyl group substituted with a hydroxy group, and examples include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl 3-hydroxypropyl, 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, hydroxy-C\textsubscript{3}-alkyl is preferred; hydroxymethyl is more preferred.

Where the substituent of R\textsubscript{1} is the hydroxy-substituted C\textsubscript{3}-C\textsubscript{7} cycloalkyl group, this hydroxy-substituted C\textsubscript{3}-C\textsubscript{7} cycloalkyl group represents a C\textsubscript{3}-C\textsubscript{7} cycloalkyl group which is substituted with hydroxy group(s) and the C\textsubscript{3}-C\textsubscript{7} cycloalkyl is aforementioned above. Examples of a hydroxy-substituted C\textsubscript{3}-C\textsubscript{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\textsubscript{3}-C\textsubscript{5} cycloalkyl is preferred; 1-hydroxycyclopropyl is more preferred.

Where the substituent of R\textsubscript{1} is the hydroxy-C\textsubscript{r}-alkyl-substituted C\textsubscript{3}-C\textsubscript{7} cycloalkyl group, this hydroxy-C\textsubscript{r}-C\textsubscript{6} alkyl-substituted C\textsubscript{3}-C\textsubscript{7} cycloalkyl group represents a C\textsubscript{3}-C\textsubscript{7} cycloalkyl group which is substituted with hydroxy-C\textsubscript{r}-alkyl group(s), and the hydroxy-C\textsubscript{r}-alkyl and the C\textsubscript{3}-C\textsubscript{7} cycloalkyl are aforementioned above. Examples of a hydroxy-C\textsubscript{r}-alkyl-substituted C\textsubscript{3}-C\textsubscript{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-hydroxymethylcyclohexyl, 2-hydroxymethylcyclohexyl, 3-hydroxymethylcyclohexyl, 4-hydroxymethylcyclohexyl, 1-hydroxymethylcycloheptyl, 2-hydroxymethylcycloheptyl, 3-hydroxymethylcycloheptyl and 4-hydroxymethylcycloheptyl. Of these, hydroxy-C\textsubscript{3}-alkyl-substituted C\textsubscript{3}-C\textsubscript{5} cycloalkyl is preferred; 1-hydroxymethylcyclopropyl and 1-(2-hydroxyethyl)-cyclopropyl are more preferred.

Where the substituent of R\textsubscript{1} is the aryl group, it may be phenyl, naphthyl or anthracenyl. Of these, phenyl is preferred.

Where the substituent of R\textsubscript{1} is the 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 R³, R⁴ and the substituent of R¹ is the heteroaryl group, this heteroaryl group 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-thiazoyl, 4-thiazoyl, 2-furyl, 2-oxazoyl, 1-pyrazoyl, 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-thiazoyl, 4-thiazoyl and 1-pyrazoyl are more preferred for the substituent of R¹.

Where the substituent of R¹ is the 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-thiazoyl, 2-fluoro-4-thiazoyl, 4-fluoro-2-furyl, 4-fluoro-2-oxazoyl, 4-fluoro-1-pyrazoyl, 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-pyridinyl, 4-chloro-2-thienyl, 4-chloro-2-thiazoyl, 2-chloro-4-thiazoyl, 4-chloro-2-furyl, 4-chloro-2-oxazoyl, 4-chloro-1-pyrazoyl, 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 the 4 to 6 membered heterocyclic group is the CrC₆ acyl group, this Ci-C₅ acyl group represents a carbonyl group substituted with hydrogen atom or CrC₅ alkyl group, and examples include, but are not limited to, a formyl, acetyl, propionyl, butyryl, pentanoyl and hexanoyl. Of these, C₂-C₆ acyl is preferred and acetyl is more preferred.

The term "-A-" in the compound of formula (I), as used herein, represents that the left bond of A is attached to quaternary carbon and the right bond is attached to adjacent aromatic carbon. (i.e. The compound of formula (I) wherein -A- represents -0-CH₂O⁻, O is linked to the quaternary carbon and CH₂ is linked to the adjacent aromatic carbon.)

The term "R¹" in the compound of formula (I), as used herein, represents that R¹ is attached to either one of aromatic nitrogens.

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

(a) \(-A- \equiv \text{-CH}_2\text{-CH}_2\text{-, -CH}_2\text{-CH}_2\text{-CH}_2\text{-, -CH}_2\text{-O-}, \text{-CH}_2\text{-O-CH}_2\text{-, or -CH}_2\text{CH}_2\text{O-};}

(b) \(-A- \equiv \text{-CH}_2\text{-CH}_2\text{-, -CH}_2\text{-O-}, \text{-CH}_2\text{-O-CH}_2\text{-, or -CH}_2\text{CH}_2\text{O-};}

(c) \(-A- \equiv \text{-CH}_2\text{-CH}_2\text{-, -CH}_2\text{-O- or -CH}_2\text{CH}_2\text{O-};}

(d) \(R^1\) is a hydrogen atom or a CrC\(_6\) alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a C\(_1\)\(-C_6\) alkoxy group, a hydroxy-substituted C3\(-C_7\) 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;

(e) \(R^1\) is hydrogen atom or a CrC\(_6\) alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC\(_6\) alkoxy group or a heteroaryl group;

(f) \(R^1\) is a hydrogen atom or a CrC\(_6\) alkyl group being substituted with a hydroxy group, C\(_1\)\(-C_6\) alkoxy group or a heteroaryl group;

(g) \(R^1\) is a hydrogen atom or a C\(_2\)-C\(_3\) alkyl group being substituted with a hydroxy group, a CrC\(_3\) alkoxy group, an isoxazole group, a thiazolyl group or a pyrazolyl group;

(h) \(R^1\) is a hydrogen atom or a C\(_2\)-C\(_3\) alkyl group being substituted with a hydroxy group, a methoxy group or an isoxazole group;

(i) \(R^1\) is a hydrogen atom or methoxyethyl;

(j) \(R^2\) is a hydrogen atom or a d-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 CrC\(_6\) alkoxy group;

(k) \(R^2\) is a CrC\(_6\) alkyl group;

(l) \(R^2\) is a C\(_1\)-C\(_3\) alkyl group;

(m)\(R^2\) is a methyl group;

(n) \(R^3\) and \(R^4\) are independently a hydrogen atom or a CrC\(_6\) alkyl being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a deuterium, a hydroxy group and a CrC\(_6\) alkoxy group;
(o) \( R^3 \) and \( R^4 \) are independently a CrC\(_6\) alkyl group being unsubstituted or substituted with one substituent selected from the group consisting of a hydroxy group and a C1-C\(_6\) alkoxy group or -CD\(_3\);
(p) \( R^3 \) and \( R^4 \) are independently a hydrogen atom, a C1-C\(_3\) alkyl group being unsubstituted or substituted with a hydroxy group or -CD\(_3\);
(q) \( R^3 \) and \( R^4 \) are independently a hydrogen atom, a methyl group, -CD\(_3\) or 2-hydroxyethyl group;
(r) \( R^3 \) and \( R^4 \) are independently a methyl group, -CD\(_3\) or 2-hydroxyethyl 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 CrC\(_6\) alkyl group, a C\(_r\) C\(_6\) acyl group, and a hydroxy-Ci-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, a halogen atom, an oxo group, a CrC\(_6\) alkyl group, a Ci-C\(_6\) acyl group and a hydroxy-Ci-C\(_6\) alkyl group;
(u) \( R^3 \) and \( R^4 \) taken together with the nitrogen atom to which they are attached form an azetidinyl, pyrrolidinyl 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-Ci-C\(_3\) alkyl group;
(v) \( R^3 \) and \( R^4 \) taken together with the nitrogen atom to which they are attached form a pyrrolidino group, a azetidino group or a morpholino group;
(w) \( R^3 \) and \( R^4 \) taken together with the nitrogen atom to which they are attached form a pyrrolidino group;
(x) \( R^5 \), \( R^6 \), \( R^7 \) and \( R^8 \) are independently a hydrogen atom, a halogen atom or a C\(_r\) C\(_6\) alkyl group;
(y) \( R^5 \) and \( R^7 \) are independently a hydrogen atom, a halogen atom or a CrC\(_6\) alkyl group;
(z) \( R^5 \) and \( R^7 \) are independently a hydrogen atom, a halogen atom or a methyl group;
(aa) \( R^5 \) and \( R^7 \) are independently a hydrogen atom or a halogen atom;
(bb) \( R^5 \) and \( R^7 \) are independently a hydrogen atom, a fluorine atom or a chlorine atom;
(cc) \( R^5 \) and \( R^8 \) are independently a hydrogen atom, a halogen atom or a CrC\(_6\) alkyl group;
group;
(dd) R^6 and R^8 are independently a hydrogen atom or a halogen atom;
(ee) R^6 and R^8 are independently a hydrogen atom, a fluorine atom or a chlorine atom;
(ff) R^5 is a hydrogen atom or a fluorine atom;
(gg) R^5 is a hydrogen atom;
(hh) R^7 is a hydrogen atom or a fluorine atom; and
(ii) R^8 is a hydrogen atom;

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

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

(A) -A- is \(-\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{O}\), \(-\text{O-CH}_2\), \(-\text{O-CH}_2\text{CH}_2\), \(-\text{CH}_2\text{O-CH}_2\) or \(-\text{CH}_2\text{CH}_2\text{O}\); R^1 is hydrogen atom or a CrC_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC_6 alkoxy group or a heteroaryl group; R^2 is a CrC_6 alkyl group; R^3 and R^4 are independently a hydrogen atom or a CrC_6 alkyl being unsubstituted or substituted with 1 to 3 substituents independently selected from the group consisting of a deuterium, a hydroxy group and a CrC_6 alkoxy group; 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 CrC_6 alkyl group, a C_r C_6 acyl group, and a hydroxy-d-C_6 alkyl group; R^5, R^6, R^7 and R^8 are independently a hydrogen atom, a halogen atom or a CrC_6 alkyl group;

(B) -A- is \(-\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{CH}_2\text{CH}_2\), \(-\text{CH}_2\text{O}\), \(-\text{O-CH}_2\), \(-\text{O-CH}_2\text{CH}_2\), \(-\text{CH}_2\text{O-CH}_2\) or \(-\text{CH}_2\text{CH}_2\text{O}\); R^1 is hydrogen atom or a CrC_6 alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC_6 alkoxy group or a heteroaryl group; R^2 is a CrC_6 alkyl group; R^3 and R^4 are independently a hydrogen atom, a C_r C_3 alkyl group being unsubstituted or substituted with a hydroxy group or -CD_3; 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, a halogen atom, an oxo group, a CrC_6 alkyl group, a CrC_6 acyl group and a hydroxy-C_1-C_6 alkyl group; R^5, R^6, R^7 and R^8
are independently a hydrogen atom, a halogen atom or a CrC₆ alkyl group;
(C) -A- is -CH₂-CH₂-, -CH₂-O-, -O-CH₂-, -CH₂-O-CH₂- or -CH₂-CH₂-O-; R¹ is hydrogen atom or a CrC₆ alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC₆ alkoxy group or a heteroaryl group; R² is a CrC₆ alkyl group; R³ and R⁴ are independently a hydrogen atom, a C₁-C₃ alkyl group being substituted with a hydroxy group or -CH₂-O-; R³ and R⁴ 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, a halogen atom, an oxo group, a CrC₆ alkyl group, a CrC₆ acyl group and a hydroxy-CrC₆ alkyl group; R⁵ and R⁷ are independently a hydrogen atom or a halogen atom; R⁶ and R⁸ are independently a hydrogen atom or a halogen atom;
(D) -A- is -CH₂-CH₂-, -CH₂-O-, -O-CH₂-, -CH₂-O-CH₂- or -CH₂-CH₂-O-; R¹ is hydrogen atom or a CrC₆ alkyl group being substituted with 1 to 2 substituents independently selected from the group consisting of a hydroxy group, a CrC₆ alkoxy group or a heteroaryl group; R² is a methyl group; R³ and R⁴ are independently a hydrogen atom, a methyl group, -CD₃ or 2-hydroxyethyl group; R³ and R⁴ 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, a halogen atom, an oxo group, a CrC₆ alkyl group, a C₁-C₆ acyl group and a hydroxy-CrC₆ alkyl group; R⁵ and R⁷ are independently a hydrogen atom or a halogen atom; R⁶ and R⁸ are independently a hydrogen atom or a halogen atom;
(E) -A- is -CH₂-CH₂-, -CH₂-O-, -O-CH₂-, -CH₂-O-CH₂- or -CH₂-CH₂-O-; R¹ is a hydrogen atom or a CrC₆ alkyl group being substituted with a hydroxy group, CrC₆ alkoxy group or a heteroaryl group; R² is a CrC₆ alkyl group; R³ and R⁴ are independently a hydrogen atom, a methyl group, -CD₃ or 2-hydroxyethyl group; R³ and R⁴ taken together with the nitrogen atom to which they are attached form a pyrrolidino group, an azetidinyl group or a morpholino group; R⁵ and R⁷ are independently a hydrogen atom or a halogen atom; R⁶ and R⁸ are independently a hydrogen atom or a halogen atom;
(F) -A- is -CH₂-CH₂-, -CH₂-O- or -CH₂-CH₂-O-; R¹ is a hydrogen atom or a C₂-C₃ alkyl group being substituted with a hydroxy group, a methoxy group or an isoxazole
group; R² is a CrC₆ alkyl group; R³ and R⁴ are independently a hydrogen atom, a methyl group, -CD₃ or 2-hydroxyethyl group; R³ and R⁴ taken together with the nitrogen atom to which they are attached form a pyrrolidino group, an azetidino group or a morpholino group; R⁵ and R⁷ are independently a hydrogen atom, a fluorine atom, a chlorine atom or a methyl group; R⁶ and R⁸ are independently a hydrogen atom, a fluorine atom or a chlorine atom.

