

DESCRIPTION

[Title of the Invention]

5 α -SUBSTITUTED GLYCINAMIDE DERIVATIVE

[Technical Field]

[0001]

10 The present invention relates to an α -substituted glycine derivative which is useful as a pharmaceutical, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the same, and a pharmaceutical use thereof.

[Background Art]

[0002]

15 Transient Receptor Potential (TRP) channels are non-selective cation channels activated by various stimuli such as temperature, chemical compounds, etc., and divided into TRPM, TRPA, TRPV, TRPC, TRPP, TRPML, and TRPN families. Further, the TRPM family includes TRPM1, TRPM2, TRPM3, TRPM4a, TRPM4b, TRPM5, TRPM6, TRPM7 and TRPM8 channels (See, for example, Non-patent literature 1).

20 TRPM8, also known as CMR1 (cold and menthol sensitive receptor-1), is the eighth member of the TRPM family cloned in 2002 (See, for example, Non-patent literature 2), and is activated by cold temperature (8°C -28°C) or chemical compounds which evoke cold sensation such as menthol or icilin (See, for example, Non-patent literature 1 and 2). In addition to the primary afferent nerve (A-delta and C-fibers) and the trigeminal nerve, TRPM8 expression is also reported in taste papillae, vascular
25 endothelium, the aorta, pulmonary arteries, the prostate, the male genital tract (See, for example, Non-patent literature 3), nerve fibers scattered in the human suburothelium (See, for example, Non-patent literature 4), prostate cancer (See, for example, Non-patent literature 5) and oral squamous carcinoma (See, for example, Non-patent literature 6).

30 In TRPM8 knockout mice, both lack of cold perception and deficiency in hypersensitivity to cold stimulation after nerve injury or inflammation are observed (See, for example, Non-patent literature 3).

 In nervous system disorders, increase of TRPM8 expression and involvement in the hypersensitivity to cold in rats with sciatic nerve injury was reported (See, for example, Non-patent literature 7). It is reported that peripheral nerve injury evoked by oxaliplatin
35 increases TRPM8 expression in mice and rats, and that TRPM8 is involved in the cold hypersensitivity evoked by oxaliplatin (See, for example, Non-patent literature 8 and 9). From the fact that patients taking oxaliplatin have increased reactivity to menthol compared with healthy volunteers, TRPM8 is considered to be involved in peripheral neuropathic pain evoked by oxaliplatin in humans as well as in rodents (See, for example,
40 Non-patent literature 10).

 In regards to the urinary tract diseases, TRPM8 is reported to be involved in the frequent urination symptoms evoked by cold temperature in rats (See, for example, Non-patent literature 11). Because of the expression in neurons projecting dichotomizing axons into both the skin and the bladder of rats, TRPM8 is considered to be involved in the
45 urinary urgency evoked by cold (See, for example, Non-patent literature 12). In cats and patients with upper central nervous disorders such as stroke and spinal cord injury, infusion of a small amount of cold water into the bladder evokes micturition reflex that is not observed in normal volunteers, and this reflex is increased by the addition of menthol (See, for example, Non-patent literature 13 and 14). In cats, this reflex is decreased according to

desensitization of C-fibers, so menthol-sensitive C-fibers are considered to be involved in the reflex (See, for example, Non-patent literature 13).

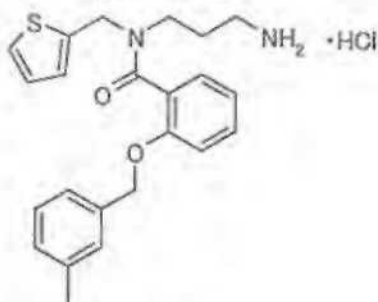
In patients with idiopathic detrusor overactivity or painful bladder syndrome, it is reported that TRPM8 expression is increased in nerve fibers in the suburothelium, and that TRPM8 expression correlates with the frequency of urination and pain scores (See, for example, Non-patent literature 15). Therefore, it is likely that TRPM8 plays an important role in the bladder afferent pathway during the bladder filling.

Accordingly, treatment or prevention of diseases or symptoms caused by the activation of TRPM8 are expected by inhibiting TRPM8.

In the meantime, as a compound of inhibiting TRPM8, *N*-(3-aminopropyl)-2-[[3-methylphenyl)methyl]oxy]-*N*-(2-thienylmethyl)benzamide hydrochloride (hereinafter sometimes referred to as AMTB) is known.

[0003]

[Chem.1]



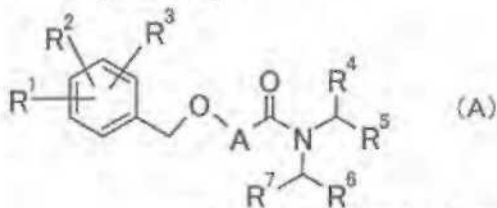
[0004]

In anesthetized rats, AMTB suppresses the frequency of rhythmic bladder contractions and nociceptive reflex responses to bladder distension. However, after a high dose of AMTB administration, the decrease of the average blood pressure is observed, so there are still problems (See, for example, Non-patent literature 16).

AMTB has been also disclosed as Examples of a compound represented by the general formula (A) (see Patent literature 1, Example 24).

[0005]

[Chem.2]



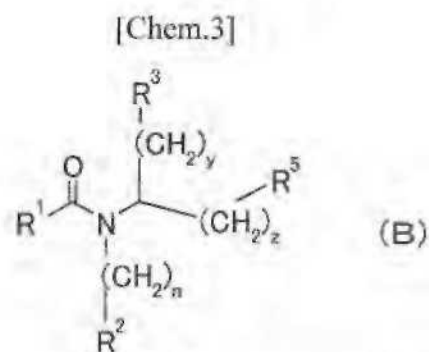
[wherein, R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and A have the same meanings as defined in Patent literature 1.]

However, general formula (A) has a different structure from the compounds of the present invention. Further, anything is neither described nor suggested about the compounds of the present invention in Patent literature 1.

[0006]

In the meantime, a compound represented by the general formula (B) has been described as a α -substituted glycine derivative (see Patent literature 2).

[0007]



[0008]

5 [wherein, R¹, R², R³, R⁵, n, y and z have the same meanings as defined in Patent literature 2.]

However, the compounds described in Patent literature 2 have a different structure from the compounds of the present invention. Further, the compounds of the present invention are different in the point that they are TRPM8 inhibitors relative to that the compound described in Patent literature 2 are oxytocin inhibitors.

10 [Citation List]

[Patent Literature]

[0009]

[Patent literature 1] International publication No. WO2007/ 017093

[Patent literature 2] International publication No. WO2004/ 020414

15 [Non-Patent Literature]

[0010]

[Non-patent literature 1] Makoto Tominaga, "Folia Pharmacologica Japonica," 2004, Vol. 124, p. 219-227

[Non-patent literature 2] McKemy DD. et al., "Nature" 2002, Vol. 416, p. 52-58

20 [Non-patent literature 3] Broad LM. et al., "Expert Opin Ther Targets", 2009, Vol. 13, p. 69-81

[Non-patent literature 4] Andersson KE. et al., "BJU Int", 2010, Vol. 106, p.1114-1127

[Non-patent literature 5] Zhang L. et al., "Endocr Relat Cancer", 2006, Vol. 13, p.27-38

[Non-patent literature 6] Okamoto Y. et al., "Int J Oncol", 2012, Vol. 40, p.1431-1440

25 [Non-patent literature 7] Su L. et al., "BMC Neurosci", 2011, Vol.12, p.120

[Non-patent literature 8] Kawashiri T. et al., "Mol Pain", 2012, Vol. 8, p.7

[Non-patent literature 9] Gauchan P. et al., "Neurosci Lett", 2009, Vol. 458, p.93-95

[Non-patent literature 10] Kono T. et al., "Brain Behav", 2012, Vol. 2, 68-73

[Non-patent literature 11] Lei Z. et al., "Neurol Urodyn", 2012, doi:10.1002/nau.22325

30 [Non-patent literature 12] Shibata Y. et al., "Neuroreport", 2011, Vol. 22, p.61-67

[Non-patent literature 13] Lindstrom S. et al., "Acta Physiol Scand", 1991, Vol.141, p.1-10

[Non-patent literature 14] Geirsson G. et al., "J Urol", 1993, Vol. 150, 427-430

[Non-patent literature 15] Mukerji G. et al., "BMC Urol", 2006, Vol. 6, p.6

35 [Non-patent literature 16] Lashinger ES. et al., "Am J Physiol Renal Physiol", 2008, Vol. 295, p.F803-F810

[Summary of the Invention]

[Objects to Be Solved by the Invention]

[0011]

40 The present invention is to provide a novel α -substituted glycine derivative, or a pharmaceutically acceptable salt thereof, a pharmaceutical composition comprising the same, and a pharmaceutical use thereof.

[Means for Solving the Objects]

[0012]

The present inventors have conducted extensive studies to find α -substituted glycinamide derivatives, and as a result found that compound (I) of the present invention or a pharmaceutically acceptable salt thereof have a potent TRPM8 inhibition, thereby completing the present invention.

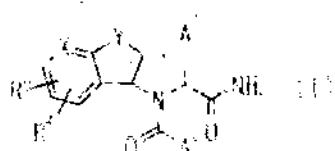
[0013]

That is, the means for solving the above-described objects are as shown below.

[1] A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

[0014]

(Chem 4)



wherein

A¹ is a group selected from the group consisting of the following (a) to (c).

a) C₁₋₆-aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, C₁₋₆-alkoxycarbonyl, cyano, hydroxy-C₁₋₆-alkyl, carbamoyl, nitro, amino, C₁₋₆-alkoxycarbonylamino, C₁₋₆-alkyl, monodifluoroalkylamino, C₁₋₆-alkylhecarbonylamino, C₁₋₆-alkylsulfonylamino and C₁₋₆-alkylsulfonyl.

b) 5-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, cyano and halo-C₁₋₆-alkoxy, and

c) 6-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, cyano and halo-C₁₋₆-alkoxy;

A² is a group selected from the group consisting of the following (d) to (f).

d) C₁₋₆-aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, cyano, amino, nitro, carboxy, (C₁₋₆-alkyl)hecarbonylamino, (C₁₋₆-alkyl)hecarbonyloxy, (C₁₋₆-alkyl)carbonyl and (C₁₋₆-aryl)alkoxy carbonyl.

e) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, cyano, monodifluoroalkylamino, C₁₋₆-alkylsulfonyl, amino, (C₁₋₆-aryl)alkoxy carbonyl, hydroxy-C₁₋₆-alkyl, hydroxy-C₁₋₆-alkoxy, C₁₋₆-alkenyl, morpholino and (C₁₋₆-alkyl)hecarbonyl, and

f) C₃₋₆-cycloalkyl.

X is CH or N;

Y is -CR¹R²- or an oxygen atom;

R¹ and R² independently represent a hydrogen atom, a halogen atom or C₁₋₆-alkyl;

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkyl, halo-C₁₋₆-alkoxy, hydroxy-C₁₋₆-alkoxy, C₃₋₆-cycloalkyl, C₃₋₆-cycloalkoxy, C₂₋₆-alkenyl or cyano with the proviso that when X is CH, and R¹ and R² are hydrogen atoms, R³ and R⁴ are not hydrogen atoms at the same time; and

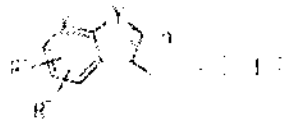
n is 1 or 2

[2] The compound according to [1] or a pharmaceutically acceptable salt thereof wherein X is CH and n is 1.

[3] The compound according to [2] or a pharmaceutically acceptable salt thereof wherein a group represented by the general formula

[0015]

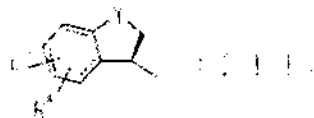
[Chem.5]



is a group represented by the following general formula:

[0016]

[Chem.6]



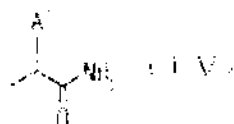
(wherein R¹ and R² independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, C₁₋₆ cycloalkyl, C₁₋₆ cycloalkoxy, C₂₋₆ alkenyl or cyano with the proviso that R¹ and R² are not hydrogen atoms at the same time).

[4] The compound according to [3] or a pharmaceutically acceptable salt thereof wherein Y is -CR(R³)₂.

[5] The compound according to [4] or a pharmaceutically acceptable salt thereof wherein a group represented by the general formula,

[0017]

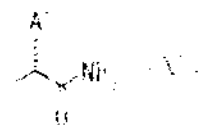
[Chem.7]



is a group represented by the following general formula:

[0018]

[Chem.8]



(wherein A' is a group selected from the group consisting of the following (a), (b) and (c).

a) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom,

hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl, cyano, hydroxy-C₁₋₆ alkyl, carbonyl, nitro, amino, C₁₋₆ alkoxy carbonyl amino, C₁₋₆ alkyl, mono-di-C₁₋₆ alkyl amino, (C₁₋₆ alkyl) carbonyl amino, C₁₋₆ alkyl sulfonyl amino and C₁₋₆ alkyl sulfonyl,

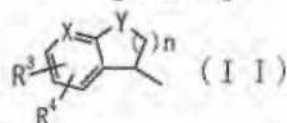
b) 5-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, cyano and halo-C₁₋₆ alkoxy, and

c) 6-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, cyano and halo-C₁₋₆ alkoxy).

- 5 [6] The compound according to [5] or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[0019]

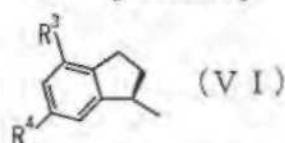
[Chem.9]



- 10 is a group represented by the following general formula:

[0020]

[Chem.10]



- 15 (wherein R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time).

[7] The compound according to [6] or a pharmaceutically acceptable salt thereof, wherein A² is a group selected from the group consisting of the following d1) and e):

- 20 d1) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, amino, nitro, carboxy, (C₁₋₅ alkyl)carbonylamino, (C₁₋₆ alkyl)carbonyloxy, (C₁₋₆ alkyl)carbonyl and (C₇₋₁₀ aralkyloxy)carbonyl, and

- 25 e) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, (C₇₋₁₀ aralkyloxy)carbonyl, hydroxy-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkoxy, C₂₋₆ alkenyl, morpholino and (C₁₋₆ alkyl)carbonyl.

- 30 [8] The compound according to [7] or a pharmaceutically acceptable salt thereof, wherein A¹ is a group selected from the group consisting of the following a2), b1) and c1):

a2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, hydroxy-C₁₋₆ alkyl, cyano, amino, mono(di)C₁₋₆ alkylamino and C₁₋₆ alkoxy,

- 35 b1) thiazolyl, and

c1) a group selected from the group consisting of pyridyl, pyrimidinyl or pyrazinyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy and cyano;

- 40 A² is a group selected from the group consisting of the following d2) and e1):

d2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, (C₁₋₆ alkyl)carbonyloxy and amino, and

e1) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, mono(difluoroalkyl)amino, C_{1-6} alkylsulfanyl, amino, hydroxy- C_{1-6} alkyl and C_{1-6} alkenyl; and

R^1 and R^2 independently represent a hydrogen atom, a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo- C_{1-6} alkoxy, C_{1-6} cycloalkyl or cyano with the proviso that R^1 and R^2 are not hydrogen atoms at the same time.

[9] The compound according to [8] or a pharmaceutically acceptable salt thereof, wherein A^1 is a group selected from the group consisting of the following d2) and e2).

d2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy- C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo- C_{1-6} alkoxy, cyano, (C₁₋₆ alkyl)carbonyloxy and amino; and

e2) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, furazanyl and benzo[1,3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, mono(difluoroalkyl)amino, C_{1-6} alkylsulfanyl, amino, hydroxy- C_{1-6} alkyl and C_{1-6} alkenyl.

[10] The compound according to [9] or a pharmaceutically acceptable salt thereof, wherein A^1 is phenyl, pyridyl or pyrazinyl, in which the each ring is unsubstituted or substituted with selected from the group consisting of the following: a halogen atom, amino, mono(difluoroalkyl)amino or hydroxy;

A^2 is a group selected from the group consisting of the following d3) and e3).

d3) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy and amino; and

e3) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, isoxazolyl and benzo[1,3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, mono(difluoroalkyl)amino, C_{1-6} alkylsulfanyl, and amino; and

R^1 and R^2 independently represent a hydrogen atom, a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkoxy, C_{1-6} cycloalkyl or cyano with the proviso that R^1 and R^2 are not hydrogen atoms at the same time.

[1021]

[11] The compound according to [9] or a pharmaceutically acceptable salt thereof, wherein A^1 is phenyl, pyridyl or pyrazinyl, in which the each ring is unsubstituted or substituted with selected from the group consisting of the following: a halogen atom or hydroxy;

A^2 is a group selected from the group consisting of the following d4) and e3);

d4) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} alkoxy and amino; and

e3) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, isoxazolyl and benzo[1,3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, mono(difluoroalkyl)amino, C_{1-6} alkylsulfanyl, and amino; and

R^3 and R^4 independently represent a hydrogen atom, a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkoxy, C_{3-6} cycloalkyl or cyano with the proviso that R^3 and R^4 are not hydrogen atoms at the same time.

[0022]

- 5 [12] The compound according to [1] selected from the following group or a pharmaceutically acceptable salt thereof:

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide (Example 1-1);

- 10 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]nicotinamide (Example 1-6);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide (Example 2-21LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]benzamide (Example 2-4LP);

- 15 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropylindan-1-yl]benzamide (Example 2-5LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]benzamide (Example 2-11LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide (Example 2-26LP);

- 20 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide (Example 2-27LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide (Example 2-31LP);

- 25 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide (Example 2-33LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]nicotinamide (Example 2-39LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]nicotinamide (Example 2-40LP);

- 30 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]nicotinamide (Example 2-56LP);

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-66LP);

- 35 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-5-carboxamide (Example 2-71LP);

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide (Example 2-76LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluoronicotinamide (Example 2-86LP);

- 40 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide (Example 2-221LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]-2-hydroxybenzamide (Example 3-2);

- 45 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide (Example 4-2);

2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide (Example 6-1);

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 12);

2-amino-N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide (Example 1-3);

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-6) P;.

5 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 2-23) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-4,6-difluoroindan-1-yl]-2-methoxynicotinamide (Example 2-36) P;.

10 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloroindan-1-yl]-2-methoxynicotinamide (Example 2-46) P;.

N-[(*R*)-carbamoyl(pyridin-3-ylmethyl)]-N-[(*R*)-6-chloroindan-1-yl]benzamide (Example 2-87) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 2-88) P;.

15 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide (Example 2-89) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-2-chloro-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 2-93) P;.

20 N-[(*R*)-carbamoyl(pyridin-3-ylmethyl)]-2-chloro-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-97) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylnicotinamide (Example 2-100) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylaminonicotinamide (Example 2-107) P;.

25 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydrobenzofuran-7-carboxamide (Example 2-111) P;.

N-[(*R*)-carbamoyl(pyridin-3-ylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide (Example 2-118) P;.

30 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloroindan-1-yl]-2-methylsulfanylnicotinamide (Example 2-125) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylsulfanylnicotinamide (Example 2-128) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-4,6-difluoroindan-1-yl]-2-methylnicotinamide (Example 2-131) P;.

35 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-4,6-difluoroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 2-132) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methyl-2H-pyrazole-3-carboxamide (Example 2-133) P;.

40 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloroindan-1-yl]-2-methylnicotinamide (Example 2-137) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methylthiazole-4-carboxamide (Example 2-147) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylisoxazole-5-carboxamide (Example 2-150) P;.

45 N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyridine-2-carboxamide (Example 2-152) P;.

N-[(*R*)-carbamoyl(phenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylpyrimidine-5-carboxamide (Example 2-154) P;.

50 N-[(*R*)-carbamoyl-(3-fluorophenylmethyl)]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 2-161) P;.

- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylisonicotinamide (Example 2-167LP);
- N*-[(*R*)-carbamoyl-(3-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 2-168LP);
- 5 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide (Example 2-172LP);
- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide (Example 2-173LP);
- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyrazine-2-carboxamide (Example 2-175LP);
- 10 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyrazine-2-carboxamide (Example 2-179LP);
- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide (Example 2-180LP);
- 15 *N*-[(*RS*)-carbamoylphenylmethyl]-*N*-[(*SR*)-5-chloro-7-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide (Example 2-252M);
- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 4-5, 19-1LP);
- N*-[(*R*)-carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 4-8);
- 20 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide (Example 4-9);
- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide (Example 11);
- 25 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 13);
- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 14LP);
- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 15LP);
- 30 *N*-[(*R*)-carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 18-13LP);
- N*-[(*R*)-carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 19-6LP);
- 35 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-methylbenzamide (Example 19-12LP);
- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-fluoro-6-hydroxybenzamide (Example 19-15LP);
- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-fluoro-2-hydroxybenzamide (Example 19-16LP);
- 40 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-4-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 19-17LP);
- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-fluoro-2-hydroxybenzamide (Example 19-25LP);
- 45 *N*-[(*R*)-3-aminophenylcarbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 21-1);
- N*-[(*R*)-3-aminophenylcarbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 21-2);
- N*-[(*R*)-carbamoyl(5-fluoropyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 19-31LP); and
- 50

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluorindan-1-yl]-2-hydroxy-3-methylbenzamide(Example 19-41I.P).

[0023]

[13] A pharmaceutical composition comprising the compound according to any one of [1] to [12] or a pharmaceutically acceptable salt thereof.

[14] The pharmaceutical composition according to [13], which is an agent for the treatment or prevention of a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons.

[15] A method for preventing or treating a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons, comprising administering an effective amount of the compound according to any one of [1] to [12] or a pharmaceutically acceptable salt thereof.

[16] Use of the compound according to any one of [1] to [12] or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for preventing or treating a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons.

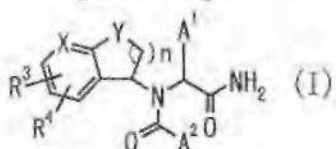
[0024]

As another embodiment,

[17] A compound represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

[0025]

[Chem.11]



(wherein A¹ is a group selected from the group consisting of the following aa) to

cc):

aa) C₆₋₁₀ aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, C₁₋₆ alkoxy carbonyl and C₁₋₆ alkylsulfonyl,

bb) 5-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl and halo-C₁₋₆ alkoxy, and

cc) 6-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl and halo-C₁₋₆ alkoxy);

A² is a group selected from the group consisting of the following dd), ee) and f):

dd) C₆₋₁₀ aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, amino, nitro, carboxy and (C₇₋₁₀ aralkyloxy)carbonyl,

ee) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfonyl, amino, (C₇₋₁₀ aralkyloxy)carbonyl, hydroxy-C₁₋₆ alkyl, C₂₋₆ alkenyl, morpholino and (C₁₋₆ alkyl)carbonyl, and

f) C₃₋₆ cycloalkyl;

X is CH or N;

Y is $-\text{CR}^1\text{R}^2-$ or an oxygen atom;

R^1 and R^2 independently represent a hydrogen atom, a halogen atom or C_{1-6} alkyl;

R^3 and R^4 independently represent a hydrogen atom, a halogen atom, C_{1-6} alkyl,

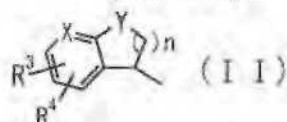
- 5 C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo- C_{1-6} alkoxy, hydroxy- C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-6} alkenyl or cyano with the proviso that when X is CH, and R^1 and R^2 are hydrogen atoms, R^3 and R^4 are not hydrogen atoms at the same time; and n is 1 or 2).

[18] The compound according to [17] or a pharmaceutically acceptable salt thereof, wherein X is CH; and n is 1.

- 10 [19] The compound according to [18] or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[0026]

[chem.12]

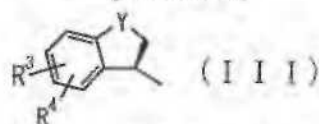


is a group represented by the following general formula:

15

[0027]

[Chem.13]



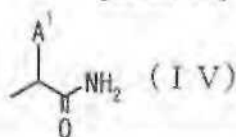
- 20 (wherein R^3 and R^4 independently represent a hydrogen atom, a halogen atom, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo- C_{1-6} alkoxy, hydroxy- C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{3-6} cycloalkoxy, C_{2-6} alkenyl or cyano with the proviso that R^3 and R^4 are not hydrogen atoms at the same time).

[20] The compound according to [19] or a pharmaceutically acceptable salt thereof, wherein Y is $-\text{CR}^1\text{R}^2-$.

- 25 [21] The compound according to [20] or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[0028]

[chem.14]

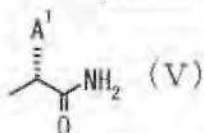


is a group represented by the following general formula:

30

[0029]

[chem.15]



(wherein A^1 is a group selected from the group consisting of the following aa1), bb) or cc):

35

aa1) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, halo- C_{1-6} alkyl, halo- C_{1-6} alkoxy, C_{1-6} alkoxycarbonyl and C_{1-6} alkylsulfonyl,

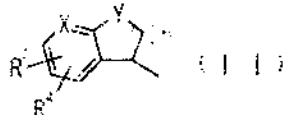
bb) 5-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl and halo-C₁₋₆ alkoxy, and

cc) 6-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl and halo-C₁₋₆ alkoxy).

[22] The compound according to [21] or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[0030]

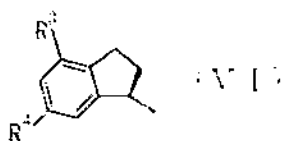
[chem.16]



is a group represented by the following general formula:

[0031]

[chem.17]



(wherein R¹ and R² independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, C₂₋₆ cycloalkyl, C₂₋₆ alkenyl or cyano with the proviso that R¹ and R² are not hydrogen atoms at the same time).

[23] The compound according to [22] or a pharmaceutically acceptable salt thereof, wherein A² is a group selected from the group consisting of the following dd1) and ee).

dd1) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, amino, nitro, carboxy and (C₂₋₆ aralkyloxy)carbonyl, and

ee) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, (C₂₋₆ aralkyloxy)carbonyl, hydroxy-C₁₋₆ alkyl, C₂₋₆ alkenyl, morpholino and (C₂₋₆ alkyl)carbonyl.

[24] The compound according to [23] or a pharmaceutically acceptable salt thereof wherein A¹ is a group selected from the group consisting of the following aa2), bb1) and cc1):

aa2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy and C₁₋₆ alkoxy,

bb1) thiazolyl, and

cc1) a group selected from the group consisting of pyridyl, pyrimidinyl and pyrazinyl, wherein the each ring is unsubstituted or substituted with 1 to 2 halogen atoms;

A² is a group selected from the group consisting of the following dd2) and e1):

dd2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2

substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano and amino, and

e1) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, hydroxy-C₁₋₆ alkyl and C₂₋₆ alkenyl; and

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[25] The compound according to [24] or a pharmaceutically acceptable salt thereof, wherein A² is a group selected from the group consisting of dd2) and e2):

dd2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano and amino, and

e2) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, furazanyl and a benzo[1, 3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, hydroxy-C₁₋₆ alkyl and C₂₋₆ alkenyl.

[26] The compound according to [25] or a pharmaceutically acceptable salt thereof, wherein A¹ is phenyl, pyridyl or pyrazinyl, in which the each ring is unsubstituted or substituted with selected from the group consisting of the following: a halogen atom or hydroxy;

A² is a group selected from the group consisting of d4) and e3):

d4) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkoxy and amino, and

e3) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, isoxazolyl and benzo[1, 3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, and amino, and

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[0032]

[27] The compound according to [17] selected from the following group or a pharmaceutically acceptable salt thereof:

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide (Example 1-1);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]nicotinamide (Example 1-6);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide (Example 2-2LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]benzamide (Example 2-4LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropylindan-1-yl]benzamide (Example 2-5LP);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]benzamide (Example 2-11LP);

- N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide (Example 2-26LP);
 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide (Example 2-27LP);
- 5 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide (Example 2-31LP);
 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide (Example 2-33LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]nicotinamide
- 10 (Example 2-39LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]nicotinamide (Example 2-40LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]nicotinamide (Example 2-56LP);
- 15 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-66LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-5-carboxamide (Example 2-71LP);
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide (Example
- 20 2-76LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluoronicotinamide (Example 2-86LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide (Example 2-221LP);
- 25 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]-2-hydroxybenzamide (Example 3-2);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide (Example 4-2);
 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide
- 30 (Example 6-1);
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 12);
 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide (Example 1-3);
- 35 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-6LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 2-23LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-methoxynicotinamide
- 40 (Example 2-36LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methoxynicotinamide (Example 2-46LP);
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide (Example 2-87LP);
- 45 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 2-88LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide (Example 2-89LP);
N-[(*R*)-carbamoylphenylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 2-93LP);
- 50

- N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide (Example 2-97LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylnicotinamide (Example 2-100LP);
5 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylamino)nicotinamide (Example 2-107LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydrobenzofuran-7-carboxamide (Example 2-111LP);
10 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide (Example 2-118LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-(methylsulfanyl)nicotinamide (Example 2-125LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylsulfanyl)nicotinamide (Example 2-128LP);
15 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-methylnicotinamide (Example 2-131LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 2-132LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methyl-2H-pyrazole-3-carboxamide (Example 2-133LP);
20 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methylnicotinamide (Example 2-137LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methylthiazole-4-carboxamide (Example 2-147LP);
25 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylisoxazole-5-carboxamide (Example 2-150LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyridine-2-carboxamide (Example 2-152LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylpyrimidine-5-carboxamide (Example 2-154LP);
30 *N*-[(*R*)-carbamoyl-(3-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 2-161LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylisonicotinamide (Example 2-167LP);
35 *N*-[(*R*)-carbamoyl-(3-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 2-168LP);
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide (Example 2-172LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide (Example 2-173LP);
40 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyrazine-2-carboxamide (Example 2-175LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyrazine-2-carboxamide (Example 2-179LP);
45 *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide (Example 2-180LP);
N-[(*RS*)-carbamoylphenylmethyl]-*N*-[(*SR*)-5-chloro-7-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide (Example 2-252M);
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 4-5);
50

N-[(*R*)-carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide (Example 4-8);

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide (Example 4-9);

5 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide (Example 11);

2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (Example 13);

10 *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 14LP); and

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide (Example 15LP).

[0033]

15 [28] A pharmaceutical composition comprising the compound according to any one of [17] to [27] or a pharmaceutically acceptable salt thereof.

[29] The pharmaceutical composition according to [28], which is an agent for the treatment or prevention of a disease or a symptom caused by hyperexcitability or a disorder of the afferent neuron.

20 [30] A method for preventing or treating a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons, comprising administering an effective amount of the compound according to any one of [17] to [27] or a pharmaceutically acceptable salt thereof.

25 [31] Use of the compound according to any one of [17] to [27] or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for preventing or treating a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons.

[Effects of the Invention]

[0034]

30 The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits a potent inhibitory effect in for example a confirmation test of inhibitory effects on icilin-induced wet-dog shakes which is a similar method described in International publication No. WO2009/ 012430. Therefore, the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is useful as an agent for treating or preventing diseases or symptoms caused by hyperexcitability or disorder of afferent

35 neurons.
[Embodiments for Carrying Out the Invention]

[0035]

The terms in the specification are defined.

[0036]

40 The "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom. It is preferably a fluorine atom or a chlorine atom.

[0037]

The term "C₁₋₆ alkyl" means alkyl having 1 to 6 carbon atoms, which may be branched. Examples thereof include methyl, ethyl, propyl, isopropyl, *n*-butyl, isobutyl, 45 *sec*-butyl, *tert*-butyl, *n*-pentyl, isopentyl, neopentyl, *tert*-pentyl, 1-methylbutyl, 2-methylbutyl, 1,2-dimethylpropyl, *n*-hexyl, isohexyl, and the like.

[0038]

50 The term "C₁₋₆ alkoxy" means alkoxy having 1 to 6 carbon atoms, which may be branched. Examples thereof include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, pentyloxy, hexyloxy, and the like.

[0039]

The term "halo-C₁₋₆ alkyl" means the above C₁₋₆ alkyl substituted by 1 to 5 of the same or different halogen atoms. Examples thereof include monofluoromethyl, difluoromethyl, trifluoromethyl, 2-chloroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 1,1-difluoroethyl, 1,2-difluoroethyl, 2,2,2-trifluoroethyl, 1,1,2,2,2-pentafluoroethyl, 2,2,2-trichloroethyl, 3-fluoropropyl, 2-fluoropropyl, 1-fluoropropyl, 3,3-difluoropropyl, 2,2-difluoropropyl, 1,1-difluoropropyl, 1-fluorobutyl, 1-fluoropentyl, 1-fluorohexyl, and the like.

[0040]

The term "halo-C₁₋₆ alkoxy" means the above C₁₋₆ alkoxy substituted by 1 to 5 of the same or different halogen atoms. Examples thereof include monofluoromethoxy, difluoromethoxy, trifluoromethoxy, 2-chloroethoxy, 2-fluoroethoxy, 2,2-difluoroethoxy, 1,1-difluoroethoxy, 1,2-difluoroethoxy, 2,2,2-trifluoroethoxy, 1,1,2,2,2-pentafluoroethoxy, 2,2,2-trichloroethoxy, 3-fluoropropoxy, 2-fluoropropoxy, 1-fluoropropoxy, 3,3-difluoropropoxy, 2,2-difluoropropoxy, 1,1-difluoropropoxy, 4-fluorobutoxy, 5-fluoropentyloxy, 6-fluorohexyloxy, and the like.

[0041]

The term "hydroxy-C₁₋₆ alkyl" means the above C₁₋₆ alkyl substituted by hydroxy. Examples thereof include hydroxymethyl, 1-hydroxyethyl, 1-hydroxy-1,1-dimethylmethyl, 2-hydroxyethyl, 2-hydroxy-2-methylpropyl, 3-hydroxypropyl, and the like.

[0042]

The term "hydroxy-C₁₋₆ alkoxy" means the above C₁₋₆ alkoxy substituted by hydroxy. Examples thereof include hydroxymethoxy, 1-hydroxyethoxy, 1-hydroxy-1,1-dimethylmethoxy, 2-hydroxyethoxy, 2-hydroxy-2-methylpropoxy, 3-hydroxypropoxy, and the like.

[0043]

The term "C₆₋₁₀ aryl" means phenyl or naphthyl.

[0044]

The term "(C₁₋₆ aralkyloxy)carbonyl" means carbonyl substituted by alkoxy having 1 to 4 carbon atoms substituted by phenyl. Examples thereof include benzyloxycarbonyl, phenethylloxycarbonyl, 1-phenylethylloxycarbonyl, 3-phenylpropylloxycarbonyl, 4-phenylbutylloxycarbonyl, and the like.

[0045]

The term "mono(di)C₁₋₆ alkylamino" means amino mono- or di-substituted by the above C₁₋₆ alkyl. These C₁₋₆ alkyl may be different in the case of di-substitution.

[0046]

The term "C₁₋₆ alkylsulfanyl" means a group represented by (C₁₋₆ alkyl)-S-. Examples thereof include methylsulfanyl, ethylsulfanyl, propylsulfanyl, isopropylsulfanyl, butylsulfanyl, isobutylsulfanyl, *sec*-butylsulfanyl, pentylsulfanyl, hexylsulfanyl, and the like.

[0047]

The term "C₁₋₆ alkylsulfonyl" means a group represented by (C₁₋₆ alkyl)-SO₂-. Examples thereof include methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, isobutylsulfonyl, *sec*-butylsulfonyl, pentylsulfonyl, hexylsulfonyl, and the like.

[0048]

The term "(C₁₋₆ alkyl)carbonyl" means carbonyl substituted by the above C₁₋₆ alkyl. Examples thereof include acetyl, ethylcarbonyl, propylcarbonyl, isopropylcarbonyl, isobutylcarbonyl, butylcarbonyl, *sec*-butylcarbonyl, *tert*-butylcarbonyl, pentylcarbonyl, hexylcarbonyl, and the like.

[0049]

The term " C_{1-6} alkoxy" means carbonyl substituted by the above C_{1-6} alkoxy. Examples thereof include methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, isobutoxycarbonyl, butoxycarbonyl, *sec*-butoxycarbonyl, *tert*-butoxycarbonyl, pentyloxycarbonyl, hexyloxycarbonyl, and the like.

[0050]

The term " C_{3-6} cycloalkyl" means monocyclic saturated alicyclic hydrocarbon having 3 to 6 carbon atoms. Examples thereof include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0051]

The term " C_{3-6} cycloalkoxy" means alkoxy having monocyclic saturated alicyclic hydrocarbon having 3 to 6 carbon atoms. Examples thereof include cyclopropoxy, cyclobutyloxy, cyclopentyloxy, and cyclohexyloxy.

[0052]

The term "heterocycle" means 5 or 6-membered heterocycle having any 1 to 4 atoms selected from a sulfur atom, an oxygen atom and a nitrogen atom, examples thereof include aromatic heterocycle such as furyl, thienyl, pyrrolyl, azepinyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyranyl, pyridyl, 1-oxidopyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, furazanyl and the like, unsaturated heterocycle such as pyrrolinyl, imidazolinyl, pyrazolinyl, dihydropyranyl, dihydrothiopyranyl, dihydropyridyl and the like, and saturated heterocycle such as morphonyl, thiomorphonyl, pyrrolidinyl, imidazolinyl, pyrazolidinyl, piperidyl, piperazinyl, tetrahydrofuranlyl and the like. Furthermore, the above "heterocycle" may be fused with other cyclic groups, examples thereof include isobenzofuranyl, benzoxazolyl, benzoisoxazolyl, benzothiazolyl, benzoisothiazolyl, chromenyl, chromanonyl, xanthenyl, phenoxathiinyl, indoliziny, isoindoliziny, indolyl, indazolyl, purinyl, quinoliziny, isoquinolyl, quinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, carbazolyl, carbolinyl, acridinyl, isoindolinyl, 2,3-dihydrobenzofuranyl, imidazo[1,2-a]pyridyl, imidazo[1,2-a]pyrazinyl, benzo[1,3]dioxolyl, benzothienyl, 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazinyl, and the like.

Preferably, examples of the "heterocycle" of A^2 include thienyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, pyrazinyl, furazanyl, 2,3-dihydrobenzofuranyl or benzo[1,3]dioxolyl, further preferably pyrazolyl, thiazolyl, pyridyl or benzo[1,3]dioxolyl.

[0053]

As "5-membered heterocycle" of A^1 , isoxazolyl or thiazolyl is preferable.

[0054]

As "6-membered heterocycle" of A^1 , pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl is preferable, and pyridyl, pyrimidinyl or pyrazinyl is more preferable.

[0055]

The term " $(C_{1-4}$ aralkyloxy) C_{1-6} alkoxy" means the above C_{1-6} alkoxy substituted by alkoxy having 1 to 4 carbon atoms substituted by phenyl.

[0056]

The term " C_{2-6} alkenyl" means straight chained or branched unsaturated hydrocarbon having 2 to 6 carbon atoms, which has at least one double bond. Examples thereof include vinyl, 2-propenyl, 1-propenyl, 1-buten-1-yl, 1-buten-2-yl, 1-buten-3-yl, 1-buten-4-yl, 2-buten-1-yl, 2-buten-2-yl, 1-penten-1-yl, 1-penten-2-yl, 1-penten-3-yl, 2-penten-1-yl, 2-penten-2-yl, 2-penten-3-yl, 1-hexen-1-yl, 1-hexen-2-yl, 1-hexen-3-yl, 2-methyl-1-propen-1-yl, and the like.

[0057]

The term "(C₁₋₆ alkyl)carbonylamino" means amino substituted by the above (C₁₋₆ alkyl)carbonyl.

[0058]

5 The term "(C₁₋₆ alkyl)sulfonylamino" means amino substituted by the above C₁₋₆ alkylsulfonyl.

[0059]

The term "(C₁₋₆ alkoxy)carbonylamino-C₁₋₆ alkyl" means the above C₁₋₆ alkyl substituted by amino substituted by the above (C₁₋₆ alkoxy)carbonyl.

[0060]

10 The term "(C₁₋₆ alkyl)carbonyloxy" means carbonyloxy substituted by the above C₁₋₆ alkyl.

Hereinafter, the present invention is described in more detail.

[0061]

15 The compound (I) of the present invention also include stereoisomers such as optical isomers, geometric isomers and the like thereof.

The optical isomer of the compound (I) of the present invention may have either of an R configuration and an S configuration at the respective asymmetric carbon atoms. Also, any of the optical isomers thereof and a mixture of the optical isomers are encompassed by the present invention. Further, in the mixture of the optical active bodies, 20 racemic bodies including equal amounts of the respective optical isomers are also encompassed within the scope of the present invention. In the case where the compound (I) of the present invention is a solid or crystal racemic body, the racemic compound, the racemic mixture, and the racemic solid solution are also encompassed within the scope of the present invention.

25 In the case where geometric isomers of the compound (I) of the present invention exist, the present invention includes any of the geometric isomers.

Furthermore, in the case where tautomers of the compound (I) of the present invention exist, the present invention includes any of the tautomers.

[0062]

30 The compound (I) of the present invention can be converted to a pharmaceutically acceptable salt thereof according to a usual method, as necessary. Such a salt may be presented as an acid addition salt or a salt with a base.

[0063]

35 Examples of the acid addition salt can include acid addition salts with mineral acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and acid addition salts with organic acids such as formic acid, acetic acid, trifluoroacetic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, propionic acid, citric acid, succinic acid, tartaric acid, fumaric acid, butyric acid, oxalic acid, malonic acid, maleic acid, lactic acid, malic acid, carbonic acid, 40 glutamic acid, aspartic acid, and the like.

[0064]

Examples of the salt with a base can include salts with inorganic bases, such as a sodium salt, a potassium salt, a calcium salt, a magnesium salt, and the like, and salts with organic bases such as piperidine, morpholine, pyrrolidine, arginine, lysine, and the like

45 [0065]

In addition, the compound (I) of the present invention or a pharmaceutically acceptable salt thereof also encompasses hydrates, and solvates with pharmaceutically acceptable solvents such as ethanol and the like.

[0066]

TRPM8 is a cation channel that expression is observed in dorsal root ganglion and trigeminal ganglion. The TRPM8 inhibitor reduces the amount of cations influxing into cells through TRPM8 and thus suppresses the increase of the intracellular cation concentration. Based on this mechanism, the TRPM8 inhibitor is useful as an agent for treating or preventing lower urinary tract symptoms (LUTS), in particular overactive bladder syndrome (OAB) and the like by suppression of hyperexcited afferent neuron activity.

Further, TRPM8 inhibitory activity can be evaluated by the efficiency inhibiting the wet-dog shake action which is induced by the administration of icilin, TRPM8 agonist. Furthermore, an effect on overactive bladder (OAB) can be evaluated by an elongation of micturition interval against overactive bladder induced by acetic acid in accordance with a method described in J.Urol., 2001, 166, 1142.

[0067]

As other embodiment of a compound represented by the general formula (I) of the present invention,

A is a group selected from the group consisting of the following (a3), (b2) and (c2):

(a3) C_{1-6} -aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, C_{1-6} -alkoxycarbonyl and C_{1-6} -alkylsulfonyl,

(b2) isoxazolyl or thiazolyl, and

(c2) 6-membered heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom and C_{1-6} -alkyl.

A' is a group selected from the group consisting of the following (dd), (ee) and (ff):

(dd) C_{1-6} -aryl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, cyano, amino, nitro, carboxy and (C_{1-6}) -alkyloxycarbonyl,

(ee) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, cyano, mono- or di- (C_{1-6}) -alkylamino, C_{1-6} -alkylsulfonyl, amino, (C_{1-6}) -alkyloxycarbonyl, hydroxy- C_{1-6} -alkyl, C_{1-6} -alkenyl, morpholino and (C_{1-6}) -alkylcarbonyl, and

(f) C_{3-6} -cycloalkyl;

X is CH or N;

Y is $-CR^2R^3-$ or an oxygen atom;

R^2 and R^3 independently represent a hydrogen atom, a halogen atom or C_{1-6} -alkyl;

R^4 and R^5 independently represent a hydrogen atom, a halogen atom, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkyl, halo- C_{1-6} -alkoxy, hydroxy- C_{1-6} -alkoxy, C_{3-6} -cycloalkyl, C_{3-6} -alkenyl or cyano with the proviso that when X is CH, and R^2 and R^3 are hydrogen atoms, R^4 and R^5 are not hydrogen atoms at the same time; and

n is 1 or 2.

[0068]

Methods for Producing Compound (I) of the Present Invention

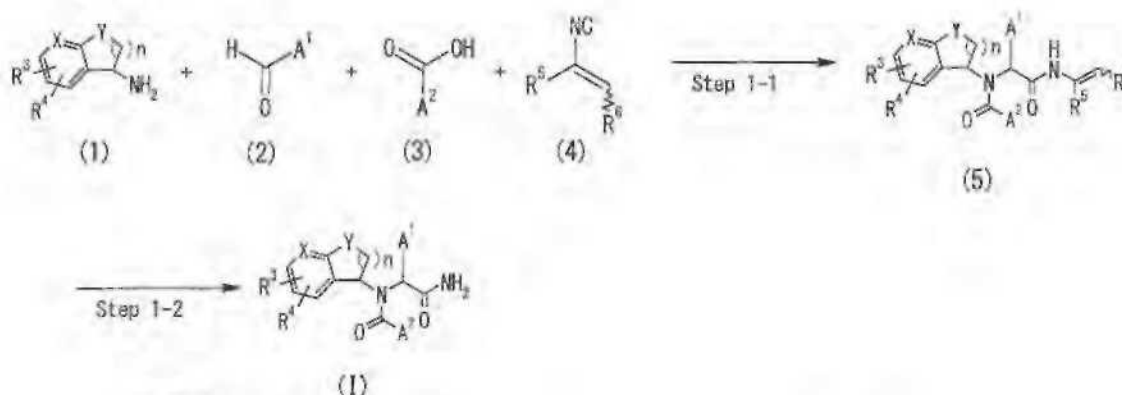
[0069]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof can be prepared by a method shown in the following or a similar method thereto, or a method described in literatures or a similar method thereto.

[0070]

[Chem.18]

Scheme 1



[0071]

(wherein, A¹, A², R¹ to R⁴, X, Y and n have the same meanings as defined above; R⁵ and R⁶ respectively represent C₁₋₆ alkyl group or R⁵ and R⁶ are bound to form a group represented by -(CH₂)_m-(CHR⁷)_m-(CH₂)_m-;

m is 1 or 2; and

R⁷ represent a hydrogen atom or a phenyl group.)

[0072]

Step 1-1

Compound (5) can be prepared by allowing Compound (1), Compound (2) and Compound (3) to react with Compound (4) in a solvent. Such reaction is well-known to those skilled in the art as Ugi reaction, and can be prepared, for example, by using the methods described in Domling A., Ugi I. *Angewandte Chemie International Edition* 2000, 39, 3168-3210. The reaction temperature is at -78°C to solvent reflux temperature, and the reaction time is usually from 10 minutes to 6 days, varying based on a used starting material, solvent and reaction temperature or the like.

[0073]

Step 1-2

The compound (I) can be prepared by hydrolysis of Compound (5) in a solvent under acidic condition. Examples of the solvent include tetrahydrofuran, 1,4-dioxane, and the like. Examples of the acid include hydrochloric acid, sulfuric acid, trifluoroacetic acid, and the like. The reaction temperature is at room temperature to solvent reflux temperature, and the reaction time is usually from 10 minutes to 1 day, varying based on a used starting material, solvent and reaction temperature or the like.

[0074]

Respectively, Compound (2) and Compound (3) can be commercially available, or can be prepared by a method described in literature or a similar method thereto.

Compound (1) can be commercially available, and can be prepared, for example, by using the methods described in Jonathan A. Ellman et al., *Accounts of Chemical Research* 2002, 35, 984-995 or a similar method thereto. Compound (4) can be commercially available, and can be prepared, for example, by using the methods described in W. Maison et al., *Bioorganic Medicinal Chemistry* 2000, 8, 1343-1360 or a similar method thereto.

[0075]

The schemes shown above are exemplifications of methods for preparing the compound (I) of the present invention or production intermediates thereof. These can be variously modified into schemes which can be easily understood by those skilled in the art.

[0076]

Moreover, where a protecting group is required depending on the type of the functional group, introduction and removal operations can be appropriately carried out in combination according to conventional methods. Examples regarding the type of protecting groups, introduction, and removal can include the methods described in Theodora W. Greene & Peter G.M. Wuts Eds., "Greene's Protective Groups in Organic Synthesis," fourth edition, Wiley-Interscience, 2006.

[0077]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof, and a manufacturing intermediate used for preparing these compounds can be isolated/purified, as necessary, by solvent extraction, crystallization/recrystallization, chromatography, preparative high performance liquid chromatography, or the like, which are isolation/purification means well-known to a skilled person in the art of the relevant field.

[0078]

A pharmaceutical composition comprising the compound (I) of the present invention or a pharmaceutically acceptable salt thereof as an active ingredient is used in various dosage forms according to the usage. Examples of such dosage forms include powders, granules, fine granules, dry syrups, tablets, capsules, injections, liquids, ointments, suppositories, plasters, sublinguals, and the like, which are administered orally or parenterally.

[0079]

These pharmaceutical compositions can be prepared by appropriately mixing or diluting/dissolving with appropriate pharmaceutical additives such as an excipient, a disintegrant, a binder, a lubricant, a diluent, a buffering agent, a tonicity agent, a preservative, a wetting agent, an emulsifier, a dispersant, a stabilizer, a solubilizing aid, and the like by a publicly-known method according to the dosage form. In addition, when the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is used in combination with agents other than the TRPM8 inhibitor, the pharmaceutical compositions can be prepared by formulating the respective active ingredients simultaneously or separately in the same way as described above.

[0080]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof exhibits potent inhibitory effects based on its TRPM8 inhibition in the confirmation test of inhibitory effects on icilin-induced wet-dog shakes. Accordingly, a pharmaceutical comprising the compound (I) of the present invention or a pharmaceutically acceptable salt thereof as an active ingredient can be used as an agent for treating or preventing diseases or symptoms caused by the activation of TRPM8.

[0081]

"A disease or a symptom caused by the activation of TRPM8" means a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons.

Examples of "a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons" include anxiety, depression, lower urinary tract symptoms (LUTS), algia, circulatory disorder, itch, pins-and-needles sensation, hives and the like.

[0082]

"Lower urinary tract symptoms (LUTS)" means symptom caused by lower urinary tract dysfunction and the like, and examples of "lower urinary tract dysfunction" include overactive bladder, detrusor overactivity, nocturia, cystitis such as interstitial cystitis and the like, prostatitis such as chronic prostatitis and the like, painful bladder syndrome,

hypersensitive bladder syndrome, urinary incontinence, benign prostatic hyperplasia, ankylurethria and the like.

[0083]

Examples of "circulatory disorder" include cold-induced rhinitis, Raynaud disease and the like.

[0084]

The compound (I) of the present invention or a pharmaceutically acceptable salt thereof can also be appropriately used in combination with at least one agent other than the TRPM8 inhibitor.

[0085]

Examples of the agent that can be used in combination with the compound (I) of the present invention or a pharmaceutically acceptable salt thereof include an opioid analgesic agent, a non-steroidal anti-inflammatory drug (NSAID), a barbiturate sedative, a benzodiazepine drug having sedating properties, a H_1 blocker having sedating properties, a sedative, a skeletal muscle relaxant, a NMDA receptor antagonist, an α -adrenoceptor modulator, a tricyclic antidepressant, an anti-seizure drug, a tachykinin antagonist (NK antagonist), a muscarinic receptor antagonist, a COX-2 selective inhibitor, a coal tar analgesic, a neuroleptic agent, a TRPV1 agonist, a TRPV1 inhibitor, a β blocker, a local anesthetic agent, a corticosteroid, a 5-HT receptor agonist, a 5-HT_{2A} receptor antagonist, a cholinergic analgesic, PDE5 inhibitor, PDE9 inhibitor, $\alpha 2\delta$ ligand, a cannabinoid, a metabotropic glutamate receptor 1 antagonist (mGluR1 antagonist), a metabotropic glutamate receptor 5 antagonist (mGluR5 antagonist), a serotonin reuptake inhibitor, a noradrenaline reuptake inhibitor, a serotonin-noradrenaline reuptake inhibitor, an inducible nitric oxide synthase inhibitor (iNOS inhibitor), an acetylcholine esterase inhibitor (AChE inhibitor), an EP4 antagonist, a leukotriene B4 antagonist, a 5-lipoxygenase inhibitor, a sodium channel blocker, a 5-HT3 antagonist, a chemotherapeutic agent, an EP1 antagonist, a $\beta 3$ adrenoceptor agonist, a TRPA1 inhibitor, a TRPV3 inhibitor, a TRPV4 inhibitor, a T-type calcium channel inhibitor, a an ASIC inhibitor, a P2X inhibitor, a Trk inhibitor, a FAAH inhibitor, a botulinus toxin, a 5 α -reductase inhibitor, an anti-NGF antibody, a NGF modulator, an depressant of IgE production, a histamine H2 inhibitor, a bladder mucosal protectant, a NOS activity regulator, a bladder muscle relaxant, a GABA reuptake inhibitor, a GABA receptor regulator, GABA aminotransferase inhibitor and the like.

[0086]

Furthermore, concrete examples of the agent that is used in combination are illustrated as below, but the content of the present invention is not limited thereto. Further, examples of the concrete compounds include a free form thereof and other pharmaceutically acceptable salts.

[0087]

Examples of "an α -adrenoceptor modulator" can include doxazosin, tamsulosin, silodosin, clonidine, guanfacine, dexmedetomidine, modafinil, tizanidine, moxonidine, and the like.

[0088]

Examples of "a muscarinic receptor antagonist" can include oxybutynin, tolterodine, propiverine, darifenacin, solifenacin, temiverine, ipratropium bromide, trospium, propantheline, temiverine, imidafenacin, fesoterodine, and the like.

[0089]

Examples of "EP1 antagonist" can include GSK-269984A, ONO-8539 and the like.

[0090]

Examples of "a $\beta 3$ adrenoceptor agonist" can include mirabegron, solabegron, TRK-380, and the like.

[0091]

5 Examples of "a bladder mucosal protectant" can include pentosan polysulphate, hyaluronic acid, chondroitin sulfate, and the like.

[0092]

When the compound (I) of the present invention or a pharmaceutically acceptable salt thereof is administrated in combination with one or more of the above-described agents, the present invention includes all administration methods following 1) to 5):

- 10 1) simultaneous administration by a combination preparation,
- 2) simultaneous administration by the same administration pathway as a separate formulation,
- 3) simultaneous administration by a different administration pathway as a separate formulation,
- 15 4) administration at different times by the same administration pathway as a separate formulation, and
- 5) administration at different times by a different administration pathway as a separate formulation.

Further, in the case of administration at different times as a separate formulation as in 4) or 20 5), the order of administration of the compound (I) of the present invention or a pharmaceutically acceptable salt thereof and the above-described agents that is administrated in combination is not particularly limited.

[0093]

Furthermore, the compounds of the present invention or a pharmaceutically acceptable salt thereof can be administrated appropriately in combination with one or more 25 of the above-described agents to achieve an advantageous effect that is equal to or more than an additive effect in prevention or treatment of the above-described diseases. Alternatively, as compared with a case of being administrated alone, the amount used can be reduced, or the side effect of the agent(s) without TRPM8 inhibitor used together can be mitigated, or the side effect of the agent(s) without TRPM8 inhibitor used together can 30 be avoided or mitigated.

[0094]

The pharmaceutical composition of the present invention can be administered systemically or locally, and orally or parenterally (nasal, pulmonary, intravenous, rectal, 35 subcutaneous, intramuscular, transdermal routes, and the like).

[0095]

When the pharmaceutical composition of the present invention is employed for actual therapy, the administration amount of the active ingredient, which is the compound (I) of the present invention or a pharmaceutically acceptable salt thereof, is appropriately 40 determined depending on the age, gender, and weight of the patient, the extent of disease and therapy and the like. For example, in the case of oral administration, it can be appropriately administered in the range of about 6 to 3000 mg per day for an adult (regarded as a body weight of 60 kg), in one portion or in several divided portions. The daily dose as an oral administration agent is preferably from 10 to 1000 mg, and more 45 preferably from 60 to 600 mg. For example, in the case of parenteral administration, it can be appropriately administered in the range of about 0.6 to 300 mg per day for an adult, in one portion or in several divided portions. The daily dose as a parenteral administration agent is preferably from 1 to 100 mg, and more preferably from 6 to 60 mg. In addition, the administration amount of the compound (I) or a pharmaceutically acceptable salt

thereof which is the active ingredient of the TRPM8 inhibitor of the present invention can be reduced according to the administration amount of agents other than TRPM8 inhibitor.

[0096]

Hereinbelow, the present invention is illustrated in detail with reference to

5 Examples, Reference Examples, and Test Examples, but the scope of the present invention is not limited thereto.

[0097]

Among the symbols used in each of the Reference Examples, Examples, and Tables, Ref. Ex. means Reference Example Number, Ex. No. means Example Number,

10 Sirc. means a chemical structural formula, ¹H-NMR means a proton nuclear magnetic resonance spectrum, CDCl₃ means chloroform-d, and DMSO-d₆ means dimethylsulfoxide-d₆, CD₃OD means methanol-d₄. Further, ESI-MS means electrospray ionization mass spectrometry, RT means retention time of high-performance liquid chromatography. When a mixture of two diastereomer was separated/purified using normal-phase column chromatography, low polarity product means a former eluted compound, high polarity product means a latter eluted compound. In the end of Example Number, LP means low polarity product, HP means high polarity product, and M means a mixture of optical isomers. [α]_D means specific optical rotation.

[0098]

20 In each Reference Example, the irradiation of the microwave used Biorage Initiator.

[0099]

In each Example, high-performance liquid chromatography and mass spectrometry analysis was performed on the following conditions.

25 Instrument: 6520 Accurate-Mass Q-TOF instrument (Agilent)

Column: Inertsil ODS-4 (GL Science) 2.1 x 50 mm, 3 μm

Flow rate: 0.75 mL/min.

Gradient:

[Table 1]

Time (minutes)	0.1% HCO ₂ H/H ₂ O	0.1% HCO ₂ H/MeCN
0	80	20
5	10	90
6	10	90

30

[1-NAMPI-18]

[0100]

Reference Example 1-1

6-Cyclopropylindan-1-one

35

[0101]

To a suspension of 6-bromindan-1-one (0.60 g), cyclopropylboronic acid monohydrate (0.47 g), tricyclohexylphosphine (0.081 g) and tripotassium phosphate (2.11 g) in toluene (10 mL) and distilled water (0.5 mL) was added palladium(II) acetate (0.064 g), and the mixture was stirred for 1 hour at 150 °C under microwave irradiation. The reaction mixture was allowed to cool to room temperature, and water was added. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 0/100 to 20/80) to afford the title compound (0.402 g).

40

[0102]

¹H-NMR(CDCl₃) δ: 0.68-0.75 (2H, m), 0.95-1.05 (2H, m), 1.90-2.00 (1H, m), 2.64-2.73 (2H, m), 3.05-3.13 (2H, m), 7.34-7.38 (2H, m), 7.40-7.43 (1H, m).

[0103]

Reference Example 1-2

6-Cyclopropyl-4-fluorindan-1-one

The title compound was synthesized in a manner similar to that of Reference Example 1-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 2.

[0104]

¹H-NMR(CDCl₃) δ: 0.69-0.76 (2H, m), 0.99-1.07 (2H, m), 1.90-1.98 (1H, m), 2.67-2.75 (2H, m), 3.05-3.13 (2H, m), 7.02 (1H, dd, J = 1.3, 9.9 Hz), 7.24 (1H, d, J = 1.3 Hz).

[0105]

Reference Example 2

4-Fluoro-6-vinylindan-1-one

[0106]

A mixture of 6-bromo-4-fluorindan-1-one (0.30g), tetrakis(triphenylphosphine)palladium(0) (0.182g), tributylvinyltin (600μl) and toluene (6ml) was stirred overnight under reflux. The reaction mixture was allowed to cool to room temperature, to the mixture were added an aqueous solution of 0.5mol/L potassium fluoride and ethyl acetate, and the mixture was stirred for 0.5 hours at room temperature. The insoluble material was removed by filtration through a pad of Celite. The organic layer of the filtrate was washed with water and brine successively, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 0/100 to 15/85) to afford the title compound (0.235g). The structural formula is shown in Table 2.

[0107]

¹H-NMR(CDCl₃) δ: 2.72-2.77 (2H, m), 3.11-3.17 (2H, m), 5.37 (1H, d, J = 10.8 Hz), 5.81 (1H, d, J = 17.5 Hz), 6.72 (1H, dd, J = 10.8, 17.5 Hz), 7.33 (1H, dd, J = 1.2, 9.8 Hz), 7.56-7.59 (1H, m).

[0108]

Reference Example 3-1

(*R*)-6-Chloro-4-fluorindan-1-ylamine hydrochloride

[0109]

To a solution of 6-chloro-4-fluorindan-1-one (0.43g) in toluene (5ml) were added (*R*)-*tert*-butylsulfonamide (0.79g) and tetraethyl orthosilicate (0.79g), and the mixture was stirred for 23 hrs at 60°C under argon atmosphere. The reaction mixture was poured into a saturated aqueous solution of sodium bicarbonate, and the obtained two-layer mixture was stirred vigorously. The insoluble material was removed by filtration through a pad of Celite. The organic layer was separated, and the water layer was extracted with toluene. The combined organic layer was washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 14/86 to 35/65) to afford (*R*)-*N*-(6-chloro-4-fluorindan-1-ylidene)-*tert*-butylsulfonamide (0.18g).

To a solution of (*R*)-*N*-(6-chloro-4-fluorindan-1-ylidene)-*tert*-butylsulfonamide (0.32g) in tetrahydrofuran (5.4ml) were added water (0.1ml) and sodium borohydride (0.13g) at 0°C, and the mixture was stirred for 15 minutes at same temperature, and for 45 minutes at room temperature. The reaction mixture was partitioned between dichloromethane and water, and the organic layer was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 19/81 to

40/60) to afford (*R*)-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-*tert*-butylsulfonamide (0.26g). To a solution of (*R*)-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-*tert*-butylsulfonamide (0.39g) in methanol (3.4mL) was added a solution of 4mol/L hydrogen chloride in 1,4-dioxane (1.0mL) at room temperature, and the mixture was stirred for 1hr at same temperature. Diisopropyl ether (approx. 20mL) was added dropwise to the reaction mixture, and the precipitated salt was collected by filtration to afford the title compound (0.26g). The structural formula is shown in Table 2.

[0110]

¹H-NMR(DMSO-d₆)δ: 1.98-2.11 (1H, m), 2.44-2.59 (1H, m), 2.83-2.93 (1H, m), 3.00-3.11 (1H, m), 4.74-4.81 (1H, m), 7.44 (1H, dd, J=1.6, 9.0Hz), 7.51-7.55 (1H, m), 8.25-8.55 (3H, m).

[0111]

Reference Examples 3-2 to 3-6

Reference Examples 3-2 to 3-6 were synthesized in a manner similar to that of Reference Example 3-1 by using the corresponding starting materials. The spectrum data of Reference Example 3-2 to 3-6 are shown as follows, and the structural formulae are shown in Table 2.

[0112]

Reference Example 3-2

(*R*)-4-Fluoroindan-1-ylamine hydrochloride

[0113]

¹H-NMR(DMSO-d₆)δ: 1.95-2.15 (1H, m), 2.40-2.60 (1H, m), 2.80-3.00 (1H, m), 3.00-3.15 (1H, m), 4.70-4.80 (1H, m), 7.10-7.25 (1H, m), 7.30-7.55 (2H, m), 8.20-8.70 (2H, m).

[0114]

Reference Example 3-3

(*R*)-5-Fluoroindan-1-ylamine hydrochloride

[0115]

¹H-NMR(DMSO-d₆)δ: 1.95-2.10 (1H, m), 2.40-2.60 (1H, m), 2.80-2.95 (1H, m), 3.00-3.15 (1H, m), 4.60-4.75 (1H, m), 7.05-7.25 (2H, m), 7.55-7.70 (1H, m), 8.20-8.65 (2H, m).

[0116]

Reference Example 3-4

(*R*)-4,6-Difluoroindan-1-ylamine hydrochloride

[0117]

¹H-NMR(DMSO-d₆)δ: 1.95-2.15 (1H, m), 2.40-2.60 (1H, m), 2.80-2.95 (1H, m), 2.95-3.10 (1H, m), 4.76 (1H, dd, J=7.0Hz), 7.20-7.40 (2H, m), 8.15-8.60 (2H, m).

[0118]

Reference Example 3-5

(*R*)-3,3-Dimethylindan-1-ylamine hydrochloride

[0119]

¹H-NMR(DMSO-d₆)δ: 1.17 (3H, s), 1.38 (3H, s), 1.83 (1H, dd, J=8.5, 13.3Hz), 2.38 (1H, dd, J=7.5, 13.3Hz), 4.75-4.81 (1H, m), 7.27-7.40 (3H, m), 7.54-7.61 (1H, m), 8.47 (3H, br s).

[0120]

Reference Example 3-6

(*R*)-6-Cyclopropylindan-1-ylamine hydrochloride

[0121]

¹H-NMR(DMSO-d₆)δ: 0.55-0.72 (2H, m), 0.90-1.00 (2H, m), 1.86-2.03 (2H, m), 2.37-2.52 (1H, m), 2.74-2.87 (1H, m), 2.92-3.05 (1H, m), 4.60-4.67 (1H, m), 7.08 (1H, dd, J=1.6, 8.0Hz), 7.19 (1H, d, J=8.0Hz), 7.29 (1H, s), 8.33 (3H, br s).

[0122]

Reference Example 4-1

(R)-N-[(R)-6-Cyclopropyl-4-fluoroindan-1-yl]-tert-butylsulfonamide

[0123]

To a solution of 6-cyclopropyl-4-fluoroindan-1-one (0.083g) and *(R)-tert*-butylsulfonamide (0.053g) in tetrahydrofuran (1ml) was added tetraethyl orthotitanate (180 μ l) at room temperature, and the mixture was stirred for a day under reflux. The reaction mixture was allowed to cool to 0°C, and sodium borohydride (0.017g) was added. The mixture was stirred for 0.5 hours under ice-cooling, and for 1 hour at room temperature. To the reaction mixture were added water and methanol, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate, then filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 2/8 to 1/1) to afford the title compound (0.032g). The structural formula is shown in Table 2.

[0124]

¹H-NMR(CDCl₃) δ : 0.61-0.73 (2H, m), 0.91-1.00 (2H, m), 1.23 (9H, s), 1.84-1.94 (1H, m), 1.95-2.05 (1H, m), 2.30-2.54 (1H, m), 2.71-2.82 (1H, m), 2.93-3.03 (1H, m), 3.39 (1H, d, J = 6.0 Hz), 4.80-4.90 (1H, m), 6.62 (1H, d, J = 10.4 Hz), 7.10 (1H, s).

[0125]

Reference Example 4-2

(R)-N-[(R)-4-Fluoro-6-vinylindan-1-yl]-tert-butylsulfonamide

The title compound was synthesized in a manner similar to that of Reference Example 4-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 2.

[0126]

¹H-NMR(CDCl₃) δ : 1.24 (9H, s), 1.98-2.09 (1H, m), 2.45-2.57 (1H, m), 2.75-2.87 (1H, m), 2.97-3.08 (1H, m), 3.42 (1H, d, J = 6.2 Hz), 4.85-4.95 (1H, m), 5.26 (1H, d, J = 10.9 Hz), 5.74 (1H, d, J = 17.6 Hz), 6.68 (1H, dd, J = 10.9, 17.6 Hz), 7.00 (1H, d, J = 10.0 Hz), 7.40 (1H, s).

[0127]

Reference Example 5

[(R)-6-(2-Benzoyloxyethoxy)indan-1-yl]carbamic acid tert-butyl ester

[0128]

To a mixture of *N-[(R)-6-hydroxyindan-1-yl]carbamic acid tert*-butyl ester (0.148g), cesium carbonate (0.386g) and sodium iodide (0.018g) in *N,N*-dimethylformamide (2ml) was added (2-bromoethoxymethyl)benzene (117 μ l) at room temperature, and the mixture was stirred for 3 hours at 70°C. The reaction mixture was allowed to cool to room temperature. To the mixture was added water, and this was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 1/9 to 9/1) to afford the title compound (0.20g). The structural formula is shown in Table 2.

[0129]

¹H-NMR(CDCl₃) δ : 1.39 (9H, br s), 1.71-1.85 (1H, m), 2.50-2.64 (1H, m), 2.69-2.95 (2H, m), 3.75-3.86 (2H, m), 4.08-4.20 (2H, m), 4.58-4.77 (2H, m), 5.06-5.21 (1H, m), 6.81 (1H, dd, J = 2.4, 8.3 Hz), 6.88 (1H, d, J = 1.9 Hz), 7.10 (1H, d, J = 8.3 Hz), 7.24-7.42 (5H, m).

[0130]

[Table 2]

Ex. No.	Structure	Yield (%)	Structure
1-1		9-1	
1-2		1-3	
1-3		1-4	
1-4		1-5	
1-5		1-6	
1-6		1-7	
1-7		1-8	
1-8		1-9	

[0131]

Example 1-1

5 N-[(R)-Carbamoylphenylmethyl]-N-[(R)-4,6-difluoroindan-1-yl]nicotinamide

[0132]

To a solution of (*R*)-4,6-difluoroindan-1-ylamine (0.1g) in methanol (1mL) was added benzaldehyde (0.063g), and the mixture was stirred for 1 hour at 60°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added nicotinic acid (0.073g) and 4-phenylcyclohexen-1-ylisocyanide (0.108g). The mixture was stirred overnight at 60°C, allowed to cool to room temperature, and concentrated under reduced pressure. To the residue were added tetrahydrofuran (3mL), water (12μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (440μL), and the mixture was stirred for 1.5 hours at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: methanol / ethyl acetate / *n*-hexane = 0/70/30 to 0/100/0 to 20/80/0) to afford the title compound (0.076g). The structural formula is shown in Table 3.

[0133]

RT(min.): 2.727

MS(ESI, *m/z*): 406.1371 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.69-1.90 (1H, m), 1.93-2.15 (1H, m), 2.42-2.90 (2H, m), 4.54-4.88 (1H, br), 5.28-5.70 (3H, m), 6.65-6.79 (1H, m), 7.34-7.66 (7H, m), 7.77-7.97 (1H, m), 8.64-8.73 (1H, m), 8.82 (1H, br s).

[0134]

Examples 1-2 to 1-6

Examples 1-2 to 1-6 were synthesized in a manner similar to that of Example 1-1 by using the corresponding starting materials. The spectrum data of Examples 1-2 to 1-6 are shown as follows, and the structural formulae are shown in Table 3.

[0135]

Example 1-2

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]nicotinamide

RT(min.): 2.356

MS(ESI, *m/z*): 395.1513 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.74-2.19 (2H, m), 2.57-2.90 (2H, m), 4.56-5.78 (4H, m), 7.21-7.61 (8H, m), 7.81-7.92 (1H, m), 8.19-8.37 (1H, m), 8.64-8.75 (1H, m), 8.81 (1H, br s).

[0136]

Example 1-3

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide

RT(min.): 2.161

MS(ESI, *m/z*): 421.1480 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.61-1.82 (1H, m), 1.92-2.18 (1H, m), 2.43-2.80 (2H, m), 4.50-4.80 (1H, br), 5.23-5.62 (5H, m), 6.62-6.78 (2H, m), 7.35-7.55 (7H, m), 8.13 (1H, dd, *J*=1.9, 5.0Hz).

[0137]

Example 1-4

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]nicotinamide

RT(min.): 1.813

MS(ESI, *m/z*): 410.1621 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.63-1.86 (1H, m), 1.93-2.20 (1H, m), 2.58-2.90 (2H, m), 4.46-4.77 (1H, br), 5.08-5.81 (5H, m), 6.65-6.75 (1H, m), 7.35-7.62 (8H, m), 8.14 (1H, dd, *J*=1.5, 5.1Hz), 8.21 (1H, br s).

[0138]

Example 1-5

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-trifluoromethylindan-1-yl]nicotinamide

RT(min.): 2.964

MS(ESI, *m/z*): 438.1435 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.76-1.94 (1H, m), 2.05-2.20 (1H, m), 2.58-2.90 (2H, m), 4.55-4.97 (1H, br), 5.20-5.81 (3H, m), 7.20-7.63 (8H, m), 7.78-7.97(1H, m), 8.26 (1H, br s), 8.62-8.73 (1H, m), 8.82 (1H, br s).

[0139]

Example 1-6

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]nicotinamide

RT(min.): 2.432

MS(ESI, *m/z*): 400.1663 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.67-1.82 (1H, m), 1.97-2.09 (1H, m), 2.47-2.75 (2H, m), 3.89 (3H, s), 4.66-4.82 (1H, br), 5.28-5.67 (3H, m), 6.81-6.88 (1H, m), 7.07 (1H, d, *J*=8.4Hz), 7.34-7.54 (6H, m), 7.60-7.65 (1H, m), 7.90-7.96 (1H, m), 8.69 (1H, dd, *J*=1.6, 5.0Hz), 8.86-8.89 (1H, m).

[0140]

Example 2-1

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide

[0141]

To a solution of (*R*)-5-chloroindan-1-ylamine hydrochloride (0.05g) in methanol (1mL) were added triethylamine (35μL) and benzaldehyde (0.026g), and the mixture was stirred for 1.5hours at 50°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added benzoic acid (0.03g) and 4-phenylcyclohexen-1-ylisocyanide (0.045g). The mixture was stirred for 3days at 50°C, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (2mL), water (5μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (185μL), and the mixture was stirred for 1hour at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25 to 100/0) to afford *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide (Example 2-1LP, 0.040g) as low polarity product and *N*-[(*S*)-carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide (Example 2-1HP, 0.023g) as high polarity product. The structural formulae are shown in Table 4.

[0142]

Example 2-1LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide

RT(min.): 3.627

MS(ESI, *m/z*): 403.1217 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.64-1.88 (1H, m), 1.95-2.15 (1H, m), 2.46-2.84 (2H, m), 4.63 (1H, br s), 5.20-5.90 (3H, m), 7.15 (1H, br s), 7.25-7.65 (11H, m), 7.91 (1H, d, *J*=8.0Hz).

[0143]

Example 2-1HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide

RT(min.): 3.534

MS(ESI, *m/z*): 403.1219 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 2.34-2.53 (1H, m), 2.58-2.86 (2H, m), 2.98-3.15 (1H, m), 4.35-4.53

(1H, m), 5.31-6.05 (3H, m), 6.51-6.70 (1H, m), 6.78 (1H, dd, J=1.8, 8.2Hz), 7.16 (1H, br s), 7.27-7.63 (10H, m).

[0144]

Examples 2-2 to 2-260

- 5 Examples 2-2 to 2-260 were synthesized in a manner similar to that of Example 2-1 by using the corresponding starting materials. The spectrum data of Examples 2-2 to 2-260 are shown as follows, and the structural formulae are shown in Tables 4 to 28.

[0145]

Example 2-2LP

- 10 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide

RT(min.): 3.583

MS(ESI, m/z): 403.1219 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.86 (1H, m), 2.00-2.14 (1H, m), 2.48-2.78 (2H, m), 4.66 (1H, s), 5.23-5.93 (3H, m), 7.09 (1H, d, J=7.8Hz), 7.17-7.65 (11H, m), 7.97 (1H, s).

- 15 [0146]

Example 2-2HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide

RT(min.): 3.447

MS(ESI, m/z): 403.1213 (M-H)⁺

- 20 ¹H-NMR (CDCl₃) δ: 2.35-2.56 (1H, m), 2.59-2.83 (2H, m), 2.95-3.13 (1H, m), 4.40 (1H, br s), 5.31-5.92 (3H, m), 6.49-6.64 (1H, m), 7.04-7.14 (2H, m), 7.27-7.63 (10H, m).

[0147]

Example 2-3LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-trifluoromethylindan-1-yl]benzamide

- 25 RT(min.): 3.760

MS(ESI, m/z): 437.1482 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.90 (1H, m), 2.00-2.20 (1H, m), 2.60-2.85 (1H, m), 2.85-3.05 (1H, m), 4.63 (1H, br s), 5.20-5.85 (3H, m), 7.30-7.65 (12H, m), 8.15-8.30 (1H, m).

[0148]

- 30 Example 2-3HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-trifluoromethylindan-1-yl]benzamide

RT(min.): 3.641

MS(ESI, m/z): 437.1483 (M-H)⁺

- 35 ¹H-NMR (CDCl₃) δ: 2.40-2.60 (1H, m), 2.60-2.80 (1H, m), 2.80-3.00 (1H, m), 3.15-3.35 (1H, m), 4.30-4.55 (1H, m), 5.25-5.90 (3H, m), 6.75-6.95 (2H, m), 7.20-7.35 (4H, m), 7.35-7.50 (5H, m), 7.50-7.65 (2H, m).

[0149]

Example 2-4LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]benzamide

- 40 RT(min.): 3.332

MS(ESI, m/z): 399.1711 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.82 (1H, m), 1.96-2.11 (1H, m), 2.46-2.75 (2H, m), 3.90 (3H, s), 4.69 (1H, br s), 5.20-5.90 (3H, m), 6.78-6.87 (1H, m), 7.06 (1H, d, J=8.3Hz), 7.24-7.67 (11H, m).

- 45 [0150]

Example 2-5LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropylindan-1-yl]benzamide

RT(min.): 3.803

MS(ESI, m/z): 409.1919 (M-H)⁺

¹H-NMR (CDCl₃) δ: 0.74-1.06 (4H, m), 1.63-1.82 (1H, m), 1.91-2.11 (2H, m), 2.44-2.76 (2H, m), 4.65 (1H, br s), 5.19-5.98 (3H, m), 6.97-7.09 (2H, m), 7.29-7.68 (11H, m).

[0151]

Example 2-5HP

5 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropylindan-1-yl]benzamide

RT(min.): 3.653

MS(ESI, *m/z*): 409.1913 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ: -0.03-0.09 (1H, m), 0.26-0.36 (1H, m), 0.61-0.79 (2H, m), 1.46-1.59 (1H, m), 2.29-2.47 (1H, m), 2.56-2.78 (2H, m), 2.93-3.08 (1H, m), 4.45 (1H, br s), 5.25-5.95 (3H, m), 6.35 (1H, br s), 6.89 (1H, dd, *J*=1.3, 8.0Hz), 7.02-7.08 (1H, m), 7.27-7.66 (10H, m).

[0152]

Example 2-6LP

15 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.720

MS(ESI, *m/z*): 421.1130 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.90 (1H, m), 1.90-2.20 (1H, m), 2.40-2.65 (1H, m), 2.65-2.90 (1H, m), 4.66 (1H, br s), 5.20-5.85 (3H, m), 6.75-7.05 (1H, m), 7.25-7.90 (11H, m).

[0153]

20 Example 2-6HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.595

MS(ESI, *m/z*): 421.1129 (M-H)⁺

25 ¹H-NMR (CDCl₃) δ: 2.35-2.60 (1H, m), 2.60-2.90 (2H, m), 2.95-3.25 (1H, m), 4.30-4.50 (1H, m), 5.20-5.90 (3H, m), 6.25-6.45 (1H, m), 6.83 (1H, d, *J*=8.3Hz), 7.25-7.60 (10H, m).

[0154]

Example 2-7LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]benzamide

RT(min.): 3.627

30 MS(ESI, *m/z*): 403.1217 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.87 (1H, m), 1.99-2.16 (1H, m), 2.47-2.64 (1H, m), 2.74-2.92 (1H, m), 4.65 (1H, br s), 5.19-5.98 (3H, m), 7.23-7.62 (12H, m), 7.83-7.95 (1H, m).

[0155]

35 Example 2-7HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]benzamide

RT(min.): 3.526

MS(ESI, *m/z*): 403.1216 (M-H)⁺

40 ¹H-NMR (CDCl₃) δ: 2.34-3.23 (4H, m), 4.47 (1H, br s), 5.31-5.93 (3H, m), 6.52-6.68 (1H, m), 6.74-6.80 (1H, m), 7.11 (1H, d, *J*=7.9Hz), 7.23-7.63 (10H, m).

[0156]

Example 2-8LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-chloro-6-fluoroindan-1-yl]benzamide

RT(min.): 3.779

45 MS(ESI, *m/z*): 421.1115 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.90 (1H, m), 1.90-2.15 (1H, m), 2.40-2.65 (1H, m), 2.65-2.85 (1H, m), 4.50-4.80 (1H, m), 5.20-5.85 (3H, m), 6.85-7.10 (1H, m), 7.25-7.80 (11H, m).

[0157]

Example 2-8HP

50 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-chloro-6-fluoroindan-1-yl]benzamide

RT(min.): 3.609

MS(ESI, m/z): 421.1121 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.40-2.60 (1H, m), 2.60-2.85 (2H, m), 2.95-3.20 (1H, m), 4.35-4.55 (1H, m), 5.30-5.90 (3H, m), 6.10-6.35 (1H, m), 6.75-6.95 (1H, m), 7.25-7.60 (10H, m).

5 [0158]

Example 2-9LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 2.882

MS(ESI, m/z): 371.1406 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 4.12 (1H, dd, J=5.3, 10.2Hz), 4.26 (1H, br s), 4.66 (1H, br s), 5.28-5.88 (3H, m), 6.78 (1H, d, J=8.1Hz), 6.93-7.04 (1H, m), 7.19-7.73 (12H, m).

[0159]

Example 2-9HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*S*)-2,3-dihydrobenzofuran-3-yl]benzamide

15 RT(min.): 2.900

MS(ESI, m/z): 371.1402 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.48-4.61 (2H, m), 5.13-5.22 (1H, m), 5.43-5.70 (3H, m), 6.51 (1H, t, J=7.5Hz), 6.68 (1H, br s), 6.80 (1H, d, J=8.2Hz), 7.07-7.54 (11H, m).

[0160]

20 Example 2-10LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-chloro-6-methoxyindan-1-yl]benzamide

RT(min.): 3.671

MS(ESI, m/z): 433.1329 (M-H)⁻

25 ¹H-NMR (CDCl₃) δ: 1.60-1.80 (1H, m), 1.95-2.10 (1H, m), 2.45-2.70 (2H, m), 4.03 (3H, s), 4.55-4.70 (1H, m), 5.20-5.75 (3H, m), 7.17 (1H, s), 7.30-7.65 (10H, m), 7.75 (1H, br s).

[0161]

Example 2-11LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]benzamide

RT(min.): 3.562

30 MS(ESI, m/z): 435.1535 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.75-1.95 (1H, m), 2.05-2.25 (1H, m), 2.50-2.85 (2H, m), 4.55-4.70 (1H, m), 5.25-5.65 (2H, m), 5.80-6.10 (1H, m), 6.67 (1H, dd, J=74.6, 74.6Hz), 6.95-7.20 (2H, m), 7.30-7.65 (10H, m), 7.65-7.75 (1H, m).

[0162]

35 Example 2-11HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]benzamide

RT(min.): 3.351

MS(ESI, m/z): 435.1527 (M-H)⁻

40 ¹H-NMR (CDCl₃) δ: 2.40-2.60 (1H, m), 2.65-2.85 (2H, m), 3.00-3.15 (1H, m), 4.35-4.50 (1H, m), 5.30-5.90 (4H, m), 6.30-6.45 (1H, m), 6.87 (1H, dd, J=2.0, 8.0Hz), 7.14 (1H, d, J=8.3Hz), 7.25-7.65 (10H, m).

[0163]

Example 2-12LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5,6-difluoroindan-1-yl]benzamide

45 RT(min.): 3.469

MS(ESI, m/z): 405.1423 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.68-1.86 (1H, m), 1.99-2.19 (1H, m), 2.46-2.79 (2H, m), 4.55-4.77 (1H, br), 5.21-5.94 (3H, m), 6.83-7.01 (1H, m), 7.32-7.62 (10H, m), 7.71-7.88 (1H, m).

[0164]

50 Example 2-12HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5,6-difluoroindan-1-yl]benzamide

RT(min.): 3.330

MS(ESI, *m/z*): 405.1424 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 2.36-2.56 (1H, m), 2.62-2.81 (2H, m), 2.94-3.15 (1H, m), 4.35-4.47 (1H, br), 5.32-5.87 (3H, m), 6.29-6.48 (1H, m), 6.88-7.00 (1H, m), 7.27-7.40 (5H, m) 7.41-7.60 (5H, m).

[0165]

Example 2-13LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]benzamide

10 RT(min.): 3.144

MS(ESI, *m/z*): 394.1567 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.16-2.24 (2H, m), 2.56-3.22 (2H, m), 4.48-5.95 (4H, m), 7.12-7.64 (12H, m), 8.15-8.34 (1H, m).

[0166]

15 Example 2-14LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-difluoromethoxyindan-1-yl]benzamide

RT(min.): 3.470

MS(ESI, *m/z*): 435.1531 (*M*-H)⁺

20 ¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 2.00-2.15 (1H, m), 2.45-2.65 (1H, m), 2.75-2.90 (1H, m), 4.66 (1H, br s), 5.20-6.00 (3H, m), 6.49 (1H, dd, *J*=74.0, 74.0Hz), 6.95-7.10 (1H, m), 7.30-7.65 (11H, m), 7.80-7.90 (1H, m).

[0167]

Example 2-14HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-difluoromethoxyindan-1-yl]benzamide

25 RT(min.): 3.382

MS(ESI, *m/z*): 435.1533 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 2.35-2.55 (1H, m), 2.60-2.85 (2H, m), 3.05-3.25 (1H, m), 4.40-4.55 (1H, m), 5.30-6.00 (3H, m), 6.49 (1H, dd, *J*=73.9, 73.9Hz), 6.55-6.65 (1H, m), 6.75-6.95 (2H, m), 7.20-7.65 (10H, m).

[0168]

Example 2-15LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.292

MS(ESI, *m/z*): 405.1019 (*M*-H)⁺

35 ¹H-NMR (CDCl₃) δ: 3.61-5.90 (6H, m), 6.65 (1H, d, *J*=8.6Hz), 7.05-7.19 (1H, m), 7.36-7.80 (11H, m).