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 and geometric isomers of the compounds of formula (I), including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition salts wherein the counterion is optically active, for example, D-lactate or L-lysine, or racemate, DL-tartrate or DL-arginine.

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

- Λ/Λ,2-Thmethyl-2',3',6,7-tetrahydro-1/-/-spiro[chromeno[7,8-of]imidazole-8,1'-indene]-5-carboxamide;
- (-)-Λ/Λ,2-Trimethyl-2\3\6J-tetrahydro-1H-spiro[chromeno[7 8-cf]imidazole-8,1'-inclene]-5-carboxamide;
- (+)-Λ/Λ,2-Thmethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8,1'-indene]-5-carboxamide;
- S'-Fluoro-Λ,Λ'-trimethyl^'.S'.ey-tetrahydro-IH-spirotchromeno^.'δ-cdimidazole-S.r-indene]-5-carboxamide;
- (-)-5'-Fluoro-Λ,Λ',2-trimethyl-2',3',6,7-tetrahydro-1 H-spiro[chromeno[7,8-c]imidazole-8, 1'- indene]-5-carboxamide;
- (+)-5'-Fluoro-Λ,Λ',2-thmethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8,r -indene]-5-carboxamide;
- 5J7'-Difluoro-/V,/V,2-trimethyl-2,3',6,7-tetrahydro-1 H-spiro[chromeno[7,8-c]imidazole-8, 1'- indene]-5-carboxamide;
- (-J-S'J'-Difluoro- Λ,Λ'-thmethyl^'.S'. 6J-tetrahydro-1H-spirolchromeno^.'δ-cdimidazole-8, 1'-indene]-5-carboxamide;
- (+)-5',7'-Difluoro-Λ,Λ',2-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8, 1'-indene]-5-carboxamide;
5J-Difluoro-/V, Λ,2'-trimethyl-2,3,6,7-tetrahydro-rH-spiro[chromene-4,8-l-chromeno[7,8-djimidazole]-5'-carboxamide;
4,6-Difluoro-A/, Λ,2'-trimethyl-6',7'-dihydro-1'//-spiro[1-benzofuran-3,8-l-chromeno[7,8-c/]imidazole]-5'-carboxamide;

or a pharmaceutically acceptable salt thereof.

More preferred embodiment of the invention is (+)-Λ,Λ,2-Trimethyl-2',3,6,7-tetrahydro-1'/-/-spiro[chromeno[7,8-c(/)]imidazole-8,1-l-indene]-5-carboxamide or a pharmaceutically acceptable salt thereof.

Another embodiment of the invention is a compound of the formula (I'):

```
   O
  ^ R^3
 /   \\     \               
N   R^4  |    |  R^1  R^2
     |\   |    |               
     \|   |    |               
    R^5
        |                 
        |                 
    R^6
```

or a pharmaceutically acceptable salt thereof, wherein;

R^1 represents 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, a CrC_6 alkoxy group, a hydroxy-substituted C_3-C_7 cycloalkyl group, a hydroxy-Ci-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;

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

R^3 and R^4 independently represent a hydrogen atom, a CrC_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 deuterium, a halogen atom, a hydroxy group, a CrC_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, a halogen atom, an oxo group, a CrC_6...
alkyl group, a CrC₆ acyl group, and a hydroxy-Ci-C6 alkyl group;
R⁵, R⁶, R⁷ and R⁸ independently represent a hydrogen atom, a halogen atom or a C-i-C₆ alkyl group; and

-A- represents \(-\text{CH}_2\text{-CH}_2\text{-}, \text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}, \text{-CH}_2\text{-O-}, \text{-0-CH}_2\text{-}, \text{-0-CH}_2\text{-CH}_2\text{-},\)
\(-\text{CH}_2\text{-O-CH}_2\text{-}, \text{-CH}_2\text{-CH}_2\text{-O-}, \text{-CH}_2\text{-S-}, \text{-S-CH}_2\text{-}, \text{-S-CH}_2\text{-CH}_2\text{-}, \text{-CH}_2\text{-S-CH}_2\text{-} or \text{-CH}_2\text{-CH}_2\text{-S-}.\)

Pharmaceutically acceptable salts of a compound of formula (I) include the acid addition 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.

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 the invention 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. D₂O, de-acetone, d₆-DivISO.
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 Halebian (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 $^{36}$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**

The compounds of the present invention may be prepared by a variety of processes well known for the preparation of compounds of this type, for example as shown in the following Method A.

Unless otherwise indicated, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸ and A in the following methods are as defined above. All starting materials in the following general syntheses may be commercially available or obtained by the following Method B or conventional methods known to those skilled in the art, such as WO 2004054984 and the disclosures which are incorporated herein by reference.

**Method A**

This figure illustrates the preparation of compounds of formula (I).

**Reaction Scheme A**
In Reaction Scheme A, \( R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 \) and \( A \) are each as defined above; \( A^a \) is \(-\text{CH}_2-\text{CH}_2-, -\text{CH}_2-\text{CH}_2-\text{CH}_2-, -\text{CH}_2-\text{O}, -\text{CH}_2-\text{O}-\text{CH}_2-, -\text{CH}_2-\text{CH}_2-\text{O}, -\text{CH}_2-\text{S}, -\text{CH}_2-\text{S}-\text{CH}_2-\text{S} \) or \(-\text{CH}_2-\text{CH}_2-\text{S}; A^b \) is \(-\text{O}-\text{CH}_2-, -\text{O}-\text{CH}_2-\text{CH}_2-, -\text{S}-\text{CH}_2- or -\text{S}-\text{CH}_2-\text{CH}_2-; \) Hal is a halogen atom, preferably a bromine atom; Prot\(^1\) is a hydroxy-protecting group; Prot\(^2\) is a nitrogen-protecting group; \( L_v \) is a leaving group; \( R_1^a \) is \( R_1 \) as defined above or \( R_1^a \) wherein hydroxy group is protected by a hydroxy-protecting group; \( R_2^a \) is \( R_2 \) as defined above, \( R_2^a \) wherein hydroxy group is protected by a hydroxy-protecting group; \( R_3^a \) is \( R_3 \) as defined above, \( R_3^a \) wherein hydroxy group is protected by a hydroxy-protecting group; \( R_4^a \) is \( R_4 \) as defined above or \( R_4^a \) 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, an 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, CrC₄ alkoxycarbonyl, CrC₄ alkylcarbonyl, tri-CrC₄ alkylsilyl or tri-CrC₄ alkylaryl silyl groups, and CrC₄ alkoxy- CrC₄ alkyl groups. Suitable hydroxy-protecting groups include acetyl and tert-butyl(dimethyl)silyl. The term "nitrogen-protecting groups", as used herein, signifies a protecting group capable of being cleaved by various means to yield a nitrogen moiety, such as hydrogenolysis, hydrolysis, electrolysis or photolysis, and such nitrogen-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, Ci-C₄ alkoxycarbonyl, CrC₄ alkylcarbonyl, tri-CrC₄ alkylsilyl, phenylsulfonyloxy group or aralkyl groups. Suitable amino or nitrogen-protecting groups include benzyl, tert-butoxycarbonyl and toluensulfonyl.

(Step A1)

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; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; amides, such as formamide, \(\Lambda,\Lambda\)-dimethylformamide, \(\Lambda,\Lambda\)-dimethylacetamide and hexamethylphosphoric triamide; carboxylic acids, such as acetic acid, formic acid, propanoic acid; Of these solvents, acetic acid or the reaction in the absence of solvents 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 \(\Lambda\)-methylmorpholine, triethylamine, thproplyamine, tributylamine, diisopropylethylamine, dicyclohexylamine, \(\Lambda\)-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(\(\Lambda,\Lambda\)-dimethylamino)pyridine, 2,6-di(tert-butyl)-4-methylpyridine, quinoline, \(\Lambda,\Lambda\)-dimethylaniline, \(\Lambda,\Lambda\)-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 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 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 10 minutes to about 24 hours will usually suffice.

(Step A2)

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

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 hexamethylenephosphoric 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 ethanol 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 or iron, and acids, such as hydrochloric acid, acetic acid and acetic acid-ammonium chloride.
complex. Of these, the combination of iron and 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 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.

(Step A3)

This reaction is described in detail by T. W. Greene et al., in 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 of alkoxy carbonyl or arylsulfonfyl.

Examples of the nitrogen-protecting group halide or anhydride usable in the above reaction include 4-methylphenylsulfonyl chloride, phenylsulfonyl chloride or di-terf-butyl-dicarbonate; of these 4-methylphenylsulfonyl chloride or di-terf-butyl-dicarbonate is preferred.

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 hexamethylphosphohc triamide; nitriles, such as acetonitile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; alcohols, such as methanol, ethanol, propanol, 2-propanol, ethylene glycol and butanol; or mixed solvents thereof. Of these, N,N-dimethylformamide is preferred.

Examples of such bases include: alkali metal hydroxides, such as lithium hydroxide, sodium hydroxide and potassium hydroxide; alkali metal hydrides, such as lithium hydride, sodium hydride and potassium hydride; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium tert-butoxide; alkali metal carbonates, such as lithium carbonate, sodium carbonate and potassium carbonate; alkali metal hydrogenocarbonates, such as lithium hydrogenocarbonate, sodium
hydrogencarbonate and potassium hydrogencarbonate; amines, such as
Ν-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, 
dicyclohexylamine, Ν-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 
4-(Ν,Ν-dimethylamino)pyridine, 2,6-di(te/f-butyl)-4-methylpyridine, quinoline, 
Ν,Ν-dimethylanilne, Ν,Ν-diethylaniline, DBN, DABCO and DBU; 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; or mixed bases thereof. Of these, sodium 
hydride or triethylamine 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 8 hours, will usually suffice.

(Step A4)

In this step, the compound of formula (VIII) is prepared by amidation of the 
compound of formula (VI) with the compound of formula (VII) in a carbon monoxide 
atmosphere. 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, 
Ν,Ν-dimethylformamide, Ν,Ν-dimethylacetamide and hexamethyolphosphoric triamide; 
nitriles, such as acetonitrile and benzonitrile; and ketones, such as acetone and 
diethylketone. Of these solvents, tetrahydrofuran 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 (II) acetate, tris(dibenzylideneacetone)dipalladiumchloroform, [1,2-bis(diphenylphosphino)ethane]palladium dichloride, bis(tri-o-toluy phosphoryne)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, tri-o-toluy phosphoryne, triphenylphosphine, 2-diphenylphosphino-2'-methoxy-1,1'-binaphthyl or 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. The above palladium catalyst is preferably tetrakis(triphenylphosphine)palladium.

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°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 60 minutes to about 72 hours, will usually suffice.

(Step A5)

In this step, deprotection of Prot^1 of the compound formula (VIII) is carried out. This reaction is described in detail by T. W. Greene et al., in 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 of benzyl.

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, \(\Lambda,N\)-dimethylformamide, \(\Lambda,N\)-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol and butanol; carboxylic acid, such as acetic acid or formic acid; Of these solvents, acetic acid or tetrahydrofuran is preferred.

The reaction is carried out in the presence of a palladium catalyst under the hydrogen gas. 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, 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 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 10 minutes to about 24 hours, will usually suffice.

(Step A6)

In this step, the compound (X) is prepared by Mannich reaction of the compound of formula (IX) with Eshenmoser's salt (\(\Lambda,N\)-dimethylmethyleneiminium iodide).

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, \(\Lambda,N\)-dimethylformamide, \(\Lambda,N\)-dimethylacetamide and hexamethylphosphoric triamide; nitriles, such as acetonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents, \(\Lambda,N\)-dimethylformamide or dichloromethane 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 hydroxides, such as lithium hydroxide, sodium hydroxide and
potassium hydroxide; alkali metal carbonates, such as lithium carbonate, sodium
carbonate and potassium carbonate; alkali metal hydrogenocarbonates, such as lithium
hydrogenocarbonate, sodium hydrogenocarbonate and potassium hydrogenocarbonate.
Of these, the reaction in the absence of base or potassium carbonate 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°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 10
minutes to about 24 hours, will usually suffice.

(Step A7)

In this step, the compound (XII) is prepared by Diels Alder reaction of the
compound of formula (X) with formula (Xla) or (Xlb). The compounds of formula (Xla),
which are commercially available or maybe prepared by Method B or methods described
in Heterocycles, 28, 55; 1989, Tetrahedron, 60, 1791; 2004 and Tetrahedron Letters, 43,
8269; 2002. The compounds of formula (Xlb) may be prepared by the methods

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:
aromatic hydrocarbons, such as benzene, toluene, xylene, chlorobenzene and
nitrobenzene; amides, such as formamide, \( \Lambda,\Lambda \)-dimethylformamide,
\( \Lambda,\Lambda \)-dimethylacetamide and hexamethylphosphoric triamide; nitiles, such as acetonitrile
and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane. Of these solvents,
xylene or chlorobenzene 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°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 effectuated under the preferred conditions outlined above, a period of from about 10 minutes to about 24 hours, will usually suffice.

(Step A8)

In this step, deprotection of Prot₂ of the compound formula (XII) is carried out.

The deprotection reaction is normally and preferably effectuated in the presence of a base. 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; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; alcohols, such as methanol, ethanol, propanol, 2-propanol, ethylene glycol and butanol; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; water; or mixed solvents thereof. Of these solvents, 2-propanol, water, or mixed solvents thereof 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, lithium hydroxide or sodium hydroxide is preferred. 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°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 10 minutes to about 24 hours, will usually suffice.  

(Step A9)

The compound of formula (I) is prepared by nucleophilic substitution of the compound of formula (Ia) with the compound of formula (XIII) followed by deprotection of the hydroxy-protecting group (A9b).  

(A9a) Alkylation

In the case where R¹ represents a substituent instead of a hydrogen atom, alkylation reaction will be carried out. 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°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 30 minutes to about 24 hours, will usually suffice.
(A9b) Deprotection of hydroxy-protecting group

In the case where R^1a, R^2a, R^3a, R^4a 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 tert-butyldimethylsilyl.

The deprotection of the hydroxyl groups is carried out with an acid, such as acetic acid, hydrogen fluoride, hydrogen fluohde-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°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 10 minutes to about 24 hours, will usually suffice.

**Method B**

This figure illustrates the preparation of compounds of formula (XIa).

**Reaction Scheme B**

![Reaction Scheme B](image)

(Step B1 )

In this step, the compound of formula (XIV) is prepared by halogenation (B1-a) followed by Friedel Crafts reaction (B1-b) or by cyclization (B1-c) of the compound of formula (XIII).
(B1-a) Halogenation

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; amides, such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoric triamide; amines, such as nitriles, such as acetonitrile and benzonitrile; or mixed solvents thereof. Of these, 1,2-dichloroethane or dichloromethane is preferred.

The reaction is carried out in the presence of a halogenating agent. There is likewise no particular restriction on the nature of the halogenating agents used, and any halogenating agent commonly used in reactions of this type may equally be used here. Examples of such halogenating agents include: thionyl chloride, oxalyl chloride and phosphorus oxychloride. Of these, thionyl chloride 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.

(B1-b) Friedel Crafts reaction

The reaction is normally and preferably effected in the presence or the absence 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, 1,1,2,2-tetrachlorohane and 1,2-dichloroethane; aromatic hydrocarbons, such as benzene, toluene and nitrobenzene; carbon disulfide; or mixed solvents thereof. Of
these, dichloromethane or carbon disulfide 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: Lewis acids, such as BF$_3$, AlCl$_3$, AlBr$_3$, FeCl$_3$, AgCl, ZnI$_2$, ZnCl$_2$, Fe(NO$_3$)$_3$, CF$_3$SO$_2$Si(CH$_3$)$_3$, Yb(CF$_3$SO$_3$)$_3$, and SnCl$_4$. Of these, AlCl$_3$ 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 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.

(B1-c) Cyclization

The reaction is normally and preferably effected in the presence or absence 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,N-dimethylformamide, N,N-dimethylacetamide and hexamethylphosphoramic triamide; or mixed solvents thereof. Of these, dichloromethane or the absence of solvent 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; acids, such as trifluoroacetic acid, or polyphosphoric acid. Of these, polyphosphoric 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 20°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.

(Step B2)

In this step, the compound of formula (Xla) is prepared by Wittig reaction from formula (XIV) with methyltriphenylphosphonium iodide. The compound of formula (Xla) may be prepared alternatively by methods described in Tetrahedron Letters, 26, 5579; 1985. The following exemplifies Wittig reaction.

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, 1,1-dimethylformamide, 1,1-dimethylacetamide and hexamethylphosphoril triamide; nitriles, such as acetonitrile and benzonitrile; sulfoxides, such as dimethyl sulfoxide and sulfolane; Of these solvents, diethyl ether or tetrahydrofuran 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; alkali metal alkoxides, such as sodium methoxide, sodium ethoxide and potassium f-butoxide; alkali metal amides, such as lithium amide, sodium amide, potassium amide, lithium diisopropyl amide, lithium bis(trimethylsilyl)amide and potassium bis(trimethylsilyl)amide, sodium hexamethyldisilazane, potassium hexamethyldisilazane; Of these, potassium f-butoxide 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°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 10 minutes to about 24 hours will usually suffice.

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 performance 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.

The preparation/isolation of individual enantiomers can be prepared by conventional techniques, such as chiral synthesis from a suitable optically pure precursor which may be prepared according to the Method C or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high-pressure liquid chromatography (HPLC) and supercritical fluid chromatography (SFC).

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.

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.

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).

**ORAL ADMINISTRATION**

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, pregelatinised 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, pregelatinised 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 tableting. The final formulation may comprise one or more layers and may be coated or uncoated; it may even be encapsulated.


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. 6,106,864. Details of other suitable release technologies such as high energy dispersions and osmotic and coated particles are to be found in Verma et al, Pharmaceutical Technology On-line, 25(2), 1-14 (2001). The use of chewing gum to achieve controlled release is described in WO00/35298.

PARENTERAL ADMINISTRATION

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, intrastemal, 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.

**TOPICAL ADMINISTRATION**

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, atomiser (preferably an atomiser 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 homogenization, 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 atomiser 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 100µl. 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 flavors, 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.

**RECTAL/INTRAVAGINAL ADMINISTRATION**

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 WO91/11172, WO94/02518 and WO98/55148.

**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 0.05 mg to about 500 mg depending, of course, on the mode of administration, preferred in the range of about 0.1 mg to about 400 mg and more preferred in the range of about 0.5 mg to about 300 mg. For example, oral administration may require a total daily dose of from about 1 mg to about 300 mg, while an intravenous dose may only require from about 0.5 mg to about 100 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 65 kg to about 70 kg. 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. A n 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), or a pharmaceutically acceptable salt thereof, as defined above, may be administered simultaneously, sequentially or separately in combination with one or more agents selected from:

(i) histamine H₂ receptor antagonists, e.g. ranitidine, lutfudine, 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\textsubscript{3} antagonists, e.g. dolasetron, palonosetron, alosetron, azasetron, ramosetron, mitrazapine, granisetron, tropisetron, E-3620, ondansetron and indisetron;

(vii) 5-HT\textsubscript{4} agonists, e.g. tegaserod, mosapride, cinitapride and oxtriptane;

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

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

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

(xi) calcium channel blockers, e.g. aranidipine, lacidipine, falodipine, azelnidipine, clinidipine, lomerizine, diltiazem, gallopamil, efondipine, nisoldipine, amlodipine, lercanidipine, bevantolol, nicardipine, isradipine, benidipine, verapamil, nitrendipine, bamidipine, 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,9Rk7-[3.S-bis^rifluoromethyloBenzyll]-δ.9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2, 1-g][1,7]naphthridine-6-1 3-dione (TAK-637), 5-[[2(R,3S)-2-[(1 R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholiny]meth yl]-1,2-dihydro-3H-1 ,2,4-thiazol-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. clarithromycin, roxithromycin, rokitamycin, fluhromycins, telithromycin, amoxicillin, ampicillin, temocillin, bacampicillin, aspoxicillin, sultamicillin, pipercillin, lenampicillin, tetracycline, metronidazole, bithmuth citrate and bithmuth subsalicylate;

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

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

(xvii) muscarinic receptor antagonists, e.g. trosprim, solifenacin, tolterodine, tiotropium, cimeropium, oxitropium, ipratropium, tiquizium, 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;
(xxii) 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. isoprotoreno and terbutaline;
(xxxii) alpha-2 agonists, e.g. clonidine, medetomidine, lofexidine, moxonidine, tizanidine, guanfacine, guanabenz, talipexole and dexmedetomidine;
(xxiv) endothelin 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) ghrelin agonists, e.g. capromorelin and TZP-101;
(xxix) AchE release stimulants, e.g. Z-338 and KW-5092;
(xxxx) CCK-B antagonists, e.g. ithglumide, 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) mGluR5 antagonists, e.g. ADX-10059 and AFQ-056;
(xxxvi) 5-HT3 agonists, e.g. pumosetrag (DDP733);
(xxxvii) mGluRδ 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: ml_ (milliliter(s)), µL (microlitter(s)), Kg (kirogram(s)), g (gram(s)), mg
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°C. 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-freeze until use. For enzyme assay, lyophilized vesicles were reconstituted with 3 mM MgSO\(_4\) containing 40 mM Bis-ths (pH 6.4 at 37°C).

Enzyme reaction was performed incubating 5 mM KCl, 3 mM Na\(_2\)ATP, 3 mM MgSO\(_4\) and 1.0 µg of reconstituted vesicles for 30 minutes at 37°C 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. All example compounds showed potent inhibitory activity.

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 MgSO₄ containing 5 mM Tris (pH 7.4 at 37°C).

Enzyme reaction was performed incubating 150 mM KCl, 3 mM Na₂ATP, 3 mM MgSO₄, 15 µM valinomycin and 3.0 µg of vesicles for 30 minutes at 37°C in a final 60 µl of reaction mixture (5 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.

The results of IC₅₀ values of the inhibitory activity for the compounds of following examples are shown in Table 1.

Table 1.

<table>
<thead>
<tr>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
<th>Example No.</th>
<th>IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>7</td>
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<td>13</td>
<td>0.130</td>
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<td>0.019</td>
<td>25</td>
<td>0.020</td>
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<td>8</td>
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<td>14</td>
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<td>0.025</td>
<td>26</td>
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<td>3</td>
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<td>9</td>
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<td>15</td>
<td>0.098</td>
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<td>0.067</td>
<td>27</td>
<td>0.041</td>
</tr>
<tr>
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<tr>
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<td>0.027</td>
</tr>
<tr>
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<td>18</td>
<td>0.036</td>
<td>24</td>
<td>0.027</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All the tested compounds showed acid pump antagonistic activity.