[0169]

Example 2-15HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]benzamide

40 RT(min.): 3.215

MS(ESI, *m/z*): 405.1016 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 4.45-4.65 (2H, m), 5.07-5.21 (1H, m), 5.42-5.72 (3H, m), 6.51 (1H, br s), 6.65-6.74 (1H, m), 7.03 (1H, d, *J*=8.2Hz), 7.13-7.53 (10H, m).

[0170]

45 Example 2-16LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-ethylindan-1-yl]benzamide

RT(min.): 3.752

MS(ESI, *m/z*): 397.1924 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.29 (3H, t, *J*= 7.6Hz), 1.66-1.87 (1H, m), 1.97-2.13 (1H, m), 2.49-

2.80 (4H, m), 4.67 (1H, br s), 5.20-6.05 (3H, m), 7.05-7.15 (2H, m), 7.30-7.53 (8H, m), 7.57-7.65 (2H, m), 7.77 (1H, br s).

[0171]

Example 2-17LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-methylindan-1-yl]benzamide

RT(min.): 3.516

MS(ESI, *m/z*): 383.1769 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.82 (1H, m), 1.98-2.11 (1H, m), 2.43 (3H, s), 2.48-2.78 (2H, m), 4.67 (1H, br s), 5.38-5.98 (3H, m), 7.02-7.12 (2H, m), 7.30-7.53 (8H, m), 7.58-7.66 (2H, m), 7.74 (1H, br s).

[0172]

Example 2-18LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-methylindan-1-yl]benzamide

RT(min.): 3.493

15 MS(ESI, *m/z*): 383.1766 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.66-1.83 (1H, m), 2.00-2.13 (1H, m), 2.20 (3H, s), 2.41-2.77 (2H, m), 4.70 (1H, br s), 5.21-6.01 (3H, m), 7.09 (1H, d, *J* = 7.2Hz), 7.22-7.29 (1H, m), 7.31-7.64 (10H, m), 7.77 (1H, d, *J* = 7.2Hz).

[0173]

20 Example 2-19LP

N-[(*R*)-6-Bromoindan-1-yl]-*N*-[(*R*)-carbamoylphenylmethyl]benzamide

RT(min.): 3.654

MS(ESI, *m/z*): 447.0716 (M-H)⁺

25 ¹H-NMR (CDCl₃) δ: 1.68-1.86 (1H, m), 1.97-2.14 (1H, m), 2.46-2.77 (2H, m), 4.66 (1H, br s), 5.25-5.94 (3H, m), 6.98-7.07 (1H, m), 7.30-7.63 (11H, m), 8.11 (1H, br s).

[0174]

Example 2-20LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-trifluoromethylindan-1-yl]benzamide

RT(min.): 3.737

30 MS(ESI, *m/z*): 437.1487 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.77-1.94 (1H, m), 2.06-2.26 (1H, m), 2.59-2.92 (2H, m), 4.56-4.74 (1H, m), 5.22-6.03 (3H, m), 7.17-7.65 (12H, m), 8.23 (1H, br s).

[0175]

Example 2-21LP

35 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-trifluoromethoxyindan-1-yl]benzamide

RT(min.): 3.822

MS(ESI, *m/z*): 453.1434 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.75-1.95 (1H, m), 2.00-2.20 (1H, m), 2.50-2.85 (2H, m), 4.55-4.80 (1H, m), 5.20-6.00 (3H, m), 7.05-7.20 (2H, m), 7.30-7.65 (10H, m), 7.85 (1H, br s).

[0176]

40 Example 2-22LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-nitrobenzamide

RT(min.): 3.534

MS(ESI, *m/z*): 450.1273 (M-H)⁺

45 ¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 2.05-2.20 (1H, m), 2.35-2.50 (1H, m), 2.65-2.80 (1H, m), 4.63 (1H, s), 5.05-5.20 (1H, m), 5.35-5.50 (2H, m), 6.65-6.80 (1H, m), 7.35-7.85 (9H, m), 8.25 (1H, d, *J* = 8.2Hz).

[0177]

Example 2-23LP

50 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 2.937

MS(ESI, m/z): 422.1074 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 1.95-2.20 (1H, m), 2.40-2.65 (1H, m), 2.65-2.90 (1H, m), 4.55-4.90 (1H, m), 5.25-5.75 (3H, m), 6.90-7.10 (1H, m), 7.30-7.55 (6H, m),
 5 7.70-7.95 (2H, m), 8.65-8.75 (1H, m), 8.82 (1H, br s).

[0178]

Example 2-23HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 2.767

10 MS(ESI, m/z): 422.1077 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.40-2.65 (1H, m), 2.65-2.85 (2H, m), 3.00-3.20 (1H, m), 4.30-4.55 (1H, m), 5.30-5.70 (3H, m), 6.20-6.40 (1H, m), 6.85 (1H, d, J=8.3Hz), 7.25-7.45 (6H, m), 7.80-7.95 (1H, m), 8.71 (1H, dd, J=1.6, 4.9Hz), 8.75-8.85 (1H, br s).

[0179]

15 Example 2-24LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]nicotinamide

RT(min.): 2.486

MS(ESI, m/z): 406.0972 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 4.05-4.20 (2H, m), 5.00-5.90 (4H, m), 6.40-6.80 (1H, m), 7.00-7.95 (9H, m), 8.45-8.90 (2H, m).

[0180]

Example 2-24HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]nicotinamide

25 RT(min.): 2.507

MS(ESI, m/z): 406.0960 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.40-5.80 (5H, m), 6.35-6.80 (2H, m), 7.06 (1H, d, J=1.7, 8.6Hz), 7.15-7.60 (7H, m), 7.65-7.90 (1H, m), 8.60-8.75 (2H, m).

[0181]

30 Example 2-25LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]nicotinamide

RT(min.): 1.824

35 MS(ESI, m/z): 421.1071 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.01 (1H, dd, J=4.7, 10.1Hz), 5.35-5.65 (5H, m), 6.65-6.75 (2H, m), 7.16-7.23 (1H, m), 7.40-7.58 (6H, m), 7.70-7.72 (1H, m), 8.14 (1H, dd, J=1.8, 5.1Hz).

[0182]

Example 2-26LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide

40 RT(min.): 2.778

MS(ESI, m/z): 436.1476 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.75-1.90 (1H, m), 2.05-2.20 (1H, m), 2.55-2.80 (2H, m), 4.55-4.85 (1H, m), 5.25-5.90 (3H, m), 6.65 (1H, dd, J=74.1, 74.1Hz), 6.95-7.20 (2H, m), 7.35-7.55 (6H, m), 7.75 (1H, br s), 7.85-7.95 (1H, m), 8.65-8.75 (1H, m), 8.84 (1H, br s).

[0183]

Example 2-27LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide

50 RT(min.): 2.243

MS(ESI, m/z): 451.1583 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.40-1.90 (1H, m), 1.95-2.20 (1H, m), 2.50-2.80 (2H, m), 4.50-4.75 (1H, m), 5.30-5.60 (5H, m), 6.58 (1H, dd, J=74.1, 74.1Hz), 6.68 (1H, dd, J=5.0, 7.3Hz), 6.95-7.10 (1H, m), 7.16 (1H, d, J=8.2Hz), 7.35-7.55 (6H, m), 7.70 (1H, br s), 8.12 (1H, dd, J=1.8, 5.0Hz).

[0184]

Example 2-28LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.030

MS(ESI, m/z): 389.1307 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.10-5.84 (6H, m), 6.60-6.99 (2H, m), 7.32-7.66 (11H, m).

[0185]

Example 2-28HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 2.979

MS(ESI, m/z): 389.1305 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.50-4.65 (1H, m), 5.11-5.23 (1H, m), 5.40-5.66 (3H, m), 6.25-6.36 (1H, m), 6.66-6.84 (2H, m), 7.17-7.34 (4H, m), 7.43-7.50 (6H, m).

[0186]

Example 2-29LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.239

MS(ESI, m/z): 407.1211 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.16-5.86 (6H, m), 6.64-6.81 (1H, m), 7.16-7.68 (11H, m).

[0187]

Example 2-29HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.165

MS(ESI, m/z): 407.1208 (M-H)⁻

¹H-NMR (CDCl₃) δ: 4.60-6.20 (6H, m), 6.60-6.68 (1H, m), 7.24-7.50 (11H, m).

[0188]

Example 2-30LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]benzamide

RT(min.): 3.499

MS(ESI, m/z): 417.1614 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.66-1.81 (1H, m), 1.99-2.11 (1H, m), 2.41-2.53 (1H, m), 2.69-2.79 (1H, m), 3.89 (3H, s), 4.67 (1H, br s), 5.30-5.78 (3H, m), 6.54 (1H, d, J=10.5Hz), 7.33-7.52 (9H, m), 7.56-7.61 (2H, m).

[0189]

Example 2-30HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]benzamide

RT(min.): 3.301

MS(ESI, m/z): 417.1618 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.39-2.51 (1H, m), 2.61-2.77 (2H, m), 2.99-3.11 (1H, m), 3.28 (3H, s), 4.47 (1H, br s), 5.37-5.54 (2H, m), 5.73 (1H, br), 5.95 (1H, br s), 6.40 (1H, dd, J=2.0, 10.4Hz), 7.28-7.39 (5H, m), 7.42-7.48 (3H, m), 7.53-7.59 (2H, m).

[0190]

Example 2-31LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide

RT(min.): 2.732

MS(ESI, *m/z*): 404.1171 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 1.90-2.15 (1H, m), 2.50-2.80 (2H, m), 4.55-4.90 (1H, m), 5.20-5.75 (3H, m), 7.05-7.15 (1H, m), 7.15-7.30 (1H, m), 7.30-7.55 (6H, m), 7.85-8.05 (2H, m), 8.60-8.75 (1H, m), 8.84 (1H, br s).

[0191]

Example 2-31HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide

RT(min.): 2.606

MS(ESI, *m/z*): 404.1170 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 2.40-2.60 (1H, m), 2.65-2.85 (2H, m), 2.95-3.15 (1H, m), 4.30-4.60 (1H, m), 5.25-5.75 (3H, m), 6.40-6.60 (1H, m), 7.10 (2H, s), 7.25-7.45 (6H, m), 7.80-7.95 (1H, m), 8.70 (1H, dd, *J*=1.5, 4.8Hz), 8.83 (1H, br s).

[0192]

Example 2-32LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]pyrimidine-5-carboxamide

RT(min.): 2.715

MS(ESI, *m/z*): 407.1326 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.91 (1H, m), 1.94-2.14 (1H, m), 2.44-2.90 (2H, m), 4.45-5.00 (1H, br), 5.25-5.77 (3H, m), 6.63-6.86 (1H, m), 7.25-7.78 (6H, m), 8.77-9.02 (2H, m), 9.22-9.36 (1H, m).

[0193]

Example 2-33LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide

RT(min.): 2.166

MS(ESI, *m/z*): 419.1276 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.45-1.80 (1H, m), 1.90-2.15 (1H, m), 2.45-2.75 (2H, m), 4.55-4.80 (1H, m), 5.25-5.65 (5H, m), 6.67 (1H, dd, *J*=5.1, 7.3Hz), 7.10 (1H, d, *J*=8.0Hz), 7.20-7.30 (1H, m), 7.35-7.55 (6H, m), 7.87 (1H, br s), 8.12 (1H, dd, *J*=1.7, 5.0Hz).

[0194]

Example 2-34LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]pyrazine-2-carboxamide

RT(min.): 2.944

MS(ESI, *m/z*): 407.1323 (*M*-H)⁺

¹H-NMR (DMSO-*d*₆) δ: 1.20-1.40 (1H, m), 2.00-2.15 (1H, m), 2.45-2.65 (1H, m), 2.80-2.95 (1H, m), 5.05-5.15 (1H, m), 5.54 (1H, s), 6.85-7.00 (1H, m), 7.20-7.55 (9H, m), 8.65-8.95 (2H, m).

[0195]

Example 2-35LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]benzamide

RT(min.): 3.586

MS(ESI, *m/z*): 401.1671 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.68-1.82 (1H, m), 2.00-2.12 (1H, m), 2.39-2.56 (4H, m), 2.71-2.82 (1H, m), 4.65 (1H, br s), 5.25-5.85 (3H, m), 6.78 (1H, d, *J*=9.6Hz), 7.25-7.63 (11H, m).

[0196]

Example 2-35HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]benzamide

RT(min.): 3.544

MS(ESI, *m/z*): 401.1669 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.93 (3H, s), 2.39-2.76 (3H, m), 3.02-3.14 (1H, m), 4.39 (1H, br s), 5.38-5.55 (2H, m), 5.67-5.79 (1H, m), 6.19 (1H, br s), 6.62 (1H, d, J = 9.9 Hz), 7.25-7.33 (4H, m), 7.42-7.47 (3H, m), 7.53-7.61 (2H, m).

[0197]

5 Example 2-36)P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]-2-methoxynicotinamide
RT(min.): 3.204

MS(ESI, m/z): 436, 4478 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.69-2.27 (2H, m), 2.44-3.08 (2H, m), 3.93-4.12 (3H, m), 4.49-4.85 (1H, m), 5.15-6.05 (3H, m), 6.51-6.79 (1H, m), 6.88-7.19 (1H, m), 7.30-7.88 (7H, m), 8.17-8.33 (1H, m).

[0198]

Example 2-37)P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-fluoroindan-1-yl]picotinamide

15 RT(min.): 2.492

MS(ESI, m/z): 388, 4468 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.69-1.88 (1H, m), 1.97-2.13 (1H, m), 2.46-2.78 (2H, m), 4.61-4.86 (1H, br), 5.28-5.75 (3H, m), 6.89-7.02 (1H, m), 7.05-7.16 (1H, m), 7.33-7.55 (6H, m), 7.66-7.79 (1H, m), 7.83-7.95 (1H, m), 8.69 (1H, dd, J = 1.5, 4.9 Hz), 8.80-8.89 (1H, m).

[0199]

Example 2-38)P

2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-6-fluoroindan-1-yl]picotinamide

RT(min.): 1.979

MS(ESI, m/z): 403, 4574 (M-H)⁺

25 ¹H-NMR (CDCl₃) δ: 1.50-2.11 (2H, m), 2.43-2.75 (2H, m), 4.54-4.79 (1H, br), 5.30-5.62 (5H, m), 6.67 (1H, dd, J = 5.0, 7.4 Hz), 6.93-7.00 (1H, m), 7.09-7.15 (1H, m), 7.36-7.54 (6H, m), 7.59-7.64 (1H, m), 8.12 (1H, dd, J = 1.7, 5.0 Hz).

[0200]

Example 2-39)P

30 N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4-fluoro-6-methoxyindan-1-yl]picotinamide

RT(min.): 2.674

MS(ESI, m/z): 418, 4569 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.67-1.81 (1H, m), 1.97-2.10 (1H, m), 2.42-2.55 (1H, m), 2.68-2.80 (1H, m), 3.88 (3H, s), 4.72 (1H, br s), 5.32-5.61 (3H, m), 6.56 (1H, d, J = 10.5 Hz), 7.34-7.53 (7H, m), 7.86-7.95 (1H, m), 8.67-8.72 (1H, m), 8.86 (1H, s).

[0201]

Example 2-39)P

N-[(*S*)-Carbamoylphenylmethyl]-N-[(*R*)-4-fluoro-6-methoxyindan-1-yl]picotinamide

RT(min.): 2.479

40 MS(ESI, m/z): 418, 4570 (M-H)⁺

¹H-NMR (CDCl₃) δ: 2.43-2.55 (1H, m), 2.64-2.80 (2H, m), 2.98-3.11 (1H, m), 3.26 (3H, s), 4.50 (1H, br), 5.37-5.62 (3H, m), 5.88 (1H, s), 6.41 (1H, dd, J = 2.0, 10.4 Hz), 7.30-7.44 (6H, m), 7.85-7.92 (1H, m), 8.69-8.73 (1H, m), 8.84 (1H, s).

[0202]

45 Example 2-40)P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4-fluoro-6-methylindan-1-yl]picotinamide

RT(min.): 2.744

MS(ESI, m/z): 402, 4670 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.69-1.83 (1H, m), 2.00-2.10 (1H, m), 2.42 (3H, s), 2.45-2.57 (1H, m),

2.70-2.83 (1H, m), 4.72 (1H, br s), 5.33-5.64 (3H, m), 6.79 (1H, d, $J=9.7\text{Hz}$), 7.35-7.60 (7H, m), 7.91 (1H, d, $J=7.8\text{Hz}$), 8.69 (1H, dd, $J=1.6, 4.9\text{Hz}$), 8.86 (1H, s).

[0203]

Example 2-40HP

5 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]nicotinamide

RT(min.): 2.672

MS(ESI, m/z): 402.1621 ($M-H$)⁻

¹H-NMR (CDCl₃) δ : 1.92 (3H, s), 2.40-2.58 (1H, m), 2.65-2.81 (2H, m), 3.00-3.15 (1H, m), 4.42 (1H, br), 5.37-5.64 (3H, m), 6.14 (1H, s), 6.63 (1H, d, $J=9.8\text{Hz}$), 7.25-7.44 (6H, m),

10 7.86-7.92 (1H, m), 8.70 (1H, dd, $J=1.7, 4.9\text{Hz}$), 8.83 (1H, s).

[0204]

Example 2-41LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5-fluoro-2,3-dihydrobenzofuran-3-yl]nicotinamide

15 RT(min.): 1.545

MS(ESI, m/z): 405.1367 ($M-H$)⁻

¹H-NMR (CDCl₃) δ : 4.01 (1H, dd, $J=4.6, 10.2\text{Hz}$), 4.07-4.85 (1H, m), 5.35-5.64 (4H, m), 6.65-6.78 (2H, m), 6.90-7.01 (1H, m), 7.39-7.60 (7H, m), 8.15 (1H, dd, $J=1.7, 5.1\text{Hz}$).

[0205]

20 Example 2-42LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]nicotinamide

RT(min.): 1.848

MS(ESI, m/z): 423.1271 ($M-H$)⁻

25 ¹H-NMR (CDCl₃) δ : 4.07-4.80 (2H, m), 5.30-5.65 (4H, m), 6.67-6.87 (2H, m), 7.30-7.60 (7H, m), 8.13-8.17 (1H, m).

[0206]

Example 2-43LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]pyridine-2-carboxamide

30 RT(min.): 3.085

MS(ESI, m/z): 406.1373 ($M-H$)⁻

¹H-NMR (CDCl₃) δ : 1.66-3.18 (4H, m), 4.69-6.24 (4H, m), 6.48-6.78 (1H, m), 6.97-8.06 (9H, m), 8.56-8.64 (1H, m).

[0207]

35 Example 2-44LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]pyridazine-4-carboxamide

RT(min.): 2.633

MS(ESI, m/z): 407.1318 ($M-H$)⁻

40 ¹H-NMR (CDCl₃) δ : 1.68-1.89 (1H, m), 1.95-2.13 (1H, m), 2.45-2.88 (2H, m), 4.48-5.76 (4H, m), 6.56-6.84 (1H, m), 7.37-7.72 (7H, m), 9.21-9.42 (2H, m).

[0208]

Example 2-45LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-6-methoxynicotinamide

RT(min.): 3.324

45 MS(ESI, m/z): 436.1470 ($M-H$)⁻

¹H-NMR (CDCl₃) δ : 1.72-1.93 (1H, m), 1.95-2.20 (1H, m), 2.47-2.94 (2H, m), 3.97 (3H, s), 4.50-5.94 (4H, m), 6.64-6.77 (1H, br), 6.80 (1H, d, $J=8.7\text{Hz}$), 7.31-7.68 (6H, m), 7.74-7.86 (1H, m), 8.43 (1H, d, $J=1.7\text{Hz}$).

[0209]

50 Example 2-46LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methoxynicotinamide
RT(min.): 3.261

MS(ESI, *m/z*): 434.1276 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 1.85-2.25 (1H, m), 2.45-2.80 (2H, m), 3.95-4.10 (3H, m), 4.55-4.90 (1H, m), 5.10-6.20 (3H, m), 6.90-7.15 (2H, m), 7.15-7.30 (1H, m), 7.30-8.05 (7H, m), 8.22 (1H, dd, *J*=1.8, 5.0Hz).

[0210]

Example 2-47LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]isonicotinamide

RT(min.): 2.620

MS(ESI, *m/z*): 406.1370 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.68-1.86 (1H, m), 1.93-2.12 (1H, m), 2.43-2.85 (2H, m), 4.50-5.05 (1H, m), 5.24-5.77 (3H, m), 6.53-6.80 (1H, m), 7.20-7.66 (8H, m), 8.66-8.80 (2H, m).

[0211]

Example 2-48LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]nicotinamide

RT(min.): 2.804

MS(ESI, *m/z*): 418.1329 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.34-1.64 (2H, m), 1.66-1.83 (2H, m), 2.55-2.65 (2H, m), 4.65 (1H, br s), 4.99-5.10 (1H, m), 5.28-5.69 (2H, m), 7.01 (1H, d, *J*=8.2Hz), 7.17-7.23 (1H, m), 7.35-7.45 (4H, m), 7.47-7.55 (2H, m), 7.89-7.95 (1H, m), 8.22 (1H, d, *J*=1.3Hz), 8.70 (1H, dd, *J*=1.6, 4.9Hz), 8.86 (1H, d, *J*=1.6Hz).

[0212]

Example 2-48HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]nicotinamide

RT(min.): 2.701

MS(ESI, *m/z*): 418.1324 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.37-1.68 (1H, m), 1.90-2.07 (1H, m), 2.14-2.35 (2H, m), 2.58-2.83 (2H, m), 4.45 (1H, br s), 4.99-5.09 (1H, m), 5.34-5.72 (2H, m), 6.77 (1H, br s), 6.93-7.02 (2H, m), 7.22-7.43 (6H, m), 7.83-7.91 (1H, m), 8.70 (1H, dd, *J*=1.5, 4.9Hz), 8.81-8.85 (1H, m).

[0213]

Example 2-49LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide

RT(min.): 3.691

MS(ESI, *m/z*): 417.1379 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.32-1.55 (2H, m), 1.70-1.84 (2H, m), 2.54-2.63 (2H, m), 4.62 (1H, br s), 5.07-5.18 (1H, m), 5.24-5.99 (2H, m), 7.00 (1H, d, *J*=8.2Hz), 7.16-7.22 (1H, m), 7.32-7.61 (10H, m), 8.13-8.18 (1H, m).

[0214]

Example 2-49HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-7-chloro-1,2,3,4-tetrahydronaphthalen-1-yl]benzamide

RT(min.): 3.583

MS(ESI, *m/z*): 417.1376 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.40-1.53 (1H, m), 1.89-2.02 (1H, m), 2.13-2.33 (2H, m), 2.56-2.67

(1H, m), 2.70-2.83 (1H, m), 4.42 (1H, br s), 5.07-5.17 (1H, m), 5.31-5.93 (2H, m), 6.85 (1H, br s), 6.93-7.02 (2H, m), 7.28-7.32 (5H, m), 7.42-7.46 (3H, m), 7.53-7.57 (2H, m).

[0215]

Example 2-50LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiophene-2-carboxamide

RT(min.): 3.682

MS(ESI, *m/z*): 427.0689 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.80-2.40 (2H, m), 2.55-2.70 (1H, m), 2.80-3.00 (1H, m), 4.40-6.30 (4H, m), 6.90-7.05 (1H, m), 7.07 (1H, dd, *J*=3.8, 5.0Hz), 7.30-7.50 (6H, m), 7.52 (1H, dd, *J*=1.0, 5.0Hz), 7.65-7.85 (1H, m).

[0216]

Example 2-51LP

15 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-5-carboxamide

RT(min.): 3.173

MS(ESI, *m/z*): 428.0639 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.75-2.30 (2H, m), 2.50-2.70 (1H, m), 2.75-3.00 (1H, m), 4.50-6.05 (4H, m), 6.85-7.10 (1H, m), 7.30-7.55 (5H, m), 7.65-7.90 (1H, m), 8.20 (1H, br s), 8.92 (1H, s).

[0217]

Example 2-52LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-isopropoxyindan-1-yl]nicotinamide

RT(min.): 2.840

25 MS(ESI, *m/z*): 428.1983 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.34-1.42 (6H, m), 1.69-1.82 (1H, m), 1.96-2.07 (1H, m), 2.44-2.73 (2H, m), 4.60-4.85 (2H, m), 5.29-5.66 (3H, m), 6.77-6.86 (1H, m), 7.02-7.10 (1H, m), 7.33-7.62 (7H, m), 7.86-7.97 (1H, m), 8.64-8.72 (1H, m), 8.84-8.92 (1H, m).

[0218]

30 Example 2-53LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-isopropoxyindan-1-yl]benzamide

RT(min.): 3.742

MS(ESI, *m/z*): 427.2028 (M-H)⁻

35 ¹H-NMR (CDCl₃) δ: 1.34-1.43 (6H, m), 1.67-1.81 (1H, m), 1.97-2.08 (1H, m), 2.45-2.71 (2H, m), 4.61-4.76 (2H, m), 5.24-5.84 (3H, m), 6.77-6.84 (1H, m), 7.05 (1H, d, *J*=8.1Hz), 7.30-7.64 (11H, m).

[0219]

Example 2-54LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-6-cyano-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide

RT(min.): 3.276

MS(ESI, *m/z*): 431.1326 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.67-2.16 (2H, m), 2.44-2.90 (2H, m), 4.50-5.85 (4H, m), 6.62-6.84 (1H, m), 7.37-8.09 (8H, m), 8.79-8.95 (1H, m).

[0220]

45 Example 2-55LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]thiazole-5-carboxamide

RT(min.): 2.959

MS(ESI, *m/z*): 412.0941 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.77-1.98 (1H, m), 2.00-2.30 (1H, m), 2.54-2.69 (1H, m), 2.77-2.96

(1H, m), 4.37-5.14 (1H, m), 5.19-6.08 (3H, m), 6.55-6.88 (1H, m), 7.53-7.70 (6H, m),
8.17-8.24 (1H, m), 8.95 (1H, s).

[0221]

Example 2-56) P

5 A-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4-fluoroindan-1-yl]nicotinamide

RT(min.): 2.502

MS(ESI, m/z): 388.1467 (M-H)⁺

¹H-NMR (CDCl₃, δ): 1.68-1.88 (1H, m), 1.97-2.15 (1H, m), 2.47-2.66 (1H, m), 2.72-2.92
(1H, m), 4.60-4.83 (1H, br), 5.29-5.73 (3H, m), 6.91-7.04 (1H, m), 7.29-7.53 (7H, m), 7.78
10 (1H, d, J = 7.7Hz), 7.91 (1H, d, J = 7.7Hz), 8.65-8.73 (1H, m), 8.80-8.90 (1H, m).

[0222]

Example 2-57) P

A-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]thiazole-2-carboxamide

RT(min.): 3.495

15 MS(ESI, m/z): 412.0940 (M-H)⁺

¹H-NMR (CDCl₃, δ): 3.55-3.79 (1H, m), 4.50-5.90 (2H, m), 6.50-7.10 (2H, m), 7.32-7.68
(8H, m), 7.85-8.00 (1H, m).

[0223]

Example 2-58) P

20 A-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-4-chloro-6-fluoroindan-1-yl]nicotinamide

RT(min.): 2.986

MS(ESI, m/z): 422.1078 (M-H)⁺

¹H-NMR (CDCl₃, δ): 1.70-1.90 (1H, m), 1.95-2.15 (1H, m), 2.40-2.65 (1H, m), 2.65-2.85
(1H, m), 4.50-5.80 (1H, m), 6.85-7.10 (1H, m), 7.30-7.95 (8H, m), 8.65-8.75 (1H, m), 8.81
25 (1H, br s).

[0224]

Example 2-59) P

2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-5-
carboxamide

30 RT(min.): 2.752

MS(ESI, m/z): 433.0751 (M-H)⁺

¹H-NMR (CDCl₃, δ): 1.75-1.35 (2H, m), 2.45-2.75 (1H, m), 2.75-3.00 (1H, m), 4.20-6.30
(6H, m), 6.85-7.10 (1H, m), 7.10-7.80 (7H, m).

[0225]

35 Example 2-60) P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-4-
carboxamide

RT(min.): 3.294

MS(ESI, m/z): 428.0643 (M-H)⁺

40 ¹H-NMR (CDCl₃, δ): 1.45-2.05 (1H, m), 2.40-2.45 (1H, m), 2.55-2.75 (1H, m), 2.75-3.20
(1H, m), 4.50-7.05 (1H, m), 7.10-7.85 (7H, m), 8.18 (1H, br s), 8.75-8.95 (1H, m).

[0226]

Example 2-61) P

45 2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]thiazole-5-
carboxamide

RT(min.): 2.540

MS(ESI, m/z): 427.1046 (M-H)⁺

¹H-NMR (CDCl₃, δ): 1.78-2.36 (2H, m), 2.51-2.73 (1H, m), 2.80-2.95 (1H, m), 4.33-5.00
(1H, m), 5.21-6.30 (1H, m), 6.56-6.81 (1H, m), 7.31-7.58 (7H, m).

[0227]

Example 2-62LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]terephthalamic acid benzyl ester

5 RT(min.): 4.269

MS(ESI, *m/z*): 539.1791 (*M*-H)⁻¹H-NMR (CDCl₃) δ: 1.63-2.12 (2H, m), 2.37-3.13 (2H, m), 4.50-5.07 (1H, m), 5.13-5.71 (5H, m), 6.53-6.73 (1H, m), 7.23-7.67 (13H, m), 8.08-8.22 (2H, m).

[0228]

10 Example 2-63LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiophene-3-carboxamide

RT(min.): 3.586

MS(ESI, *m/z*): 427.0690 (*M*-H)⁻15 ¹H-NMR (CDCl₃) δ: 1.70-2.25 (2H, m), 2.45-2.65 (1H, m), 2.70-3.00 (1H, m), 4.50-5.95 (4H, m), 6.85-7.10 (1H, m), 7.20-7.90 (9H, m).

[0229]

Example 2-64LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluorothiophene-2-carboxamide

20 RT(min.): 3.923

MS(ESI, *m/z*): 445.0597 (*M*-H)⁻25 ¹H-NMR (CDCl₃) δ: 1.22-1.34 (1H, m), 1.81-1.95 (1H, m), 2.56-2.69 (1H, m), 2.85-2.96 (1H, m), 4.10-6.30 (4H, m), 6.47 (1H, dd, *J*=1.4, 4.2Hz), 6.94-7.03 (1H, m), 7.11-7.16 (1H, m), 7.34-7.43 (5H, m), 7.70-7.78 (1H, m).

[0230]

Example 2-64HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluorothiophene-2-carboxamide

30 RT(min.): 3.747

MS(ESI, *m/z*): 445.0596 (*M*-H)⁻¹H-NMR (CDCl₃) δ: 2.63-2.94 (3H, m), 3.13-3.23 (1H, m), 4.28-6.48 (4H, m), 6.49 (1H, dd, *J*=1.4, 4.2Hz), 6.85-6.90 (1H, m), 7.13-7.18 (1H, m), 7.20-7.35 (6H, m).

[0231]

35 Example 2-65LP

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]nicotinamide

RT(min.): 1.997

MS(ESI, *m/z*): 403.1575 (*M*-H)⁻40 ¹H-NMR (CDCl₃) δ: 1.60-1.77 (1H, m), 1.97-2.16 (1H, m), 2.50-2.82 (2H, m), 4.52-4.82 (1H, br), 5.24-5.64 (5H, m), 6.67 (1H, dd, *J*=5.0, 7.4Hz), 6.93-7.01 (1H, m), 7.25-7.55 (7H, m), 7.67 (1H, d, *J*=7.4Hz), 8.12 (1H, d, *J*=1.8, 5.0Hz).

[0232]

Example 2-66LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

45 RT(min.): 2.520

MS(ESI, *m/z*): 422.1078 (*M*-H)⁻¹H-NMR (CDCl₃) δ: 1.74-1.94 (1H, m), 2.10-2.31 (1H, m), 2.48-2.68 (1H, m), 2.76-2.96 (1H, m), 4.63-4.77 (1H, m), 5.34-6.14 (3H, m), 6.95-7.06 (1H, m), 7.32-7.59 (6H, m), 7.70 (1H, br s), 7.85-8.02 (1H, m), 8.56-8.72 (2H, m).

[0233]

Example 2-66HP

N-[(*S*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 2.275

5 MS(ESI, *m/z*): 422.1079 (M-H)⁺¹H-NMR (CDCl₃) δ: 2.42-3.20 (4H, m), 4.37-4.48 (1H, m), 5.41-5.92 (3H, m), 6.86-6.92 (1H, m), 7.28-7.34 (1H, m), 7.43-7.60 (6H, m), 7.86-7.94 (1H, m), 8.30-8.38 (1H, m), 8.56-8.63 (1H, m).

[0234]

10 Example 2-67LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]isothiazole-5-carboxamide

RT(min.): 3.228

MS(ESI, *m/z*): 412.0937 (M-H)⁺15 ¹H-NMR (CDCl₃) δ: 1.71-1.93 (1H, m), 2.05-2.34 (1H, m), 2.48-2.66 (1H, m), 2.71-2.96 (1H, m), 4.45-5.90 (4H, m), 6.54-6.88 (1H, m), 7.32-7.65 (7H, m), 8.48 (1H, br s).

[0235]

Example 2-68LP

N-[(*R*)-Carbamoylpyridin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.223

20 MS(ESI, *m/z*): 422.1075 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.90-2.09 (1H, m), 2.21-2.37 (1H, m), 2.50-2.69 (1H, m), 2.80-3.11 (1H, m), 4.66-5.95 (4H, m), 6.83-7.09 (1H, m), 7.40-7.83 (9H, m), 8.49-8.65 (1H, m).

[0236]

Example 2-69LP

25 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyridine-2-carboxamide

RT(min.): 3.300

MS(ESI, *m/z*): 422.1077 (M-H)⁺30 ¹H-NMR (CDCl₃) δ: 1.60-2.10 (1H, m), 2.15-2.40 (1H, m), 2.45-3.20 (2H, m), 4.70-6.30 (3H, m), 6.80-7.00 (1H, m), 7.30-7.60 (7H, m), 7.60-8.00 (3H, m), 8.55-8.65 (1H, m).

[0237]

Example 2-70LP

N-[(*R*)-Carbamoylpyridin-4-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 2.385

35 MS(ESI, *m/z*): 422.1077 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.87-2.96 (4H, m), 4.56-4.73 (1H, br), 5.29-6.33 (3H, m), 6.94-7.09 (1H, m), 7.34-7.66 (8H, m), 8.62-8.68 (2H, m).

[0238]

Example 2-71LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-5-carboxamide

RT(min.): 2.972

MS(ESI, *m/z*): 410.0736 (M-H)⁺45 ¹H-NMR (CDCl₃) δ: 1.75-1.95 (1H, m), 2.00-2.30 (1H, m), 2.55-2.90 (2H, m), 4.50-4.90 (1H, m), 5.20-6.00 (3H, m), 7.05-7.30 (2H, m), 7.35-7.50 (5H, m), 7.90-8.00 (1H, m), 8.15-8.30 (1H, m), 8.92 (1H, s).

[0239]

Example 2-72LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiophene-3-carboxamide

RT(min.): 3.440

50 MS(ESI, *m/z*): 409.0783 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.95 (1H, m), 1.95-2.20 (1H, m), 2.50-2.85 (2H, m), 4.55-4.80 (1H, m), 5.20-5.95 (3H, m), 7.05-7.30 (2H, m), 7.30-7.65 (7H, m), 7.71 (1H, br s), 7.90-8.05 (1H, m).

[0240]

5 Example 2-73LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]pyridine-2-carboxamide

RT(min.): 3.112

MS(ESI, *m/z*): 404.1172 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ: 1.55-2.05 (1H, m), 2.15-2.40 (1H, m), 2.50-3.20 (2H, m), 4.60-5.25 (1H, m), 5.40-6.25 (3H, m), 7.00-7.25 (2H, m), 7.25-8.30 (9H, m), 8.61 (1H, d, *J*=4.6Hz).

[0241]

Example 2-74LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-4-carboxamide

RT(min.): 3.116

15 MS(ESI, *m/z*): 410.0738 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.45-2.05 (1H, m), 2.10-2.50 (1H, m), 2.55-3.20 (2H, m), 4.50-5.35 (1H, m), 5.35-6.85 (3H, m), 6.95-8.25 (9H, m), 8.75-8.95 (1H, m).

[0242]

Example 2-75LP

20 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-2-carboxamide

RT(min.): 3.711

MS(ESI, *m/z*): 428.0640 (M-H)⁺

25 ¹H-NMR (CDCl₃) δ: 1.50-2.05 (1H, m), 2.10-2.45 (1H, m), 2.45-3.20 (2H, m), 4.50-7.10 (4H, m), 7.25-8.25 (9H, m).

[0243]

Example 2-76LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide

RT(min.): 2.302

30 MS(ESI, *m/z*): 406.1371 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.74-1.92 (1H, m), 2.12-2.29 (1H, m), 2.50-2.66 (1H, m), 2.75-2.95 (1H, m), 4.59-4.84 (1H, m), 5.28-6.16 (3H, m), 6.62-6.83 (1H, m), 7.32-7.61 (7H, m), 7.86-8.04 (1H, m), 8.51-8.74 (2H, m).

[0244]

35 Example 2-77LP

N-[(*R*)-Carbamoylpyridin-2-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide

RT(min.): 3.011

MS(ESI, *m/z*): 406.1373 (M-H)⁺

40 ¹H-NMR (CDCl₃) δ: 1.90-2.04 (1H, m), 2.21-2.37 (1H, m), 2.50-2.68 (1H, m), 2.76-2.95 (1H, m), 4.69-4.86 (1H, m), 5.27-5.68 (2H, m), 6.61-6.79 (1H, m), 7.16-7.85 (10H, m), 8.54-8.62 (1H, m).

[0245]

Example 2-77HP

N-[(*S*)-Carbamoylpyridin-2-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide

45 RT(min.): 2.800

MS(ESI, *m/z*): 406.1374 (M-H)⁺

¹H-NMR (CDCl₃) δ: 2.33-2.78 (3H, m), 2.95-3.14 (1H, m), 4.69-4.84 (1H, m), 5.40-5.72 (2H, m), 6.55-6.65 (1H, m), 6.95-7.06 (1H, m), 7.16-7.83 (9H, m), 8.49-8.60 (1H, m).

[0246]

50 Example 2-78LP

N-[(*R*)-Carbamoylpyridin-2-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide

RT(min.): 2.141

MS(ESI, *m/z*): 407.1324 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.87-2.06 (1H, m), 2.22-2.40 (1H, m), 2.52-2.69 (1H, m), 2.78-2.95 (1H, m), 4.75-4.95 (1H, m), 5.39-5.68 (2H, m), 6.61-6.80 (1H, m), 7.20-7.90 (6H, m), 7.92-8.08 (1H, m), 8.53-8.65 (1H, m), 8.66-8.81 (1H, m), 8.93 (1H, br s).

[0247]

Example 2-79LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-2-carboxamide

10 RT(min.): 3.543

MS(ESI, *m/z*): 410.0736 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.45-2.00 (1H, m), 2.15-2.45 (1H, m), 2.55-3.15 (2H, m), 4.60-5.90 (2H, m), 6.95-7.65 (11H, m), 7.80-8.00 (1H, m).

[0248]

15 Example 2-80LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]isonicotinamide

RT(min.): 2.829

MS(ESI, *m/z*): 422.1075 (*M*-H)⁺

20 ¹H-NMR (CDCl₃) δ: 1.30-3.20 (4H, m), 4.35-5.70 (4H, m), 6.80-7.90 (9H, m), 8.65-8.80 (2H, m).

[0249]

Example 2-81LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide

RT(min.): 1.447

25 MS(ESI, *m/z*): 407.1326 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.71-1.92 (1H, m), 2.08-2.27 (1H, m), 2.47-2.66 (1H, m), 2.74-2.94 (1H, m), 4.46-4.95 (1H, m), 5.33-5.84 (3H, m), 6.65-6.84 (1H, m), 7.35-7.62 (3H, m), 7.79-8.08 (2H, m), 8.57-8.91 (4H, m).

[0250]

30 Example 2-82LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]isothiazole-5-carboxamide

RT(min.): 3.444

MS(ESI, *m/z*): 428.0640 (*M*-H)⁺

35 ¹H-NMR (CDCl₃) δ: 1.70-1.95 (1H, m), 2.00-2.25 (1H, m), 2.50-2.65 (1H, m), 2.70-2.95 (1H, m), 4.50-5.90 (4H, m), 6.85-7.10 (1H, m), 7.30-7.90 (7H, m), 8.48 (1H, s).

[0251]

Example 2-83LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

40 RT(min.): 1.774

MS(ESI, *m/z*): 423.1029 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 2.05-2.30 (1H, m), 2.45-2.70 (1H, m), 2.70-2.95 (1H, m), 4.65-4.90 (1H, m), 5.30-5.85 (3H, m), 6.95-7.10 (1H, m), 7.25-7.50 (2H, m), 7.70-8.05 (3H, m), 8.60-8.85 (4H, m).

[0252]

45 Example 2-84LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluorothiophene-2-carboxamide

RT(min.): 2.650

50 MS(ESI, *m/z*): 446.0547 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.85-1.98 (1H, m), 2.06-2.41 (1H, m), 2.64-2.78 (1H, m), 2.90-3.04 (1H, m), 4.41-6.23 (4H, m), 6.49 (1H, dd, J = 1.4, 4.2 Hz), 7.04 (1H, d, J = 8.5 Hz), 7.15-7.19 (1H, m), 7.35 (1H, dd, J = 4.8, 8.0 Hz), 7.67 (1H, s), 7.84-7.90 (1H, m), 8.59-8.64 (2H, m), [0253]

5 Example 2-851.P

N-[(*R*)-Carbamoylpyridin-2-ylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide
RT(min.): 2.381

MS(ESI, m/z): 423.1031 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ: 1.87-3.16 (4H, m), 4.52-5.86 (3H, m), 6.79-8.09 (8H, m), 8.44-8.98 (3H, m), [0254]

Example 2-861.P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluoronicotinamide
RT(min.): 3.319

15 MS(ESI, m/z): 440.0983 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.72-2.17 (2 H, m), 2.44-2.86 (2H, m), 4.58-5.82 (4H, m), 6.87-7.09 (1H, m), 7.30-7.90 (7H, m), 8.50-8.70 (2H, m), [0255]

20 Example 2-871.P

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-N-[(*R*)-6-chloroindan-1-yl]benzamide
RT(min.): 2.518
MS(ESI, m/z): 404.1171 (M-H)⁺

25 ¹H-NMR (CDCl₃) δ: 1.70-1.95 (1H, m), 2.10-2.50 (1H, m), 2.55-2.70 (1H, m), 2.70-2.90 (1H, m), 4.60-4.80 (1H, m), 5.20-5.30 (3H, m), 7.05-7.20 (1H, m), 7.20-7.30 (1H, m), 7.30-7.40 (1H, m), 7.40-7.50 (3H, m), 7.50-7.65 (2H, m), 7.80-7.90 (1H, m), 7.90-8.05 (1H, m), 8.55-8.70 (2H, m), [0256]

Example 2-881.P

30 N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-chloroindan-1-yl]-4-methylthiazole-5-carboxamide
RT(min.): 3.052
MS(ESI, m/z): 424.0892 (M-H)⁺

35 ¹H-NMR (CDCl₃) δ: 1.65-2.20 (2H, m), 2.45-2.90 (5H, m), 4.50-4.90 (1H, m), 5.20-5.70 (3H, m), 7.05-7.15 (1H, m), 7.20-7.50 (6H, m), 7.90 (1H, s), 8.76 (1H, s), [0257]

Example 2-891.P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide
40 RT(min.): 3.654
MS(ESI, m/z): 451.1227 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 1.95-2.25 (1H, m), 2.40-3.10 (2H, m), 3.85-3.95 (3H, m), 4.50-6.35 (4H, m), 6.80-7.15 (3H, m), 7.20-7.80 (8H, m), [0258]

45 Example 2-901.P

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]cyclohexylcarboxamide
RT(min.): 4.058
MS(ESI, m/z): 427.1595 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.05-3.04 (15H, m), 4.31-6.60 (4H, m), 6.90-7.06 (1H, m), 7.25-7.85 (6H, m).