**Canine kidney Na⁺/K⁺-ATPase inhibition**

The powdered canine kidney Na₇K⁺-ATPase (Sigma) was reconstituted with 3 mM MgSO₄ containing 40 mM Tris (pH 7.4 at 37°C). Enzyme reaction was performed incubating 100 mM NaCl, 2 mM KCl, 3 mM Na₂ATP, 3 mM MgSO₄ 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 °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.

All example compounds showed potent inhibitory activity.

**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.

**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 °C with 2 M HCl containing 1 mM MgCl₂, 10 mM KCl. 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 -80°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 [³H]-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 -10µM 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 °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 °C) containing 1 mM MgCl₂, 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.

**PAMPA (parallel artificial membrane permeation assay)**

Experiments were performed in 96-well acceptor and donor plates. Such
96-well system was described in *J. Med. Chem.*, 1998, 41, 1007. 4% phosphatidylcholine and 1% stearic acid in dodecane were used as artificial membrane material. The acceptor plate (96 well hydrophobic filter plate (MAIP N45, Millipore)) was prepared by adding 5 µL of artificial membrane material on the top of the filter and the plate was filled with 250 µL of 2-(N-morpholino)ethanesulfonic acid (MES) buffered Hank’s balanced salt solution (HBSS) (pH 6.5). The donor plate (Transport Receiver plate (MATRNPS50, Millipore)) was filled with 300 µL of MES buffered HBSS (pH 6.5) containing 10 µM of the test compounds. The acceptor plate was placed onto the donor plate to form a "sandwich" and was incubated at 30°C for 2.5 hours. After the incubation period, acceptor, donor and initial donor solution (reference) were analyzed via LC-MS/MS. Data were reported as the effective permeability value in cm X 106/sec and the membrane retention value.

**Half-life in human liver microsomes (HLM)**

Test compounds (1 µM) were incubated with 1 mM MgCl₂, 1 mM NADP+, 5 mM isocitric acid, 1U/mL isocitric dehydrogenase and 0.8 mg/mL HLM in 100 mM potassium phosphate buffer (pH 7.4) at 37°C on a number of 384-well plates. At several time points, a plate was removed from the incubator and the reaction was terminated with two incubation volumes of acetonitrile. The compound concentration in supernatant was measured by LC/MS/MS system. The intrinsic clearance value was calculated using following equations:

\[
C_{\text{li,nt}} \frac{\text{ul/min/mg protein}}{\text{Protein concentration}} = k \times \text{incubation volume}
\]

Where, \(k\) = - slope of ln(concentration) vs. time (min-1)

**hERG patch clamp assay**

To determine the potential of compounds to inhibit the hERG channel, the cloned counterpart of the rapidly inactivating delayed rectifier potassium current (IKr).

HEK293 cells stably expressing the hERG channel were used in whole-cell patch clamp electrophysiology studies at ambient temperature (26.5-28.5°C). The methodology for stable transfection of this channel in HEK293 cells can be found elsewhere (Zhou et al 1998, Biophysical Journal, 74, pp230-241). The solutions used for experimentation were standard extracellular solution of the following composition
(mM); NaCl, 137; KCl, 4; CaCl$_2$, 1.8; MgCl$_2$, 1; Glucose, 10; HEPES, 10; pH 7.4 ± 0.05 with NaOH/HCl; and standard intracellular solution of the following composition (mM); KCl, 130; MgCl$_2$, 1; HEPES, 10; EGTA, 5; MgATP, 5; pH 7.2 ± 0.05 with KOH. The voltage protocol applied was designed to activate the hERG channel and allow the measurement of drug block of the channel and is as follows. First the membrane potential was stepped from a holding potential of -80mV to +30mV for 1s. This was followed by a descending voltage ramp at a rate of 0.5mV/ms back to holding potential of -80mV and the peak outward current observed during the repolarizing ramp was measured. This protocol was evoked repeatedly every 4 seconds (0.25Hz). After establishing a stable baseline period in the presence of vehicle (0.1 % v/v DMSO), four increasing concentrations of test compound were then bath-applied sequentially until the response reached steady-state or 10 minutes (whichever occurred first). 10 micromol/L dofetilide was used at the end of each experiment as an internal positive control and to define maximum block.

**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 °C 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:

\[ \text{fu} = 1 - \left( \frac{[\text{plasma}]_{eq} - [\text{buffer}]_{eq}}{[\text{plasma}]_{eq}} \right) \]

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 KH₂PO₄, 2.84 g of Na₂HPO₄ 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 1-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 % CO₂ with target cell density of 0.5 x 10⁶ 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 \( (k_o) \).

This value was scaled to take hepatocellularity, liver and body weight into account to give an intrinsic clearance value \( (\text{CL}_{int}) \) in ml/min/kg as illustrated in Equation 1. Hepatic clearance \( (\text{CL}_h) \) 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).

\[
\text{Equation 1: } k_o \times (\text{g liver/kg body weight}) \times (\text{ml incubation/number of cells in incubation}) \times (\text{cells/g liver})
\]

\[
\text{Equation 2: } \text{CL}_h = Q_h \times \left\{ 1 - \exp \left( -\frac{\text{CL}_{int}}{Q_h} \right) \right\}
\]

\[
\text{Equation 3: } E_h = \frac{\text{CL}_h}{Q_h}
\]

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 \( (\text{AUC}_{po}) \) after oral administration is calculated using Equation 4.

\[
\text{Equation 4: } \text{AUC}_{po} = \frac{\text{Dose} \times (1-E_h)}{\text{CL}_h}
\]

**RMS (Reactive Metabolite Screening)**

Tested compounds (100 µM) were incubated with 5 mM glutathione (GSH) and human liver microsomes (HL-101 : 2.0 mg/mL) in 100 mM phosphate buffer (pH 7.4). The reaction was initiated by addition of cofactors (3.3 mM glucose 6-phosphate, 3.3 mM MgCl₂, 10 unit/mL glucose 6-phosphate dehydrogenase, 1.3 mM NADP⁺ and 0.93 mM NADH). The final incubation volume was 1.5 ml. After 2 hr incubation at 37 °C, the reaction was stopped by addition of 1mL of 0.2 M monochloroacetic acid (MCA) and centrifuged at 3000 rpm for 15 min. The supernatant was attempted to solid phase extraction (isolute C18 SPE, International Sorbent Technology). This included
removing proteins, washing 3 times with 1mL of 0.2 M MCA and eluting twice with 2.5 mL of methanol. Following solvent dry-up, the residues were dissolved in 150 μL of 10% methanol containing 2 mM ammonium acetate and 0.027% formic acid and filtrated using centrifugal filter device (Ultrafree MC, Millipore). Analyses were measured by LC/MS/MS systems.

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 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 °C; evaporation of solvent was carried out using a rotary evaporator under reduced pressure with a bath temperature of up to 60 °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 F<sub>254</sub> precoated TLC plates or Merck NH<sub>2</sub> gel (an amine coated silica gel) F<sub>254</sub> 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). Preparative TLC was carried out using Merck silica gel 60 F<sub>254</sub> 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 dimethylsulfoxide (99.9%) as solvent unless indicated otherwise, relative to tetramethylsilane (TMS) as internal standard in parts per million (ppm); conventional abbreviations used are: s = singlet, d = doublet, m = multiplet, dd = doublet of doublet, sep = septet, br.s = broad singlet, br.d = broad doublet, etc. IR spectra were measured by a Fourier transform infrared spectrophotometer (Shimazu FTIR-8300). Optical rotations were measured using a P-1020 Digital Polarimeter (Japan Spectroscopic CO, Ltd.). Microwave irradiation was
carried out using Initiator 60 (Biotage).

### Example 1

\( \text{\textit{N,N'}}\text{-Trimethyl-2',a'ej-tetrahdro-IH-spirochromenory.S-c \text{\pi}imidazole-S.l'-inden} \) 5-carboxamide

#### STEP 1: \( \text{\textit{N}}'\text{-}(4\text{-Bromo-2-nitro-6}\text{-r(phenylmethyl)oxylphenyl})\text{acetamide} \)

To a solution of 4-bromo-2-nitro-6-[\( \text{\pi} \text{oxy}\text{]aniline} \) (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 give the title compound as a brown solid (30.9 g, 83%).

\(^1\text{H NMR} \) (\( \text{CDCl}_3 \), 270 MHz) \( \delta \): 7.69 (d, \( J = 2.0 \text{ Hz} \), 1H), 7.56 (br. s, 1H), 7.47-7.38 (m, 5H), 7.34 (d, \( J = 2.0 \text{ Hz} \), 1H), 5.14 (s, 2H), 2.16 (s, 3H) ppm.

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

#### STEP 2: 6-Bromo-2-methyl-4-r(phenylmethyl)oxyl-1/-/-benzimidazole

A mixture of \( \text{\textit{N}}'\text{-}(4\text{-Bromo-2-nitro-6}\text{-r(phenylmethyl)oxylphenyl})\text{acetamide} \) (120 g, 329 mmol, STEP 1) and iron powder (55.1 g, 986 mmol) in acetic acid (500 ml) was refluxed with stirring for 6 hours. After cooling to room temperature, the mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuum. The residue was diluted with ethyl acetate (1.5 L). The resulted precipitates were filtered through a pad of Celite, and washed with ethyl acetate (500 ml). The filterate was concentrated in vacuum, and the residue was diluted with ethyl acetate (200 ml). The brine (800 ml) was added to the organic mixture, the resulted white precipitates were collected by filtration, and washed with water (200 ml) and diethyl ether (200 ml). The white solid was dissolved with dichloromethane/methanol (10 : 1, 1.0 L), dried over magnesium sulfate, and concentrated. The solid was triturated with diethyl ether (300
mL), collected by filtration, and dried in vacuum to afford the title compound as a white solid (54.7 g, 53%).

\(^1\)H NMR (DMSO-\textit{d}_6, 270 MHz) \(\delta: 7.63-7.28\) (m, 7H), 5.38 (s, 2H), 2.69 (s, 3H) ppm. (NH was not observed.)

MS (ESI) m/z: 317 (M+H)\(^+\), 315 (M-H)\(^-\).

STEP 3:

6-Bromo-2-methyl-1-r(4-methylphenyl)sulfonyl-4-f(phenylmethyloxy)-1H-benzimidazole

To a suspension of 6-bromo-2-methyl-4-[(phenylmethyl)oxy]-1H-benzimidazole (79.2 g, 250 mmol, STEP 2) in \(\Lambda, \Lambda\)-dimethylformamide (500 mL) was added sodium hydride (60% in mineral oil, 12.0 g, 300 mmol) at 0 °C. After stirring at room temperature for 20 minutes, the reaction mixture was cooled to 0 °C. To the mixture was added 4-methylbenzenesulfonyl chloride (47.6 g, 250 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 30 minutes. The mixture was quenched with water (800 mL), and the white precipitates were collected by filtration, washed with diisopropyl ether (500 mL), and dried in vacuum at 70 °C for 7 hours to afford the title compound as a white solid (116 g, 98%).

\(^1\)H NMR (DMSO-cf, 270 MHz) \(\delta: 7.98\) (d, \(J = 8.1\) Hz, 2H), 7.64 (d, \(J = 1.9\) Hz, 1H), 7.53-7.34 (m, 7H), 7.22 (d, \(J = 1.9\) Hz, 1H), 5.28 (s, 2H), 2.74 (s, 3H), 2.38 (s, 3H) ppm.

MS (ESI) m/z: 471 (M+H)\(^+\), 469 (M-H)\(^-\).

STEP 4: \(\Lambda, \Lambda, 2\)-Trimethyl-1-r(4-methylphenyl)sulfonyl-1-4-r(phenylmethyloxy)-1H-benzimidazole-6-carboxamide

A mixture of 6-bromo-2-methyl-1-[(4-methylphenyl)sulfonyl]-4-[(phenylmethyl)oxy]-1H-benzimidazole (53.0 g, 112 mmol, STEP 3) and tetrakis(triphenylphosphine) palladium(O) (25.9 g, 22.4 mmol) in 2M dimethylamine tetrahydrofuran solution (580 mL) was stirred at 65 °C under carbon mono-oxide gas (1 atmosphere) for 32 hours. The mixture was cooled to room temperature, and diluted with ethyl acetate (600 mL). The organic mixture was washed with saturated ammonium chloride aqueous solution (800 mL) and brine (500 mL), dried over magnesium sulfate and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate gradient elution from 1 : 2 to 1 : 3) to affor
d the title compound as a white solid (21.8 g, 42%).

1H NMR (CDCl₃, 270 MHz) δ: 7.80 (d, J = 8.1 Hz, 2H), 7.70 (s, 1H), 7.45 (d, J = 8.1 Hz, 2H), 7.40-7.22 (m, 5H), 6.86 (s, 1H), 5.32 (s, 2H), 3.11 (br. s, 3H), 2.89 (br. s, 3H), 2.81 (s, 3H), 2.40 (s, 3H) ppm.

MS (ESI) m/z: 464 (M+H)+.

STEP 5:

4-Hydroxy- N,N,2-trimethyl-1-[(4-methylphenyl)sulfonyl]-1/-/-benzimidazole-6-carboxamide

A mixture of N,N,2-trimethyl-1-[(4-methylphenyl)sulfonyl]-4-[[phenylmethyl]oxy]-1H-benzimidazole-6-carboxamide (29.0 g, 62.6 mmol, STEP 4) and 10% palladium on carbon (6.0 g) in tetrahydrofuran (200 ml) was stirred under hydrogen gas (1 atmosphere) at room temperature for 24 hours. Another 4.0 g of 10% palladium on carbon was added, and the mixture was stirred under hydrogen gas (1 atmosphere) at room temperature for additional 6 hours. The resulted mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuum to afford the title compound as a white solid (23.0 g, 98%).

1H NMR (CDCl₃, 270 MHz) δ: 7.82 (d, J = 8.1 Hz, 2H), 7.63 (s, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.92 (s, 1H), 3.14 (br. s, 3H), 3.01 (br. s, 3H), 2.79 (s, 3H), 2.40 (s, 3H) ppm (-OH was not observed).

MS (ESI) m/z: 374 (M+H)\ 372 (M-H)⁻.

Step 6: 5-(Dimethylamino)methyl-4-hydroxy- N,N,2-trimethyl-1 -r(4-methylphenyl)sulfonyl-\ 1/-/-benzimidazole-6-carboxamide

A mixture of 4-hydroxy- N,N,2-trimethyl-1-[(4-methylphenyl)sulfonyl]-1/-/-benzimidazole-6-carboxamide (15 g, 40 mmol, STEP 5) and N,N-dimethylmethyleniminium iodide (8.9 g, 48 mmol) in dichloromethane (200 ml) was stirred at 40 °C for 15 hours. The reaction mixture was cooled to room temperature, and quenched with saturated sodium hydrogen carbonate aqueous solution (200 ml). The mixture was extracted with dichloromethane (200 ml x 2). The combined organic layer was dried over magnesium sulfate and concentrated in vacuum. The residue was purified by column chromatography on amino gel (hexane : ethyl acetate gradient elution from 1 : 1 to ethyl
acetate only) to afford the title compound as a white amorphous (15.5 g, 90%).

$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.79-7.76 (d, $J = 8.1$ Hz, 2H), 7.35-7.30 (m, 3H), 3.90-3.50 (br. s, 2H), 3.17 (s, 3H), 2.86 (s, 3H), 2.77 (s, 3H), 2.40 (s, 3H), 2.35 (s, 6H) ppm (-OH was not observed).

MS (ESI) m/z: 431 (M+H$^+$), 429 (M-H$^-$).

**Step 7**:  \(N,N\_2\text{-Trimethyl-3-r(4-methylphenyl)sulfonyl}-2\_3\_6\_7\text{-tetrahydro-3H-spiro[chromeno[7,8-c]imidazole-8,1\_indene]-5-carboxamide}\)

A mixture of

\[5-[(\text{dimethylamino})\text{methyl}]-4\text{-hydroxy-} \ N,N\_2\text{-thmethyl-1-[(4-methylphenyl)sulfonyl]}\] 1/-/-benzimidazole-6-carboxamide (2.0 g, 4.7 mmol, STEP 6) and 1-methyleneindane (1.2 g, 9.3 mmol, *Molecules*, 2005, 10, 217.) in o-xylene (50 ml) was stirred at 150 $^\circ$C for 10 hours. The reaction mixture was cooled to room temperature, the solvent was removed in vacuum. The residue was purified by column chromatography on amino gel (hexane : ethyl acetate gradient elution from 1 : 1 to ethyl acetate only) to afford the title compound as a white amorphous (1.2 g, 50%).

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$: 7.80-7.77 (d, $J = 8.8$ Hz, 2H), 7.51 (s, 1H), 7.30-7.17 (m, 6H), 3.19 (s, 3H), 3.13-3.08 (m, 1H), 2.92 (s, 3H), 2.95-2.85 (m, 2H), 2.75 (s, 3H), 2.40 (s, 3H), 2.49-2.02 (m, 5H) ppm.

MS (ESI) m/z: 516 (M+H$^+$), 514 (M-H$^-$).

**Step 8**:  \(N,N\_2\text{-2\_trimethyl-2\_3\_6\_7\text{-tetrahydro-1\_H-spirochromenor7.8-c\_imidazole-8,1\_indene}-5\text{-carboxamide}}\)

A mixture of \(N,N\_2\text{-2\_trimethyl-3-[(4-methylphenyl)sulfonyl]}\_2\_3\_6\_7\text{-tetrahydro-3\_/-/-spiro[chromeno[7,8-c]imidazole-8,1\_indene]-5\text{-carboxamide}}\) (1.2 g, 2.3 mmol, STEP 7) in 2M sodium hydroxide aqueous solution (30 ml) and 2-propanol (30 ml) was stirred at 40 $^\circ$C for 8 hours. The reaction mixture was cooled to room temperature, and diluted with water (30 ml). The mixture was extracted with dichloromethane (50 mL x 2), dried over magnesium sulfate and concentrated in vacuum. The residue was purified by column chromatography on amino gel (ethyl acetate : methanol = 30 : 1 as an eluent) to afford the title compound as a white amorphous (0.85 g, quant.).

$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 8.97 (br. s, 1H), 7.34-7.15 (m, 5H), 3.16 (s, 3H), 3.18-3.07
Example 2

(-)-N,N,2-Trimethyl^'.S'.βJ-tetrahdro-IH-spirochromenor/S-c πimidazole-8.i'-indo
enei-5-carboxamide and

Example 3

(+)-N,yV,2-Trimethyl-2'.3'.6,7-tetrahdro-1H-spirochromenor7,8-cπimidazole-8,1'-Ind
enel-5-carboxamide

The fraction-1 (332 mg) and fraction-2 (334 mg) were prepared from racemic
N,N,2-trimethyl-2',3',6,7-tetrahydro-1/-/spiro[chromeno[7,8-c]imidazole-8,1 '^'-indene]-5-ca
rbboxamide (850 mg, STEP 8 of Example 1) by HPLC as follows.

Isolation condition

Column: CHIRALPAK AD-H (20 mm x 250 mm, DAICEL)

Mobile phase: n-Hexane / Ethanol / Diethylamine (90 / 10 / 0.1)

Flow rate: 20 mL/min

(-)-N,N,2-Trimethyl-2',3',6,7-tetrahdro-1 H-spirochromenor7,8-cπimidazole-8,1'-Ind
enel-5-carboxamide (fraction-1)

NMR: spectrum data were identical with those of the racemate

optical rotation: [α]23D = -48 ° (C = 0.51, Methanol)

optical purity: >99 %e.e.

retention time: 10.6 min

(+)-N,N,2-Trimethyl-2',3',6,7-tetrahdro-1 H-spirochromenor7,8-cπimidazole-8,1'-Ind
enel-5-carboxamide (fraction-2)

NMR: spectrum data were identical with those of the racemate

optical rotation: [α]23D = +43° (C =0.54, Methanol)

optical purity: >99 %e.e.

retention time: 14.8 min

Example 4

5'-Fluoro-/V,yV,2-trimethyl-2',3',6,7-tetrahdro-1H-spirochromenor7,8-c πimidazole-8
,1'-indene1-5-carboxamide
Step 1: 5-Fluoro-1-methyleneindane

To a suspension of methyltriphenylphosphonium iodide (6.48 g, 16.0 mmol) in diethyl ether (70 ml) was added potassium tert-butoxide (1.80 g, 16.0 mmol) at room temperature. The reaction mixture was stirred for 30 minutes. To this mixture was added 5-fluoroindan-1-one (2.00 g, 13.3 mmol) in diethyl ether (30 ml) over 5 minutes. The reaction suspension was stirred for 15 hours at the same temperature and filtered. The filtrate was concentrated in vacuum, and the residue was purified by column chromatography on silica gel (hexane as an eluent) to afford the title compound as a colorless oil.

$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.45-7.40 (m, 1H), 6.94-6.85 (m, 2H), 5.36 (s, 1H), 4.99 (s, 1H), 2.99-2.79 (m, 4H) ppm.

Step 2:

5'-Fluoro-$\Lambda,\Lambda$/2-trimethyl-3-f(4-methylphenyl)sulfonyl-2',3',6,7-tetrahydro-3H-spirochromeno[7,8-Cf]imidazole-8,1'-indenel-5-carboxamide

The title compound was prepared as a white amorphous (1.4 g, 56%) from 5-[(dimethylamino)methyl]-4-hydroxy-$\Lambda,\Lambda$/2-trimethyl-1-[(4-methylphenyl)sulfonyl]-1/-/-benzimidazole-6-carboxamide (2.0 g, 4.7 mmol, STEP 6 of Example 1) and 5-fluoro-1-methyleneindane (1.7 g, 11.5 mmol, STEP 1) by the same manner in STEP 7 of Example 1.

$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.80-7.77 (d, $J = 8.8$ Hz, 2H), 7.52 (s, 1H), 7.30-7.22 (m, 3H), 6.95-6.84 (m, 2H), 3.19 (s, 3H), 3.12-3.07 (m, 1H), 2.92 (s, 3H), 2.98-2.79 (m, 2H), 2.75 (s, 3H), 2.40 (s, 3H), 2.51-2.18 (m, 4H), 2.08-2.00 (m, 1H) ppm.

MS (ESI) m/z: 534 (M+H$^+$).

Step 3: 5'-Fluoro-$\Lambda,\Lambda$/2-trimethyl-2',3',6.7-tetrahydro-1'H-spirochromeno[8,1'-indenel-5-carboxamide

The title compound was prepared as a white amorphous (658 mg, 67%) from
5'-fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-3-[(4-methylphenyl)sulfonyl]-2',3',6,7-tetrahydro-3/-/-spiro[chromeno[7,8-c][imidazole-8,1'-indenene]-5-carboxamide (1.39 g, 2.61 mmol, STEP 2) by the same manner in STEP 8 of Example 1.

\[ \delta : 9.06 \text{ (br. s, 1H), 7.31-7.29 \text{ (m, 1H), 7.16 \text{ (s, 1H), 7.02-6.92 \text{ (m, 2H), 3.17 \text{ (s, 3H), 3.11-3.06 \text{ (m, 2H), 2.91 \text{ (s, 3H), 2.96-2.88 \text{ (m, 2H), 2.54 \text{ (s, 3H), 2.42-2.19 \text{ (m, 3H), 2.09-2.02 \text{ (m, 1H ppm.}} \]

MS (ESI) m/z: 380 (M+H)\(^+\), 378 (M-H).

Example 5

(-)-5'-Fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-2',3',6,7-tetrahydro-1H-spirochromeno7,8-imidazole-8,1'-indenene-5-carboxamide and Example 6

(+)-5'-Fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-2',3',6,7-tetrahydro-1H-spirochromeno7,8-imidazole

The fraction-1 (278 mg) and fraction-2 (231 mg) were prepared from racemic S'-fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-2',3',6,7-tetrahydro-1H-spirochromeno7,8-imidazole-δ-c/limidazole-δ.i'-indenene]-5-carboxamide (650 mg, STEP 3 of Example 4) by SFC as follows.