[0259]

Example 2-91LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-trifluoromethylnicotinamide

RT(min.): 3.845

MS(ESI, m/z): 490.0953 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ: 1.69-1.87 (1H, m), 1.95-2.12 (1H, m), 2.45-3.15 (2H, m), 4.58-5.78 (4H, m), 6.84-7.06 (1H, m), 7.37-7.56 (5H, m), 7.69-7.88 (2H, m), 7.98-8.11 (1H, m), 8.89 (1H, br s).

[0260]

Example 2-91HP

15 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-trifluoromethylnicotinamide

RT(min.): 3.694

MS(ESI, m/z): 490.0953 (M-H)⁺

20 ¹H-NMR (CDCl₃) δ: 2.46-2.61 (1H, m), 2.69-2.83 (2H, m), 3.02-3.17 (1H, m), 4.47 (1H, br s), 5.27-5.57 (3H, m), 6.26 (1H, br s), 6.86 (1H, d, J=8.3Hz), 7.25-7.43 (5H, m), 7.79 (1H, d, J=8.0Hz), 8.00-8.08 (1H, m), 8.89 (1H, br s).

[0261]

Example 2-92LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5,7-difluoroindan-1-yl]benzamide

RT(min.): 3.970

25 MS(ESI, m/z): 405.1422 (M-H)⁺

¹H-NMR (CDCl₃) δ: 2.00-2.30 (1H, m), 2.30-2.65 (1H, m), 2.65-2.90 (1H, m), 2.90-3.15 (1H, m), 4.40-4.80 (1H, m), 5.00-6.20 (2H, m), 6.60-6.80 (2H, m), 6.90-7.15 (1H, m), 7.25-7.55 (8H, m), 7.55-7.65 (2H, m).

[0262]

30 Example 2-92HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5,7-difluoroindan-1-yl]benzamide

RT(min.): 3.259

MS(ESI, m/z): 405.1422 (M-H)⁺

35 ¹H-NMR (CDCl₃) δ: 2.40-2.60 (1H, m), 2.65-3.00 (2H, m), 3.15-3.40 (1H, m), 4.28 (1H, br s), 5.40-5.90 (3H, m), 6.10-6.20 (1H, m), 6.65-6.75 (1H, m), 7.15-7.30 (5H, m), 7.40-7.50 (3H, m), 7.55-7.65 (2H, m).

[0263]

Example 2-93LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 3.441

MS(ESI, m/z): 456.0688 (M-H)⁺

45 ¹H-NMR (CDCl₃) δ: 1.72-1.86 (1H, m), 2.25-2.60 (2H, m), 2.75-3.13 (1H, m), 4.56 (1H, br s), 5.13-5.26 (1H, m), 5.34-5.50 (2H, m), 6.86-7.04 (1H, m), 7.34-7.94 (8H, m), 8.41-8.50 (1H, m).

[0264]

Example 2-94LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-trifluoromethylnicotinamide

50 RT(min.): 3.722

MS(ESI, m/z): 490.0951 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.67-2.15 (2H, m), 2.43-3.11 (2H, m), 4.56 (1H, s), 5.03-5.20 (1H, m), 5.31-5.53 (2H, m), 6.85-7.05 (1H, m), 7.35-8.14 (8H, m), 8.78-8.82 (1H, m).

[0265]

5 Example 2-95LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]isothiazole-5-carboxamide

RT(min.): 3.551

MS(ESI, m/z): 410.0735 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.45-2.00 (1H, m), 2.15-2.45 (1H, m), 2.55-3.15 (2H, m), 4.60-5.90 (2H, m), 6.90-7.65 (11H, m), 7.80-8.00 (1H, m).

[0266]

Example 2-96LP

N-[(*S*)-Carbamoylthiazol-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.358

15 MS(ESI, m/z): 428.0639 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.85-2.04 (1H, m), 2.18-2.33 (1H, m), 2.48-2.67 (1H, m), 2.84-2.99 (1H, m), 4.94-5.07 (1H, m), 5.36-5.66 (2H, m), 6.83-7.05 (2H, m), 7.38-7.91 (8H, m).

[0267]

Example 2-97LP

20 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 2.778

MS(ESI, m/z): 456.0686 (M-H)⁻

25 ¹H-NMR (CDCl₃) δ: 1.66-2.96 (4H, m), 4.55-5.70 (4H, m), 6.80-7.07 (1H, m), 7.30-8.81 (9H, m).

[0268]

Example 2-98LP

N-[(*R*)-Carbamoylphenylmethyl]-3-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]isonicotinamide

30 RT(min.): 3.402

MS(ESI, m/z): 456.0687 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.71-3.17 (4H, m), 4.52-5.82 (4H, m), 6.83-7.07 (1H, m), 7.30-7.88 (7H, m), 8.50-8.80 (2H, m).

[0269]

35 Example 2-99LP

N-[(*R*)-Carbamoyl-(2-chlorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 3.170

MS(ESI, m/z): 456.0685 (M-H)⁻

40 ¹H-NMR (CDCl₃) δ: 1.60-3.18 (4H, m), 4.80-5.80 (4H, m), 6.79-7.01 (1H, m), 7.28-8.02 (7H, m), 8.57-8.89 (2H, m).

[0270]

Example 2-100LP

45 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylnicotinamide

RT(min.): 2.796

MS(ESI, m/z): 436.1237 (M-H)⁻

50 ¹H-NMR (CDCl₃) δ: 1.68-2.17 (2H, m), 2.40-2.62 (4H, m), 2.71-3.14 (1H, m), 4.58-5.11 (1H, m), 5.19-5.28 (1H, m), 5.36-5.53 (2H, m), 6.86-7.03 (1H, m), 7.17-7.60 (6H, m), 7.71-7.90 (1H, m), 8.48-8.72 (2H, m).

[0271]

Example 2-101LP

N-[(*R*)-Carbamoylphenylmethyl]-4-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

5 RT(min.): 3.312

MS(ESI, *m/z*): 456.0687 (M-H)⁺¹H-NMR (DMSO-*d*₆) δ: 1.30-1.44 (1H, m), 2.01-2.21 (1H, m), 2.48-2.66 (1H, m), 2.83-2.94 (1H, m), 4.92-5.00 (0.5H, m), 5.22-5.30 (1H, m), 5.40 (0.5H, s), 7.10-7.17 (1H, m), 7.35-7.81 (9H, m), 8.33 (0.5H, s), 8.62-8.68 (1H, m), 8.90 (0.5H, s).

10 [0272]

Example 2-102LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-ethoxynicotinamide

RT(min.): 3.596

15 MS(ESI, *m/z*): 466.1339 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.47 (3H, t, *J*=7.1Hz), 1.65-1.90 (1H, m), 2.10-2.30 (1H, m), 2.40-2.65 (1H, m), 2.65-3.10 (1H, m), 4.30-4.70 (3H, m), 5.20-5.80 (3H, m), 6.80-7.05 (2H, m), 7.30-7.90 (7H, m), 8.15-8.30 (1H, m).

[0273]

20 Example 2-103LP

N-[(*R*)-Carbamoyl-(2-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 3.039

MS(ESI, *m/z*): 440.0982 (M-H)⁺25 ¹H-NMR (CDCl₃) δ: 1.69-3.21 (4H, m), 4.82-5.82 (4H, m), 6.78-8.00 (8H, m), 8.62-8.86 (2H, m).

[0274]

Example 2-104LP

5-[(*N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}pyridine-2-carboxylic acid benzyl ester

30 RT(min.): 3.976

MS(ESI, *m/z*): 556.1451 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.64-2.11 (2H, m), 2.40-2.87 (2H, m), 4.56-5.71 (6H, m), 6.80-7.10 (1H, m), 7.28-8.28 (13H, m), 8.85-8.99 (1H, m).

35 [0275]

Example 2-105LP

N-[(*R*)-Carbamoylphenylmethyl]-3-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyridine-2-carboxamide

RT(min.): 3.500

40 MS(ESI, *m/z*): 456.0688 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.61-3.17 (4H, m), 4.66-6.08 (4H, m), 6.78-7.01 (1H, m), 7.22-7.90 (8H, m), 8.48-8.62 (1H, m).

[0276]

Example 2-106LP

45 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-methoxynicotinamide

RT(min.): 3.510

MS(ESI, *m/z*): 452.1181 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.68-2.23 (2H, m), 2.43-2.95 (2H, m), 3.97 (3H, s), 4.38-4.95 (1H, m),

5.22-5.88 (3H, m), 6.80 (1H, d, $J=8.6\text{Hz}$), 6.89-7.06 (1H, m), 7.31-7.53 (5H, m), 7.69-7.90 (2H, m), 8.38-8.48 (1H, m).

[0277]

Example 2-106HP

5 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-methoxynicotinamide

RT(min.): 3.366

MS(ESI, m/z): 452.1187 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ : 2.48-2.83 (3H, m), 3.03-3.19 (1H, m), 3.97 (3H, s), 4.22-4.63 (1H, m), 5.32-5.83 (3H, m), 6.18-6.53 (1H, m), 6.75-6.89 (2H, m), 7.18-7.49 (5H, m), 7.73-7.85 (1H, m), 8.33-8.46 (1H, m).

[0278]

Example 2-107LP

15 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylamino)nicotinamide

RT(min.): 2.362

MS(ESI, m/z): 451.1341 (M-H)⁺

20 ¹H-NMR (CDCl₃) δ : 1.62-2.14 (2H, m), 2.45-2.83 (2H, m), 3.00-3.13 (3H, m), 4.48-4.82 (1H, m), 5.19-5.67 (3H, m), 6.00-6.31 (1H, m), 6.57 (1H, dd, $J=5.1, 7.2\text{Hz}$), 6.91-7.05 (1H, m), 7.34-7.68 (7H, m), 8.20 (1H, dd, $J=1.7, 5.1\text{Hz}$).

[0279]

Example 2-107HP

25 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylamino)nicotinamide

RT(min.): 2.357

MS(ESI, m/z): 451.1343 (M-H)⁺

30 ¹H-NMR (CDCl₃) δ : 2.49-2.90 (3H, m), 2.99-3.15 (4H, m), 4.21-4.56 (1H, m), 5.32-5.66 (3H, m), 5.89-6.32 (1H, m), 6.56 (1H, dd, $J=5.1, 7.3\text{Hz}$), 6.81 (1H, dd, $J=1.3, 8.6\text{Hz}$), 7.25-7.43 (7H, m), 8.20 (1H, dd, $J=1.7, 5.1\text{Hz}$).

[0280]

Example 2-108LP

35 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-trifluoromethylnicotinamide

RT(min.): 3.616

MS(ESI, m/z): 490.0952 (M-H)⁺

¹H-NMR (CDCl₃) δ : 1.65-3.13 (4H, m), 4.56-4.78 (1H, m), 5.05-5.20 (1H, m), 5.30-6.03 (2H, m), 6.85-7.05 (1H, m), 7.33-7.56 (5H, m), 7.60-7.93 (2H, m), 8.76-9.10 (2H, m).

[0281]

Example 2-109LP

40 *N*-[(*R*)-Carbamoyl-(5-fluoropyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.217

MS(ESI, m/z): 440.0984 (M-H)⁺

45 ¹H-NMR (CDCl₃) δ : 1.71-2.00 (1H, m), 2.13-2.40 (1H, m), 2.50-3.02 (2H, m), 4.64-4.86 (1H, m), 5.34-6.35 (3H, m), 6.92-7.08 (1H, m), 7.42-7.87 (7H, m), 8.40-8.56 (2H, m).

[0282]

Example 2-110LP

50 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]imidazo[1,2-*a*]pyrazine-3-carboxamide

RT(min.): 2.970

MS(ESI, m/z): 462.1140 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.61-3.13 (4H, m), 4.40-6.40 (4H, m), 6.86-7.14 (1H, m), 7.36-8.22 (8H, m), 8.80-9.30 (2H, m).

[0283]

5 Example 2-111LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydrobenzofuran-7-carboxamide

RT(min.): 3.737

MS(ESI, m/z): 463.1227 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ : 1.76-2.33 (2H, m), 2.45-2.90 (2H, m), 3.20-3.35 (2H, m), 4.56-6.17 (6H, m), 6.80-7.02 (2H, m), 7.19-7.72 (8H, m).

[0284]

Example 2-112LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]nicotinamide

15 RT(min.): 1.615

MS(ESI, m/z): 405.1139 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.68-1.86 (1H, m), 2.07-2.23 (1H, m), 2.57-2.72 (1H, m), 2.79-2.99 (1H, m), 4.66-4.92 (1H, m), 5.26-5.91 (3H, m), 7.24-7.45 (4H, m), 7.77-8.05 (3H, m), 8.62-8.74 (3H, m), 8.81-8.87 (1H, m).

20 [0285]

Example 2-113LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-fluorobenzamide

RT(min.): 2.623

25 MS(ESI, m/z): 440.0983 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.74-1.89 (1H, m), 2.17-2.40 (1H, m), 2.54-2.67 (1H, m), 2.79-2.93 (1H, m), 4.57-4.87 (1H, m), 5.33-6.10 (3H, m), 6.98-7.04 (1H, m), 7.14-7.21 (1H, m), 7.24-7.68 (5H, m), 7.90-8.03 (1H, m), 8.59-8.72 (2H, m).

[0286]

30 Example 2-114LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methoxynicotinamide

RT(min.): 2.295

MS(ESI, m/z): 452.1177 (M-H)⁻

35 ¹H-NMR (CDCl₃) δ : 1.68-2.21 (2H, m), 2.38-3.09 (2H, m), 3.89-4.03 (3H, m), 4.44-5.89 (4H, m), 6.80-7.05 (2H, m), 7.24-7.89 (6H, m), 8.40-8.66 (2H, m).

[0287]

Example 2-115LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]imidazo[1,2-*a*]pyridine-6-carboxamide

40 RT(min.): 2.250

MS(ESI, m/z): 461.1184 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.69-3.14 (4H, m), 4.45-6.60 (4H, m), 6.83-7.10 (1H, m), 7.27-8.00 (10H, m), 8.40-8.56 (1H, m).

45 [0288]

Example 2-116LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxymethylnicotinamide

RT(min.): 2.665

50 MS(ESI, m/z): 452.1184 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.69-1.82 (1H, m), 2.00-2.18 (1H, m), 2.45-3.12 (2H, m), 4.55-5.71 (6H, m), 6.85-7.04 (1H, m), 7.25-7.87 (8H, m), 8.59-8.67 (1H, m).

[0289]

Example 2-117LP

5 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylbenzamide

RT(min.): 2.788

MS(ESI, *m/z*): 436.1235 (M-H)⁺

10 ¹H-NMR (CDCl₃) δ: 1.68-1.81 (1H, m), 2.03-2.22 (1H, m), 2.37-2.58 (4H, m), 2.77-3.17 (1H, m), 4.61-4.70 (1H, m), 5.23-5.96 (3H, m), 6.85-7.03 (1H, m), 7.20-7.49 (5H, m), 7.61-7.82 (1H, m), 7.97-8.15 (1H, m), 8.51-8.74 (2H, m).

[0290]

Example 2-118LP

15 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

RT(min.): 2.518

MS(ESI, *m/z*): 452.1183 (M-H)⁺

20 ¹H-NMR (CDCl₃) δ: 1.75-1.91 (1H, m), 2.09-2.32 (1H, m), 2.52-2.67 (1H, m), 2.79-3.13 (1H, m), 3.90-3.97 (3H, m), 4.68-4.77 (1H, m), 5.31-6.75 (3H, m), 6.84-7.10 (3H, m), 7.25-7.58 (4H, m), 7.89-8.02 (1H, m), 8.50-8.76 (2H, m).

[0290]

Example 2-119LP

25 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-trifluoromethylbenzamide

RT(min.): 3.003

MS(ESI, *m/z*): 490.0953 (M-H)⁺

¹H-NMR (DMSO-*d*₆) δ: 1.22-2.22 (2H, m), 2.46-2.70 (1H, m), 2.82-2.94 (1H, m), 4.94-5.28 (1H, m), 5.31-5.36 (1H, m), 7.10-7.56 (5H, m), 7.63-8.03 (5H, m), 8.39-8.73 (2H, m).

[0292]

30 Example 2-120LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-ethylbenzamide

RT(min.): 3.028

MS(ESI, *m/z*): 450.1387 (M-H)⁺

35 ¹H-NMR (CDCl₃) δ: 1.28-1.35 (3H, m), 1.66-1.83 (1H, m), 2.01-2.25 (1H, m), 2.45-2.59 (1H, m), 2.70-3.14 (3H, m), 4.61-4.69 (1H, m), 5.18-6.04 (3H, m), 6.85-7.03 (1H, m), 7.19-7.84 (6H, m), 7.98-8.13 (1H, m), 8.53-8.73 (2H, m).

[0293]

Example 2-121LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-oxo-1,6-dihydropyridazine-3-carboxamide

RT(min.): 2.761

MS(ESI, *m/z*): 439.0979 (M-H)⁺

45 ¹H-NMR (CDCl₃) δ: 1.35-2.14 (2H, m), 2.51-2.64 (1H, m), 2.73-3.07 (1H, m), 5.04-6.35 (4H, m), 6.77-7.03 (2H, m), 7.35-7.79 (7H, m), 11.52 (1H, br).

[0294]

Example 2-122LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-cyanobenzamide

50 RT(min.): 2.498

MS(ESI, m/z): 447.1031 (M-H)⁻

¹H-NMR (DMSO-d₆) δ: 1.29-2.14 (2H, m), 2.42-2.69 (1H, m), 2.84-2.97 (1H, m), 5.05-5.42 (2H, m), 7.11-8.09 (10H, m), 8.48-8.73 (2H, m).

[0295]

5 Example 2-123LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-trifluoromethoxybenzamide

RT(min.): 3.072

MS(ESI, m/z): 506.0900 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.65-1.97 (1H, m), 2.13-2.24 (1H, m), 2.48-2.66 (1H, m), 2.77-3.16 (1H, m), 4.57-5.00 (1H, m), 5.20-5.78 (3H, m), 6.85-7.05 (1H, m), 7.32-7.77 (6H, m), 7.87-8.11 (1H, m), 8.59-8.69 (2H, m).

[0296]

Example 2-124LP

15 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-methoxyindan-1-yl]nicotinamide

RT(min.): 0.998

MS(ESI, m/z): 401.1626 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.69-1.83 (1H, m), 2.08-2.25 (1H, m), 2.57-2.87 (2H, m), 3.81 (3H, s), 4.71-4.83 (1H, m), 5.24-6.05 (3H, m), 6.72-6.76 (1H, m), 6.86-6.91 (1H, m), 7.34-7.42 (2H, m), 7.73 (1H, d, J=8.4Hz), 7.87-7.94 (1H, m), 7.96-8.05 (1H, m), 8.60-8.73 (3H, m), 8.83-8.88 (1H, m).

[0297]

Example 2-125LP

25 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-(methylsulfanyl)nicotinamide

RT(min.): 3.518

MS(ESI, m/z): 450.1050 (M-H)⁻

30 ¹H-NMR (CDCl₃) δ: 1.65-1.90 (1H, m), 2.10-2.35 (1H, m), 2.45-2.75 (5H, m), 4.45-4.90 (1H, m), 5.10-5.65 (3H, m), 7.00-7.15 (2H, m), 7.20-7.30 (1H, m), 7.30-7.80 (6H, m), 7.95 (1H, s), 8.49 (1H, dd, J=1.6, 4.9Hz).

[0298]

Example 2-126LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]imidazo[1,2-*a*]pyrazine-2-carboxamide

35 RT(min.): 2.961

MS(ESI, m/z): 462.1148 (M-H)⁻

¹H-NMR (DMSO-d₆) δ: 1.19-1.36 (1H, m), 1.91-2.07 (1H, m), 2.42-2.64 (1H, m), 2.78-2.95 (1H, m), 5.06-5.17 (1H, m), 6.63 (1H, s), 7.08-7.15 (1H, m), 7.33-7.64 (8H, m), 7.96-8.01 (1H, m), 8.46 (1H, s), 8.60-8.67 (1H, m), 9.14 (1H, s).

40 [0299]

Example 2-127LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydrobenzofuran-7-carboxamide

RT(min.): 2.574

45 MS(ESI, m/z): 464.1186 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.82-2.00 (1H, m), 2.26-2.43 (1H, m), 2.56-2.71 (1H, m), 2.80-2.96 (1H, m), 3.20-3.38 (2H, m), 4.60-4.86 (3H, m), 5.30-5.80 (2H, m), 6.87-7.07 (2H, m), 7.22-7.57 (5H, m), 7.85-7.98 (1H, m), 8.50-8.75 (2H, m).

[0300]

50 Example 2-128LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylsulfanyl)nicotinamide

RT(min.): 3.627

MS(ESI, *m/z*): 468.0959 (*M*-H)⁺

- 5 ¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 2.10-2.45 (1H, m), 2.45-2.60 (1H, m), 2.65 (3H, s), 2.65-3.15 (1H, m), 4.40-4.95 (1H, m), 5.00-5.75 (3H, m), 6.80-7.15 (2H, m), 7.35-7.85 (7H, m), 8.45-8.55 (1H, m).

[0301]

Example 2-129LP

- 10 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxynicotinamide

RT(min.): 2.598

MS(ESI, *m/z*): 438.1035 (*M*-H)⁺

- 15 ¹H-NMR (CDCl₃) δ: 1.35-2.00 (2H, m), 2.15-3.15 (3H, m), 4.70-5.20 (1H, m), 5.35-5.65 (1H, m), 6.05-6.80 (2H, m), 6.80-7.05 (1H, m), 7.25-7.85 (9H, m).

[0302]

Example 2-130LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylthiazole-4-carboxamide

- 20 RT(min.): 3.464

MS(ESI, *m/z*): 442.0805 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.59-3.24 (7H, m), 4.44-7.06 (4H, m), 7.12-8.06 (8H, m).

[0303]

Example 2-131LP

- 25 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.495

MS(ESI, *m/z*): 420.1532 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.56-2.22 (2H, m), 2.34-3.18 (5H, m), 4.46-5.68 (4H, m), 6.55-6.86 (1H, m), 7.14-7.83 (8H, m), 8.51-8.65 (1H, m).

- 30 [0304]

Example 2-132LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 3.005

- 35 MS(ESI, *m/z*): 426.1101 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.61-2.23 (2H, m), 2.44-2.95 (5H, m), 4.43-4.90 (1H, m), 5.27-5.84 (3H, m), 6.57-6.86 (1H, m), 7.28-7.81 (6H, m), 8.77 (1H, s).

[0305]

Example 2-133LP

- 40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methyl-2*H*-pyrazole-3-carboxamide

RT(min.): 3.183

MS(ESI, *m/z*): 425.1189 (*M*-H)⁺

- 45 ¹H-NMR (CDCl₃) δ: 1.68-2.25 (2H, m), 2.51-3.10 (2H, m), 3.86-4.18 (3H, m), 4.50-6.00 (4H, m), 6.46 (1H, br s), 6.80-7.11 (1H, m), 7.29-7.85 (7H, m).

[0306]

Example 2-134LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methyl-3*H*-imidazole-4-carboxamide

- 50 RT(min.): 2.272

MS(ESI, m/z): 425.1193 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.75-2.36 (2H, m), 2.51-3.00 (2H, m), 3.86 (3H, br s), 4.30-6.50 (4H, m), 6.88-7.07 (1H, m), 7.33-7.85 (8H, m).

[0307]

5 Example 2-135LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methylisoxazole-4-carboxamide

RT(min.): 3.377

MS(ESI, m/z): 426.1032 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.69-2.25 (2H, m), 2.40-3.04 (5H, m), 4.38-5.10 (1H, m), 5.16-5.90 (3H, m), 6.87-7.13 (1H, m), 7.30-7.53 (5H, m), 7.61-7.87 (1H, m), 8.26 (1H, br s).

[0308]

Example 2-136LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-2-chloro-*N*-[(*R*)-6-chloroindan-1-yl]benzamide

15 RT(min.): 2.567

MS(ESI, m/z): 438.0787 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.65-1.99 (1H, m), 2.11-2.34 (1H, m), 2.53-2.90 (2H, m), 4.60-4.85 (1H, m), 5.17-5.80 (3H, m), 7.07-8.22 (9H, m), 8.56-8.74 (2H, m).

[0309]

20 Example 2-137LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.483

MS(ESI, m/z): 418.1332 (M-H)⁻

25 ¹H-NMR (CDCl₃) δ: 1.60-1.85 (1H, m), 1.90-2.15 (1H, m), 2.40-2.60 (1H, m), 2.60-2.85 (4H, m), 4.55-4.80 (1H, m), 5.19 (1H, dd, J=8.6, 8.6Hz), 5.25-5.65 (2H, m), 7.05-7.15 (1H, m), 7.15-7.30 (2H, m), 7.30-7.90 (6H, m), 7.90-8.05 (1H, m), 8.50-8.65 (1H, m).

[0310]

Example 2-138LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methoxybenzamide

30 RT(min.): 2.331

MS(ESI, m/z): 434.1285 (M-H)⁻

35 ¹H-NMR (CDCl₃) δ: 1.70-1.90 (1H, m), 2.05-2.30 (1H, m), 2.55-2.70 (1H, m), 2.70-2.85 (1H, m), 3.94 (3H, s), 4.72 (1H, s), 5.20-5.80 (2H, m), 5.90-6.95 (1H, m), 6.97 (1H, d, J=8.4Hz), 7.06 (1H, ddd, J=0.7, 7.5, 7.5Hz), 7.11 (1H, dd, J=8.0, 17.4Hz), 7.15-7.50 (4H, m), 7.68 (1H, s), 7.90-8.05 (1H, m), 8.50-8.80 (2H, m).

[0311]

Example 2-139LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-ethylnicotinamide

RT(min.): 3.006

40 MS(ESI, m/z): 450.1399 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.35-1.45 (3H, m), 1.67-1.83 (1H, m), 1.97-2.08 (1H, m), 2.43-3.21 (4H, m), 4.53-4.72 (1H, m), 5.16-5.57 (3H, m), 6.84-7.04 (1H, m), 7.16-7.86 (8H, m), 8.58-8.66 (1H, m).

[0312]

45 Example 2-140LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-vinylnicotinamide

RT(min.): 3.366

MS(ESI, m/z): 448.1238 (M-H)⁻

50 ¹H-NMR (CDCl₃) δ: 1.64-1.85 (1H, m), 1.91-2.13 (1H, m), 2.40-3.18 (2H, m), 4.50-4.98 (1H, m), 5.13-5.78 (4H, m), 6.48-6.63 (1H, m), 6.85-7.87 (10H, m), 8.60-8.69 (1H, m).

[0313]

Example 2-141LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methyloxazole-5-carboxamide

5 RT(min.): 3.196

MS(ESI, *m/z*): 426.1034 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.82-2.32 (2H, m), 2.46 (3H, br s), 2.54-3.05 (2H, m), 4.46-5.27 (1H, m), 5.30-6.19 (3H, m), 6.84-7.05 (1H, m), 7.33-7.52 (5H, m), 7.54-7.87 (2H, m).

[0314]

10 Example 2-142LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,4-dimethylthiazole-5-carboxamide

RT(min.): 3.333

MS(ESI, *m/z*): 456.0961 (M-H)⁺15 ¹H-NMR (CDCl₃) δ: 1.67-1.93 (1H, m), 1.94-2.23 (1H, m), 2.45-2.96 (8H, m), 4.37-5.93 (4H, m), 6.87-7.08 (1H, m), 7.33-7.52 (5H, m), 7.63-7.79 (1H, m).

[0315]

Example 2-143LP

2-{*N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}pyridine *N*-oxide

20 RT(min.): 2.727

MS(ESI, *m/z*): 438.1036 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.75-2.25 (1H, m), 2.40-3.20 (3H, m), 4.60-6.00 (4H, m), 6.85-7.10 (1H, m), 7.25-7.70 (9H, m), 8.20-8.35 (1H, m).

[0316]

25 Example 2-144LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]imidazo[1,2-*a*]pyridine-8-carboxamide

RT(min.): 2.221

30 MS(ESI, *m/z*): 461.1193 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.90-3.20 (4H, m), 4.76-5.97 (3H, m), 6.78-6.99 (2H, m), 7.22-7.48 (5H, m), 7.49-7.82 (4H, m), 8.15-8.28 (1H, m).

[0317]

Example 2-145LP

35 3-{*N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}pyridine *N*-oxide

RT(min.): 2.536

MS(ESI, *m/z*): 438.1030 (M-H)⁺40 ¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 1.90-2.15 (1H, m), 2.45-3.20 (2H, m), 4.50-5.90 (4H, m), 6.80-7.20 (1H, m), 7.25-7.55 (7H, m), 7.60-7.90 (1H, m), 8.15-8.30 (1H, m), 8.36 (1H, s).

[0318]

Example 2-146LP

45 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 2.101

MS(ESI, *m/z*): 443.0758 (M-H)⁺50 ¹H-NMR (CDCl₃) δ: 1.69-1.89 (1H, m), 1.99-2.29 (1H, m), 2.54-2.69 (4H, m), 2.80-2.97 (1H, m), 4.52-4.97 (1H, m), 5.32-5.75 (3H, m), 6.97-7.06 (1H, m), 7.39 (1H, dd, *J*=4.8, 8.0Hz), 7.69 (1H, br s), 7.85-8.00 (1H, br), 8.59-8.71 (2H, m), 8.78 (1H, s).

[0319]

Example 2-147LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methylthiazole-4-carboxamide

5 RT(min.): 3.225

MS(ESI, *m/z*): 442.0803 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.69-1.92 (1H, m), 1.95-2.23 (1H, m), 2.47-2.70 (4H, m), 2.71-3.00 (1H, m), 4.45-4.91 (1H, m), 5.22-5.77 (3H, m), 6.85-7.08 (1H, m), 7.32-7.54 (5H, m), 7.72 (1H, br s), 8.77 (1H, s).

10 [0320]

Example 2-148LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methyloxazole-4-carboxamide

RT(min.): 3.435

15 MS(ESI, *m/z*): 426.1031 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.80-3.19 (7H, m), 4.26-6.11 (2H, m), 6.40-8.11 (10H, m).

[0321]

Example 2-149LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-morpholin-4-yl nicotinamide

20 RT(min.): 3.170

MS(ESI, *m/z*): 507.1618 (*M*-H)⁺25 ¹H-NMR (CDCl₃) δ: 1.76-2.25 (2H, m), 2.47-2.97 (2H, m), 3.54-3.64 (4H, m), 3.75-3.86 (4H, m), 4.42-6.08 (3H, m), 6.64 (1H, d, *J*=8.8Hz), 6.90-7.03 (1H, m), 7.30-7.51 (6H, m), 7.70-7.82 (2H, m), 8.45 (1H, d, *J*=2.0Hz).

[0322]

Example 2-149HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-morpholin-4-yl nicotinamide

30 RT(min.): 3.004

MS(ESI, *m/z*): 507.1613 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 2.48-2.81 (3H, m), 3.05-3.17 (1H, m), 3.56-3.63 (4H, m), 3.78-3.86 (4H, m), 4.27-4.71 (1H, m), 5.34-5.98 (3H, m), 6.19-6.51 (1H, m), 6.65 (1H, d, *J*=8.9Hz), 6.82-6.88 (1H, m), 7.27-7.37 (5H, m), 7.74 (1H, dd, *J*=2.1, 8.9Hz), 8.42 (1H, d, *J*=2.1Hz).

35 [0323]

Example 2-150LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylisoxazole-5-carboxamide

RT(min.): 3.507

40 MS(ESI, *m/z*): 426.1034 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.85-2.30 (5H, m), 2.50-2.67 (1H, m), 2.81-3.06 (1H, m), 4.82-5.92 (4H, m), 6.80-7.00 (1H, m), 7.34-7.72 (6H, m), 7.93-8.25 (1H, m).

[0324]

Example 2-151LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-3-methylpyridine-2-carboxamide

45 RT(min.): 3.205

MS(ESI, *m/z*): 418.1330 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.70-1.95 (1H, m), 2.10-2.30 (1H, m), 2.45-2.60 (4H, m), 2.60-2.75

(1H, m), 4.65-4.95 (1H, m), 5.17 (1H, dd, $J=8.5$, 8.5Hz), 5.25-5.95 (2H, m), 7.00-7.50 (6H, m), 7.50-7.65 (3H, m), 7.92 (1H, br s), 8.40-8.50 (1H, m).

[0325]

Example 2-152LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyridine-2-carboxamide

RT(min.): 3.372

MS(ESI, m/z): 436.1240 ($M-H$)⁻

10 ¹H-NMR (CDCl₃) δ : 1.70-2.00 (1H, m), 2.10-2.40 (1H, m), 2.40-3.20 (5H, m), 4.60-5.90 (4H, m), 6.80-7.00 (1H, m), 7.15-7.25 (1H, m), 7.25-7.70 (6H, m), 7.76 (1H, s), 8.40-8.50 (1H, m).

[0326]

Example 2-153LP

15 *N*-[(*R*)-Carbamoyl-(2-methylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 3.165

MS(ESI, m/z): 436.1241 ($M-H$)⁻

20 ¹H-NMR (CDCl₃) δ : 1.79-3.13 (7H, m), 4.76-5.08 (1H, m), 5.26-5.73 (3H, m), 6.79-7.00 (1H, m), 7.17-7.50 (5H, m), 7.60-7.99 (2H, m), 8.54-8.90 (2H, m).

[0327]

Example 2-154LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylpyrimidine-5-carboxamide

RT(min.): 2.937

25 MS(ESI, m/z): 437.1192 ($M-H$)⁻

¹H-NMR (CDCl₃) δ : 1.68-1.84 (1H, m), 1.95-2.13 (1H, m), 2.44-2.92 (5H, m), 4.54-4.87 (1H, m), 5.09-5.62 (3H, m), 6.95-7.06 (1H, m), 7.38-7.61 (5H, m), 7.78 (1H, s), 8.50-8.80 (1H, m), 9.05-9.20 (1H, m).

[0328]

30 Example 2-155LP

N-[(*R*)-Carbamoyl-(3-methylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.965

MS(ESI, m/z): 450.1399 ($M-H$)⁻

35 ¹H-NMR (CDCl₃) δ : 1.38-1.87 (1H, m), 1.94-2.14 (1H, m), 2.38 (3H, s), 2.41-3.13 (5H, m), 4.52-5.00 (1H, m), 5.14-5.68 (3H, m), 6.84-7.40 (6H, m), 7.51-7.83 (2H, m), 8.52-8.60 (1H, m).

[0329]

Example 2-156LP

40 *N*-[(*R*)-Carbamoyl-(4-methylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.975

MS(ESI, m/z): 450.1395 ($M-H$)⁻

45 ¹H-NMR (CDCl₃) δ : 1.39-1.88 (1H, m), 1.94-2.14 (1H, m), 2.35-2.41 (3H, m), 2.42-2.55 (1H, m), 2.61-3.13 (4H, m), 4.49-5.62 (4H, m), 6.84-7.02 (1H, m), 7.13-7.28 (3H, m), 7.34-7.82 (4H, m), 8.51-8.60 (1H, m).

[0330]

Example 2-157LP

50 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-6-(2,2,2-trifluoroethoxy)nicotinamide

RT(min.): 3.951

MS(ESI, m/z): 502.1156 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.65-2.20 (2H, m), 2.50-2.85 (2H, m), 4.55-4.90 (3H, m), 5.25-5.80 (3H, m), 6.92 (1H, d, J=8.5Hz), 7.05-7.15 (1H, m), 7.15-7.30 (1H, m), 7.30-7.55 (5H, m),
 5 7.88 (1H, dd, J=2.0, 8.6Hz), 7.97 (1H, br s), 8.37-8.45 (1H, m).

[0331]

Example 2-158LP

3-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]pyrazine-2-carboxamide

10 RT(min.): 2.928

MS(ESI, m/z): 420.1241 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.70-1.95 (1H, m), 2.05-2.35 (1H, m), 2.50-2.90 (2H, m), 4.55-4.95 (1H, m), 5.30-5.95 (5H, m), 7.08 (1H, d, J=8.0Hz), 7.10-7.25 (1H, m), 7.30-7.55 (5H, m),
 15 7.70-7.95 (2H, m), 7.95-8.15 (1H, m).

[0332]

Example 2-159LP

N-[(*R*)-Carbamoyl-(2-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.815

20 MS(ESI, m/z): 454.1144 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.40-2.20 (2H, m), 2.40-3.20 (5H, m), 4.85-5.65 (4H, m), 6.80-8.10 (8H, m), 8.50-8.60 (1H, m).

[0333]

Example 2-160LP

25 *N*-[(*R*)-Carbamoyl-(2-trifluoromethylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 3.031

MS(ESI, m/z): 504.1114 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.40-1.75 (1H, m), 1.80-2.10 (1H, m), 2.35-2.55 (1H, m), 2.55-2.85 (4H, m), 4.80-5.60 (4H, m), 6.90-7.05 (1H, m), 7.15-7.30 (1H, m), 7.50-7.90 (5H, m),
 30 8.15-8.40 (1H, m), 8.50-8.70 (1H, m).

[0334]

Example 2-161LP

35 *N*-[(*R*)-Carbamoyl-(3-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.836

MS(ESI, m/z): 454.1147 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.64-1.83 (1H, m), 2.00-2.15 (1H, m), 2.45-2.87 (5H, m), 4.53-4.74 (1H, m), 5.21 (1H, t, J=8.7Hz), 5.37-5.67 (2H, m), 6.86-7.82 (8H, m), 8.54-8.62 (1H, m).

40 [0335]

Example 2-162LP

N-[(*R*)-Carbamoyl-(4-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.839

45 MS(ESI, m/z): 454.1147 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.40-1.85 (1H, m), 1.96-2.13 (1H, m), 2.44-3.16 (5H, m), 4.52-4.96 (1H, m), 5.16-5.66 (3H, m), 6.86-7.34 (4H, m), 7.46-7.81 (4H, m), 8.53-8.62 (1H, m).

[0336]

Example 2-163LP

N-[(*R*)-Carbamoyl-(3-methoxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.785

MS(ESI, *m/z*): 466.1347 (M-H)⁺

- 5 ¹H-NMR (CDCl₃) δ: 1.68-1.88 (1H, m), 1.97-2.15 (1H, m), 2.42-3.16 (5H, m), 3.82 (3H, s), 4.50-4.99 (1H, m), 5.15-5.62 (3H, m), 6.77-7.40 (6H, m), 7.51-7.83 (2H, m), 8.53-8.61 (1H, m).

[0337]

Example 2-164LP

- 10 *N*-[(*R*)-Carbamoyl-(4-methoxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.760

MS(ESI, *m/z*): 466.1347 (M-H)⁺

- 15 ¹H-NMR (CDCl₃) δ: 1.42-1.90 (1H, m), 1.94-2.11 (1H, m), 2.42-3.14 (5H, m), 3.84 (3H, s), 4.46-4.95 (1H, m), 5.13-5.60 (3H, m), 6.84-7.03 (3H, m), 7.14-7.81 (5H, m), 8.52-8.61 (1H, m).

[0338]

Example 2-165LP

- 20 *N*-[(*R*)-Carbamoyl-(3-trifluoromethylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 3.239

MS(ESI, *m/z*): 504.1115 (M-H)⁺

- 25 ¹H-NMR (CDCl₃) δ: 1.61-1.75 (1H, m), 2.03-2.14 (1H, m), 2.46-2.58 (1H, m), 2.61-2.87 (4H, m), 4.65-4.83 (1H, m), 5.23 (1H, t, J=8.7Hz), 5.33-5.70 (2H, m), 6.99-7.05 (1H, m), 7.20-7.30 (1H, m), 7.48-7.94 (6H, m), 8.55-8.63 (1H, m).

[0339]

Example 2-166LP

- 30 *N*-[(*R*)-Carbamoyl-(4-trifluoromethylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 3.298

MS(ESI, *m/z*): 504.1113 (M-H)⁺

- 35 ¹H-NMR (CDCl₃) δ: 1.62-1.77 (1H, m), 2.03-2.15 (1H, m), 2.46-2.58 (1H, m), 2.61-3.15 (4H, m), 4.62-4.98 (1H, m), 5.15-5.73 (3H, m), 6.86-7.30 (2H, m), 7.41-7.83 (6H, m), 8.54-8.64 (1H, m).

[0340]

Example 2-167LP

- 40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylisonicotinamide

RT(min.): 2.769

MS(ESI, *m/z*): 436.1235 (M-H)⁺

- ¹H-NMR (CDCl₃) δ: 1.67-1.84 (1H, m), 1.92-2.12 (1H, m), 2.35-3.12 (5H, m), 4.52-4.72 (1H, m), 5.09-5.62 (3H, m), 6.83-7.65 (7H, m), 7.69-7.87 (1H, m), 8.50-8.60 (2H, m).

[0341]

Example 2-168LP

- 45 *N*-[(*R*)-Carbamoyl-(3-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.314

MS(ESI, *m/z*): 452.1191 (M-H)⁺

- ¹H-NMR (DMSO-*d*₆) δ: 1.36-1.57 (1H, m), 2.02-2.15 (1H, m), 2.35-2.69 (4H, m), 2.85-

2.97 (1H, m), 4.93-5.30 (2H, m), 6.66-7.49 (8H, m), 7.57-7.86 (2H, m), 8.51-8.59 (1H, m), 9.65 (1H, br).

[0342]

Example 2-169LP

5 *N*-[(*R*)-Carbamoyl-(4-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.212

MS(ESI, *m/z*): 452.1178 (M-H)⁺

10 ¹H-NMR (DMSO-*d*₆) δ: 1.31-1.51 (1H, m), 1.98-2.10 (1H, m), 2.35-2.68 (4H, m), 2.84-2.95 (1H, m), 4.91-5.27 (2H, m), 6.75-6.86 (2H, m), 7.02-7.17 (3H, m), 7.25-7.90 (5H, m), 8.50-8.58 (1H, m), 9.68 (1H, br).

[0343]

Example 2-170LP

15 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylfuran-3-carboxamide

RT(min.): 3.830

MS(ESI, *m/z*): 427.0986 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.80-3.05 (7H, m), 5.06-5.87 (4H, m), 6.76-6.97 (1H, m), 7.40-7.55 (5H, m), 7.58-7.67 (1H, m).