Isolation condition

Apparatus: Berger MultiGram II™, Mettler-Toledo
Column: CHIRALPAK® AD-H (20 x 250 mm, DAICEL)
Column temp: 35 \(^{\circ}\)C
Outlet pressure: 100 bar
Mobile phase: Carbon dioxide/[Methanol/Diethylamine = 100/0.1 (v/v)] = 85/15 (v/v)
Flow rate: 40 mL/min

(-)-5'-Fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-2',3',6,7-tetrahydro-1H-spirochromeno7,8-c/limidazole-8,1'-indenene-5-carboxamide (fraction-1)

NMR: spectrum data were identical with those of the racemate
optical rotation: \([\alpha]_D^{23} = -42 ^{\circ} \text{ (C = 0.51 , Methanol)}\)
optical purity: 87 %e.e.
retention time: 7.4 min

(+)-5'-Fluoro-\( \Lambda, \Lambda', 2\)-trimethyl-2',3',6,7-tetrahydro-1H-spirochromeno7,8-Qf1imidazole e-8,1'-
NMR: spectrum data were identical with those of the racemate
optical rotation: \([\alpha]_D^{23} = +38^\circ\) (C = 0.51, Methanol)
optical purity: 96 %e.e.
retention time: 8.4 min

**Example 7**

**δJ'-Difluoro-  \(\Lambda,\Lambda\)-trimethyl\',\',a\'-tetrahydro-IH-spirochromenory. δ-\(\text{imidazo} \leq 8,1\'-\text{indenel-5-carboxamide} \)**

![Chemical Structure](image)

**Step 1: 5.7-Difluoro-1-methyleneindane**

The title compound was prepared as a colorless oil (1.75 g, 88%) from 5,7-Difluoroindan-1-one (2.00 g, 11.9 mmol) by the same manner in STEP 1 of Example 4.

\(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta: 6.86-6.36 \text{ (m, 2H)}, 5.61 \text{ (s, 1H)}, 5.19 \text{ (s, 1H)}, 3.18-2.52 \text{ (m, 4H)} \) ppm.

**Step 2:**

**5',7'-Difluoro- \(\Lambda,\Lambda\),2-thmethyl-3-[(4-methylphenyl)sulfonyl]-2\',3\',6\',7-tetrahydro-3H-**

**spirochromenory7,8-c \(\text{imidazole-8,1'}\)-indenel-5-carboxamide**

The title compound was prepared as a white amorphous (1.0 g, 42%) from 5-[(dimethylamino)methyl]-4-hydroxy- \(\Lambda,\Lambda,2\)-thmethyl-1-[(4-methylphenyl)sulfonyl]-1/-/-be \nmimidazole-6- carboxamide (2.0 g, 4.7 mmol, STEP 6 of Example 1) and 5,7-difluoro-1-methyleneindane (1.6 g, 9.6 mmol, STEP 1) by the same manner in STEP 7 of Example 1.

\(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta: 7.80-7.77 \text{ (d, } J = 8.8 \text{ Hz, 2H)}, 7.52 \text{ (s, 1H)}, 7.30-7.27 \text{ (d, } J = 8.8 \text{ Hz, 2H), 6.77-6.74 \text{ (dd, } J = 8.1, 1.5 \text{ Hz, 1H)}, 6.65-6.58 \text{ (dt, } J = 9.5, 1.5 \text{ Hz, 1H)}, 3.19 \text{ (s, 3H), 3.14-3.12 \text{ (m, 1H)}}, 2.91 \text{ (s, 3H)}, 2.94-2.86 \text{ (m, 2H)}, 2.75 \text{ (s, 3H)}, 2.79-2.68 \text{ (m, 1H)}, 2.40 \text{ (s, 3H)}, 2.47-2.43 \text{ (m, 1H)}, 2.27-2.18 \text{ (m, 1H)}, 2.12-2.02 \text{ (m, 2H)} \) ppm.
MS (ESI) m/z: 552 (M+H)^+, 550 (M-H)^-.

Step 3: 5',Z'-Difluoro-Λ,Λ'-trimethyl',S'. 6J-tetrahydro-IH-spirochromenofy. δ-cηimidazole-δ.i'

5'-indenel -5-carboxamide

The title compound was prepared as a white amorphous (684 mg, 90%) from 5'J'-difluoro- Λ,Λ',2-
trimethyl-3-[(4-methylphenyl)sulfonyl]-2',3',6,7-tetrahydro-3/-/spiro[chromeno[7,8-c/limid
azole-8,1'-indene]-5-carboxamide (1.06 g, 1.92 mmol, STEP 2) by the same manner in
STEP 8 of Example 1.

'H NMR (CDCl₃, 270 MHz) δ: 9.10 (br. s, 1H), 7.15 (s, 1H), 6.88-6.61 (m, 2H), 3.16 (s,
3H), 3.20-3.06 (m, 1H), 2.90 (s, 3H), 3.02-2.70 (m, 3H), 2.54 (s, 3H), 2.46-2.30 (m, 1H),
2.25-2.02 (m, 3H) ppm.

MS (ESI) m/z: 398 (M+H)^+, 396 (M-H)^-.

Example 8
(-)-5',7'-Difluoro- Λ,Λ'/2-trimethyl-2',3',6,7-tetrahydro-1H-spirochromenor7,8-c ηimid
azole-8,1'-indenel-5-carboxamide and

Example 9
(+)-5',7'-Difluoro-yV,yV/2-trimethyl-2',3',6,7-tetrahydro-1H-spirochromenor7,8-c πimid
azole-8,1'-indene1-5-carboxamide

The fraction-1 (155 mg) and fraction-2 (278 mg) were prepared from racemic
S'J'-difluoro- Λ,Λ'-trimethyl',S'.ej-tetrahydro-1H-spirochromeno^A.S-c/limidazole-
δ.r
-indene]-5-carboxamide (680 mg, STEP 3 of Example 7) by SFC as follows.

Isolation condition

| Apparatus: | Berger MultiGram II™, Mettler-Toledo |
| Column:    | CHIRALPAK® AD-H (20 x 250 mm, DAICEL) |
| Column temp: | 35 °C |
| Outlet pressure: | 100 bar |
| Mobile phase: | Carbon dioxide/[Methanol/Diethylamine =100/0.1(v/v)] = 90/10 (v/v) |
| Flow rate: | 40 mL/min |

(-V5',7'-Difluoro- Λ,Λ'/2-trimethyl-2',3',6,7-tetrahydro-1H-spirochromenor7,8-c/limidazole-
8.1'-indenel-5-carboxamide (fraction-1)
NMR: spectrum data were identical with those of the racemate
optical rotation: $[\alpha]_D^{23} = -15.6^\circ$ (C = 0.52, Methanol)
optical purity: >99 %e.e.
retention time: 6.7 min

(+)-5'.7'-Difluoro-N,N,2-trimethyl-2',3',6',7'-tetrahydro-1H-spirorchromenor7.8-(/limidazole-8,1'-indenei-5-carboxamide (fraction-2)
NMR: spectrum data were identical with those of the racemate
optical rotation: $[\alpha]_D^{23} = +17.8^\circ$ (C = 0.53, Methanol)
optical purity: 97 %e.e.
retention time: 7.7 min

Example 10
5.7-Difluoro-/V,/V,2'-trimethyl-2,3,6',7'-tetrahydro-1'tf-spirorchromene-4.8'-chromen or7,8-tf1imidazole1-5'-carboxamide

STEP 1: 5.7-Difluoro-4-methylenechromane

To a suspension of zinc powder (activated by washing with aqueous hydrochloric acid) (40.0 g, 612 mmol) in tetrahydrofuran (100 ml) was added diiodomethane (0.4 ml) at room temperature. After stirring at room temperature for 5 minutes, the mixture was treated with sonication for 1 minute. To the mixture was added dropwise a solution of diiodomethane (18.1 ml, 225 mmol) in tetrahydrofuran (100 ml) at room temperature with keeping the inner temperature below 26°C. After stirring at room temperature for additional 30 minutes, the mixture was stood overnight. A part of the supernatant (49 ml) was transferred to another reaction vessel. To this was added dropwise a solution of titanium tetrachloride (2.40 mL, 21.7 mmol) in dichloromethane (20 mL) at 0°C. After stirring at the same temperature for 20 minutes, a solution of 5,7-difluoro-2,3-dihydro-4H-chromen-4-one (2.00 g, 10.9 mmol, US2005038032) in dichloromethane (30 mL) was added to the mixture. After stirring at
the same temperature for 30 minutes, the mixture was quenched with saturated aqueous ammonium chloride solution (300 ml), and the aqueous layer was extracted with diisopropyl ether (200 ml x 3). The combined organic layer was dried over magnesium sulfate, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 20 : 1 as an eluent) to afford the title compound as a colorless oil (1.19 g, 60%).

\(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta: 6.47-6.36 \text{ (m, 2H)}, 5.73 \text{ (s, 1H)}, 5.14 \text{ (br. s, 1H)}, 4.25 \text{ (t, } J = 5.9 \text{ Hz, 2H)}, 2.62 \text{ (t, } J = 5.9 \text{ Hz, 2H)}.

STEP 2: 5.7-Difluoro-\(\Lambda,\Lambda\)'-trimethyl-3'-\(\Lambda,\Lambda\)'-trimethyl-3'-r(4-methylphenylsulfonvnyl)-2.3.6'-7'-tetrahydro-3'H-spirorchromene-4,8'-chromeno[7,8-c]\(\pi\)imidazole1-5'-carboxamide

The title compound was prepared as a white amorphous (317 mg, 17%) from 5-[(dimethylamino)methyl]-4-hydroxy-\(\Lambda,\Lambda\)'-trimethyl-1-[(4-methylphenyl)sulfonyl]-1\(\text{H}\)-benzimidazole-6-carboxamide (1.41 g, 3.27 mmol, STEP 6 of Example 1) and 5,7-difluoro-4-methylenechromane (1.19 g, 6.53 mmol, STEP 1) by the same manner in STEP 7 of Example 1.

\(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta: 7.80 \text{ (d, } J = 8.6 \text{ Hz, 2H)}, 7.54 \text{ (s, 1H)}, 7.29 \text{ (d, } J=8.6 \text{ Hz, 2H)}, 6.46-6.34 \text{ (m, 2H)}, 4.31-4.10 \text{ (m, 2H)}, 3.19 \text{ (s, 3H)}, 3.0-2.6 \text{ (m, 2H)}, 2.92 \text{ (s, 3H)}, 2.77 \text{ (s, 3H)}, 2.40 \text{ (s, 3H)}, 2.4-1.8 \text{ (m, 4H)}.

MS (ESI) m/z: 568 (M+H)\(^+\), 566 (M-H)\(^-\).

STEP 3: 5.7-Difluoro-\(\Lambda,\Lambda\)'-trimethyl-2.3.6'-7'-tetrahydro-1\(\text{H}\)-spirorchromene-4,8'-chromeno7.8-\(\pi\)imidazole1-5'-carboxamide

The title compound was prepared as a white amorphous (233 mg, 86%) from 5,7-difluoro-4-methylenechromane (1.41 g, 6.53 mmol, STEP 1) by the same manner in STEP 8 of Example 1.

\(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta: 9.35 \text{ (br. s, 1H)}, 7.16 \text{ (s, 1H)}, 6.55-6.35 \text{ (m, 2H)}, 4.35-4.07 \text{ (m, 2H)}, 3.15 \text{ (s, 3H)}, 3.0-2.5 \text{ (m, 2H)}, 2.92 \text{ (s, 3H)}, 2.53 \text{ (s, 3H)}, 2.5-1.9 \text{ (m, 4H)}.

MS (ESI) m/z: 414 (M+H)\(^+\), 412 (M-H)\(^-\).

Example 11

4.6-Difluoro-\(\Lambda,\Lambda\)'-trimethyl-6',7'-dihydro-1\(\text{H}\)-Sdiron-benzofuran-3.8'-chromen...nor7.
δ-imidazol-5'-carboxamide

**STEP 1:** 1-(Allyloxy)-3,5-difluoro-2-iodobenzene

A mixture of 3,5-difluoro-2-iodophenol (10.6 g, 41.3 mmol, *Synthesis, 2006, 1578*), allyl bromide (5.4 mL, 61.9 mmol), and potassium carbonate (11.4 g, 82.5 mmol) in \(Λ,Λ\)-dimethylformamide (100 mL) was stirred at 70°C for 5 hours. After cooling to room temperature, the mixture was poured onto water (300 mL), and the aqueous layer was extracted with diisopropyl ether (200 mL x 2). The combined organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane : ethyl acetate = 30 : 1 as an eluent) to afford the title compound as a colorless oil (10.9 g, 89%).

\(^1\)H NMR (CDCl\(_3\), 270 MHz) δ: 6.57-6.38 (m, 2H), 6.12-5.96 (m, 1H), 5.53 (d, \(J = 17.1\) Hz, 1H), 5.36 (d, \(J = 10.6\) Hz, 1H), 4.62-4.57 (m, 2H).

**STEP 2:** 4,6-Difluoro-3-methylene-2,3-dihydro-1-benzofuran

A mixture of 1-(allyloxy)-3,5-difluoro-2-iodobenzene (5.15 g, 17.4 mmol, STEP 1), tetrakis(triphenylphosphine)palladium(0) (2.01 g, 1.74 mmol), and silver carbonate (9.59 g, 34.8 mmol) in \(Λ,Λ\)-dimethylformamide (100 mL) was stirred at 70°C for 1.5 hours under nitrogen atmosphere. After cooling to room temperature, the mixture was poured onto water (300 mL), and the aqueous layer was extracted with diethyl ether (300 mL x 2). The combined organic layer was washed with water, dried over magnesium sulfate, and concentrated in vacuum. The residue was purified by column chromatography on silica gel (hexane as an eluent) to afford the title compound as a colorless oil (1.03 g, 35%).

\(^1\)H NMR (CDCl\(_3\), 270 MHz) δ: 6.58-6.32 (m, 2H), 5.57-5.48 (m, 1H), 5.18-5.08 (m, 3H).

**STEP 3:** 4,6-Difluoro- \(Λ,Λ\)-2’-trimethyl-3’-f(4-methylphenylsulfonyl)-6’,7’-dihydro-3’H-spiro-benzofuran-3,8’-chromenor7,8-c/lmidazol-5’-carboxamide
The title compound was prepared as a white amorphous (84 mg, 2%) from 5-[(dimethylamino)methyl]-4-hydroxy-Λ,Λ,2-trimethyl-1-[(4-methylphenyl)sulfonyl]-1H-benzimidazole-6-carboxamide (1.32 g, 3.1 mmol, STEP 6 of Example 1) and 4,6-difluoro-3-methylene-2,3-dihydro-1-benzofuran (1.03 g, 6.1 mmol, STEP 2) by the same manner in STEP 7 of Example 1.

1H NMR (CDCl₃, 270 MHz) δ: 7.78 (d, J = 8.6 Hz, 2H), 7.56 (s, 1H), 7.29 (d, J = 7.9 Hz, 2H), 6.45-6.31 (m, 2H), 4.68 (d, J = 10.6 Hz, 1H), 4.42 (d, J = 10.6 Hz, 1H), 3.19 (s, 3H), 3.0-2.7 (m, 2H), 2.92 (s, 3H), 2.77 (s, 3H), 2.5-2.2 (m, 2H), 2.40 (s, 3H).

MS (ESI) m/z: 554 (M+H)+ 552 (M-H)-.

STEP 4: 4,6-Difluoro-Λ,Λ,2-trimethyl-6',7'-dihydro-1'/-/spiroπ-benzofuran-3,8'-chrome nor7,8-cimidazole-5'-carboxamide

The title compound was prepared as a white amorphous (45 mg, 75%) from 4,6-difluoro-Λ,Λ,2-trimethyl-3'-[(4-methylphenyl)sulfonyl]-6',7'-dihydro-1'H-spiro[1-benzofuran-S.δ'-chromenoδ'-imidazole-S'-carboxamide (83 mg, 0.15 mmol, STEP 3) by the same manner in STEP 8 of Example 1.

1H NMR (CDCl₃, 270 MHz) δ: 9.11 (br. s, 1H), 7.18 (s, 1H), 6.52-6.30 (m, 2H), 4.63 (d, J = 10.6 Hz, 1H), 4.38 (d, J = 10.6 Hz, 1H), 3.16 (s, 3H), 2.95-2.75 (m, 2H), 2.92 (s, 3H), 2.60-2.22 (m, 2H), 2.56 (s, 3H).

MS (ESI) m/z: 400 (M+H)+, 398 (M-H)-.

Following Examples from 12 to 18 and from 21 to 24 were prepared according to the procedure described in Example 1.

Example 19 and 20 were prepared by the alkylation between methoxyethylbromide and Λ,Λ-thymethylS'.6y-tetrahydro-lH-spiro*chromeno*δ-cimidazole-δ.i'-indenel-S-carboxamide (Example 1) or Λ,Λ,2-Trimethyl-6',7'-dihydro-1'/-/spiro[1-benzofuran-3,8'-chromeno[7, δ-c]imidazole-5'-carboxamide (Example 14) respectively.

<p>| Example 12 | 7'-Fluoro-N,N,2-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide |</p>
<table>
<thead>
<tr>
<th>Example</th>
<th>Compound Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>4-Fluoro-N,N,2'-trimethyl-6',7'-dihydro-1'H-spiro[1-benzo furan-3,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</td>
</tr>
<tr>
<td>14</td>
<td>N,N,2'-Trimethyl-6',7'-dihydro-1'H-spiro[1-benzofuran-3,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</td>
</tr>
<tr>
<td>15</td>
<td>N,N,2'-Trimethyl-2,3,6',7'-tetrahydro-1'H-spiro[chromene-4,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</td>
</tr>
<tr>
<td>Example 16</td>
<td>5-Fluoro-N,N,2'-trimethyl-2,3,6',7'-tetrahydro-1'H-spiro[chromene-4,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>White amorphous</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.21-6.56 (m, 4H); 4.16-4.08 (m, 2H), 3.10 (s, 3H), 3.00-2.80 (m, 2H), 2.87 (s, 3H), 2.39 (s, 3H), 2.30-2.15 (m, 1H), 1.99-1.87 (m, 3H) ppm (NH was not observed).</td>
</tr>
<tr>
<td></td>
<td>MS (ESI) m/z: 396 (M+H)$^+$, 394 (M-H)$^-$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 17</th>
<th>$N,N,2'$-Trimethyl-6',7'-dihydro-1'H,3H-spiro[2-benzofuran-1,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White amorphous</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.41-7.27 (m, 5H), 5.24-5.20 (d, $J = 12.5$ Hz, 1H), 5.04-5.00 (d, $J = 12.5$ Hz, 1H), 3.12 (s, 3H), 3.16-3.05 (m, 1H), 2.95-2.80 (m, 1H), 2.86 (s, 3H), 2.42-2.30 (m, 1H), 2.36 (s, 3H), 2.25-2.20 (m, 1H) ppm (NH was not observed).</td>
</tr>
<tr>
<td></td>
<td>MS (ESI) m/z: 364 (M+H)$^+$, 362 (M-H)$^-$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 18</th>
<th>2-Methyl-5-(pyrrolidin-1-ylcarbonyl)-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White solid</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.38-7.10 (m, 5H), 3.72-3.52 (m, 2H), 3.28-2.79 (m, 6H), 2.48-2.21 (m, 2H), 2.38 (s, 3H), 2.20-1.78 (m, 6H) ppm (NH was not observed).</td>
</tr>
<tr>
<td></td>
<td>MS (ESI) m/z: 388 (M+H)$^+$, 386 (M-H)$^-$</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 19</th>
<th>1-(2-Methoxyethyl)-N,N,2-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White amorphous</td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (CDCl$_3$, 270 MHz) $\delta$: 7.52-7.48 (m, 4H), 7.12 (s, 1H), 4.40-4.18 (m, 2H), 3.61-3.38 (m, 2H), 3.29-2.71 (m, 4H), 3.16 (s, 3H), 3.07 (s, 3H), 2.92 (s, 3H), 2.53 (s,</td>
</tr>
<tr>
<td>Example 20</td>
<td>1'-(2-Methoxyethyl)-N,N,2'-trimethyl-6',7'-dihydro-1'H-spiro[1-benzofuran-3,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>NMR</strong></td>
<td>White amorphous</td>
</tr>
<tr>
<td>1H NMR (CDCl₃, 270 MHz) δ: 7.42-7.22 (m, 2H), 7.16 (s, 1H), 7.03-6.74 (m, 2H), 4.67 (d, J = 10.8 Hz, 2H), 4.27-4.21 (m, 2H), 3.57-3.26 (m, 2H), 3.26-2.78 (m, 11H), 2.52 (s, 3H), 2.65-2.43 (m, 1H), 2.42-2.19 (m, 1H) ppm.</td>
<td></td>
</tr>
<tr>
<td><strong>MS</strong></td>
<td>MS (ESI) m/z: 422 (M+H)⁺.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 21</th>
<th>N,N,2',4-Tetramethyl-6',7'-dihydro-3'H-spiro[1-benzofuran-3,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NMR</strong></td>
<td>White amorphous</td>
</tr>
<tr>
<td>1H NMR (CDCl₃, 270 MHz) δ: 9.51 (br s, 1H), 7.46-6.98 (m, 2H), 6.98-6.50 (m, 2H), 4.50 (d, J = 8.1 Hz, 1H), 4.36 (d, J = 8.1 Hz, 1H), 3.36-2.65 (m, 3H), 3.15 (s, 3H), 2.91 (s, 3H), 2.50 (s, 3H), 2.38 (s, 3H) 2.29-2.09 (m, 1H) ppm</td>
<td></td>
</tr>
<tr>
<td><strong>MS</strong></td>
<td>MS (ESI) m/z: 378 (M+H)⁺, 376 (M-H)⁻.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 22</th>
<th>6-Fluoro-N,N,2'-trimethyl-6',7'-dihydro-3'H-spiro[1-benzofuran-3,8'-chromeno[7,8-d]imidazole]-5'-carboxamide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NMR</strong></td>
<td>White amorphous</td>
</tr>
<tr>
<td>1H NMR (CDCl₃, 270 MHz) δ: 9.15 (br s, 1H), 7.30-7.15 (m, 2H), 6.75-6.50 (m, 2H), 4.85-4.36 (m, 2H), 3.16 (s, 3H), 3.0-2.8 (m, 2H), 2.92 (s, 3H), 2.55-2.18 (m, 2H), 2.53 (s, 3H) ppm.</td>
<td></td>
</tr>
<tr>
<td><strong>MS</strong></td>
<td>MS (ESI) m/z: 382 (M+H)⁺, 380 (M-H)⁻.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Example 23</th>
<th>N,N,2',7'-Tetramethyl-2',3',6,7-tetrahydro-3'H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide</th>
</tr>
</thead>
</table>
Example 25

\[
\text{N.N'-a-Tetramethyl^'.a'.-6J-tetrahydro-aH-spirochromenorZ.S-cimidazole-S.I'-indene-S-carboxamide}
\]

The title compound was prepared as a gray solid (312 mg, 55%) from 5-[(dimethylamino)methyl]-4-hydroxy-\(N,N\)-1,2-tetramethyl-1H-benzimidazole-6-carboxamide (437 mg, 1.50 mmol, WO 2004087701) by the same manner in STEP 7 of Example 1.

\[
^1\text{H NMR (CDCl}_3\text{, 270 MHz)} \delta: 7.36-7.10 \text{ (m, 4H), 6.78 (s, 1H), 3.66 (s, 3H), 3.25-2.80 (m, 2H), 3.16 (s, 3H), 2.90 (s, 3H), 2.6-2.0 (m, 6H), 2.55 (s, 3H).}
\]

MS (ESI) m/z: 376 (M+H)^+. 374 (M-H)^-.