20 [0344]

Example 2-171LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-cyanonicotinamide

RT(min.): 3.372

25 MS(ESI, *m/z*): 447.1035 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.78-1.91 (1H, m), 2.12-2.33 (1H, m), 2.45-3.16 (2H, m), 4.50-5.64 (4H, m), 6.85-7.02 (1H, m), 7.36-7.66 (6H, m), 7.72-8.12 (2H, m), 8.72-8.81 (1H, m).

[0345]

Example 2-172LP

30 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide

RT(min.): 2.594

MS(ESI, *m/z*): 466.0982 (M-H)⁺

35 ¹H-NMR (CDCl₃) δ: 1.79-1.99 (1H, m), 2.21-2.42 (1H, m), 2.58-2.71 (1H, m), 2.79-2.98 (1H, m), 4.65-4.82 (1H, m), 5.37-5.78 (2H, m), 5.98-6.36 (3H, m), 6.85-7.08 (4H, m), 7.31-7.39 (1H, m), 7.49-7.62 (1H, m), 7.82-7.97 (1H, m), 8.55-8.70 (2H, m).

[0346]

Example 2-173LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide

RT(min.): 3.674

MS(ESI, *m/z*): 465.1034 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.69-1.92 (1H, m), 2.10-2.31 (1H, m), 2.50-2.63 (1H, m), 2.71-2.89 (1H, m), 4.56-5.95 (4H, m), 5.98-6.12 (2H, m), 6.81-7.03 (4H, m), 7.29-7.80 (6H, m).

45 [0347]

Example 2-174LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-methoxyindan-1-yl]-2-methylnicotinamide

RT(min.): 0.838

MS(ESI, *m/z*): 415.1781 (M-H)⁺

50 ¹H-NMR (CDCl₃) δ: 1.61-1.76 (1H, m), 2.01-2.14 (1H, m), 2.51-2.87 (5H, m), 3.80 (3H, s),

4.61-4.80 (1H, m), 5.14-5.83 (3H, m), 6.70-6.76 (1H, m), 6.84-6.91 (1H, m), 7.17-7.24 (1H, m), 7.32-8.22 (4H, m), 8.50-8.73 (3H, m).

[0348]

Example 2-175LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyrazine-2-carboxamide

RT(min.): 3.170

MS(ESI, *m/z*): 437.1194 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.80-2.30 (2H, m), 2.40-2.55 (1H, m), 2.60-2.85 (4H, m), 5.10-5.25 (1H, m), 5.35-5.80 (2H, m), 6.85-7.00 (1H, m), 7.35-7.50 (4H, m), 7.50-7.60 (2H, m), 7.77 (1H, s), 8.30-8.60 (2H, m).

[0349]

Example 2-176LP

15 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,2-dimethyl-2,3-dihydrobenzofuran-7-carboxamide

RT(min.): 4.092

MS(ESI, *m/z*): 491.1551 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.29-1.65 (6H, m), 1.76-1.94 (1H, m), 2.12-2.36 (1H, m), 2.47-2.66 (1H, m), 2.73-2.88 (1H, m), 2.94-3.14 (2H, m), 4.58-4.77 (1H, m), 5.24-6.33 (3H, m), 6.87-7.01 (2H, m), 7.17-7.23 (1H, m), 7.28-7.76 (7H, m).

[0350]

Example 2-177LP

3-[(*R*)-Carbamoyl-[(*R*)-6-chloro-4-fluoroindan-1-yl]-(2-methylpyridin-3-carbonyl)amino}methyl]benzoic acid methyl ester

25 RT(min.): 2.776

MS(ESI, *m/z*): 494.1296 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.60-1.78 (1H, m), 2.00-2.12 (1H, m), 2.43-2.56 (1H, m), 2.62-2.87 (4H, m), 3.94 (3H, m), 4.63-4.85 (1H, m), 5.26-5.76 (3H, m), 6.92-7.27 (2H, m), 7.43-7.92 (4H, m), 7.95-8.27 (2H, m), 8.54-8.64 (1H, m).

30 [0351]

Example 2-177HP

3-[(*S*)-Carbamoyl-[(*R*)-6-chloro-4-fluoroindan-1-yl]-(2-methylpyridin-3-carbonyl)amino}methyl]benzoic acid methyl ester

RT(min.): 2.513

35 MS(ESI, *m/z*): 494.1294 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.30-3.23 (7H, m), 3.93 (3H, m), 4.35-4.45 (1H, m), 5.06-5.76 (3H, m), 6.80-8.14 (8H, m), 8.60 (1H, dd, *J*=1.6, 5.0Hz).

[0352]

Example 2-178LP

40 *N*-[(*R*)-Carbamoyl-(3-methanesulfonylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.342

MS(ESI, *m/z*): 514.1018 (M-H)⁻

45 ¹H-NMR (CDCl₃) δ: 1.40-1.80 (1H, m), 2.05-2.25 (1H, m), 2.45-2.90 (5H, m), 3.10 (3H, s), 4.70-4.90 (1H, m), 5.25 (1H, dd, *J*=8.5, 8.5Hz), 5.30-6.10 (2H, m), 6.99-7.06 (1H, m), 7.20-7.32 (1H, m), 7.53-8.22 (6H, m), 8.55-8.67 (1H, m).

[0353]

Example 2-179LP

50 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyrazine-2-carboxamide

RT(min.): 3.081

MS(ESI, m/z): 423.1028 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.85-2.30 (2H, m), 2.45-2.70 (1H, m), 2.70-3.15 (1H, m), 4.50-6.70 (4H, m), 6.80-7.05 (1H, m), 7.30-7.85 (6H, m), 8.40-9.20 (3H, m).

5 [0354]

Example 2-180LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide

RT(min.): 2.219

10 MS(ESI, m/z): 453.1144 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.70-3.10 (4H, m), 3.97-4.10 (3H, m), 4.60-6.50 (4H, m), 6.95-8.75 (9H, m).

[0355]

Example 2-181LP

15 3-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyrazine-2-carboxamide

RT(min.): 3.074

MS(ESI, m/z): 438.1146 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.70-2.35 (2H, m), 2.45-3.20 (2H, m), 4.50-6.00 (6H, m), 6.85-7.00 (1H, m), 7.35-7.55 (6H, m), 7.80-7.92 (1H, m), 7.95-8.13 (1H, m).

[0356]

Example 2-182LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[*b*]thiophene-2-carboxamide

25 RT(min.): 4.158

MS(ESI, m/z): 477.0856 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.79-2.35 (2H, m), 2.54-3.06 (2H, m), 4.39-4.97 (1H, m), 5.26-6.33 (3H, m), 6.84-7.09 (1H, m), 7.32-7.54 (7H, m), 7.64 (1H, s), 7.77-7.91 (3H, m).

[0357]

30 Example 2-183LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]naphthalene-2-carboxamide

RT(min.): 4.087

MS(ESI, m/z): 471.1290 (M-H)⁻

35 ¹H-NMR (CDCl₃) δ: 1.73-2.22 (2H, m), 2.35-2.87 (2H, m), 4.45-5.88 (4H, m), 6.83-7.04 (1H, m), 7.34-7.99 (12H, m), 8.05 (1H, s).

[0358]

Example 2-184LP

40 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]quinoline-3-carboxamide

RT(min.): 3.463

MS(ESI, m/z): 472.1243 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.73-2.22 (2H, m), 2.37-3.17 (2H, m), 4.50-5.89 (4H, m), 6.80-7.09 (1H, m), 7.35-7.69 (6H, m), 7.75-7.98 (3H, m), 8.

45 14 (1H, d, *J*=8.6Hz), 8.37 (1H, s), 9.09 (1H, s).

[0359]

Example 2-185LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]isoquinoline-4-carboxamide

50 RT(min.): 3.206

MS(ESI, m/z): 472.1239 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.73-1.82 (1H, m), 2.10-2.18 (1H, m), 2.38-2.48 (1H, m), 2.69-2.76 (1H, m), 4.70 (1H, br), 5.50 (2H, br), 5.23-5.27 (1H, m), 6.93-6.96 (1H, m), 7.43-7.75 (7H, m), 7.93-8.04 (2H, m), 8.52-8.57 (2H, m), 9.31 (1H, br).

5 [0360]

Example 2-186LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]naphthalene-1-carboxamide

RT(min.): 4.078

10 MS(ESI, m/z): 471.1294 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.67-1.75 (1H, m), 2.00-2.08 (1H, m), 2.28-2.41 (1H, m), 2.28-2.41 (1H, m), 2.64-2.70 (1H, m), 4.67 (1H, br), 5.19-5.28 (2H, m), 6.90-6.92 (1H, m), 7.34-7.92 (12H, m), 8.48-8.51 (1H, m).

[0361]

15 Example 2-187LP

4-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-5-carboxamide

RT(min.): 3.131

MS(ESI, m/z): 443.0761 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.82-3.08 (4H, m), 4.45-6.40 (6H, m), 6.94-7.05 (1H, m), 7.30-7.56 (5H, m), 7.64 (1H, s), 8.56 (1H, s).

[0362]

Example 2-187HP

4-Amino-*N*-[(*S*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]thiazole-5-carboxamide

25 RT(min.): 3.009

MS(ESI, m/z): 443.0759 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.67-2.97 (3H, m), 3.12-3.27 (1H, m), 4.33-4.60 (1H, m), 5.34-5.56 (1H, br), 5.92-6.23 (3H, m), 6.39-6.56 (1H, br), 6.87 (1H, dd, *J*=1.5, 8.6Hz), 7.24-7.45 (6H, m), 8.58 (1H, s).

30 [0363]

Example 2-188LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxy-3-methylbenzamide

35 RT(min.): 3.939

MS(ESI, m/z): 465.1397 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.63-3.18 (7H, m), 3.69-4.01 (3H, m), 4.55-5.96 (4H, m), 6.80-7.89 (10H, m).

[0364]

40 Example 2-189LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 0.979

MS(ESI, m/z): 403.1590 (M-H)⁻

45 ¹H-NMR (CDCl₃) δ: 1.62-1.80 (1H, m), 2.01-2.16 (1H, m), 2.54-2.88 (5H, m), 4.56-4.83 (1H, m), 5.17-5.89 (3H, m), 6.86-6.94 (1H, m), 6.98-7.07 (1H, m), 7.18-7.24 (1H, m), 7.32-8.23 (4H, m), 8.50-8.74 (3H, m).

[0365]

Example 2-190LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

50

RT(min.): 1.527

MS(ESI, m/z): 409.1151 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.68-1.83 (1H, m), 2.10-2.27 (1H, m), 2.60-2.89 (5H, m), 4.59-4.85 (1H, m), 5.24-5.79 (3H, m), 6.89-6.94 (1H, m), 6.99-7.06 (1H, m), 7.35-7.40 (1H, m),
5 7.75-7.81 (1H, m), 7.94-8.00 (1H, m), 8.61 (1H, d, J=2.3Hz), 8.64 (1H, dd, J=1.5, 4.8Hz), 8.78 (1H, s).

[0366]

Example 2-191LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-fluoroindan-1-yl]benzamide

10 RT(min.): 2.057

MS(ESI, m/z): 388.1475 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.74-1.90 (1H, m), 2.11-2.28 (1H, m), 2.60-2.89 (2H, m), 4.62-4.82 (1H, m), 5.21-6.25 (3H, m), 6.85-6.94 (1H, m), 6.96-7.07 (1H, m), 7.32-7.39 (1H, m),
15 7.41-7.50 (3H, m), 7.53-7.61 (2H, m), 7.77-7.84 (1H, m), 7.91-8.00 (1H, m), 8.61 (1H, dd, J=1.6, 4.8Hz), 8.65 (1H, d, J=2.3Hz).

[0367]

Example 2-192LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]benzamide

RT(min.): 1.908

20 MS(ESI, m/z): 395.1525 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.67-1.78 (1H, m), 1.84-1.94 (1H, m), 2.20-2.28 (1H, m), 2.86-2.95 (1H, m), 4.66 (1H, br), 5.43-6.11 (3H, m), 7.34-7.55 (8H, m), 8.17 (1H, s), 8.62 (3H, br).

[0368]

Example 2-192HP

25 *N*-[(*S*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]benzamide

RT(min.): 1.749

MS(ESI, m/z): 395.1524 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.51-2.60 (1H, m), 2.68-2.77 (1H, m), 2.85-2.93 (1H, m), 3.18-3.26 (1H, m), 4.33-4.41 (1H, m), 5.53-5.74 (3H, m), 6.89 (1H, br), 7.31-7.57 (8H, m), 7.91-7.93 (1H, m),
30 8.21 (1H, br), 8.61-8.62 (1H, m).

[0369]

Example 2-193LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]benzamide

RT(min.): 2.078

35 MS(ESI, m/z): 388.1474 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.78-1.92 (1H, m), 2.13-2.27 (1H, m), 2.56-2.68 (1H, m), 2.71-2.89 (1H, m), 4.63-4.80 (1H, m), 5.26-6.25 (3H, m), 6.92-7.03 (1H, m), 7.09-7.17 (1H, m), 7.32-7.37 (1H, m),
40 7.42-7.50 (3H, m), 7.53-7.62 (3H, m), 7.91-8.02 (1H, m), 8.59-8.68 (2H, m).

[0370]

40 Example 2-193HP

N-[(*S*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]benzamide

RT(min.): 1.895

MS(ESI, m/z): 388.1473 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.43-2.54 (1H, m), 2.62-2.83 (2H, m), 3.05-3.16 (1H, m), 4.41-4.57 (1H, m),
45 5.35-5.73 (2H, m), 5.83-6.18 (1H, m), 6.35-6.53 (1H, m), 6.85-6.91 (1H, m), 7.13-7.19 (1H, m), 7.25-7.31 (1H, m), 7.44-7.50 (3H, m), 7.52-7.59 (2H, m), 7.87-7.93 (1H, m), 8.30 (1H, s), 8.53-8.58 (1H, m).

[0371]

Example 2-194LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]nicotinamide

RT(min.): 1.139

MS(ESI, *m/z*): 389.1429 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.75-1.88 (1H, m), 2.09-2.23 (1H, m), 2.56-2.86 (2H, m), 4.64-4.94 (1H, m), 5.28-5.95 (3H, m), 6.93-7.04 (1H, m), 7.09-7.19 (1H, m), 7.34-7.44 (2H, m), 7.58-7.68 (1H, m), 7.84-8.07 (2H, m), 8.60-8.73 (3H, m), 8.83 (1H, s).

[0372]

Example 2-195LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 0.987

MS(ESI, *m/z*): 403.1586 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.66-1.81 (1H, m), 2.04-2.14 (1H, m), 2.52-2.85 (5H, m), 4.56-4.83 (1H, m), 5.07-5.90 (3H, m), 6.93-7.04 (1H, m), 7.10-7.25 (2H, m), 7.32-8.25 (4H, m), 8.50-8.75 (3H, m).

[0373]

Example 2-196LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.539

MS(ESI, *m/z*): 409.1147 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.73-1.83 (1H, m), 2.08-2.27 (1H, m), 2.60-2.85 (5H, m), 4.57-4.95 (1H, m), 5.24-5.86 (3H, m), 6.95-7.04 (1H, m), 7.12-7.19 (1H, m), 7.34-7.40 (1H, m), 7.53-7.60 (1H, m), 7.90-8.04 (1H, m), 8.61 (1H, d, *J*=2.2Hz), 8.64 (1H, dd, *J*=1.3, 4.8Hz), 8.78 (1H, s).

[0374]

Example 2-197LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]-2-methylnicotinamide

RT(min.): 0.834

MS(ESI, *m/z*): 410.1634 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.71-1.80 (1H, m), 2.09-2.16 (1H, m), 2.65-2.86 (5H, m), 4.59-4.70 (1H, m), 5.26 (1H, t, *J* = 8.6 Hz), 5.37-5.79 (2H, m), 7.21-7.80, (5H, m), 8.00-8.25 (2H, m), 8.59-8.67 (3H, m).

[0375]

Example 2-198LP

N-[(*R*)-Carbamoyl-(2-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 2.367

MS(ESI, *m/z*): 436.1249 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.00-3.22 (7H, m), 4.65-5.78 (4H, m), 6.75-8.16 (9H, m), 8.49-8.61 (1H, m).

[0376]

Example 2-199LP

N-[(*R*)-Carbamoyl-(2-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.566

MS(ESI, *m/z*): 451.1357 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.38-1.62 (1H, m), 1.93-2.08 (1H, m), 2.24-2.88 (8H, m), 4.76-5.06 (1H, m), 5.14-5.62 (3H, m), 6.96-7.07 (1H, m), 7.17-7.34 (2H, m), 7.48-7.88 (2H, m), 8.02-8.29 (1H, m), 8.51-8.66 (2H, m).

[0377]

Example 2-200LP

N-[(*R*)-Carbamoyl-(6-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 2.317

5 MS(ESI, *m/z*): 436.1246 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.75-1.99 (1H, m), 2.06-2.30 (1H, m), 2.40-2.96 (5H, m), 4.53-4.82 (1H, m), 5.21-6.07 (3H, m), 6.88-7.24 (2H, m), 7.39-7.60 (5H, m), 7.64-7.93 (2H, m), 8.39-8.60 (1H, m).

[0378]

10 Example 2-201LP

N-[(*R*)-Carbamoyl-(6-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

RT(min.): 1.643

MS(ESI, *m/z*): 437.1196 (*M*-H)⁻

15 ¹H-NMR (CDCl₃) δ: 1.75-1.93 (1H, m), 2.05-2.23 (1H, m), 2.48-2.93 (5H, m), 4.53-4.93 (1H, m), 5.28-5.81 (3H, m), 6.91-7.08 (1H, m), 7.23 (1H, d, *J*=8.1Hz), 7.35-7.44 (1H, m), 7.68-7.96 (3H, m), 8.44-8.56 (1H, m), 8.66-8.74 (1H, m), 8.76-8.83 (1H, m).

[0379]

Example 2-202LP

20 *N*-[(*R*)-Carbamoyl-(6-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.545

MS(ESI, *m/z*): 451.1353 (*M*-H)⁻

25 ¹H-NMR (CDCl₃) δ: 1.66-1.86 (1H, m), 2.00-2.17 (1H, m), 2.44-2.89 (8H, m), 4.52-4.78 (1H, m), 5.14-5.71 (3H, m), 6.96-7.07 (1H, m), 7.13-7.31 (2H, m), 7.43-8.08 (3H, m), 8.41-8.66 (2H, m).

[0380]

Example 2-203LP

30 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.378

MS(ESI, *m/z*): 419.1290 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.62-1.81 (1H, m), 2.00-2.14 (1H, m), 2.50-2.87 (5H, m), 4.60-4.80 (1H, m), 5.17-5.76 (3H, m), 7.09-7.16 (1H, m), 7.17-8.23 (6H, m), 8.51-8.74 (3H, m).

[0381]

35 Example 2-204LP

N-[(*R*)-Carbamoylpyridazin-4-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

RT(min.): 2.708

MS(ESI, *m/z*): 453.1148 (*M*-H)⁻

40 ¹H-NMR (CDCl₃) δ: 1.50-3.02 (4H, m), 3.89-4.07 (3H, m), 4.61-4.74 (1H, m), 5.32-5.82 (3H, m), 6.96-7.72 (7H, m), 9.17-9.23 (2H, m).

[0382]

Example 2-205LP

45 *N*-[(*R*)-Carbamoylpyridazin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

RT(min.): 2.807

MS(ESI, *m/z*): 453.1147 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.49-3.31 (4H, m), 3.93-3.99 (3H, m), 4.93-5.05 (1H, m), 5.24-5.82 (2H, m), 6.93-7.72 (8H, m), 7.94-8.14 (1H, m), 9.08-9.17 (1H, m).

[0383]

Example 2-206LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]benzamide

RT(min.): 2.349

5 MS(ESI, *m/z*): 404.1182 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.71-1.87 (1H, m), 2.06-2.26 (1H, m), 2.58-2.88 (2H, m), 4.60-4.79 (1H, m), 5.27-6.20 (3H, m), 7.17-7.21 (1H, m), 7.25-7.40 (2H, m), 7.40-7.50 (3H, m), 7.52-7.62 (2H, m), 7.81 (1H, d, *J*=8.0Hz), 7.91-8.02 (1H, m), 8.58-8.68 (2H, m).

[0384]

10 Example 2-207LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.496

MS(ESI, *m/z*): 419.1294 (*M*-H)⁻

15 ¹H-NMR (CDCl₃) δ: 1.61-1.80 (1H, m), 2.00-2.16 (1H, m), 2.50-2.88 (5H, m), 4.56-4.77 (1H, m), 5.15-5.77 (3H, m), 7.13-7.34 (3H, m), 7.34-8.20 (4H, m), 8.52-8.73 (3H, m).

[0380]

Example 2-208LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-chloroindan-1-yl]-4-methylthiazole-5-carboxamide

20 RT(min.): 1.901

MS(ESI, *m/z*): 425.0856 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.66-1.81 (1H, m), 2.02-2.23 (1H, m), 2.60-2.89 (5H, m), 4.54-4.86 (1H, m), 5.31-5.75 (3H, m), 7.18-7.23 (1H, m), 7.28-7.33 (1H, m), 7.35-7.40 (1H, m), 7.75-7.81 (1H, m), 7.92-8.00 (1H, m), 8.59-8.67 (2H, m), 8.78 (1H, s).

25 [0386]

Example 2-209LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide

RT(min.): 1.490

MS(ESI, *m/z*): 405.1134 (*M*-H)⁻

30 ¹H-NMR (CDCl₃) δ: 1.67-2.26 (2H, m), 2.54-2.98 (2H, m), 4.64-4.92 (1H, m), 5.28-6.05 (3H, m), 7.09-7.15 (1H, m), 7.18-7.44 (3H, m), 7.85-8.05 (3H, m), 8.61-8.67 (2H, m), 8.71 (1H, dd, *J*=1.6, 5.0Hz), 8.81-8.86 (1H, m).

[0387]

Example 2-210LP

35 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.819

MS(ESI, *m/z*): 425.0851 (*M*-H)⁻

40 ¹H-NMR (CDCl₃) δ: 1.71-1.84 (1H, m), 2.07-2.27 (1H, m), 2.57-2.87 (5H, m), 4.57-4.95 (1H, m), 5.31-5.81 (3H, m), 7.10-7.17 (1H, m), 7.23-7.30 (1H, m), 7.34-7.40 (1H, m), 7.82 (1H, s), 7.90-8.00 (1H, m), 8.61 (1H, d, *J*=2.3Hz), 8.64 (1H, dd, *J*=1.5, 4.8Hz), 8.78 (1H, s).

[0388]

Example 2-211LP

45 *N*-[(*R*)-Carbamoylpyrimidin-5-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

RT(min.): 2.770

MS(ESI, *m/z*): 453.1147 (*M*-H)⁻

50 ¹H-NMR (CDCl₃) δ: 1.58-3.00 (4H, m), 3.92-4.04 (3H, m), 4.64-4.79 (1H, m), 5.04-6.00 (3H, m), 6.96-7.56 (6H, m), 8.82-8.95 (2H, m), 9.16-9.24 (1H, m).

[0389]

Example 2-212LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]benzamide

RT(min.): 2.046

5 MS(ESI, *m/z*): 400.1679 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.70-1.84 (1H, m), 2.06-2.22 (1H, m), 2.52-2.80 (2H, m), 3.88 (3H, s), 4.67-4.82 (1H, m), 5.28-6.20 (3H, m), 6.85 (1H, dd, *J*=2.3, 8.3Hz), 7.10 (1H, d, *J*=8.3Hz), 7.32-7.37 (1H, m), 7.41-7.51 (4H, m), 7.55-7.64 (2H, m), 7.92-8.04 (1H, m), 8.60 (1H, dd, *J*=1.5, 4.8Hz), 8.65 (1H, d, *J*=2.3Hz).

10 [0390]

Example 2-213LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]nicotinamide

RT(min.): 1.154

MS(ESI, *m/z*): 401.1633 (*M*-H)⁻

15 ¹H-NMR (CDCl₃) δ: 1.67-1.82 (1H, m), 2.05-2.18 (1H, m), 2.53-2.79 (2H, m), 3.88 (3H, s), 4.72-4.87 (1H, m), 5.28-5.83 (3H, m), 6.83-6.90 (1H, m), 7.07-7.14 (1H, m), 7.34-7.44 (2H, m), 7.50-7.56 (1H, m), 7.88-8.05 (2H, m), 8.61-8.73 (3H, m), 8.84-8.89 (1H, m).

[0391]

Example 2-214LP

20 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]-2-methylnicotinamide

RT(min.): 1.017

MS(ESI, *m/z*): 415.1790 (*M*-H)⁻

25 ¹H-NMR (CDCl₃) δ: 1.61-1.77 (1H, m), 1.99-2.11 (1H, m), 2.47-2.89 (5H, m), 3.80-3.94 (3H, m), 4.64-4.83 (1H, m), 5.15-5.85 (3H, m), 6.81-6.89 (1H, m), 7.04-7.14 (1H, m), 7.18-7.24 (1H, m), 7.32-8.23 (4H, m), 8.50-8.72 (3H, m).

[0392]

Example 2-215LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]-4-methylthiazole-5-carboxamide

30 RT(min.): 1.517

MS(ESI, *m/z*): 421.1352 (*M*-H)⁻

35 ¹H-NMR (CDCl₃) δ: 1.64-1.79 (1H, m), 2.07-2.22 (1H, m), 2.55-2.81 (5H, m), 3.86 (3H, s), 4.68-4.83 (1H, m), 5.32-5.70 (3H, m), 6.84-6.89 (1H, m), 7.08-7.14 (1H, m), 7.33-7.40 (1H, m), 7.43-7.48 (1H, m), 7.93-8.03 (1H, m), 8.60-8.65 (2H, m), 8.77 (1H, s).

[0393]

Example 2-216LP

N-[(*R*)-Carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

40 RT(min.): 2.973

MS(ESI, *m/z*): 453.1152 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.78-3.09 (4H, m), 3.92-4.04 (3H, m), 4.72-4.80 (1H, m), 5.20-5.80 (2H, m), 6.92-7.64 (7H, m), 8.48-8.58 (2H, m), 8.90-9.13 (1H, m).

[0394]

45 Example 2-217LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]benzamide

RT(min.): 2.344

MS(ESI, *m/z*): 404.1180 (*M*-H)⁻

50 ¹H-NMR (CDCl₃) δ: 1.69-1.89 (1H, m), 2.08-2.27 (1H, m), 2.56-2.99 (2H, m), 4.60-4.80 (1H, m), 5.20-6.21 (3H, m), 7.22-7.33 (2H, m), 7.33-7.40 (1H, m), 7.41-7.50 (3H, m),

7.53-7.62 (2H, m), 7.73-7.83 (1H, m), 7.87-8.01 (1H, m), 8.62 (1H, dd, $J=1.4, 4.8\text{Hz}$), 8.64-8.68 (1H, m).

[0395]

Example 2-218LP

5 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]benzamide

RT(min.): 4.044

MS(ESI, m/z): 387.1521 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.70-1.90 (1H, m), 1.95-2.20 (1H, m), 2.45-2.80 (2H, m), 4.67 (1H, br s), 5.15-6.00 (3H, m), 6.85-7.20 (2H, m), 7.30-7.80 (11H, m).

10 [0396]

Example 2-218HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-fluoroindan-1-yl]benzamide

RT(min.): 3.879

MS(ESI, m/z): 387.1516 (M-H)⁻

15 ¹H-NMR (CDCl₃) δ : 2.35-2.55 (1H, m), 2.60-2.85 (2H, m), 2.95-3.15 (1H, m), 4.46 (1H, br s), 5.30-5.65 (2H, m), 5.70-6.05 (1H, m), 6.25-6.45 (1H, m), 6.75-6.90 (1H, m), 7.10 (1H, dd, $J=5.1, 8.1\text{Hz}$), 7.25-7.35 (5H, m), 7.40-7.50 (3H, m), 7.50-7.60 (2H, m).

[0397]

Example 2-219LP

20 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]benzamide

RT(min.): 4.008

MS(ESI, m/z): 387.1520 (M-H)⁻

¹H-NMR (CDCl₃) δ : 1.65-1.90 (1H, m), 2.00-2.20 (1H, m), 2.45-2.65 (1H, m), 2.70-2.95 (1H, m), 4.66 (1H, br s), 5.20-5.95 (3H, m), 6.85-7.05 (1H, m), 7.25-7.65 (11H, m), 7.70-7.85 (1H, m).

25 [0398]

Example 2-219HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]benzamide

RT(min.): 3.946

30 MS(ESI, m/z): 387.1517 (M-H)⁻

¹H-NMR (CDCl₃) δ : 2.35-2.55 (1H, m), 2.60-2.85 (2H, m), 3.05-3.25 (1H, m), 4.47 (1H, br s), 5.25-6.10 (3H, m), 6.40-6.65 (1H, m), 6.75-6.85 (2H, m), 7.20-7.35 (5H, m), 7.40-7.50 (3H, m), 7.50-7.65 (2H, m).

[0399]

35 Example 2-220LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-fluoroindan-1-yl]benzamide

RT(min.): 4.027

MS(ESI, m/z): 387.1521 (M-H)⁻

40 ¹H-NMR (CDCl₃) δ : 1.65-1.90 (1H, m), 2.00-2.20 (1H, m), 2.50-2.85 (2H, m), 4.65 (1H, br s), 5.20-5.95 (3H, m), 6.80-6.90 (1H, m), 6.95-7.10 (1H, m), 7.30-7.55 (8H, m), 7.55-7.65 (2H, m), 7.85-7.95 (1H, m).

[0400]

Example 2-220HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-5-fluoroindan-1-yl]benzamide

45 RT(min.): 3.932

MS(ESI, m/z): 387.1517 (M-H)⁻

¹H-NMR (CDCl₃) δ : 2.35-2.55 (1H, m), 2.60-2.85 (2H, m), 3.00-3.20 (1H, m), 4.44 (1H, br s), 5.35-5.65 (2H, m), 5.75-6.00 (1H, m), 6.45-6.55 (1H, m), 6.55-6.70 (1H, m), 6.86 (1H, dd, $J=2.0, 8.8\text{Hz}$), 7.25-7.35 (5H, m), 7.40-7.50 (3H, m), 7.50-7.60 (2H, m).

[0401]

Example 2-221LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide

RT(min.): 4.171

5 MS(ESI, *m/z*): 405.1424 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.65-1.90 (1H, m), 1.90-2.20 (1H, m), 2.40-2.65 (1H, m), 2.65-2.90 (1H, m), 4.66 (1H, br s), 5.20-5.85 (3H, m), 6.60-6.80 (1H, m), 7.30-7.65 (11H, m).

[0402]

Example 2-221HP

10 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide

RT(min.): 4.022

MS(ESI, *m/z*): 405.1426 (M-H)⁺15 ¹H-NMR (CDCl₃) δ: 2.35-2.65 (1H, m), 2.65-2.85 (2H, m), 2.95-3.20 (1H, m), 4.45 (1H, br s), 5.30-6.00 (3H, m), 6.05-6.25 (1H, m), 6.45-6.65 (1H, m), 7.25-7.40 (5H, m), 7.40-7.60 (5H, m).

[0403]

Example 2-222LP

20 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,6-dimethylnicotinamide

RT(min.): 2.439

MS(ESI, *m/z*): 450.1406 (M-H)⁺¹H-NMR (CDCl₃) δ: ¹H-NMR(CDCl₃)δppm: 1.34-1.85 (1H, m), 1.95-2.11 (1H, m), 2.41-3.13 (8H, m), 4.52-5.00 (1H, m), 5.17-5.61 (3H, m), 6.83-7.84 (9H, m).

[0404]

25 Example 2-223LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.514

MS(ESI, *m/z*): 419.1298 (M-H)⁺30 ¹H-NMR (CDCl₃) δ: 1.61-1.81 (1H, m), 2.02-2.16 (1H, m), 2.53-2.95 (5H, m), 4.60-4.83 (1H, m), 5.22-5.89 (3H, m), 7.15-7.24 (1H, m), 7.24-8.20 (6H, m), 8.52-8.75 (3H, m).

[0405]

Example 2-224LP

35 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-chloroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.911

MS(ESI, *m/z*): 425.0858 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.65-1.81 (1H, m), 2.07-2.25 (1H, m), 2.59-2.98 (5H, m), 4.56-4.91 (1H, m), 5.27-5.80 (3H, m), 7.25-7.33 (2H, m), 7.34-7.42 (1H, m), 7.72-7.80 (1H, m), 7.91-8.00 (1H, m), 8.60-8.69 (2H, m), 8.77 (1H, s).

40 [0406]

Example 2-225LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]benzamide

RT(min.): 2.070

MS(ESI, *m/z*): 388.1485 (M-H)⁺45 ¹H-NMR (CDCl₃) δ: 1.74-1.92 (1H, m), 2.11-2.28 (1H, m), 2.54-2.70 (1H, m), 2.85-3.00 (1H, m), 4.64-4.82 (1H, m), 5.21-6.20 (3H, m), 6.94-7.02 (1H, m), 7.25-7.39 (2H, m), 7.41-7.50 (3H, m), 7.53-7.70 (3H, m), 7.87-8.01 (1H, m), 8.58-8.70 (2H, m).

[0407]

Example 2-226LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]nicotinamide

RT(min.): 1.207

MS(ESI, *m/z*): 389.1432 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.70-1.87 (1H, m), 2.07-2.25 (1H, m), 2.56-2.98 (2H, m), 4.65-4.87 (1H, m), 5.28-5.93 (3H, m), 6.96-7.04 (1H, m), 7.29-7.45 (3H, m), 7.66-7.76 (1H, m), 7.85-8.05 (2H, m), 8.62-8.74 (3H, m), 8.82-8.89 (1H, m).

[0408]

Example 2-227LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.052

MS(ESI, *m/z*): 403.1592 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.63-1.82 (1H, m), 2.01-2.17 (1H, m), 2.52-2.96 (5H, m), 4.60-4.80 (1H, m), 5.20-5.85 (3H, m), 6.95-7.04 (1H, m), 7.17-7.24 (1H, m), 7.29-8.20 (5H, m), 8.52-8.76 (3H, m).

[0409]

Example 2-228LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.577

MS(ESI, *m/z*): 409.1155 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.68-1.84 (1H, m), 2.09-2.27 (1H, m), 2.60-2.74 (4H, m), 2.84-2.99 (1H, m), 4.62-4.85 (1H, m), 5.32-5.79 (3H, m), 6.95-7.04 (1H, m), 7.27-7.42 (2H, m), 7.63 (1H, d, *J*=7.7Hz), 7.92-8.01 (1H, m), 8.60-8.67 (2H, m), 8.78 (1H, s).

[0410]

Example 2-229LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-7-fluoroindan-1-yl]benzamide

RT(min.): 1.868

MS(ESI, *m/z*): 388.1492 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 2.08-2.23 (1H, m), 2.38-2.63 (1H, m), 2.79-3.21 (2H, m), 4.50-4.82 (1H, m), 5.21-6.00 (3H, m), 6.87-6.97 (1H, m), 7.01-7.09 (1H, m), 7.24-7.37 (2H, m), 7.43-7.63 (5H, m), 7.79-7.91 (1H, m), 8.52-8.58 (1H, m), 8.60-8.67 (1H, m).

[0411]

Example 2-230LP

N-[(*R*)-Carbamoylpyridin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 2.698

MS(ESI, *m/z*): 443.0770 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.90-2.45 (2H, m), 2.55-3.00 (5H, m), 4.60-5.10 (1H, m), 5.35-5.75 (2H, m), 6.90-7.05 (1H, m), 7.20-7.85 (5H, m), 8.50-8.65 (1H, m), 8.78 (1H, s).

[0412]

Example 2-231LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-methoxyindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.394

MS(ESI, *m/z*): 421.1347 (*M*-H)⁻

¹H-NMR (CDCl₃) δ: 1.65-1.79 (1H, m), 2.11-2.24 (1H, m), 2.59-2.85 (5H, m), 3.81 (3H, s), 4.67-4.80 (1H, m), 5.21-5.84 (3H, m), 6.73-6.78 (1H, m), 6.85-6.91 (1H, m), 7.33-7.40 (1H, m), 7.67 (1H, d, *J*=8.6Hz), 7.94-8.00 (1H, m), 8.58-8.65 (2H, m), 8.77 (1H, s).

[0413]

Example 2-232LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-7-chloroindan-1-yl]benzamide

RT(min.): 2.034

MS(ESI, *m/z*): 404.1175 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 2.28-2.40 (1H, m), 2.55-2.72 (1H, m), 2.92-3.04 (1H, m), 3.20-3.33 (1H, m), 4.49-4.61 (1H, m), 5.08-5.88 (2H, m), 7.17-7.34 (4H, m), 7.43-7.68 (6H, m), 7.79-7.88 (1H, m), 8.50-8.55 (1H, m), 8.64-8.70 (1H, m).

[0414]

Example 2-233LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-methylindan-1-yl]benzamide

RT(min.): 2.163

MS(ESI, *m/z*): 384.1723 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.71-1.89 (1H, m), 2.12-2.31 (4H, m), 2.47-2.86 (2H, m), 4.65-4.83 (1H, m), 5.26-6.48 (3H, m), 7.08-7.15 (1H, m), 7.20-7.30 (1H, m), 7.31-7.38 (1H, m), 7.40-7.50 (3H, m), 7.54-7.68 (3H, m), 7.92-8.00 (1H, m), 8.60 (1H, dd, *J*=1.5, 4.9Hz), 8.65 (1H, d, *J*=2.3Hz).

[0415]

Example 2-234LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-methylindan-1-yl]nicotinamide

RT(min.): 1.303

MS(ESI, *m/z*): 385.1676 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-1.84 (1H, m), 2.07-2.28 (4H, m), 2.47-2.83 (2H, m), 4.71-4.89 (1H, m), 5.25-6.03 (3H, m), 7.10-7.16 (1H, m), 7.23-7.30 (1H, m), 7.34-7.42 (2H, m), 7.65-7.74 (1H, m), 7.85-8.05 (2H, m), 8.60-8.74 (3H, m), 8.82-8.89 (1H, m).

[0416]

Example 2-235LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-2-methyl-*N*-[(*R*)-4-methylindan-1-yl]nicotinamide

RT(min.): 1.128

MS(ESI, *m/z*): 399.1831 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.62-1.77 (1H, m), 2.00-2.15 (1H, m), 2.22 (3H, s), 2.44-2.97 (5H, m), 4.63-4.87 (1H, m), 5.19-5.94 (3H, m), 7.09-8.23 (7H, m), 8.50-8.75 (3H, m).

[0417]

Example 2-236LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-methylindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.654

MS(ESI, *m/z*): 405.1397 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.67-1.80 (1H, m), 2.11-2.30 (4H, m), 2.51-2.83 (5H, m), 4.69-4.83 (1H, m), 5.28-5.93 (3H, m), 7.10-7.16 (1H, m), 7.22-7.29 (1H, m), 7.33-7.39 (1H, m), 7.59-7.65 (1H, m), 7.94-8.00 (1H, m), 8.57-8.65 (2H, m), 8.76 (1H, s).

40 [0418]

Example 2-237LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-methylindan-1-yl]benzamide

RT(min.): 2.198

MS(ESI, *m/z*): 384.1725 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.71-1.87 (1H, m), 2.08-2.25 (1H, m), 2.35 (3H, s), 2.57-2.86 (2H, m), 4.64-4.80 (1H, m), 5.17-6.47 (3H, m), 7.00-7.07 (1H, m), 7.10-7.17 (1H, m), 7.30-7.37 (1H, m), 7.40-7.49 (3H, m), 7.54-7.63 (2H, m), 7.65-7.72 (1H, m), 7.92-8.00 (1H, m), 8.56-8.68 (2H, m).

[0419]

50 Example 2-238LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-2-methyl-*N*-[(*R*)-5-methylindan-1-yl]nicotinamide
RT(min.): 1.207

MS(ESI, *m/z*): 399.1832 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.60-1.74 (1H, m), 2.00-2.12 (1H, m), 2.35 (3H, s), 2.52-2.86 (5H, m),
5 4.59-4.82 (1H, m), 5.16-5.89 (3H, m), 7.03 (1H, s), 7.10-7.18 (1H, m), 7.18-7.23 (1H, m),
7.32-7.43 (1H, m), 7.50-7.87 (2H, m), 7.95-8.20 (1H, m), 8.50-8.72 (3H, m).

[0420]

Example 2-239LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-5-methylindan-1-yl]-4-methylthiazole-5-
10 carboxamide

RT(min.): 1.695

MS(ESI, *m/z*): 405.1396 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.78 (1H, m), 2.09-2.22 (1H, m), 2.36 (3H, s), 2.60-2.83 (5H, m),
4.67-4.81 (1H, m), 5.27-5.91 (3H, m), 7.05 (1H, s), 7.12-7.17 (1H, m), 7.33-7.39 (1H, m),
15 7.66 (1H, d, *J*=7.9Hz), 7.94-8.00 (1H, m), 8.58-8.61 (1H, m), 8.62 (1H, dd, *J*=1.5, 4.8Hz),
8.77 (1H, s).

[0421]

Example 2-240LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methylindan-1-yl]benzamide

20 RT(min.): 2.168

MS(ESI, *m/z*): 384.1725 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.72-1.87 (1H, m), 2.07-2.23 (1H, m), 2.42 (3H, s), 2.55-2.84 (2H, m),
4.66-4.78 (1H, m), 5.28-6.30 (3H, m), 7.06-7.14 (2H, m), 7.31-7.36 (1H, m), 7.42-7.50
(3H, m), 7.55-7.65 (3H, m), 7.90-8.00 (1H, m), 8.59 (1H, dd, *J*=1.6, 5.0Hz), 8.64 (1H, d,
25 *J*=2.3Hz).

[0422]

Example 2-241LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methylindan-1-yl]nicotinamide

RT(min.): 1.328

30 MS(ESI, *m/z*): 385.1678 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.67-1.82 (1H, m), 2.06-2.18 (1H, m), 2.42 (3H, s), 2.53-2.83 (2H, m),
4.70-4.85 (1H, m), 5.28-5.95 (3H, m), 7.06-7.16 (2H, m), 7.33-7.44 (2H, m), 7.64-7.70
(1H, m), 7.88-8.04 (2H, m), 8.60-8.75 (3H, m), 8.84-8.91 (1H, m).

[0423]

35 Example 2-242LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-2-methyl-*N*-[(*R*)-6-methylindan-1-yl]nicotinamide

RT(min.): 1.141

MS(ESI, *m/z*): 399.1833 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.60-1.75 (1H, m), 1.98-2.12 (1H, m), 2.41 (3H, s), 2.50-2.90 (5H, m),
40 4.62-4.80 (1H, m), 5.15-5.87 (3H, m), 7.05-7.15 (2H, m), 7.17-7.24 (1H, m), 7.32-8.22
(4H, m), 8.50-8.74 (3H, m).

[0424]

Example 2-243LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-methylindan-1-yl]-4-methylthiazole-5-
45 carboxamide

RT(min.): 1.648

MS(ESI, *m/z*): 405.1398 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.66-1.78 (1H, m), 2.09-2.21 (1H, m), 2.41 (3H, s), 2.59-2.82 (5H, m),
4.67-4.81 (1H, m), 5.27-5.86 (3H, m), 7.08-7.15 (2H, m), 7.33-7.39 (1H, m), 7.55-7.60
50 (1H, m), 7.94-8.00 (1H, m), 8.58-8.64 (2H, m), 8.77 (1H, s).