Example 26

\[
(+)-N.N',2.3-Tetramethyl-2'.3'.6.7-tetrahydro-3H-spirochromenor7.8-c\text{cimidazole-8.1'-indene-S-carboxamide and}
\]

Example 27

\[
(-)-N.N',S-Tetramethyl-2'.S'.S'-tetrahydro-SH-spirochromenor/S-c\text{cimidazole-S.I'}
\]
**Indenel-5-carboxamide**

The fraction-1 (190 mg) and fraction-2 (169 mg) were prepared from racemic \( \Lambda/V,2,3\text{-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-c]/imidazole-8,1'-indene] } \)-5-carboxamide (471 mg, Example 25) by SFC as follows.

**Isolation condition**

<table>
<thead>
<tr>
<th>Apparatus</th>
<th>Berger MultiGram II™, Mettler-Toledo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column</td>
<td>CHIRALPAK® AD-H (20 x 250 mm, DAICEL)</td>
</tr>
<tr>
<td>Column temp</td>
<td>35 °C</td>
</tr>
<tr>
<td>Outlet pressure</td>
<td>100 bar</td>
</tr>
<tr>
<td>Mobile phase</td>
<td>Carbon dioxide/Methanol=80/20 (v/v)</td>
</tr>
<tr>
<td>Flow rate</td>
<td>40 mL/min</td>
</tr>
</tbody>
</table>

\((+)\)-\( \Lambda \)/\( \Lambda \)/\( \Lambda \)/\( 2,3\text{-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-c]/imidazole-8,1'-indenel-5-carboxamide} \) (fraction-1)

NMR: spectrum data were identical with those of the racemate

optical rotation: \([\alpha]_D^{25} = +47.3^\circ \) (C = 0.45, Methanol)

optical purity: >99% e.e.

retention time: 6.2 min

\((-)\)-\( \Lambda \)/\( \Lambda \)/\( \Lambda \)/\( 2,3\text{-tetramethyl-2',3',6,7-tetrahydro-3H-spirochromeno[7,8-d]/imidazole-8,1'-indenel-5-carboxamide} \) (fraction-2)

NMR: spectrum data were identical with those of the racemate

optical rotation: \([\alpha]_D^{25} = -55.4^\circ \) (C = 0.38, Methanol)

optical purity: >99% e.e.

retention time: 7.9 min

Following Examples 28 and 29 were prepared according to the procedure described in Example 25.

<p>| Example 28 | 5'-Fluoro-( \Lambda,\Lambda,2,3\text{-tetramethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]/imidazole-8,1'-indenel-5-carboxamide} |</p>
<table>
<thead>
<tr>
<th>Compound</th>
<th>Structures</th>
<th>Description</th>
<th>NMR Data</th>
<th>MS Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>White amorphous</td>
<td><img src="image1.png" alt="Structures" /></td>
<td></td>
<td>(^1)H NMR (CDCl\textsubscript{3}, 270 MHz) (\delta): 7.30-7.25 (m, 1H), 6.95-6.82 (m, 2H), 6.78 (s, 1H), 3.67 (s, 3H), 3.23-2.72 (m, 4H), 3.17 (s, 3H), 2.90 (s, 3H), 2.57-2.44 (m, 1H), 2.56 (s, 3H), 2.39-2.16 (m, 2H), 2.13-1.99 (m, 1H) ppm.</td>
<td>MS (ESI) m/z: 394 (M+H)+.</td>
</tr>
<tr>
<td>Example 29</td>
<td>(N,N,2,3,7'-\text{Pentamethyl-2',3',6,7-tetrahydro-3H-spiro[chromeno[7,8-d]imidazole-8,1'-indene]-5-carboxamide})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White amorphous</td>
<td><img src="image2.png" alt="Structures" /></td>
<td></td>
<td>(^1)H NMR (CDCl\textsubscript{3}, 270 MHz) (\delta): 7.16 (t, (J = 8.1) Hz, 1H), 7.05 (d, (J = 8.1) Hz, 1H), 6.99 (d, (J = 8.1) Hz, 1H), 6.77 (s, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 3.08-2.27 (m, 7H), 2.90 (s, 3H), 2.57 (s, 3H), 2.41 (s, 3H), 2.03-1.92 (1H) ppm.</td>
<td>MS (ESI) m/z: 390 (M+H)+.</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound of the formula (I):

or a pharmaceutically acceptable salt thereof, wherein;

- $R^1$ represents 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, a Ci-C$_6$ alkoxy group, a hydroxy-substituted C$_3$-C$_7$ cycloalkyl group, a hydroxy-d-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 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 Ci-C$_6$ alkoxy group;

- $R^3$ and $R^4$ independently represent a hydrogen atom, a CrC$_6$ 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 deuterium, a halogen atom, a hydroxy group, a Ci-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, a halogen atom, an oxo group, a CrC$_6$ alkyl group, a CrC$_6$ acyl group, and a hydroxy-CrC$_6$ alkyl group;

- $R^5$, $R^6$, $R^7$ and $R^8$ independently represent a hydrogen atom, a halogen atom or a CrC$_6$ alkyl group; and

- $-A-$ represents -CH$_2$-CH$_2$-, -CH$_2$-CH$_2$-CH$_2$-, -CH$_2$-O-, -O-CH$_2$-, -O-CH$_2$-CH$_2$-, -CH$_2$-S-, -S-CH$_2$-, -S-CH$_2$-CH$_2$-, -CH$_2$-S-CH$_2$- or -CH$_2$-CH$_2$-S-. 
2. The compound or the pharmaceutically acceptable salt, as claimed in claim 1, wherein:
   R¹ is a hydrogen atom or a CrC₆ alkyl group being substituted with 1 to 2 substituents
   independently selected from the group consisting of a hydroxy group, a CrC₆ alkoxy
   group and heteroaryl group;
   R² is a CrC₆ alkyl group;
   R³ and R⁴ are independently a hydrogen atom or a C₁-C₆ alkyl being unsubstituted or
   substituted with 1 to 3 substituents independently selected from the group consisting of a
   deuterium, a hydroxy group and a d-C₆ alkoxy group; or R³ and R⁴ 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 CrC₆ alkyl group, a C₁-C₆ acyl group,
   and a hydroxy-CrC₆ alkyl group; and
   -A⁻ is -CH₂-CH₂⁻, -CH₂-CH₂-CH₂⁻, -CH₂-O⁻, -O-CH₂⁻, -O-CH₂-CH₂⁻, -CH₂-O-CH₂⁻ or
   -CH₂-CH₂-O⁻.

3. The compound or the pharmaceutically acceptable salt, as claimed in claim 2, wherein:
   R¹ is a hydrogen atom or a C₁-C₆ alkyl group being substituted with hydroxy group, a
   CrC₆ alkoxy group or heteroaryl group;
   R³ and R⁴ are independently a hydrogen atom, a methyl group, -CD₃ or 2-hydroxyethyl
   group; or R³ and R⁴ taken together with the nitrogen atom to which they are attached
   form a pyrrolidino group, a azetidino group or a morpholino group;
   R⁵, R⁶, R⁷ and R⁸ are independently a hydrogen atom or a halogen atom; and
   -A⁻ is -CH₂-CH₂⁻, -CH₂-O⁻, -O-CH₂⁻, -CH₂-O-CH₂⁻ or -CH₂-CH₂-O⁻.

4. The compound of claim 1, which is selected from:
   Λ,Λ',2-Trimethyl-2',3',6,7-tetrahydro-1/-/spiro[chromeno][7,8-c][imidazole-8,1'-indene]-5-c
   arboxamide;
   (-)-Λ,Λ',2-Trimethyl-2',3',6,7-tetrahydro-1 H-spirolchromeno^⁻. δ-ϕ midazole- δ,1'-indene]-
   5-carboxamide;
   (+)-Λ,Λ',2-Trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno][7,8-c][imidazole-8,1]-indene]-
   5-carboxamide;
   S'-Fluoro-A/Λ'-trimethyl^⁻.S'.ej-tetrahydro-1H-spirolchromeno^⁻.e-cimidazole-S.1'-in
dene]-5-carboxamide;
(-)-5'-Fluoro-\(\Lambda,\Lambda,2\)-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8, 1'-indene]-5-carboxamide;
(+)-5'-Fluoro-\(\Lambda,\Lambda,2\)-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8,1'-indene]-5-carboxamide;
\(\delta^J\)-Difluoro- \(\Lambda,\Lambda,2\)-trimethyl-2',3',6J-tetrahydro-1H-spirochromeno\(^{\delta}\). \(\delta^J\)-imidazole- \(\delta,1\)'-indene]-5-carboxamide;
(-J-S'y-Difluoro- \(\Lambda,\Lambda\)-trimethyl\(^{\delta}\).\(\delta\)'-J-tetrahydro-1H-spirotchromeno\(^{\delta}\)\(\delta\)-imidazole-8,1'-indene]-5-carboxamide;
(+)-5',7'-Difluoro- \(\Lambda,\Lambda,2\)-trimethyl-2',3',6,7-tetrahydro-1H-spiro[chromeno[7,8-c]imidazole-8,1'-indene]-5-carboxamide;
\(\delta^J\)-Difluoro- \(\Lambda,\Lambda\)-trimethyl\(^{\delta}\)\(\delta\)'-J-tetrahydro-1H-spirotchromeno\(^{\delta}\)\(\delta\)-imidazole-8,1'-indene]-5-carboxamide;
4,6-Difluoro-\(\Lambda,\Lambda\)-trimethyl-6',7'-dihydro-1H-spiro[1-benzofuran-3,8'-chromeno[7,8-cy]imidazole]-5'-carboxamide;
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.

\(\delta\). 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.
# A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D491/107 A61K31/4188 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

# B. RELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used).

EPO-Internal, WPI Data, BEILSTEIN Data

# C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>E</td>
<td>WO 2008/058990 A (NYCOMED GMBH [DE]; BUHR WILM [DE]; ZIMMERMANN PETER JAN [DE]; BREHM CH) 22 May 2008 (2008-05-22) page 1, paragraph 4</td>
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<td>A</td>
<td>WO 2006/037759 A (ALTANA PHARMA AG [DE]; ZIMMERMANN PETER JAN [DE]; BUHR WILM [DE]; BREH) 13 April 2006 (2006-04-13) page 53, paragraph 1; claim 1</td>
<td>1-10</td>
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</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

A: document defining the general state of the art which is not considered to be of particular relevance
E: earlier document but published on or after the international filing date
L: document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
O: document referring to an oral disclosure, use, exhibition or other means
P: document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search

20 June 2008

Date of mailing of the international search report

26/06/2008

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx 31 651 epi nl,
Fax: (+31-70) 340-3016

Authorized officer
Gettins, Marc
<table>
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<td>WO 2006/100255 A (ALTANA PHARMA AG [DE]; CHIESA MARIA VITTORIA [DE]; ZIMMERMANN PETER JA) 28 September 2006 (2006-09-28) page 1, paragraph 4; claim 1</td>
<td>1-10</td>
</tr>
<tr>
<td>A</td>
<td>WO 2004/087701 A (ALTANA PHARMA AG [DE]; BUHR WILM [DE]; CHIESA M VITTORIA [DE]; ZIMMERM) 14 October 2004 (2004-10-14) page 52, line 4; claim 1</td>
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INTERNATIONAL SEARCH REPORT

Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. **X** Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

   Although claims 7-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- [ ] The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- [ ] The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- [ ] No protest accompanied the payment of additional search fees.
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<tr>
<td>UO 2008035195 A</td>
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<td>CA 2582294 A1</td>
<td>13-04-2006</td>
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<td>UO 2006100255 A</td>
<td>28-09-2006</td>
<td>AU 2006226352 A1</td>
<td>28-09-2006</td>
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<td>CA 2601388 A1</td>
<td>28-09-2006</td>
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<td>UO 2004087701 A</td>
<td>14-10-2004</td>
<td>AU 2004226180 A1</td>
<td>14-10-2004</td>
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<td>BR PI0408893 A</td>
<td>11-04-2006</td>
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<td>CA 2520581 A1</td>
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<td>CN 1764662 A</td>
<td>26-04-2006</td>
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<td>IS 8091 A</td>
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