[0425]

Example 2-244LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]-2-methylnicotinamide

5 RT(min.): 1.471

MS(ESI, *m/z*): 417.1740 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.61-1.78 (1H, m), 2.03-2.13 (1H, m), 2.33-2.88 (8H, m), 4.63-4.81 (1H, m), 5.14-5.84 (3H, m), 6.81 (1H, d, *J*=9.9Hz), 7.18-7.24 (1H, m), 7.32-8.23 (4H, m), 8.52-8.76 (3H, m).

10 [0426]

Example 2-245LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]-2-methylnicotinamide

RT(min.): 1.445

15 MS(ESI, *m/z*): 433.1691 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.61-1.77 (1H, m), 2.00-2.13 (1H, m), 2.43-2.87 (5H, m), 3.78-3.93 (3H, m), 4.63-4.83 (1H, m), 5.14-5.75 (3H, m), 6.56 (1H, dd, *J*=1.7, 10.5Hz), 7.18-7.24 (1H, m), 7.31-8.21 (4H, m), 8.52-8.75 (3H, m).

[0427]

20 Example 2-246LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,6-dimethylnicotinamide

RT(min.): 1.520

MS(ESI, *m/z*): 451.1355 (*M*-H)⁺25 ¹H-NMR (CDCl₃) δ: 1.64-1.81 (1H, m), 2.03-2.15 (1H, m), 2.47-3.17 (8H, m), 4.58-4.98 (1H, m), 5.25 (1H, t, *J*=8.7Hz), 5.32-5.78 (2H, m), 6.85-7.13 (2H, m), 7.33-7.79 (3H, m), 7.94-8.16 (1H, m), 8.60-8.72 (2H, m).

[0428]

Example 2-247LP

30 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-isopropoxybenzamide

RT(min.): 2.925

MS(ESI, *m/z*): 480.1508 (*M*-H)⁺35 ¹H-NMR (CDCl₃) δ: 1.38-1.49 (6H, m), 1.71-1.97 (1H, m), 2.14-2.37 (1H, m), 2.50-2.97 (2H, m), 4.62-4.79 (2H, m), 5.26-6.18 (3H, m), 6.92-7.08 (3H, m), 7.18-7.47 (3H, m), 7.56-7.63 (1H, m), 7.87-8.10 (1H, m), 8.54-8.67 (1H, m), 8.72-8.83 (1H, m).

[0429]

Example 2-248LP

40 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(2-hydroxyethoxy)benzamide

RT(min.): 2.232

MS(ESI, *m/z*): 482.1302 (*M*-H)⁺45 ¹H-NMR (CDCl₃) δ: 1.55-1.83 (1H, m), 1.98-2.37 (1H, m), 2.44-2.88 (2H, m), 3.89-4.41 (4H, m), 4.61-4.79 (1H, m), 5.22-5.69 (3H, m), 6.94-7.13 (3H, m), 7.31-7.46 (3H, m), 7.50-8.07 (2H, m), 8.48-8.69 (1.4H, m), 9.12-9.23 (0.6H, m).

[0430]

Example 2-249LP

50 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,5-dimethylnicotinamide

RT(min.): 2.675

MS(ESI, m/z): 450.1399 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.35-1.83 (1H, m), 1.93-2.13 (1H, m), 2.30-3.16 (8H, m), 4.52-4.97 (1H, m), 5.21 (t, 1H, J=8.7Hz), 5.31-5.60 (2H, m), 6.84-7.03 (1H, m), 7.24-7.61 (6H, m), 7.71-7.84 (1H, m), 8.34-8.43 (1H, m).

5 [0431]

Example 2-250LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,5-dimethylnicotinamide

RT(min.): 1.746

10 MS(ESI, m/z): 451.1354 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.65-1.81 (1H, m), 2.00-2.16 (1H, m), 2.26-2.39 (3H, m), 2.47-3.21 (5H, m), 4.58-4.97 (1H, m), 5.24 (t, 1H, J=8.7Hz), 5.32-5.78 (2H, m), 6.87-7.05 (1H, m), 7.21-7.80 (3H, m), 7.95-8.17 (1H, m), 8.35-8.45 (1H, m), 8.54-8.72 (2H, m).

[0432]

15 Example 2-251LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6,7-dihydro-5*H*-[1]pyrindin-5-yl]benzamide

RT(min.): 0.978

MS(ESI, m/z): 370.1559 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 1.68-1.91 (1H, m), 2.05-2.21 (1H, m), 2.65-2.98 (2H, m), 4.52-4.67 (1H, m), 5.20-5.80 (3H, m), 7.31-7.66 (11H, m), 8.20-8.55 (2H, m).

[0433]

Example 2-251HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6,7-dihydro-5*H*-[1]pyrindin-5-yl]benzamide

RT(min.): 0.811

25 MS(ESI, m/z): 370.1551 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.41-2.62 (1H, m), 2.65-3.00 (2H, m), 3.10-3.31 (1H, m), 4.37-4.53 (1H, m), 5.31-5.82 (3H, m), 6.65-6.73 (1H, m), 6.80-6.98 (1H, m), 7.24-7.64 (10H, m), 8.33 (1H, d, J=4.4Hz).

[0434]

30 Example 2-252M

N-[(*RS*)-Carbamoylphenylmethyl]-*N*-[(*SR*)-5-chloro-7-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.489

MS(ESI, m/z): 423.0914 (M-H)⁻

35 ¹H-NMR (CDCl₃) δ: 3.60-4.41 (2H, m), 5.20-5.88 (4H, m), 6.91-6.99 (1H, m), 7.15-7.68 (11H, m).

[0435]

Example 2-253M

N-(Carbamoylphenylmethyl)-*N*-[(*R*)-3,3-dimethylindan-1-yl]benzamide

40 RT(min.): 3.623

MS(ESI, m/z): 397.1920 (M-H)⁻

¹H-NMR (CDCl₃) δ: 0.94 (2H, s), 1.02 (1H, s), 1.19 (2H, s), 1.45 (1H, s), 1.64-1.73 (0.67H, m), 1.83-1.92 (0.67H, m), 2.19-2.29 (0.33H, m), 2.47-2.59 (0.33H, m), 4.52 (0.33H, s), 4.68 (0.67H, s), 5.25-6.10 (3H, m), 6.68 (0.33H, d, J=7.5Hz), 6.81-6.87 (0.33H, m), 7.10-7.66 (12.67H, m), 7.96 (0.67H, d, J=7.5Hz).

[0436]

Example 2-254M

N-(Carbamoylphenylmethyl)-*N*-(3-methylindan-1-yl)benzamide

RT(min.): 3.483

50 MS(ESI, m/z): 383.1767 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.00-1.43 (3H, m), 1.67-3.21 (3H, m), 4.50-4.63 (0.3H, br), 4.71 (0.7H, br s), 5.20-6.16 (3H, m), 6.68-8.10 (14H, m).

[0437]

Example 2-255M

5 *N*-(Carbamoylphenylmethyl)-*N*-[(*R*)-4-methoxyindan-1-yl]benzamide

RT(min.): 3.203

MS(ESI, m/z): 399.1708 (M-H)⁻

RT(min.): 3.259

MS(ESI, m/z): 399.1715 (M-H)⁻

10 ¹H-NMR (CDCl₃) δ: 1.65-3.15 (4H, m), 3.80 (1.4H, s), 3.81 (1.6H, s), 4.45-4.75 (1H, m), 5.35-6.90 (4H, m), 7.20-8.15 (12H, m).

[0438]

Example 2-256M

N-(Carbamoylphenylmethyl)-*N*-(3,3-difluoroindan-1-yl)benzamide

15 RT(min.): 3.180

MS(ESI, m/z): 405.1431 (M-H)⁻

RT(min.): 3.229

MS(ESI, m/z): 405.1432 (M-H)⁻

20 ¹H-NMR (CDCl₃) δ: 2.16-3.46 (2H, m), 4.20-4.55 (1H, m), 4.93-5.84 (3H, m), 6.64-7.11 (1H, m), 7.17-7.72 (12H, m), 7.90-8.17 (1H, m).

[0439]

Example 2-257M

N-(Carbamoylpyridin-3-ylmethyl)-*N*-[(*R*)-7-fluorolindan-1-yl]nicotinamide

RT(min.): 0.759

25 MS(ESI, m/z): 389.1434 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.08-2.24 (0.5H, m), 2.42-3.40 (3.5H, m), 4.30-4.41 (0.5H, m), 4.56-4.80 (0.5H, m), 5.24-5.86 (2.5H, m), 6.43-6.53 (0.5H, m), 6.88-7.48 (4.5H, m), 7.80-8.01 (3H, m), 8.45-8.92 (3.5H, m).

[0440]

30 Example 2-258M

N-(Carbamoylpyridin-3-ylmethyl)-*N*-[(*R*)-7-fluorolindan-1-yl]-4-methylthiazole-5-carboxamide

RT(min.): 1.046

MS(ESI, m/z): 409.1141 (M-H)⁻

35 RT(min.): 1.166

MS(ESI, m/z): 409.1146 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.08-2.22 (0.6H, m), 2.42-3.40 (6.4H, m), 4.32-4.37 (0.4H, m), 4.58-4.80 (0.6H, m), 5.32-5.88 (2.6H, m), 6.40-6.48 (0.4H, m), 6.88-7.40 (4H, m), 7.80-7.98 (1.4H, m), 8.46-8.62 (1.6H, m), 8.80 (0.4H, s), 8.82 (0.6H, s).

40 [0441]

Example 2-259M

N-(Carbamoylpyridin-3-ylmethyl)-*N*-[(*R*)-7-chlorolindan-1-yl]nicotinamide

RT(min.): 0.838

MS(ESI, m/z): 405.1122 (M-H)⁻

45 RT(min.): 1.016

MS(ESI, m/z): 405.1126 (M-H)⁻

¹H-NMR (CDCl₃) δ: 2.27-2.49 (4H, m), 4.18-4.26 (0.4H, m), 4.53-4.64 (0.6H, m), 5.18-5.70 (2.6H, m), 6.70-6.78 (0.4H, m), 7.08-7.51 (5H, m), 7.75-8.11 (2.4H, m), 8.43-8.93 (3.6H, m).

[0442]

Example 2-260HP

2-Amino-*N*-[(*S*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

5 RT(min.): 2.295

MS(ESI, *m/z*): 437.1187 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 2.50-2.85 (3H, m), 2.95-3.20 (1H, m), 4.25-4.55 (1H, m), 5.20-5.65 (4H, m), 6.10-6.35 (1H, m), 6.67 (1H, dd, *J*=5.0, 7.3Hz), 6.81 (1H, dd, *J*=1.3, 8.5Hz), 7.20-7.40 (6H, m), 7.47 (1H, dd, *J*=1.8, 7.2Hz), 8.13 (1H, dd, *J*=1.8,

10 5.0Hz).

[0443]

Example 3-1

N-[(*R*)-Carbamoylphenylmethyl]-2-hydroxy-*N*-[(*R*)-6-trifluoromethylindan-1-yl]benzamide

15 [0444]

To a solution of (*R*)-6-trifluoromethylindan-1-ylamine (0.06g) in methanol (1mL) was added benzaldehyde (0.032g), and the mixture was stirred for 20minutes under reflux. The reaction mixture was allowed to cool to room temperature. To the mixture were added acetylsalicylic acid (0.054g) and 4-phenylcyclohexen-1-ylisocyanide (0.055g). The mixture was stirred overnight under reflux, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (2mL), water (6μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (225μL), and the mixture was stirred for 3hours at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25 to 100/0) to afford 2-{*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-trifluoromethylindan-1-yl]carbamoyl}phenyl acetate as low polarity product. The product was passed through aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 0/100 to 35/65) to afford the title compound (0.039g). The structural formula is shown in Table 29.

[0445]

RT(min.): 3.397

35 MS(ESI, *m/z*): 453.1431 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.67-2.33 (2H, m), 2.61-3.00 (2H, m), 4.29-6.00 (4H, m), 6.89-6.95 (1H, m), 7.01-7.07 (1H, m), 7.22-7.57 (9H, m), 8.13 (1H, s), 8.67-8.86 (1H, m).

[0446]

Example 3-2 to 3-3

40 Examples 3-2 to 3-3 were synthesized in a manner similar to that of Example 3-1 by using the corresponding starting materials. The spectrum data of Examples 3-2 to 3-3 are shown as follows, and the structural formulae are shown in Table 29.

[0447]

Example 3-2

45 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.837

MS(ESI, *m/z*): 410.1510 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.48-1.99 (2H, m), 2.61-3.07 (2H, m), 4.40-6.21 (4H, m), 6.90-6.97 (1H, m), 7.00-7.07 (1H, m), 7.22-7.65 (9H, m), 8.15 (1H, s), 8.50-8.94 (1H, br).

[0448]

Example 3-3

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 3.165

5 MS(ESI, m/z): 421.1370 (M-H)⁺¹H-NMR (CDCl₃) δ: 1.64-2.25 (2H, m), 2.47-2.90 (7H, m), 4.50-5.00 (1H, br), 5.27-6.00 (3H, m), 6.62-6.78 (1H, m), 6.88-6.95 (1H, m), 7.06-7.06 (1H, m), 7.30-7.54 (8H, m), 8.54-8.84 (1H, br).

[0449]

10 Example 4-1

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

[0450]

15 To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (98mg) in methanol (2.2mL) were added benzaldehyde (47mg) and triethylamine (45mg), and the mixture was stirred for 3 hours at 60°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added acetylsalicylic acid (79mg) and 4-phenylcyclohexen-1-ylisocyanide (81mg). The mixture was stirred for 19 hours at 60°C and concentrated under reduced pressure. The obtained residue was suspended in tetrahydrofuran (2.2mL), and water (9μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (0.33mL) were added. The mixture was stirred for 1.5 hours at room temperature. To the reaction mixture were added a saturated aqueous solution of sodium bicarbonate and dichloromethane, and the formed two-layer mixture was stirred vigorously. The organic layer was separated by ISOLU (registered trademark) Phase Separator and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 52/48 to 73/27) to afford 2-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoylphenyl acetate as low polarity product. The product was passed through aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 14/86 to 20/80) to afford the title compound (69mg). The structural formula is shown in Table 30.

[0451]

RT(min.): 3.364

MS(ESI, m/z): 437.1070 (M-H)⁺

35 ¹H-NMR (CDCl₃) δ: 1.65-2.30 (2H, m), 2.80-2.95 (7H, m), 4.35-5.05 (1H, m), 5.20-6.00 (3H, m), 6.85-7.10 (3H, m), 7.30-7.55 (7H, m), 7.66 (1H, br s), 8.50-9.00 (1H, m).

[0452]

Example 4-2 to 4-9

40 Examples 4-2 to 4-9 were synthesized in a manner similar to that of Example 4-1 by using the corresponding starting materials. The spectrum data of Examples 4-2 to 4-9 are shown as follows, and the structural formulae are shown in Tables 30 and 31.

[0453]

Example 4-2

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzoxazin-3-yl]-2-hydroxybenzamide

45 RT(min.): 2.974

MS(ESI, m/z): 421.0959 (M-H)⁺¹H-NMR (CDCl₃) δ: 4.06 (1H, dd, J = 4.7, 9.9Hz), 4.30-6.00 (4H, m), 6.65-6.80 (1H, m), 6.90-7.00 (1H, m), 7.05 (1H, dd, J = 0.6, 8.3Hz), 7.10-7.70 (10H, m), 8.60-9.00 (1H, m).

[0454]

50 Example 4-3

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5-fluoro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide

RT(min.): 2.721

MS(ESI, *m/z*): 405.1253 (*M*-H)⁺

- 5 ¹H-NMR (CDCl₃) δ: 4.02-5.00 (2H, m), 5.45-5.75 (3H, m), 6.70-6.78 (1H, m), 6.90-6.99 (2H, m), 7.02-7.08 (1H, m), 7.23-7.30 (1H, m), 7.33-7.65 (8H, m), 8.73 (1H, br).

[0455]

Example 4-4

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide

10

RT(min.): 2.910

MS(ESI, *m/z*): 423.1162 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 3.70-4.40 (2H, m), 5.38-5.88 (3H, m), 6.73-6.83 (1H, m), 6.91-6.97 (1H, m), 7.02-7.07 (1H, m), 7.25-7.31 (2H, m), 7.34-7.68 (7H, m), 8.70 (1H, br).

15

[0456]

Example 4-5

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.155

20

MS(ESI, *m/z*): 438.1031 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-2.38 (2H, m), 2.53-2.94 (2H, m), 4.43-5.10 (1H, m), 5.27-6.41 (3H, m), 6.88-7.04 (3H, m), 7.28-7.35 (2H, m), 7.39 (1H, dd, *J*=4.8, 7.9Hz), 7.50-7.55 (1H, m), 7.86-8.07 (1H, m), 8.62 (1H, dd, *J*=1.5, 4.8Hz), 8.69-8.86 (1H, m), 8.89-9.79 (1H, m).

[0457]

25

Example 4-6

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-hydroxybenzamide

RT(min.): 1.984

MS(ESI, *m/z*): 420.1128 (*M*-H)⁺

30

¹H-NMR (CDCl₃) δ: 1.67-1.87 (1H, m), 2.00-2.38 (1H, m), 2.54-2.86 (2H, m), 4.57-4.98 (1H, m), 5.30-6.35 (3H, m), 6.87-7.02 (2H, m), 7.13 (1H, d, *J*=8.0Hz), 7.22-7.42 (4H, m), 7.70 (1H, br s), 7.96-8.06 (1H, m), 8.57-8.64 (1H, m), 8.66-8.72 (1H, m), 8.81-9.76 (1H, br).

[0458]

Example 4-7

35

N-[(*R*)-Carbamoylpyrimidin-5-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.463

MS(ESI, *m/z*): 439.0998 (*M*-H)⁺

40

¹H-NMR (DMSO-*d*₆) δ: 1.25-2.96 (4H, m), 4.64-5.61 (2H, m), 6.72-7.79 (8H, m), 8.64-8.93 (2H, m), 9.01-9.26 (1H, m), 10.09-10.49 (1H, m).

[0459]

Example 4-8

N-[(*R*)-Carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

45

RT(min.): 2.691

MS(ESI, *m/z*): 439.0998 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.88-2.02 (1H, m), 2.45-2.98 (3H, m), 4.80-4.96 (1H, m), 5.52-5.94 (2H, m), 6.94-7.07 (3H, m), 7.34-7.43 (3H, m), 7.86-8.28 (1H, m), 8.51-8.54 (1H, m), 8.60-8.64 (1H, m), 8.88 (1H, s), 9.22 (1H, s).

[0460]

Example 4-9

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide

5 RT(min.): 3.811

MS(ESI, *m/z*): 451.1236 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.67-2.22 (2H, m), 2.30 (3H, s), 2.49-2.62 (1H, m), 2.63-2.94 (1H, m), 4.46-4.91 (1H, m), 5.28-5.95 (3H, m), 6.82 (1H, t, *J*=7.6Hz), 6.91-7.06 (1H, m), 7.18-7.25 (2H, m), 7.34-7.52 (5H, m), 7.61-7.71 (1H, m), 8.60-8.95 (1H, br).

10 [0461]

Example 5-1

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-trifluoromethylindan-1-yl]benzamide

[0462]

15 To a solution of (*R*)-6-trifluoromethylindan-1-ylamine (0.06g) in methanol (1mL) was added benzaldehyde (0.032g), and the mixture was stirred for 20minutes under reflux. The reaction mixture was allowed to cool to room temperature. To the mixture were added 2-nitrobenzoic acid (0.049g) and 4-phenylcyclohexen-1-ylisocyanide (0.055g). The mixture was stirred overnight under reflux, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran

20 (2mL), water (6μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (225μL), and the mixture was stirred for 3hours at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure,

25 and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25 to 100/0) to afford *N*-[(*R*)-carbamoylphenylmethyl]-2-nitro-*N*-[(*R*)-6-trifluoromethylindan-1-yl]benzamide. To *N*-[(*R*)-carbamoylphenylmethyl]-2-nitro-*N*-[(*R*)-6-trifluoromethylindan-1-yl]benzamide (0.030g) were added ethanol (2mL) and 10% palladium carbon (0.030g) at room temperature, and the mixture was stirred for

30 4hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 45/55 to 65/35) to afford the title compound (0.015g). The structural formula is shown in Table 32.

[0463]

35 RT(min.): 3.695

MS(ESI, *m/z*): 452.1591 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.63-1.86 (1H, m), 2.00-2.25 (1H, m), 2.50-2.88 (2H, m), 4.29-4.74 (3H, m), 5.15-5.73 (3H, m), 6.67-6.80 (2H, m), 7.12-7.57 (9H, m), 8.17-8.29 (1H, br).

[0464]

40 Example 5-2

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]benzamide

The title compound was synthesized in a manner similar to that of Example 5-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 32.

45 [0465]

RT(min.): 3.124

MS(ESI, *m/z*): 409.1668 (*M*-H)⁺¹H-NMR (CDCl₃) δ: 1.59-1.82 (1H, m), 1.91-2.22 (1H, m), 2.48-2.90 (2H, m), 4.22-5.80 (6H, m), 6.64-6.88 (2H, m), 7.12-7.62 (9H, m), 8.13-8.34 (1H, m).

[0466]

Example 6-1

2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]benzamide

[0467]

To a solution of (*R*)-4,6-difluoroindan-1-ylamine hydrochloride (0.13g) in methanol (1.6mL) were added benzaldehyde (67mg) and triethylamine (64mg), and the mixture was stirred for 2hours at 60°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added 2-nitrobenzoic acid (0.11g) and 4-phenylcyclohexen-1-ylisocyanide (0.12g). The mixture was stirred for 15hours at 60°C, and concentrated under reduced pressure. The obtained residue was suspended in tetrahydrofuran (3.2mL), and water (13μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (0.47mL) were added. The mixture was stirred for 2hours at room temperature. To the reaction mixture were added a saturated aqueous solution of sodium bicarbonate and dichloromethane, and the formed two-layer mixture was stirred vigorously. The organic layer was separated by ISOLUTIF (registered trademark) Phase Separator, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 76/24) to afford N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]-2-nitrobenzamide (0.16g). A mixture of N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-4,6-difluoroindan-1-yl]-2-nitrobenzamide (0.16g), 10% palladium carbon (16mg) and tetrahydrofuran (3.5mL) was stirred vigorously for 18hours at room temperature under hydrogen atmosphere. The catalyst was removed by filtration through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 53/47 to 74/26) to afford the title compound (0.11g). The structural formula is shown in Table 33.

[0468]

RT(min.): 3.462

MS(ESI, m/z): 429.1531 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.30-2.85 (6H, m), 4.50-4.75 (1H, m), 5.30-5.65 (3H, m), 6.60-6.80 (3H, m), 7.15-7.25 (2H, m), 7.30-7.60 (6H, m).

[0469]

Example 6-2 to 6-5

Examples 6-2 to 6-5 were synthesized in a manner similar to that of Example 6-1 by using the corresponding starting materials. The spectrum data of Examples 6-2 to 6-5 are shown as follows, and the structural formulae are shown in Tables 33 and 34.

[0470]

Example 6-2

2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide

RT(min.): 3.664

MS(ESI, m/z): 436.1232 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.35-1.85 (3H, m), 1.90-2.25 (1H, m), 2.40-2.60 (1H, m), 2.60-2.80 (1H, m), 4.50-4.75 (1H, m), 5.30-5.70 (3H, m), 6.65-6.80 (2H, m), 6.90-7.05 (1H, m), 7.15-7.25 (2H, m), 7.30-7.60 (5H, m), 7.65-7.85 (1H, m).

[0471]

Example 6-3

2-Amino-N-[(*R*)-carbamoylphenylmethyl]-N-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]benzamide

RT(min.): 3.239

MS(ESI, m/z): 420.1117 (M-H)⁺

¹H-NMR (CDCl₃) δ: 3.99-4.70 (5H, m), 5.28-5.80 (3H, m), 6.66-6.80 (3H, m), 7.07-7.24 (3H, m), 7.36-7.65 (5H, m), 7.72-7.77 (1H, m).

[0472]

Example 6-4

2-Amino-N-[(*R*)-carbamoylpyridin-3-ylmethyl]-N-[(*R*)-6-chloro-4-fluorindan-1-yl]benzamide

RT(min): 2.498

MS(ESI, m/z): 437.1496 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.50-1.81 (1H, m), 1.99-2.27 (1H, m), 2.48-2.96 (2H, m), 4.00-5.00 (3H, m), 5.28-5.80 (3H, m), 6.67-6.82 (2H, m), 6.93-7.06 (1H, m), 7.17-7.24 (2H, m), 7.38 (1H, dd, J = 5.0, 8.0 Hz), 7.70 (1H, br s), 7.92-8.17 (1H, br s), 8.58-8.68 (2H, m).

[0473]

Example 6-5

2-Amino-N-[(*R*)-carbamoylpyridin-3-ylmethyl]-N-[(*R*)-6-chloro-4-fluorindan-1-yl]nicotinamide

RT(min): 1.243

MS(ESI, m/z): 438.1144 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.55-1.79 (1H, m), 1.96-2.24 (1H, m), 2.50-2.63 (1H, m), 2.68-2.87 (1H, m), 3.51-4.94 (1H, m), 5.27-5.79 (5H, m), 6.69 (1H, dd, J = 5.0, 7.2 Hz), 6.98-7.05 (1H, m), 7.39 (1H, ddd, J = 0.5, 4.7, 8.0 Hz), 7.47 (1H, dd, J = 1.6, 4.7 Hz), 7.67 (1H, s), 7.95-8.10 (1H, m), 8.14 (1H, dd, J = 1.8, 5.0 Hz), 8.60-8.63 (1H, m), 8.66 (1H, dd, J = 1.6, 4.7 Hz).

[0474]

Example 7

N-[(*R*)-Carbamoylphenylmethyl]-N-[(*R*)-6-(2-hydroxyethoxy)indan-1-yl]benzamide

[0475]

To a solution of [(*R*)-6-(2-benzyloxyethoxy)indan-1-yl]carbamoyl acid (*tert*-butyl ester) (0.20g) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL) at room temperature, and the mixture was stirred for 1 hour at same temperature. The reaction mixture was concentrated under reduced pressure. To the residue was added a saturated aqueous solution of sodium bicarbonate, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure. A mixture of the obtained residue, triethylamine (145 μL) and benzaldehyde (0.050g) in methanol (1 mL) was stirred for 2 hours at 60°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added benzoic acid (0.064g) and 4-phenylcyclohexen-1-yl isocyanide (0.095g), and the mixture was stirred for 5 days at external temperature of 60°C. The reaction mixture was concentrated under reduced pressure. To the obtained residue was added tetrahydrofuran (2 mL) to dissolve. To the mixture were added water (11 μL) and a solution of 4 mol/L hydrogen chloride in 1,4-dioxane (0.39 mL), and stirred for 1.5 hours at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25) to afford N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-6-(2-benzyloxyethoxy)indan-1-yl]benzamide (0.62g). To a solution of N-[(*R*)-carbamoylphenylmethyl]-N-[(*R*)-6-(2-benzyloxyethoxy)indan-1-yl]benzamide (0.62g) in tetrahydrofuran (1 mL) was added 10% palladium carbon (0.07g) at room temperature, and the mixture was stirred for 2 hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:

ethyl acetate / methanol = 100/0 to 85/15) to afford the title compound (0.019g). The structural formula is shown in Table 34.

[0476]

RT(min.): 2.832

5 MS(ESI, m/z): 429.1823 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.65-1.82 (1H, m), 1.97-2.13 (1H, m), 2.40-2.74 (3H, m), 3.90-4.00 (2H, m), 4.16-4.32 (2H, m), 4.67 (1H, br s), 5.34-5.90 (3H, m), 6.82-6.91 (1H, m), 7.04-7.10 (1H, m), 7.32-7.68 (11H, m).

[0477]

10 Example 8-1

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropyl-4-fluoroindan-1-yl]benzamide

[0478]

To a solution of (*R*)-*N*-[(*R*)-6-cyclopropyl-4-fluoroindan-1-yl]-*tert*-butansulfonamide (0.03g) in methanol (1mL) was added a solution of 4mol/L hydrogen chloride in 1,4-dioxane (35μL) at room temperature, and the mixture was stirred for 3hours at same temperature. The reaction mixture was concentrated under reduced pressure. A mixture of the obtained residue, triethylamine (14μL) and benzaldehyde (0.011g) in methanol (2mL) was heated under reflux for 0.5hours. The reaction mixture was allowed to cool to room temperature. Benzoic acid (0.013g) and 4-phenylcyclohexen-1-ylisocyanide (0.019g) were added, and the mixture was heated for 2days under reflux. The reaction mixture was concentrated under reduced pressure. To the residue was added tetrahydrofuran (2mL) to dissolve. To the mixture were added water (3μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (75μL), and the mixture was stirred for 1hour at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25 to 100/0) to afford the title compound (0.006g). The structural formula is shown in Table 34.

30 [0479]

RT(min.): 3.848

MS(ESI, m/z): 427.1832 (M-H)⁻

¹H-NMR (CDCl₃) δ: 0.72-1.07 (4H, m), 1.66-1.79 (1H, m), 1.90-2.12 (2H, m), 2.42-2.87 (2H, m), 4.63 (1H, br s), 5.28-5.86 (3H, m), 6.64-6.74 (1H, m), 7.29-7.63 (11H, m).

35 [0480]

Example 8-2

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-vinylindan-1-yl]benzamide

The title compound was synthesized in a manner similar to that of Example 8-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 34.

40 [0481]

RT(min.): 3.712

MS(ESI, m/z): 413.1676 (M-H)⁻

45 ¹H-NMR (CDCl₃) δ: 1.68-1.84 (1H, m), 2.00-2.14 (1H, m), 2.44-2.88 (2H, m), 4.60-4.73 (1H, m), 5.21-5.96 (5H, m), 6.76 (1H, dd, J= 11.0, 17.2Hz), 6.96-7.04 (1H, m), 7.32-7.65 (10H, m), 7.89 (1H, br s).

[0482]

Example 9

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-ethyl-4-fluoroindan-1-yl]benzamide

50 [0483]

To a solution of *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-vinylindan-1-yl]benzamide (0.04g, Example 8-2) in tetrahydrofuran (1mL) was added 10% palladium carbon (0.01g) at room temperature, and the mixture was stirred for 3hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 55/45 to 75/25 to 100/0) to afford the title compound (0.030g). The structural formula is shown in Table 34.

[0484]

RT(min.): 3.803

MS(ESI, *m/z*): 415.1832 (M-H)⁻

¹H-NMR (CDCl₃) δ: 1.28 (3H, t, J= 7.6Hz), 1.69-1.91 (1H, m), 2.00-2.16 (1H, m), 2.44-2.87 (4H, m), 4.66 (1H, br s), 5.26-5.93 (3H, m), 6.80 (1H, d, J= 9.8Hz), 7.32-7.66 (11H, m).

[0485]

Example 10

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]terephthalamidic acid

[0486]

To a solution of *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]terephthalamidic acid benzyl ester (0.068g, Example 2-62LP) in tetrahydrofuran (2mL) was added 10% palladium carbon (0.02g) at room temperature, and the mixture was stirred for 2hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / methanol = 100/0 to 80/20) to afford the title compound (0.032g). The structural formula is shown in Table 34.

[0487]

RT(min.): 3.057

MS(ESI, *m/z*): 449.1322 (M-H)⁻

¹H-NMR (DMSO-*d*₆) δ: 1.11-1.28 (1H, m), 1.88-2.08 (1H, m), 2.43-2.64 (1, m), 2.75-2.94 (1H, m), 4.96-5.08 (1H, m), 5.37 (1H, br s), 6.88-6.98 (1H, m), 7.21-7.62 (10H, m), 7.99-8.12 (2H, m), 13.08-13.33 (1H, br).

[0488]

Example 11

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide

[0489]

To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.33g) in methanol (7.5mL) were added benzaldehyde (0.16g) and triethylamine (0.15g), and the mixture was stirred for 1hour at 65°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added 2-methoxynicotinic acid (0.24g) and 4-phenylcyclohexen-1-ylisocyanide (0.27g). The mixture was stirred for 23hours at 65°C, and the reaction mixture concentrated under reduced pressure. The obtained residue was suspended in tetrahydrofuran (7.5mL), and water (30μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (1.1mL) were added. The mixture was stirred for 1hour at room temperature. To the reaction mixture were added a saturated aqueous solution of sodium bicarbonate and dichloromethane, and the formed two-layer mixture was stirred vigorously. The organic layer was separated by ISOLUTE (registered trademark) Phase Separator, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 64/36 to 85/15) to afford the crude product. The crude product was purified by aminopropyl silica gel column

chromatography (eluent: ethyl acetate / *n*-hexane = 58/42 to 100/0) to afford the title compound (0.20g). The structural formula is shown in Table 34.

[0490]

RT(min.): 3.409

5 MS(ESI, *m/z*): 452.1182 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.70-3.10 (4H, m), 3.95-4.10 (3H, m), 4.50-6.10 (4H, m), 6.80-7.10 (2H, m), 7.30-7.90 (7H, m), 8.20-8.30 (1H, m).

[0491]

Example 12

10 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

[0492]

To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (105mg) in methanol (2.3mL) were added 3-pyridinecarboxaldehyde (50mg) and triethylamine (47mg), and the mixture was stirred for 2hours at 65°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added 2-methylnicotinic acid (67mg) and 4-phenylcyclohexen-1-ylisocyanide (85mg). The mixture was stirred for 5hours at 65°C, and the reaction mixture was concentrated under reduced pressure. The obtained residue was suspended in tetrahydrofuran (2.3mL), and water (9μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (0.46mL) were added. The mixture was stirred for 1hour at room temperature. To the reaction mixture were added a saturated aqueous solution of sodium bicarbonate and dichloromethane, and the formed two-layer mixture was stirred vigorously. The organic layer was separated by ISOLATE (registered trademark) Phase Separator, and concentrated under reduced pressure. The residue was purified by aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 0/100 to 9/91) to afford a mixture of diastereomers. The mixture was purified by preparative reverse phase liquid chromatography (Inertsil ODS-3, eluent: acetonitrile / water = 10/90 to 90/10) to afford the title compound (32mg). The structural formula is shown in Table 34.

[0493]

30 RT(min.): 1.694

MS(ESI, *m/z*): 437.1191 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 2.00-2.20 (1H, m), 2.45-2.90 (5H, m), 4.55-5.00 (1H, m), 5.23 (1H, dd, *J* = 8.8, 8.8Hz), 5.30-5.80 (2H, m), 7.02 (1H, dd, *J* = 0.8, 8.6Hz), 7.15-7.30 (1H, m), 7.35-7.90 (5H, m), 7.90-8.25 (1H, m), 8.50-8.80 (3H, m).

35 [α]_D²⁵: +54.4° (*c* = 0.40, MeOH)

[0494]

Example 13

2-Amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide

40 [0495]

To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.1g) in methanol (3mL) were added triethylamine (0.046g) and benzaldehyde (0.048g), and the mixture was stirred for 0.5hours at 65°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added 2-nitronicotinic acid (0.083g) and 4-phenylcyclohexen-1-ylisocyanide (0.083g). The mixture was stirred overnight at 65°C, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (4mL), water (40μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (340μL), and the mixture was stirred for 1hour at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic

layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: methanol / ethyl acetate / *n*-hexane = 0/60/40 to 0/100/0 to 20/80/0) to afford 2-nitro-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (0.090g). A suspension of Raney catalyst was prepared as follows. A mixture of Raney (registered trademark) 2800 nickel slurry in water, active catalyst (Sigma-Aldrich) (200μl) and ethanol was stirred, and the solvent was removed by decantation. The catalyst was washed 3 times with ethanol, and ethanol (1mL) was added to form a suspension. To a solution of 2-nitro-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide (0.090g) in ethanol (1mL) was added the suspension of Raney catalyst at room temperature, and the mixture was stirred for 5 hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 90/10 to 100/0) to afford the title compound (0.071g). The structural formula is shown in Table 34.

[0496]

RT(min.): 2.330

MS(ESI, m/z): 437.1182 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.60-1.85 (1H, m), 1.90-2.20 (1H, m), 2.45-2.85 (2H, m), 4.50-4.85 (1H, m), 5.20-5.65 (5H, m), 6.69 (1H, dd, J = 5.1, 7.3Hz), 6.90-7.05 (1H, m), 7.35-7.55 (6H, m), 7.70 (1H, br s), 8.13 (1H, dd, J = 1.7, 5.1Hz).

[α]_D²⁰: +44.9° (c = 1.08, MeOH)

[0497]

Example 14

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

To a mixture of (*R*)-6-chloro-4-fluoroindan-1-amine hydrochloride (444mg) and benzaldehyde (212mg) in methanol (8mL) was added triethylamine (202mg), and the mixture was stirred for 2 hours at 60°C. The reaction mixture was allowed to cool to room temperature, and 2-methylnicotinic acid (274mg) and 4-phenylcyclohexen-1-ylisocyanide (366mg) were added, and the mixture was stirred overnight at 60°C. The solvent was removed under reduced pressure. To the residue were added 1,4-dioxane (3.5mL), water (0.5mL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (0.5mL) at room temperature, and the mixture was stirred for 3 hours. To the reaction mixture was added a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 5/1) to afford the each diastereomer as a crude. These crude products were purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 3/1) to afford *N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 14I.P, 279mg) as low polarity product and *N*-[(*S*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 14HP, 166mg) as high polarity product. The structural formulae are shown in Tables 34 and 35.

[0498]

Example 14I.P

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.728

MS(ESI, *m/z*): 436.1233(*M*-H)⁺

- 5 ¹H-NMR (CDCl₃) δ: 1.65-1.85 (1H, m), 1.96-2.11 (1H, m), 2.41-2.55 (1H, m), 2.61-3.14 (4H, m), 4.55-5.00 (1H, m), 5.17-5.24 (1H, m), 5.30-5.57 (2H, m), 6.84-7.04 (1H, m), 7.15-7.84 (8H, m), 8.53-8.61 (1H, m).

[α]_D²⁰: +24.9° (c = 0.58, MeOH)

[0499]

- 10 Example 14HP

N-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.569

MS(ESI, *m/z*): 436.1240(*M*-H)⁺

- 15 ¹H-NMR (CDCl₃) δ: 2.31-3.17 (7H, m), 4.36 (1H, br s), 5.07-5.61 (3H, m), 6.12-6.28 (1H, m), 6.76-6.87 (1H, m), 7.17-7.73 (7H, m), 8.56-8.61 (1H, m).

[α]_D²⁵: +85.3° (c = 1.18, MeOH)

[0500]

Example 15LP

- 20 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

[0501]

To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.45g) in methanol (10mL) were added benzaldehyde (0.22g) and triethylamine (0.21g), and the mixture was stirred for 2.5 hours at 65°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added 4-methylthiazole-5-carboxylic acid (0.31g) and 4-phenylcyclohexen-1-ylisocyanide (0.37g). The mixture was stirred for 20 hours at 65°C.

- 25 The reaction mixture was concentrated under reduced pressure, and the obtained residue was suspended in tetrahydrofuran (5mL), and water (40μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (1.5mL) were added. The mixture was stirred for 1 hour at room temperature. To the reaction mixture were added a saturated aqueous solution of sodium bicarbonate and dichloromethane, and the formed two-layer mixture was stirred vigorously. The organic layer was separated by ISOLUTE (registered trademark) Phase Separator, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 71/29 to 92/8) to afford the title compound (0.35g). The structural formula is shown in Table 35.

[0502]

RT(min.): 3.241

MS(ESI, *m/z*): 442.0800 (*M*-H)⁺

- 40 ¹H-NMR (CDCl₃) δ: 1.65-2.30 (2H, m), 2.45-3.05 (5H, m), 4.40-6.00 (4H, m), 6.85-7.10 (1H, m), 7.30-7.60 (5H, m), 7.72 (1H, br s), 8.77 (1H, s).

[α]_D²⁶: +33.6° (c = 1.07, MeOH)

[0503]

Example 15HP

- 45 *N*-[(*S*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide

[0504]

The title compound was synthesized in a manner similar to that of Example 15LP as the corresponding high polarity diastereomer. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 35.

[0505]

RT(min.): 3.046

MS(ESI, m/z): 442.0802 (M-H)⁺

5 ¹H-NMR (CDCl₃) δ: 2.24-2.85 (6H, m), 3.05-3.20 (1H, m), 4.20-4.70 (1H, m), 5.20-5.75 (3H, m), 6.00-6.45 (1H, m), 6.84 (1H, dd, J=1.0, 8.6Hz), 7.20-7.45 (5H, m), 8.79 (1H, s).
[α]_D²⁵: -72.3 (c = 1.04, MeOH)

[0506]

Example 16

10 7-Acetyl-N-[(R)-carbamoylphenylmethyl]-N'[(R)-6-chloro-4-fluoroindan-1-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

[0507]

To a solution of 5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid ethyl ester (0.225g) in tetrahydrofuran (3mL) was added acetic anhydride (130μL), and the mixture was stirred for 1hour at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate / n-hexane = 60/40 to 85/15) to afford 7-acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid ethyl ester (0.12g). To a solution of 7-acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid ethyl ester (0.12g) in ethanol (3mL) was added an aqueous solution of 2mol/L sodium hydroxide (330μL), and the mixture was stirred for 30minutes under reflux. The reaction mixture was allowed to cool to room temperature, and 2mol/L hydrochloric acid (330μL) was added to the mixture. The mixture was concentrated under reduced pressure to afford 7-acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid (0.106g). To a mixture of (R)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.112g) and triethylamine (0.051g) in methanol (2mL) was added benzaldehyde (0.054g), and the mixture was stirred for 30minutes at 65°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added 7-Acetyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxylic acid (0.106g) and 4-phenylcyclohexen-1-ylisocyanide (0.093g). The mixture was stirred overnight at 65°C, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (4mL), water (100μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (500μL), and the mixture was stirred for 30minutes at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 4/96) to afford the title compound (0.033g) as a low polarity diastereomer. The structural formula is shown in Table 35.

[0508]

40 RT(min.): 2.458

MS(ESI, m/z): 508.1561 (M-H)⁺

¹H-NMR (CDCl₃) δ: 1.75-2.28 (5H, m), 2.55-2.97 (2H, m), 3.70-5.08 (7H, m), 5.23-6.26 (3H, m), 6.89-7.10 (1H, m), 7.33-7.49 (6H, m), 7.57-7.81 (1H, m).

[0509]

45 Example 17

N-[(R)-Carbamoylphenylmethyl]-N'[(R)-6-chloro-4-fluoroindan-1-yl]-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine-3-carboxamide

[0510]

50 To a suspension of imidazo[1,2-a]pyrazine-3-carboxylic acid ethyl ester (0.21g) and a solution of 4mol/L hydrogen chloride in ethyl acetate (360μL) in ethanol (3mL) was

added 10% palladium carbon (0.080g) at room temperature, and the mixture was stirred overnight under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. To the residue were added tetrahydrofuran (3mL), triethylamine (460μL) and benzylloxycarbonyl chloride (250μL), and the mixture was stirred overnight at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 60/40 to 85/15) to afford 5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-3,7-dicarboxylic acid 7-benzyl-3-ethyl ester (0.16g). To a solution of 5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-3,7-dicarboxylic acid 7-benzyl-3-ethyl ester (0.16g) in ethanol (3mL) was added an aqueous solution of 2mol/L sodium hydroxide (315μL). The mixture was stirred for 30minutes under reflux, and allowed to cool to room temperature. To the mixture was added 2mol/L hydrochloric acid (315μL), and concentrated under reduced pressure to afford 5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-3,7-dicarboxylic acid 7-benzyl ester (0.146g). To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.108g) and triethylamine (0.049g) in methanol (2mL) was added benzaldehyde (0.052g), and the mixture was stirred for 30minutes at 65°C. The reaction mixture was allowed to cool to room temperature. To the mixture were added 5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-3,7-dicarboxylic acid 7-benzyl ester (0.146g) and 4-phenylcyclohexen-1-ylisocyanide (0.089g). The mixture was stirred overnight at 65°C, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added tetrahydrofuran (4mL), water (100μL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (500μL), and the mixture was stirred for 30minutes at room temperature. To the reaction mixture were added water and a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 4/96) to afford 3-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl]-5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-7-carboxylic acid benzyl ester (0.038g) as a low polarity diastereomer. To a suspension of 3-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl]-5,6-dihydro-8*II*-imidazo[1,2-*a*]pyrazine-7-carboxylic acid benzyl ester (0.038g) in tetrahydrofuran (3mL) was added 10% palladium carbon (0.020g) at room temperature, and the mixture was stirred for a day under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by aminopropyl silica gel column chromatography (eluent: methanol / ethyl acetate = 0/100 to 20/80) to afford the title compound (0.23g). The structural formula is shown in Table 35

[0511]

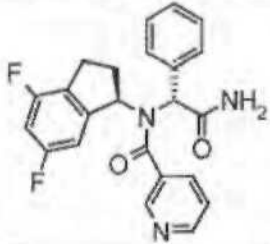
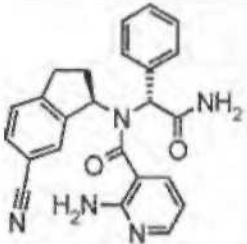
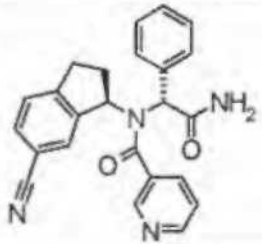
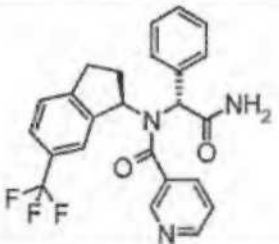
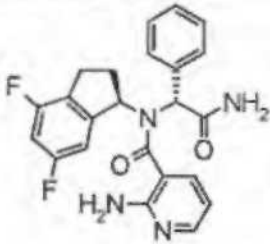
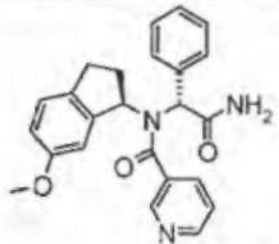
RT(min.): 2.045

MS(ESI, *m/z*): 466.1450 (*M*-H)⁺

¹H-NMR (CDCl₃) δ: 1.76-2.36 (2H, m), 2.50-3.00 (2H, m), 3.16-3.33 (2H, m), 3.56-5.00 (6H, m), 5.20-6.34 (3H, m), 6.86-7.09 (1H, m), 7.30-7.48 (6H, m), 7.55-7.81 (1H, m).

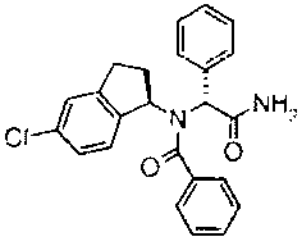
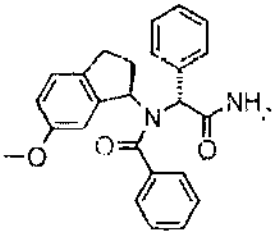
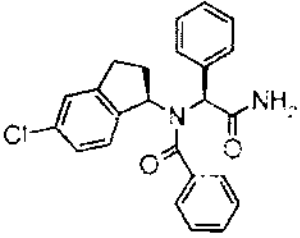
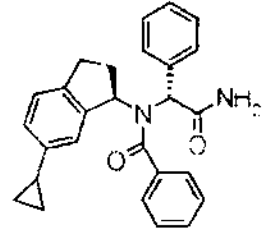
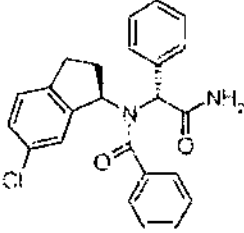
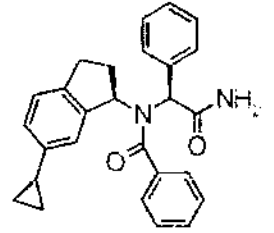
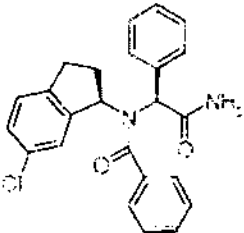
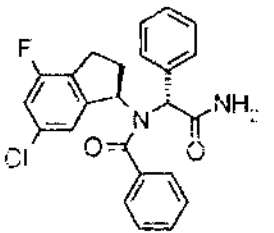
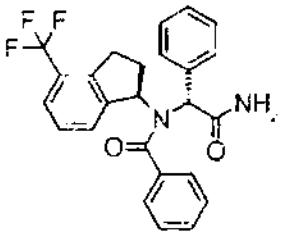
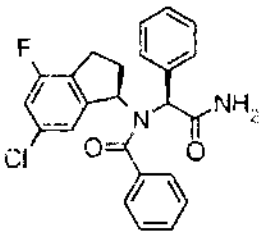
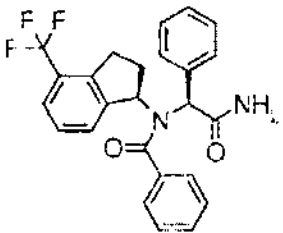
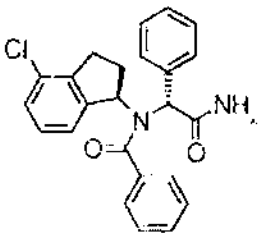
[0512]

[Table 3]

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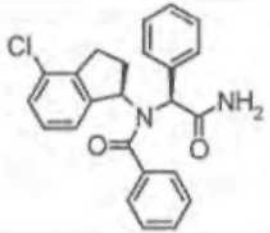
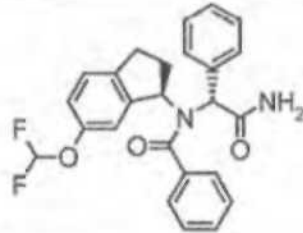
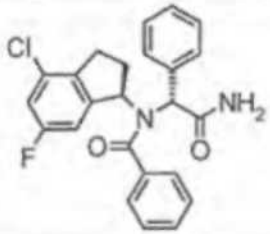
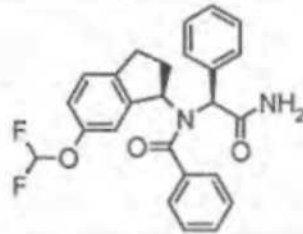
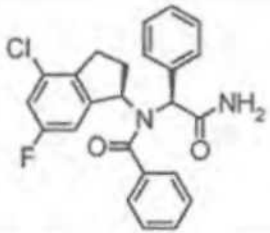
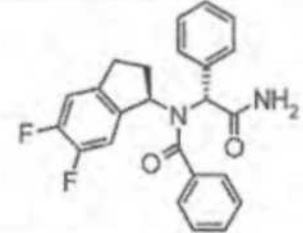
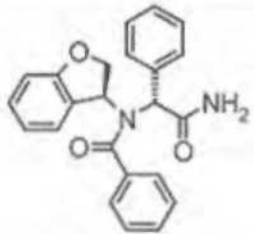
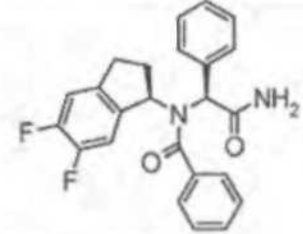
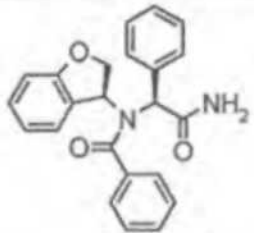
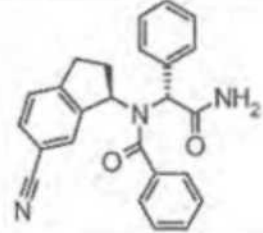
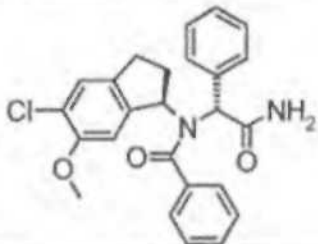
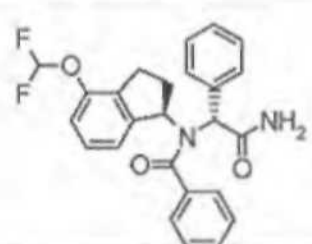
[0513]

[Table 4]

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2-21P		2-5LP	
2-23P		2-6LP	
2-31P		2-6LP	
2-31P		2-7LP	

[0514]

[Table 5]

Ex. No.	Strc.	Ex. No.	Strc.
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2-8LP		2-11HP	
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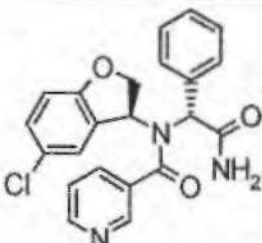
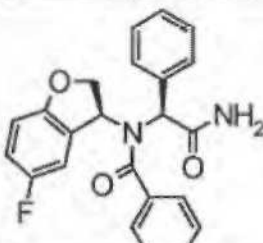
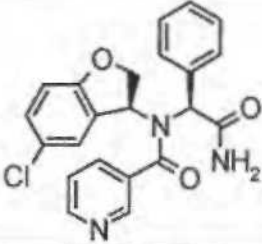
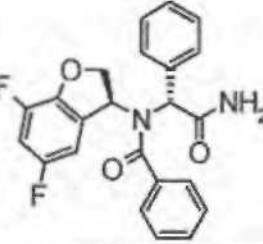
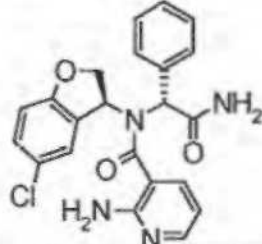
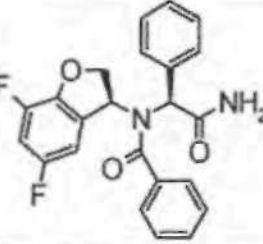
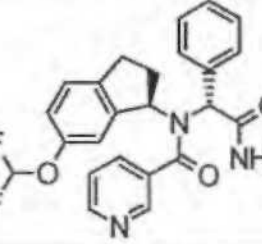
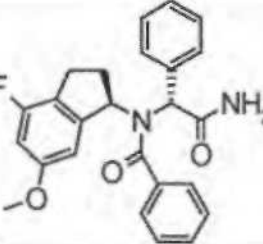
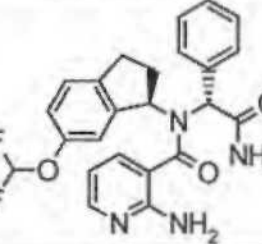
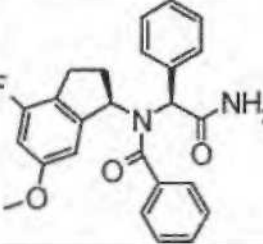
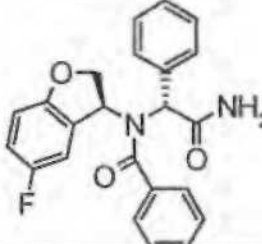
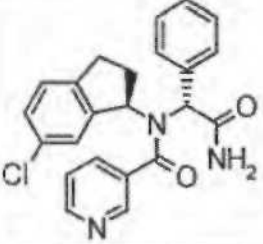
[0515]

[Table 6]

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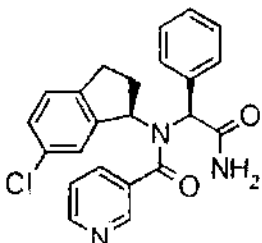
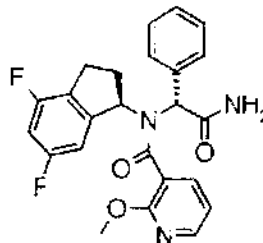
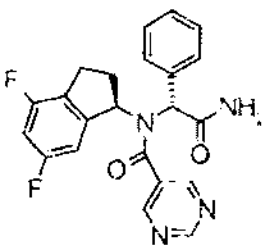
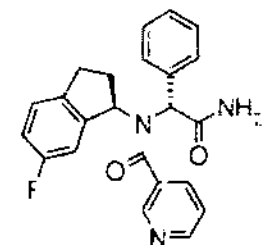
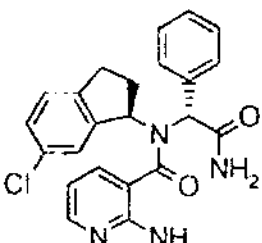
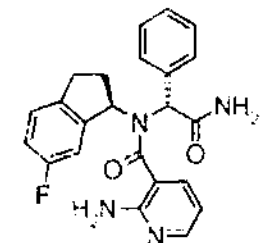
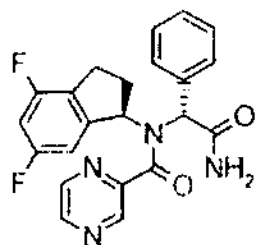
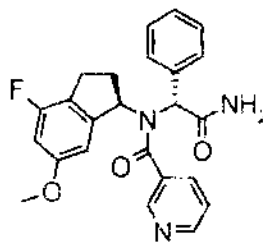
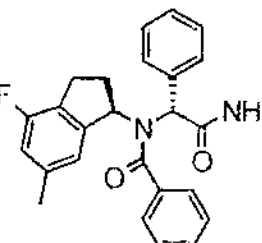
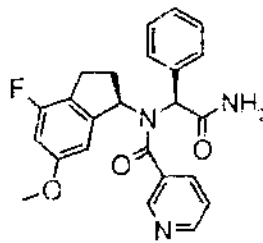
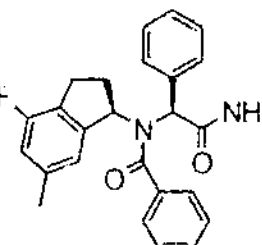
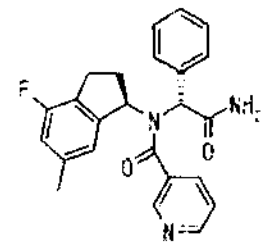
[0516]

[Table 7]

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2-28LP		2-31LP	

[0517]

[Table 8]

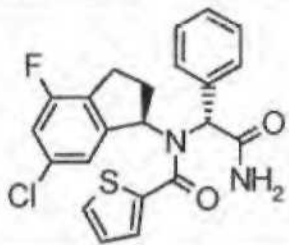
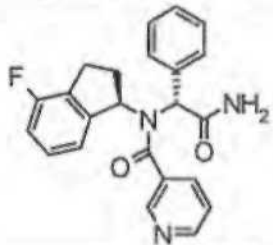
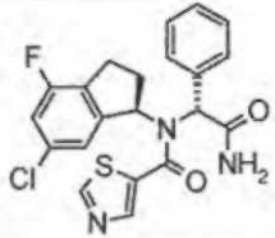
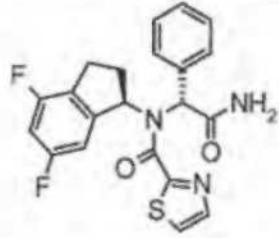
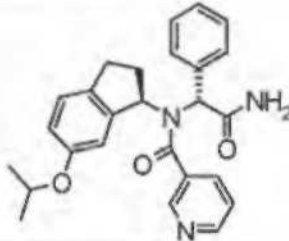
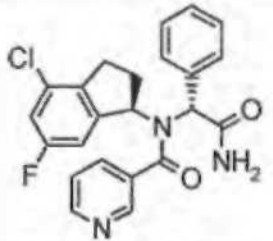
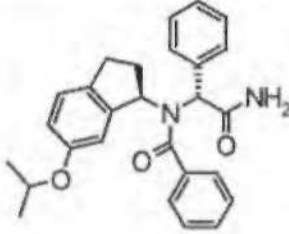
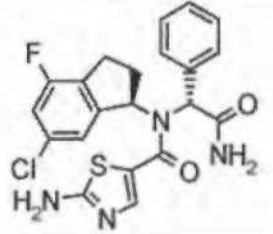
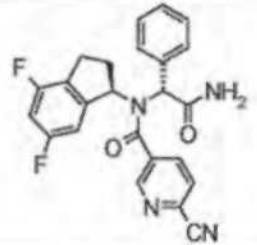
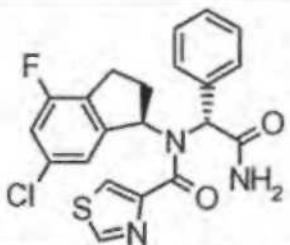
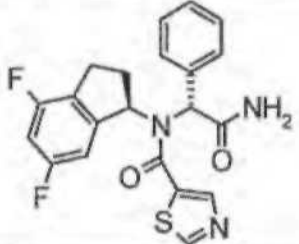
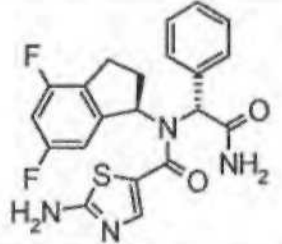
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2-34EP		2-39EP	
2-35EP		2-39EP	
2-36EP		2-40EP	

[0518]

[Table 9]

Ex. No.	Structure	Ex. No.	Structure
2-163P		2-164P	
2-165P		2-166P	
2-167P		2-168P	
2-169P		2-170P	
2-171P		2-172P	
2-173P		2-174P	

[Table 10]

Ex. No.	Strc.	Ex. No.	Strc.
2-50LP		2-56LP	
2-51LP		2-57LP	
2-52LP		2-58LP	
2-53LP		2-59LP	
2-54LP		2-60LP	
2-55LP		2-61LP	

[0520]

[Table 12]

Ex. No.	Strc.	Ex. No.	Strc.
2-72LP		2-77HP	
2-73LP		2-78LP	
2-74LP		2-79LP	
2-75LP		2-80LP	
2-76LP		2-81LP	
2-77LP		2-82LP	

[0522]

[Table 13]

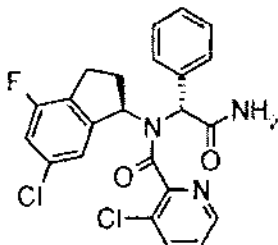
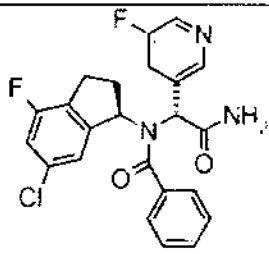
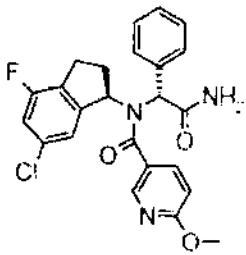
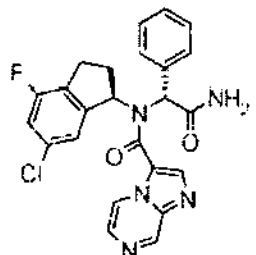
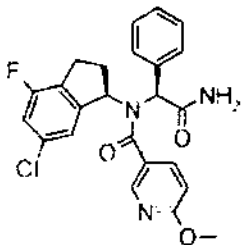
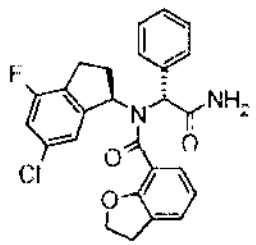
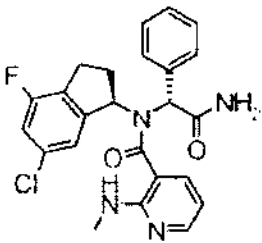
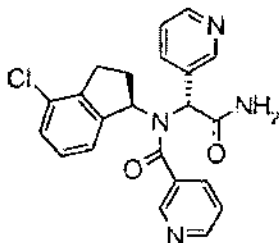
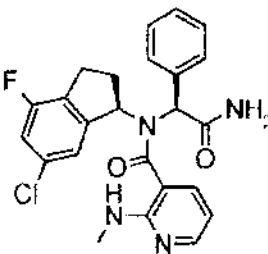
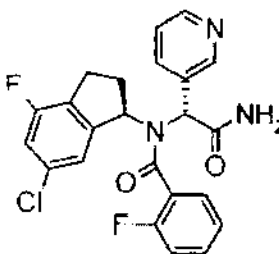
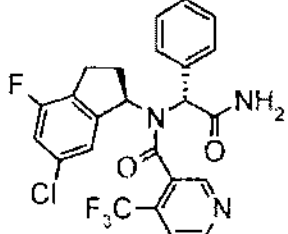
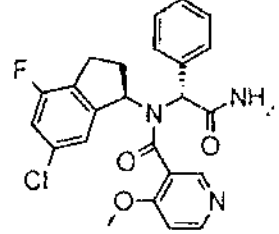
Ex. No.	Chemical structure	Ex. No.	Chemical structure
2-841F		2-842F	
2-843F		2-844F	
2-845F		2-846F	
2-847F		2-848F	
2-849F		2-850F	

[Table 14]

Ex. No.	Chemical structure	Ex. No.	Chemical structure
2-562P		2-563P	
2-564P		2-565P	
2-566P		2-567P	
2-568P		2-569P	
2-570P		2-571P	
2-568P		2-572P	

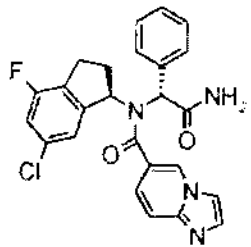
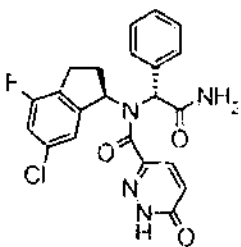
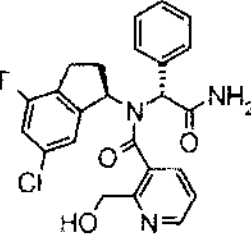
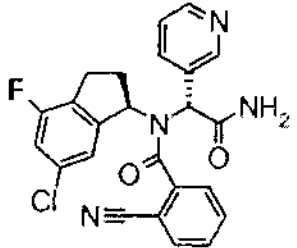
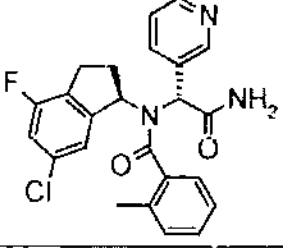
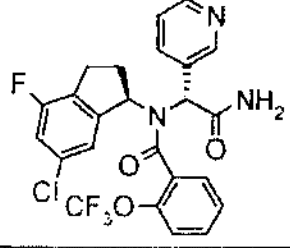
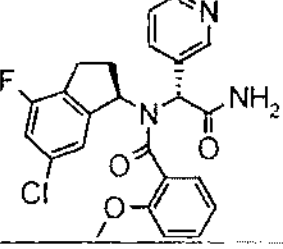
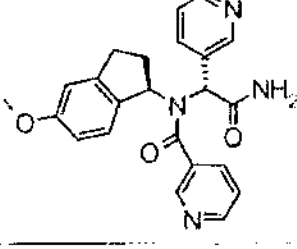
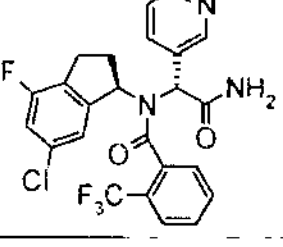
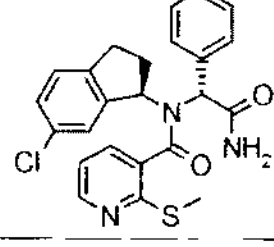
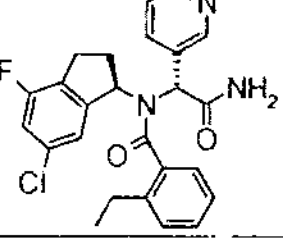
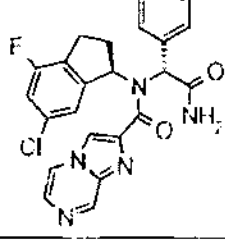
[0524]

[Table 15]

Ex. No.	Struc.	Ex. No.	Struc.
2-105LP		2-109LP	
2-106LP		2-110LP	
2-106BP		2-111LP	
2-107LP		2-112LP	
2-107BP		2-113LP	
2-108LP		2-114LP	

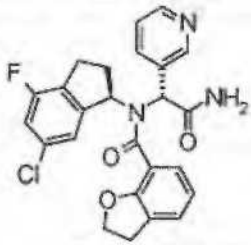
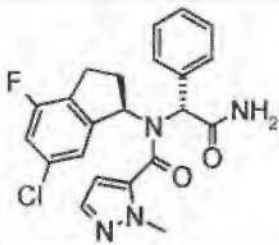
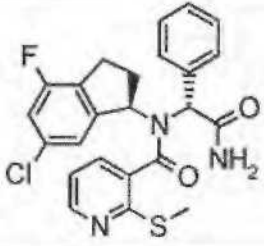
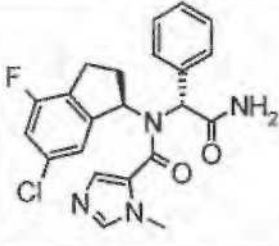
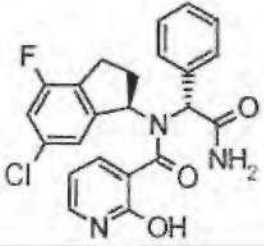
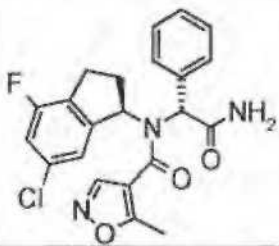
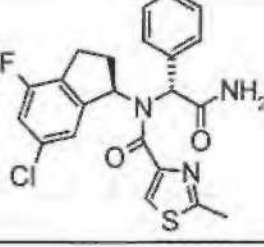
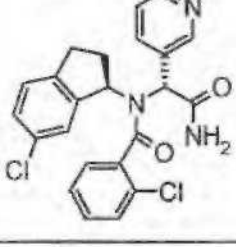
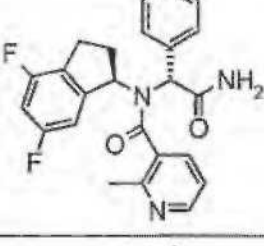
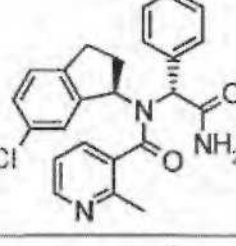
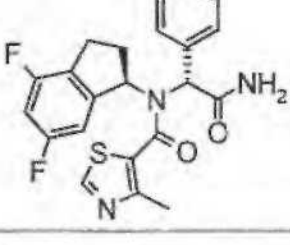
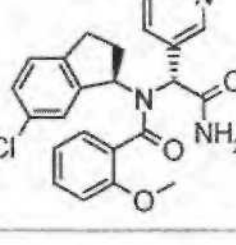
[0525]

[Table 16]

Ex. No.	Struc.	Ex. No.	Struc.
2-115LP		2-121LP	
2-116LP		2-122LP	
2-117LP		2-123LP	
2-118LP		2-124LP	
2-119LP		2-125LP	
2-120LP		2-126LP	

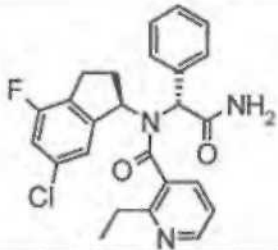
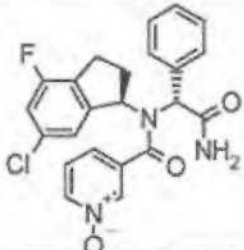
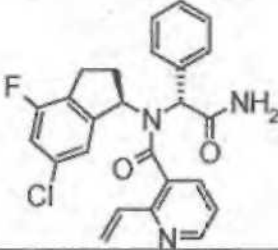
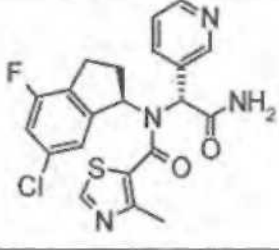
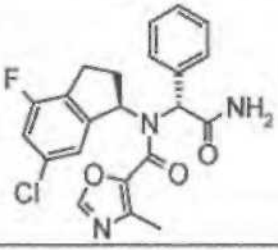
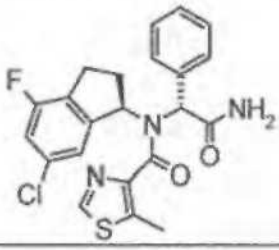
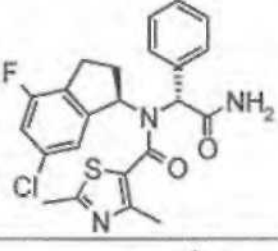
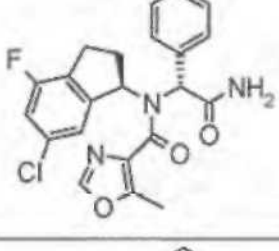
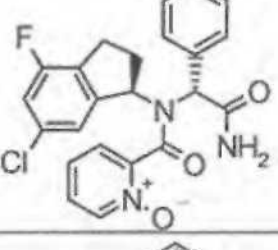
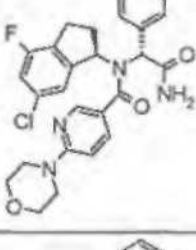
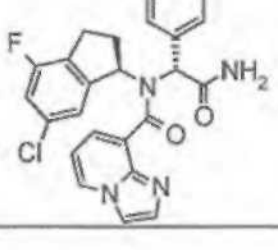
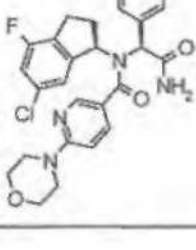
[0526]

[Table 17]

Ex. No.	Strc.	Ex. No.	Strc.
2-127LP		2-133LP	
2-128LP		2-134LP	
2-129LP		2-135LP	
2-130LP		2-136LP	
2-131LP		2-137LP	
2-132LP		2-138LP	

[0527]

[Table 18]

Ex. No.	Strc.	Ex. No.	Strc.
2-139LP		2-145LP	
2-140LP		2-146LP	
2-141LP		2-147LP	
2-142LP		2-148LP	
2-143LP		2-149LP	
2-144LP		2-149HP	

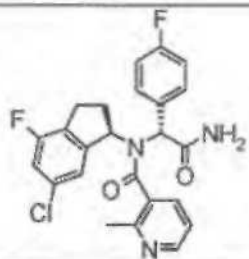
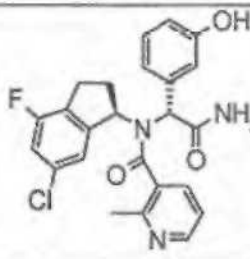
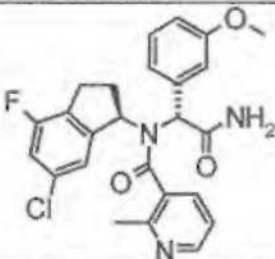
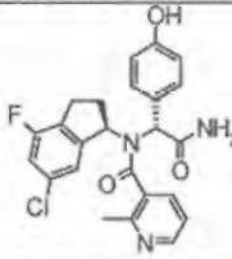
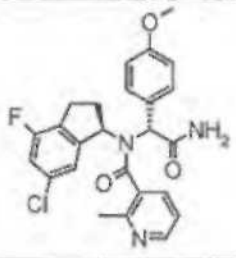
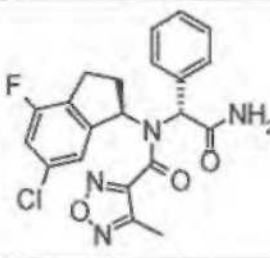
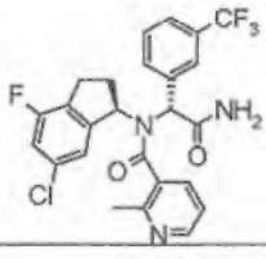
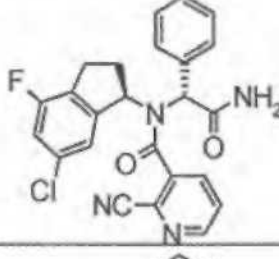
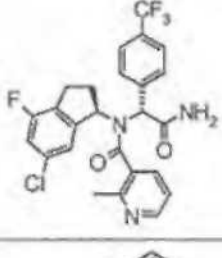
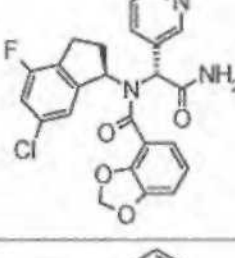
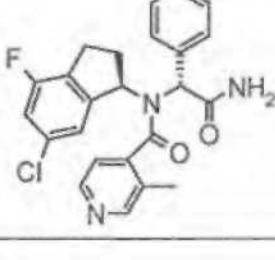
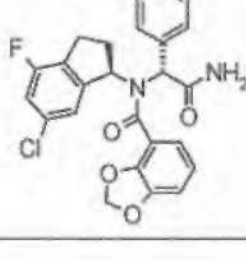
[0528]

[Table 19]

Ex. No.	Str.	Ex. No.	Str.
2-150LP		2-156LP	
2-151LP		2-157LP	
2-152LP		2-158LP	
2-153LP		2-159LP	
2-154LP		2-160LP	
2-155LP		2-161LP	

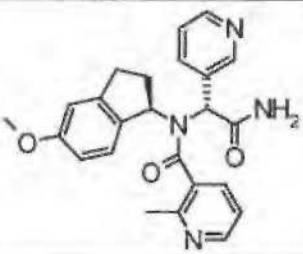
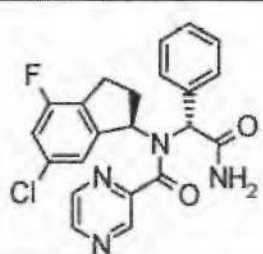
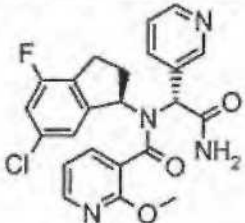
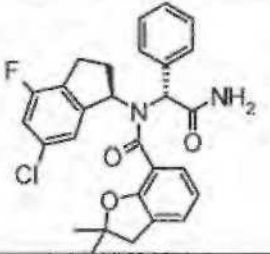
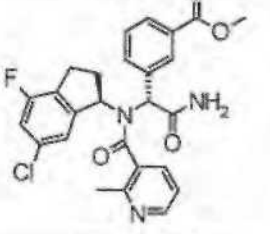
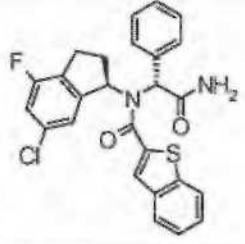
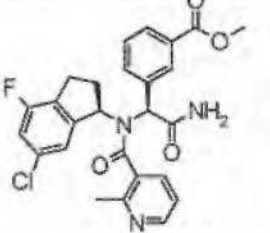
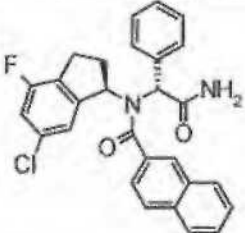
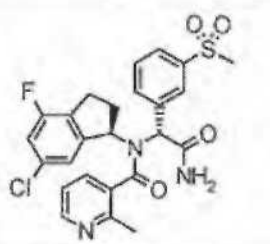
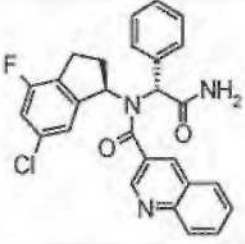
[0529]

[Table 20]

Ex. No.	Strc.	Ex. No.	Strc.
2-162LP		2-168LP	
2-163LP		2-169LP	
2-164LP		2-170LP	
2-165LP		2-171LP	
2-166LP		2-172LP	
2-167LP		2-173LP	

[0530]

[Table 21]

Ex. No.	Strc.	Ex. No.	Strc.
2-174LP		2-179LP	
2-175LP		2-180LP	
2-176LP		2-181LP	
2-177LP		2-182LP	
2-177HP		2-183LP	
2-178LP		2-184LP	

[0531]

[Table 22]

Ex. No.	Struc.	Ex. No.	Struc.
2-1851P		2-1861P	
2-1861P		2-1911P	
2-1871P		2-1921P	
2-1871P		2-1921P	
2-1881P		2-1931P	
2-1891P		2-1931P	

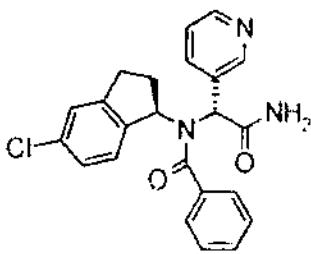
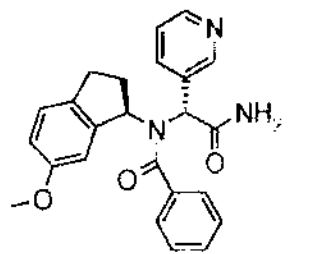
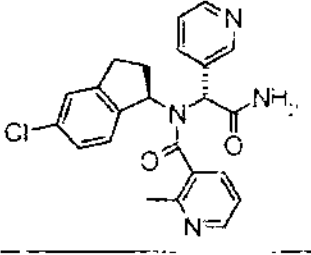
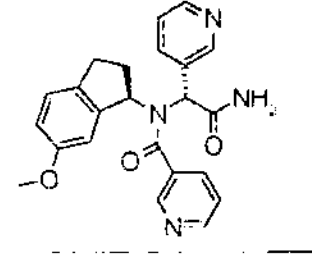
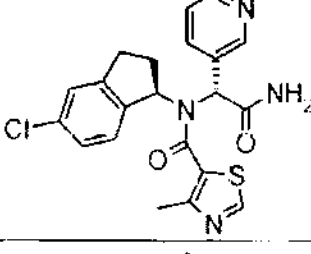
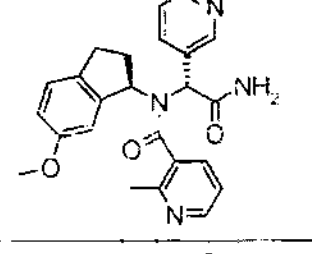
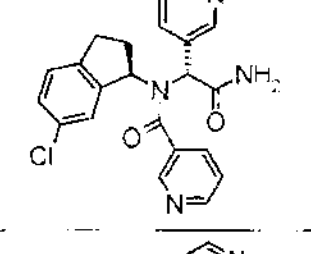
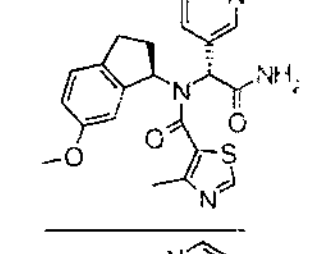
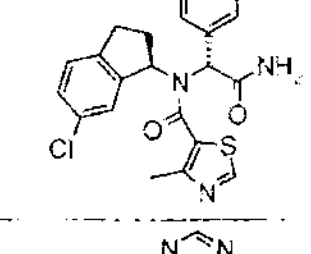
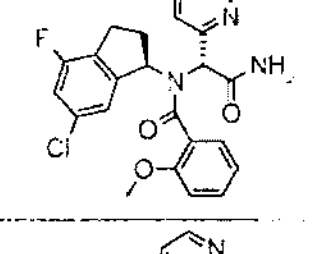
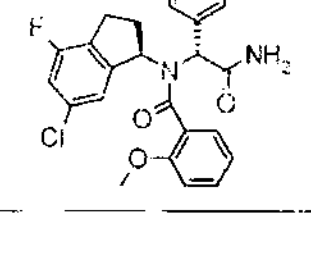
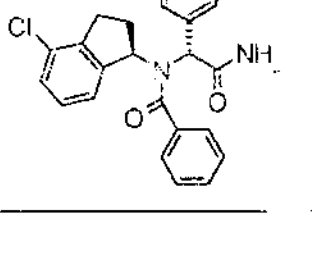
[0532]

[Table 23]

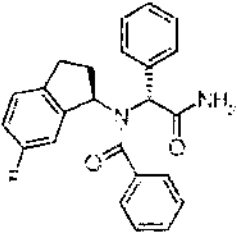
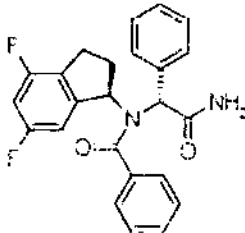
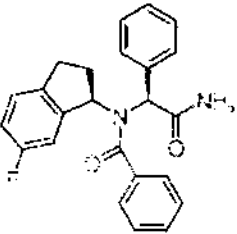
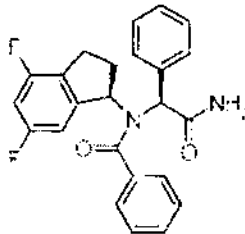
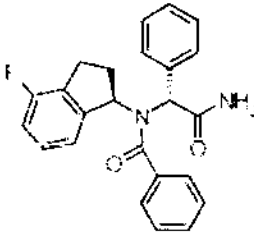
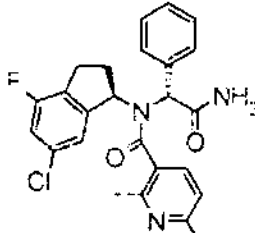
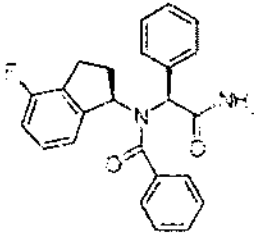
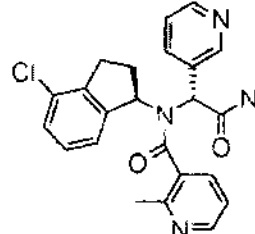
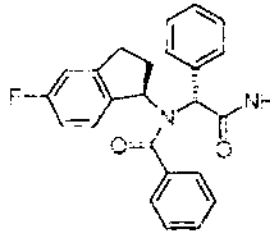
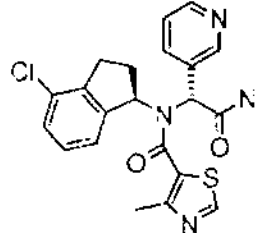
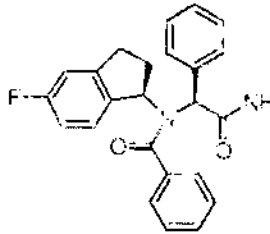
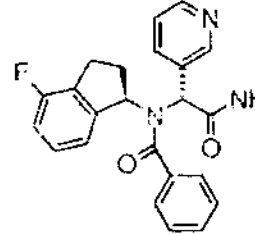
Chemical Name	Structure	Chemical Name	Structure
2-19612		2-19613	
2-19614		2-19615	
2-19616		2-19617	
2-19618		2-19619	
2-19620		2-19621	
2-19622		2-19623	

[0533]

[Table 24]

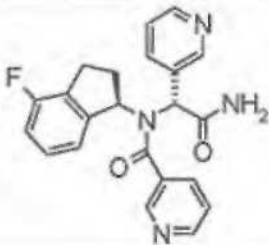
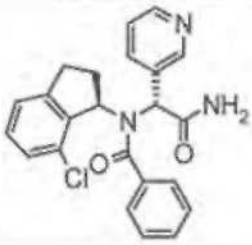
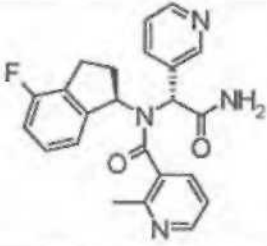
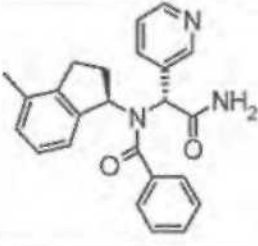
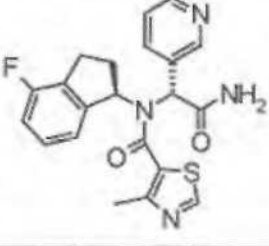
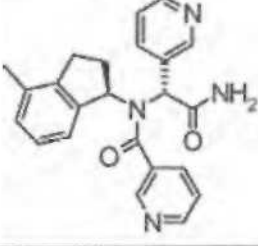
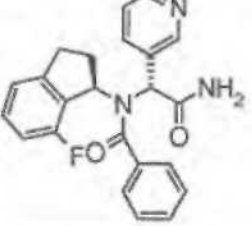
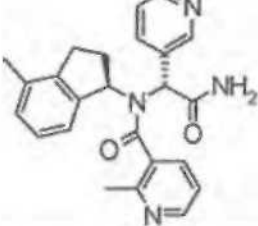
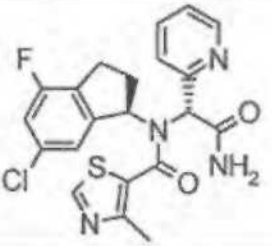
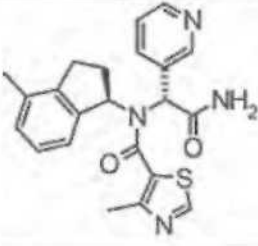
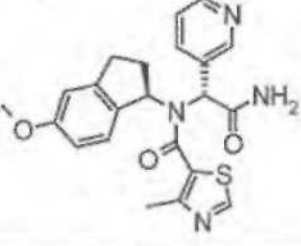
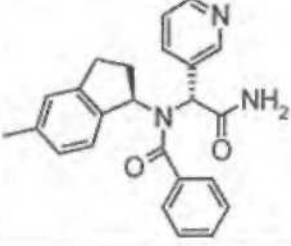
Ex. No.	Struc.	Ex. No.	Struc.
2-206LP		2-212LP	
2-207LP		2-213LP	
2-208LP		2-214LP	
2-209LP		2-215LP	
2-210LP		2-216LP	
2-211LP		2-217LP	

[Table 25]

Ex. No.	Struc.	Ex. No.	Struc.
2-2181P		2-2211P	
2-2181P		2-2211P	
2-2191P		2-2221P	
2-2191P		2-2231P	
2-2261P		2-2241P	
2-2261P		2-2251P	

[0535]

[Table 26]

Ex. No.	Strc.	Ex. No.	Strc.
2-226LP		2-232LP	
2-227LP		2-233LP	
2-228LP		2-234LP	
2-229LP		2-235LP	
2-230LP		2-236LP	
2-231LP		2-237LP	

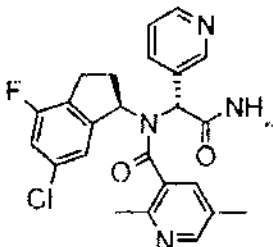
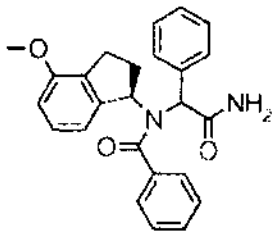
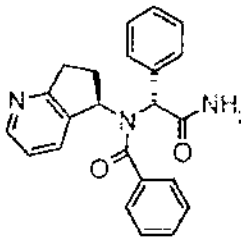
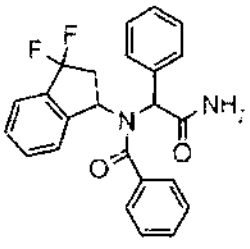
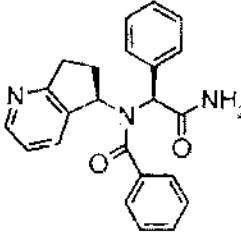
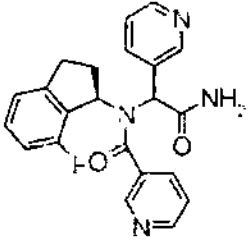
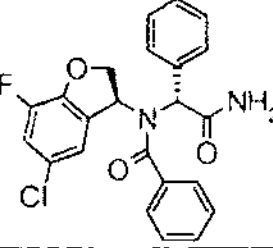
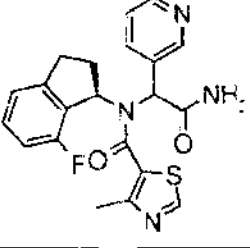
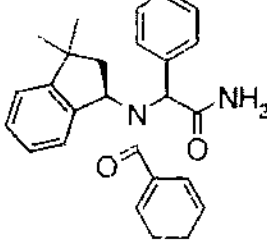
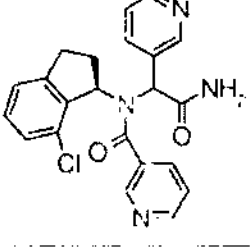
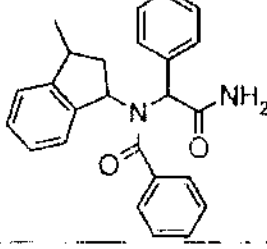
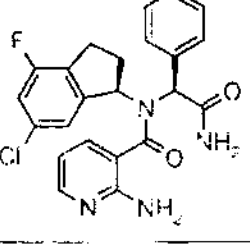
[0536]

[Table 27]

Ex. No.	Str.	Ex. No.	Str.
2-238LP		2-241LP	
2-239LP		2-245LP	
2-240LP		2-246LP	
2-241LP		2-247LP	
2-242LP		2-248LP	
2-243LP		2-249LP	

[0537]

[Table 28]

Ex. No.	Str.	Ex. No.	Str.
2-250LP		2-255M	
2-251LP		2-256M	
2-251BP		2-257M	
2-258M		2-258N	
2-259M		2-259N	
2-254M		2-260LP	

[0538]

[Table 29]

Ex. No.	Strc.	Ex. No.	Strc.
3-1		3-3	
3-2			

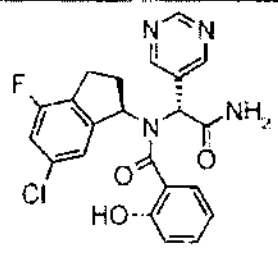
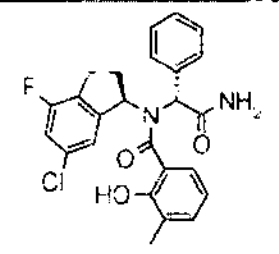
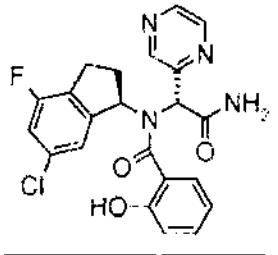
[0539]

[Table 30]

Ex. No.	Strc.	Ex. No.	Strc.
4-1		4-4	
4-2		4-5	
4-3		4-6	

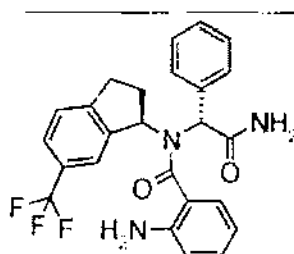
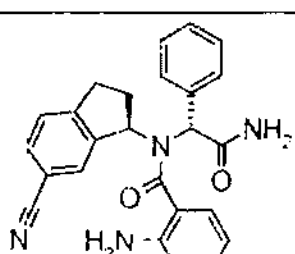
[0540]

[Table 31]

Ex. No.	Struc.	Ex. No.	Struc.
1-7		4-9	
1-8			

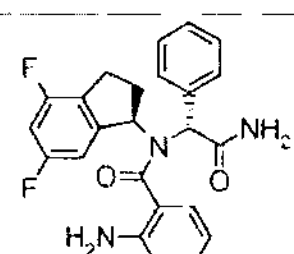
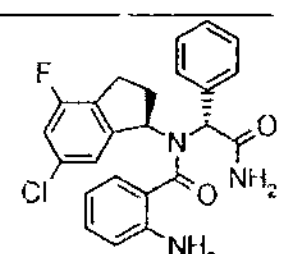
[0541]

[Table 32]

Ex. No.	Struc.	Ex. No.	Struc.
5-1		5-2	

[0542]

[Table 33]

Ex. No.	Struc.	Ex. No.	Struc.
6-1		6-2	

[0543]

[Table 34]

Ex. No.	Strc.	Ex. No.	Strc.
6-3		9	
6-4		10	
6-5		11	
7		12	
8-1		13	
8-2		14LP	

[0544]

[Table 35]

Ex. No.	Strc.	Ex. No.	Strc.
14HP		16	
15LP		17	
15HP			

[0545]

Reference Example 6-1

- 5 2-Acetyloxy-3-trifluoromethoxybenzoic acid

[0546]

To a mixture of 3-trifluoromethoxysalicylic acid (0.5g) and acetic anhydride (2mL) was added sulfuric acid (2drops), and the mixture was stirred for 1 hour at 80°C. The reaction mixture was allowed to cool to room temperature, and to the mixture was added ice. The insoluble compound was collected by filtration, and dried under reduced pressure to afford the title compound (0.519g). The structural formula is shown in Table 36.

[0547]

¹H-NMR(CDCl₃)δppm: 2.38 (3H, s), 7.36-7.42 (1H, m), 7.56-7.61 (1H, m), 8.05 (1H, dd, J=1.6, 8.0Hz).

- 15 [0548]

Reference Example 6-2

2-Acetyloxy-3-trifluoromethylbenzoic acid

The title compound was synthesized in a manner similar to that of Reference Example 6-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 36.

- 20

[0549]

¹H-NMR(CDCl₃)δppm: 2.38 (3H, s), 7.44-7.50 (1H, m), 7.90-7.94 (1H, m), 8.29-8.34 (1H, m).

[0550]

[Table 36]

Ref.Ex.	Strc.	Ref.Ex.	Strc.
6-1		6-2	

[0551]

Example 18-1 to 18-16

- 5 Examples 18-1 to 18-16 were synthesized in a manner similar to that of Example 2-1 by using the corresponding starting materials. The spectrum data of Examples 18-1 to 18-16 are shown as follows, and the structural formulae are shown in Tables 37 and 38.

[0552]

Example 18-1LP

- 10 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-difluoromethoxybenzamide

RT(min.): 2.793

MS(ESI, *m/z*) : 488.0998 (M-H)⁺

- 15 ¹H-NMR(DMSO-*d*₆)δppm: 1.22-1.37 (1H, m), 1.92-2.17 (1H, m), 2.50-2.70 (1H, m), 2.78-2.95 (1H, m), 4.78-5.45 (3H, m), 7.00-7.82 (10H, m), 8.43-8.67 (2H, m).

[0553]

Example 18-2LP

- 20 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-6-hydroxy-2-methylnicotinamide

RT(min.): 2.671

MS(ESI, *m/z*) : 452.1191 (M-H)⁺

¹H-NMR(DMSO-*d*₆)δppm: 1.05-1.35 (1H, m), 1.80-2.93 (6H, m), 4.88-5.19 (1H, m), 5.47-5.70 (1H, m), 6.23-6.31 (1H, m), 7.07-7.90 (10H, m), 11.70-12.04 (1H, m).

[0554]

- 25 Example 18-3LP

N-[(*R*)-Carbamoyl-(3-cyanophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide

RT(min.): 3.565

MS(ESI, *m/z*) : 476.1190 (M-H)⁺

- 30 ¹H-NMR(CDCl₃)δppm: 1.71-1.87 (1H, m), 2.26-2.40 (1H, m), 2.52-2.68 (1H, m), 2.79-2.93 (1H, m), 3.92 (1H, s), 4.04 (2H, m), 4.67-4.81 (1H, m), 5.33-6.81 (3H, m), 6.94-7.15 (3H, m), 7.37-7.57 (4H, m), 7.60-7.78 (2H, m), 8.03 (1H, br s).

[0555]

Example 18-4LP

- 35 *N*-[(*R*)-Carbamoyl-(3-cyanophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.655

MS(ESI, *m/z*) : 461.1196 (M-H)⁺

- 40 ¹H-NMR(CDCl₃)δppm: 1.56-1.78 (1H, m), 2.06-2.18 (1H, m), 2.47-2.89 (5H, m), 4.59-4.82 (1H, m), 5.19-5.80 (3H, m), 6.98-7.08 (1H, m), 7.19-7.29 (1H, m), 7.50-7.98 (6H, m), 8.53-8.68 (1H, br).

[0556]

Example 18-5LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-cyanobenzamide

5 RT(min.): 2.539

MS(ESI, *m/z*) : 447.1042 (*M*-H)⁺¹H-NMR(CDCl₃)δppm: 1.70-1.90 (1H, m), 2.00-2.22 (1H, m), 2.50-2.94 (2H, m), 4.62-4.93 (1H, m), 5.25-5.77 (3H, m), 6.96-7.09 (1H, m), 7.37-7.45 (1H, m), 7.54-7.65 (1H, m), 7.70-8.06 (5H, m), 8.58-8.75 (2H, m).

10 [0557]

Example 18-6LP

N-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-cyanobenzamide

RT(min.): 3.598

MS(ESI, *m/z*) : 446.1086 (*M*-H)⁺15 ¹H-NMR(CDCl₃)δppm: 1.67-2.13 (2H, m), 2.45-2.88 (2H, m), 4.53-5.80 (4H, m), 6.88-7.08 (1H, m), 7.35-7.65 (6H, m), 7.67-7.89 (4H, m).

[0558]

Example 18-7LP

N-[(*R*)-Carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-cyanobenzamide

20 RT(min.): 2.931

MS(ESI, *m/z*) : 448.0990 (*M*-H)⁺25 ¹H-NMR(CDCl₃)δppm: 2.00-2.15 (1H, m), 2.32-2.53 (1H, m), 2.61-2.74 (1H, m), 2.84-3.04 (1H, m), 4.73-4.93 (1H, m), 5.36-5.77 (3H, m), 6.97-7.07 (1H, m), 7.50-7.68 (2H, m), 7.75-7.82 (1H, m), 7.83-7.95 (2H, m), 8.52-8.63 (2H, m), 8.81 (1h, br s).

[0559]

Example 18-8LP

N-[(*R*)-Carbamoyl-(3-hydroxymethylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

30 RT(min.): 2.195

MS(ESI, *m/z*) : 512.1410 (*M*+HCO₂)⁺¹H-NMR(CDCl₃)δppm: 1.38-2.18 (3H, m), 2.38-3.13 (5H, m), 4.55-5.00 (3H, m), 5.15-5.24 (1H, m), 5.37-5.72 (2H, m), 6.83-7.03 (1H, m), 7.16-7.83 (7H, m), 8.52-8.60 (1H, m).

[0560]

35 Example 18-9LP

N-[(*R*)-Carbamoyl-(3-carbamoylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 1.969

MS(ESI, *m/z*) : 525.1359 (*M*+HCO₂)⁺40 ¹H-NMR(CDCl₃)δppm: 1.36-1.78 (1H, m), 2.00-2.12 (1H, m), 2.43-3.13 (5H, m), 4.62-4.98 (1H, m), 5.17-5.28 (1H, m), 5.32-6.50 (4H, m), 6.84-7.05 (1H, m), 7.17-7.32 (1H, m), 7.41-7.89 (5H, m), 7.94-8.11 (1H, m), 8.52-8.64 (1H, m).

[0561]

Example 18-10LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-cyanothiophene-2-carboxamide

45 RT(min.): 2.485

MS(ESI, *m/z*) : 453.0600 (*M*-H)⁺¹H-NMR(CDCl₃)δppm: 1.80-1.93 (1H, m), 2.08-2.36 (1H, m), 2.64-2.79 (1H, m), 2.89-

3.00 (1H, m), 4.57-4.98 (1H, m), 5.41-5.99 (3H, m), 7.00-7.12 (1H, m), 7.34-7.43 (1H, m), 7.57 (1H, s), 7.73 (1H, s), 7.85-7.95 (1H, m), 8.08-8.13 (1H, m), 8.61-8.70 (2H, m).

[0562]

Example 18-11LP

- 5 {3-[(*R*)-Carbamoyl-{*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-*N*-(2-methylpyridin-3-carbonyl)amino}methyl]benzyl} carbamic acid *tert*-butyl ester

RT(min.): 3.089

MS(ESI, *m/z*) : 611.2092 (*M*+HCO₂)⁺

- 10 ¹H-NMR(CDCl₃)δppm: 1.45 (9H, s), 1.63-1.82 (1H, m), 1.95-2.11 (1H, m), 2.41-3.13 (5H, m), 4.25-4.42 (2H, m), 4.55-5.05 (2H, m), 5.15-5.23 (1H, m), 5.38-5.65 (2H, m), 6.85-7.03 (1H, m), 7.15-7.53 (5H, m), 7.59-7.83 (2H, m), 8.53-8.61 (1H, m).

[0563]

Example 18-12LP

- 15 *N*-[(*R*)-Carbamoyl-(3-nitrophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.836

MS(ESI, *m/z*) : 481.1092 (*M*-H)⁺

- 20 ¹H-NMR(CDCl₃)δppm: 1.63-1.79 (1H, m), 2.09-2.22 (1H, m), 2.49-2.89 (5H, m), 4.72-4.89 (1H, m), 5.22-5.32 (1H, m), 5.38-6.00 (2H, m), 6.87-7.07 (1H, m), 7.56-7.97 (4H, m), 8.20-8.67 (3H, m).

[0564]

Example 18-13LP

- 25 *N*-[(*R*)-Carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

RT(min.): 2.572

MS(ESI, *m/z*) : 479.1655 (*M*-H)⁺

- 30 ¹H-NMR(CDCl₃)δppm: 1.73-2.20 (2H, m), 2.41-2.55 (1H, m), 2.60-2.86 (4H, m), 2.92-3.02 (6H, m), 4.45-5.70 (4H, m), 6.44-7.05 (4H, m), 7.15-7.32 (2H, m), 7.48-7.84 (2H, m), 8.52-8.60 (1H, m).

[0565]

Example 18-14LP

- 35 *N*-[(*R*)-Carbamoylphenylmethyl]-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]-2-methylnicotinamide

RT(min.): 2.298

MS(ESI, *m/z*) : 422.1331 (*M*-H)⁺

¹H-NMR(CDCl₃)δppm: 2.35-2.83 (3H, m), 3.81-4.95 (3H, m), 5.22-5.81 (3H, m), 6.64-6.88 (1H, m), 7.09-7.73 (8H, m), 8.44-8.65 (1H, m).

[0566]

Example 18-15M

- 40 *N*-(Carbamoylpyridin-3-ylmethyl)-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]-2-methylnicotinamide

RT(min.): 0.838

MS(ESI, *m/z*) : 423.1277 (*M*-H)⁺

RT(min.): 0.937

- 45 MS(ESI, *m/z*) : 423.1278 (*M*-H)⁺

¹H-NMR(CDCl₃)δppm: 2.36-2.90 (3H, m), 4.08-4.88 (2H, m), 5.20-6.22 (4H, m), 6.68-6.91 (1H, m), 7.08-8.95 (8H, m).

[0567]

Example 18-16LP

N-[*(R)*-Carbamoylphenyl-3-ylmethyl]-N-[*(S)*-5-chloro-7-fluoro-2,3-dihydrobenzodioxin-3-yl]-2-methylnicotinamide

RT (min.): 2.576

MS(ESI, m/z): 458, 1054 (M-H)⁺

¹H-NMR(CDCl₃, δppm): 2.38-2.83 (3H, m), 3.84-4.31 (2H, m), 5.20-5.63 (4H, m), 6.80-7.77 (9H, m), 8.43-8.63 (1H, m).

[0568]

Example 19-11 P

N-[*(R)*-Carbamoylpyridin-3-ylmethyl]-N-[*(R)*-6-chloro-4-fluorindan-1-yl]-2-hydroxybenzamide

To a solution of *(R)*-6-chloro-4-fluorindan-1-ylamine hydrochloride (6.66 g in methanol (100 ml)) were added triethylamine (4.80 ml) and 3-formylpyridine (3.24 g), and the mixture was stirred for 1 hour at 60°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added acetylsalicylic acid (5.41 g) and 4-phenylcyclohexen-1-ylisocyanide (5.50 g). The mixture was stirred overnight at 60°C, then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added 1,4-dioxane (150 ml), water (30 ml) and a solution of 4 mol/L hydrogen chloride in 1,4-dioxane (30 ml), and the mixture was stirred for 3 hours at room temperature. To the reaction mixture was added a saturated aqueous solution of sodium bicarbonate, and the crude product was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by aminopropyl silica gel column chromatography (eluent: ethyl acetate : methanol = 5 : 1) to afford a mixture of diastereomers. The mixture was purified by silica gel column chromatography (eluent: dichloromethane : diethyl ether : methanol = 10 : 10 : 1) to afford the title compound (4.20 g) as low polarity product. The structural formula is shown in Table 39.

¹H-NMR(CDCl₃, δppm): 1.70-2.38 (2H, m), 2.53-2.94 (2H, m), 4.45-5.10 (1H, m), 5.27-6.41 (3H, m), 6.88-7.04 (3H, m), 7.27-7.35 (2H, m), 7.36-7.42 (1H, m), 7.51-7.54 (1H, m), 7.88-8.05 (1H, m), 8.67 (1H, dd, J = 1.5, 4.8 Hz), 8.71-8.77 (1H, m), 9.10-9.75 (1H, m).

[0569]

Example 19-2 to 19-41

Examples 19-2 to 19-41 were synthesized in a manner similar to that of Example 19-1 by using the corresponding starting materials. The spectrum data of Examples 19-2 to 19-41 are shown as follows, and the structural formulae are shown in Tables 39 to 42.

[0570]

Example 19-21 P

N-[*(R)*-Carbamoyl-(3-cyanophenyl)methyl]-N-[*(R)*-6-chloro-4-fluorindan-1-yl]-2-hydroxybenzamide

RT (min.): 3.270

MS(ESI, m/z): 462, 1035 (M-H)⁺

¹H-NMR(CDCl₃, δppm): 1.67-1.83 (1H, m), 1.98-2.33 (1H, m), 2.55-2.92 (2H, m), 4.54-5.07 (1H, m), 5.31-6.00 (3H, m), 6.92-7.07 (3H, m), 7.31-7.40 (2H, m), 7.50-7.61 (2H, m), 7.65-7.76 (2H, m), 7.78-7.90 (1H, m), 8.23-8.60 (1H, br).

[0571]

Example 19-31 P

N-[*(R)*-Carbamoyl-(3-carbamoylphenyl)methyl]-N-[*(R)*-6-chloro-4-fluorindan-1-yl]-2-hydroxybenzamide

RT (min.): 2.588

MS(ESI, m/z): 480, 1143 (M-H)⁺

¹H-NMR(DMSO-d₆, δppm): 1.09-1.21 (1H, m), 1.97-2.41 (1H, m), 2.46-3.59 (1H, m), 2.76-

2.87 (1H, m), 5.01-5.11 (1H, m), 5.45 (1H, br s), 6.85-6.95 (2H, m), 7.06-7.30 (4H, m), 7.37-7.69 (5H, m), 7.82-7.93 (2H, m), 8.05 (1H, br s), 10.09 (1H, br s).

[0572]

Example 19-4LP

5 *N*-[(*R*)-Carbamoyl-(3-hydroxymethylphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.774

MS(ESI, *m/z*): 467.1188 (M-H)⁺

10 ¹H-NMR(DMSO-*d*₆)δppm: 1.10-1.27 (1H, m), 1.99-2.12 (1H, m), 2.46-2.58 (1H, m), 2.76-3.02 (1H, m), 4.51 (2H, d, *J*=5.6Hz), 5.00-5.11 (1H, m), 5.26 (1H, t, *J*=5.6Hz), 5.41 (1H, br s), 6.82-6.95 (2H, m), 6.98-7.63 (10H, m), 10.04 (1H, br s).

[0573]

Example 19-5LP

15 *N*-[(*R*)-Carbamoyl-(3-nitrophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 3.369

MS(ESI, *m/z*): 482.0940 (M-H)⁺

20 ¹H-NMR(DMSO-*d*₆)δppm: 1.14-1.33 (1H, m), 1.96-2.12 (1H, m), 2.46-2.62 (1H, m), 2.77-2.90 (1H, m), 4.97-5.58 (2H, m), 6.81-7.00 (2H, m), 7.06-8.45 (10H, m), 10.18-10.28 (1H, m).

[0574]

Example 19-6LP

25 *N*-[(*R*)-Carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.811

MS(ESI, *m/z*): 480.1507 (M-H)⁺

30 ¹H-NMR(DMSO-*d*₆)δppm: 1.21-1.35 (1H, m), 2.03-2.17 (1H, m), 2.47-2.61 (1H, m), 2.78-2.96 (7H, m), 5.02-5.13 (1H, m), 5.33 (1H, br s), 6.57-6.76 (3H, m), 6.83-6.95 (2H, m), 7.02-7.28 (5H, m), 7.42 (1H, br s), 7.58 (1H, br s), 10.02 (1H, br s).

[0575]

Example 19-7LP

35 *N*-[(*R*)-Carbamoyl-(3-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.916

MS(ESI, *m/z*): 453.1037 (M-H)⁺

¹H-NMR(DMSO-*d*₆)δppm: 1.21-1.34 (1H, m), 2.05-2.18 (1H, m), 2.46-2.61 (1H, m), 2.79-2.91 (1H, m), 5.01-5.11 (1H, m), 5.32 (1H, br s), 6.70-6.80 (3H, m), 6.84-6.94 (2H, m), 7.05-7.30 (5H, m), 7.46 (1H, br s), 7.56 (1H, br s), 9.56 (1H, br s), 10.03 (1H, br s).

[0576]

40 Example 19-8LP

{3-[(*R*)-Carbamoyl-{*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-*N*-(2-hydroxybenzoyl)amino}methyl]benzyl}carbamic acid *tert*-butyl ester

RT(min.): 3.584

MS(ESI, *m/z*): 566.1879 (M-H)⁺

45 ¹H-NMR(CDCl₃)δppm: 1.44 (9H, s), 1.71-1.89 (1H, m), 1.97-2.27 (1H, m), 2.49-2.93 (2H, m), 4.32 (2H, d, *J*=5.9Hz), 4.45-5.95 (5H, m), 6.89-7.08 (3H, m), 7.25-7.47 (6H, m), 7.64 (1H, s), 8.45-8.89 (1H, m).

[0577]

Example 19-9HP

N-[(*S*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.021

MS(ESI, *m/z*) : 438.1034 (M-H)⁺

- 5 ¹H-NMR(CDCl₃)δppm: 2.47-2.68 (2H, m), 2.73-2.85 (1H, m), 3.08-3.19 (1H, m), 4.52 (1H, br s), 5.50-5.59 (1H, m), 5.84 (1H, br s), 6.04 (1H, br s), 6.46 (1H, br s), 6.83-7.02 (3H, m), 7.28-7.36 (3H, m), 7.92-7.97 (1H, m), 8.37-8.41 (1H, m), 8.54-8.58 (1H, m), 9.10 (1H, br).

[0578]

Example 19-10M

- 10 *N*-(Carbamoylpyridin-3-ylmethyl)-*N*-[(*S*)-5,7-difluoro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide

RT(min.): 1.537

MS(ESI, *m/z*) : 424.1128 (M-H)⁺

RT(min.): 1.614

- 15 MS(ESI, *m/z*) : 424.1119 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 4.30-5.15 (3H, m), 5.55-6.57 (3H, m), 6.66-6.88 (1H, m), 6.91-7.01 (2H, m), 7.04-7.44 (4H, m), 7.81-8.02 (1H, m), 8.25-8.86 (2H, m).

[0579]

Example 19-11LP

- 20 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-5-methylbenzamide

RT(min.): 2.416

MS(ESI, *m/z*) : 452.1193 (M-H)⁺

- 25 ¹H-NMR(CDCl₃)δppm: 1.75-1.92 (1H, m), 2.17-2.40 (4H, m), 2.56-2.67 (1H, m), 2.73-2.93 (1H, m), 4.60-4.97 (1H, m), 5.46-5.95 (2H, m), 6.20-6.55 (1H, m), 6.81 (1H, d, *J*=8.1Hz), 6.94-7.03 (1H, m), 7.05-7.13 (2H, m), 7.35-7.41 (1H, m), 7.49 (1H, s), 7.96 (1H, br s), 8.58-8.63 (1H, m), 8.73 (1H, s), 9.20 (1H, br).

[0580]

Example 19-12LP

- 30 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-methylbenzamide

RT(min.): 2.416

MS(ESI, *m/z*) : 452.1195 (M-H)⁺

- 35 ¹H-NMR(CDCl₃)δppm: 1.75-1.92 (1H, m), 2.00-2.41 (4H, m), 2.55-2.68 (1H, m), 2.78-2.94 (1H, m), 4.60-5.02 (1H, m), 5.46-6.31 (3H, m), 6.71-6.76 (1H, m), 6.79 (1H, s), 6.96-7.03 (1H, m), 7.23 (1H, d, *J*=7.9Hz), 7.35-7.40 (1H, m), 7.54 (1H, s), 7.94 (1H, br s), 8.59-8.64 (1H, m), 8.69 (1H, s), 9.22 (1H, br).

[0581]

Example 19-13LP

- 40 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methoxybenzamide

RT(min.): 2.295

MS(ESI, *m/z*) : 468.1145 (M-H)⁺

- 45 ¹H-NMR(CDCl₃)δppm: 1.77-1.94 (1H, m), 2.22-2.42 (1H, m), 2.54-2.66 (1H, m), 2.77-2.95 (1H, m), 3.92 (3H, s), 4.66-4.83 (1H, m), 5.42-6.82 (3H, m), 6.90-7.03 (4H, m), 7.30-7.37 (1H, m), 7.53 (1H, s), 7.98 (1H, br s), 8.56-8.61 (1H, m), 8.67 (1H, s).

[0582]

Example 19-14LP

- 50 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-isopropylbenzamide

RT(min.): 3.092

MS(ESI, m/z) : 480.1507 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.25 (6H, t, J=6.9Hz), 1.69-2.38 (2H, m), 2.55-2.68 (1H, m), 2.75-2.94 (1H, m), 3.38 (1H, septet, J=6.9Hz), 4.59-4.92 (1H, m), 5.47-5.90 (3H, m), 6.80-6.92 (1H, m), 6.97-7.04 (1H, m), 7.18 (1H, dd, J=1.6, 7.7Hz), 7.30 (1H, dd, J=1.4, 7.7Hz), 7.36-7.40 (1H, m), 7.63 (1H, s), 7.99 (1H, br s), 8.60-8.83 (3H, m).

[0583]

Example 19-15LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-fluoro-6-hydroxybenzamide

RT(min.): 2.311

MS(ESI, m/z) : 456.0944 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.50-2.00 (1H, m), 2.24-2.94 (3H, m), 4.60-4.88 (1H, m), 5.45-5.94 (3H, m), 6.58-6.84 (2H, m), 6.96-7.07 (1H, m), 7.12-7.56 (3H, m), 7.77-8.17 (1H, m), 8.51-9.07 (2H, m).

[0584]

Example 19-16LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-fluoro-2-hydroxybenzamide

RT(min.): 2.361

MS(ESI, m/z) : 456.0941 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.70-1.90 (1H, m), 1.98-2.39 (1H, m), 2.56-2.69 (1H, m), 2.78-2.93 (1H, m), 4.64-5.05 (1H, m), 5.43-6.33 (3H, m), 6.60-6.71 (2H, m), 6.97-7.05 (1H, m), 7.31 (1H, dd, J=6.4, 8.4Hz), 7.38-7.44 (1H, m), 7.51 (1H, s), 7.92-7.99 (1H, m), 8.63 (1H, dd, J=1.4, 4.9Hz), 8.72-8.76 (1H, m).

[0585]

Example 19-17LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-4-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.589

MS(ESI, m/z) : 472.0653 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.70-1.90 (1H, m), 2.12-2.39 (1H, m), 2.56-2.69 (1H, m), 2.78-2.93 (1H, m), 4.64-5.00 (1H, m), 5.38-6.41 (3H, m), 6.87-7.06 (3H, m), 7.22-7.28 (1H, m), 7.42 (1H, dd, J=4.9, 8.0Hz), 7.48 (1H, s), 7.91-8.00 (1H, m), 8.62 (1H, dd, J=1.4, 4.8Hz), 8.76 (1H, s).

[0586]

Example 19-18LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-nitrobenzamide

RT(min.): 2.510

MS(ESI, m/z) : 483.0887 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.70-1.90 (1H, m), 2.25-2.42 (1H, m), 2.56-2.68 (1H, m), 2.75-2.89 (1H, m), 4.73-4.86 (1H, m), 5.33-5.47 (1H, m), 5.79-6.21 (2H, m), 6.97-7.06 (1H, m), 7.43-7.54 (3H, m), 7.75-7.83 (2H, m), 7.97-8.06 (1H, m), 8.66-8.70 (1H, m), 8.86 (1H, br s).

[0587]

Example 19-19LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-methoxybenzamide

RT(min.): 2.297

MS(ESI, m/z) : 468.1145 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.78-1.92 (1H, m), 1.97-2.33 (1H, m), 2.59-2.71 (1H, m), 2.84-2.96 (1H, m), 3.81 (3H, s), 4.67-5.07 (1H, m), 5.50-6.18 (3H, m), 6.47 (1H, dd, J=2.5, 8.7Hz), 6.53 (1H, d, J=2.5Hz), 6.99-7.04 (1H, m), 7.32 (1H, d, J=8.7Hz), 7.37 (1H, dd, J=4.8, 7.9Hz), 7.60 (1H, s), 7.85-7.96 (1H, m), 8.60-8.67 (2H, m), 9.69 (1H, br s).

[0588]

Example 19-20LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-3-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.523

MS(ESI, m/z) : 472.0646 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.50-2.40 (2H, m), 2.54-2.65 (1H, m), 2.76-2.90 (1H, m), 4.65-4.90 (1H, m), 5.30-5.52 (1H, m), 5.76-6.23 (2H, m), 6.90-7.03 (2H, m), 7.24-7.28 (1H, m), 7.36 (1H, dd, J=4.8, 7.9Hz), 7.40 (1H, dd, J=1.5, 8.0Hz), 7.56 (1H, s), 7.91-8.01 (1H, m), 8.56-8.61 (1H, m), 8.66-8.69 (1H, m).

[0589]

Example 19-21LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-trifluoromethylbenzamide

RT(min.): 2.813

MS(ESI, m/z) : 506.0924 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.65-1.90 (1H, m), 2.22-2.42 (1H, m), 2.55-2.67 (1H, m), 2.73-2.89 (1H, m), 4.71-4.88 (1H, m), 5.37-5.51 (1H, m), 5.94-6.52 (2H, m), 6.95-7.05 (1H, m), 7.12-7.21 (2H, m), 7.37-7.46 (2H, m), 7.48 (1H, s), 7.91-8.02 (1H, m), 8.58-8.62 (1H, m), 8.82 (1H, br s).

[0590]

Example 19-22LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluoro-2-hydroxybenzamide

RT(min.): 2.341

MS(ESI, m/z) : 456.0941 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.65-1.91 (1H, m), 2.15-2.45 (1H, m), 2.56-2.69 (1H, m), 2.74-2.91 (1H, m), 4.65-4.86 (1H, m), 5.40-5.61 (1H, m), 5.83-6.46 (2H, m), 6.86 (1H, dd, J=4.3, 8.9Hz), 6.94-7.04 (3H, m), 7.40 (1H, dd, J=4.9, 8.0Hz), 7.48 (1H, s), 7.90-8.01 (1H, m), 8.57-8.63 (1H, m), 8.75 (1H, br s).

[0591]

Example 19-23LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-trifluoromethoxybenzamide

RT(min.): 2.789

MS(ESI, m/z) : 522.0866 (M-H)⁺

¹H-NMR(CDCl₃)δppm: 1.65-1.93 (1H, m), 2.15-2.39 (1H, m), 2.55-2.67 (1H, m), 2.74-2.91 (1H, m), 4.66-4.90 (1H, m), 5.35-5.53 (1H, m), 5.70-6.21 (2H, m), 6.92-7.04 (2H, m), 7.25-7.33 (2H, m), 7.38 (1H, dd, J=4.9, 8.1Hz), 7.52 (1H, s), 7.93-8.04 (1H, m), 8.59-8.63 (1H, m), 8.69-8.73 (1H, m).

[0592]

Example 19-24LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-hydroxyisonicotinamide

RT(min.): 1.394

MS(ESI, m/z) : 439.0989 (M-H)⁻

¹H-NMR(DMSO-d₆)δppm: 1.21-2.13 (2H, m), 2.47-3.01 (2H, m), 5.01-5.45 (2H, m), 7.08-7.61 (6H, m), 7.68-7.92 (1H, m), 8.11-8.33 (2H, m), 8.47-8.67 (2H, m), 10.2-11.1 (1H, m).

[0593]

5 Example 19-25LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-fluoro-2-hydroxybenzamide

RT(min.): 2.252

MS(ESI, m/z) : 456.0941 (M-H)⁻

10 ¹H-NMR(CDCl₃)δppm: 1.86-3.06 (4H, m), 4.06-5.36 (2H, m), 5.50 (1H, br s), 6.56 (1H, br s), 6.75-7.44 (6H, m), 7.80-8.08 (1H, m), 8.58-8.66 (1H, m), 8.69-8.76 (1H, m).

[0594]

Example 19-26LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-5-methoxybenzamide

15 RT(min.): 2.240

MS(ESI, m/z) : 468.1144 (M-H)⁻

¹H-NMR(CDCl₃)δppm: 1.72-1.88 (1H, m), 2.00-2.39 (1H, m), 2.55-2.67 (1H, m), 2.74-2.92 (1H, m), 3.74 (3H, s), 4.60-4.95 (1H, m), 5.40-6.32 (3H, m), 6.82-6.89 (3H, m), 6.96-7.02 (1H, m), 7.35-7.41 (1H, m), 7.54 (1H, s), 7.92-8.01 (1H, m), 8.50-8.98 (3H, m).

[0595]

Example 19-27LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-5-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

25 RT(min.): 2.525

MS(ESI, m/z) : 472.0644 (M-H)⁻

¹H-NMR(CDCl₃)δppm: 1.70-1.90 (1H, m), 2.15-2.45 (1H, m), 2.57-2.70 (1H, m), 2.75-2.91 (1H, m), 4.60-4.97 (1H, m), 5.39-5.60 (1H, m), 5.70-6.38 (2H, m), 6.87 (1H, d, J=8.6Hz), 6.97-7.04 (1H, m), 7.21-7.28 (2H, m), 7.41 (1H, dd, J=4.9, 8.0Hz), 7.46 (1H, br s), 7.93-8.05 (1H, m), 8.60-8.66 (1H, m), 8.72-8.76 (1H, m).

[0596]

Example 19-28LP

5-Acetyl-*N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

35 RT(min.): 2.083

MS(ESI, m/z) : 480.1145 (M-H)⁻

¹H-NMR(CDCl₃)δppm: 1.75-1.92 (1H, m), 2.15-2.45 (1H, m), 2.52 (3H, s), 2.56-2.70 (1H, m), 2.75-2.91 (1H, m), 4.65-4.99 (1H, m), 5.39-5.58 (1H, m), 5.70-6.30 (2H, m), 6.96-7.03 (2H, m), 7.44 (1H, dd, J=4.9, 8.0Hz), 7.50 (1H, br s), 7.86-8.08 (3H, m), 8.65 (1H, d, J=4.5Hz), 8.75 (1H, br s).

[0597]

Example 19-29LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-ethoxy-2-hydroxybenzamide

45 RT(min.): 2.485

MS(ESI, m/z) : 482.1299 (M-H)⁻

¹H-NMR(CDCl₃)δppm: 1.41 (3H, t, J=7.0Hz), 1.79-2.36 (2H, m), 2.59-2.72 (1H, m), 2.84-2.97 (1H, m), 4.03 (2H, q, J=7.0Hz), 4.65-5.14 (1H, m), 5.50-6.20 (3H, m), 6.45 (1H, dd, J=2.4, 8.7Hz), 6.51 (1H, d, J=2.4Hz), 6.98-7.04 (1H, m), 7.30 (1H, d, J=8.7Hz), 7.36 (1H, dd, J=4.8, 8.0Hz), 7.59 (1H, s), 7.85-7.94 (1H, m), 8.60-8.67 (2H, m), 9.67 (1H, br).

50

[0598]

Example 19-30LP

5-Acetylamino-*N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

5 RT(min.): 1.746

MS(ESI, *m/z*) : 495.1254 (M-H)⁺¹H-NMR(CD₃OD)δppm: 1.33-2.36 (5H, m), 2.55-3.06 (2H, m), 4.85-5.78 (2H, m), 6.83-7.61 (5H, m), 7.64 (1H, s), 7.91-8.09 (1H, m), 8.48-8.71 (2H, m).

[0599]

10 Example 19-31LP

N-[(*R*)-Carbamoyl(5-fluoropyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.881

MS(ESI, *m/z*) : 456.0943 (M-H)⁺15 ¹H-NMR(CDCl₃)δppm: 1.70-1.89 (1H, m), 2.14-2.38 (1H, m), 2.58-2.70 (1H, m), 2.79-2.92 (1H, m), 4.67-4.95 (1H, m), 5.49-6.34 (3H, m), 6.91-6.97 (2H, m), 6.99-7.04 (1H, m), 7.28-7.35 (2H, m), 7.50 (1H, s), 7.76-7.86 (1H, m), 8.46-8.51 (2H, m), 8.90 (1H, br).

[0600]

Example 19-32LP

20 *N*-[(*R*)-Carbamoyl(5-methoxypyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.520

MS(ESI, *m/z*) : 468.1147 (M-H)⁺25 ¹H-NMR(CDCl₃)δppm: 1.73-1.91 (1H, m), 2.01-2.36 (1H, m), 2.55-2.68 (1H, m), 2.77-2.93 (1H, m), 3.88 (3H, s), 4.64-4.94 (1H, m), 5.47-6.10 (3H, m), 6.89-6.95 (1H, m), 6.96-7.05 (2H, m), 7.29-7.36 (2H, m), 7.53-7.63 (2H, m), 8.24 (1H, d, *J*=1.8Hz), 8.32 (1H, d, *J*=2.8Hz), 8.94 (1H, br).

[0601]

Example 19-33LP

30 *N*-[(*R*)-Carbamoyl(5-methylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.185

MS(ESI, *m/z*) : 452.1190 (M-H)⁺35 ¹H-NMR(CDCl₃)δppm: 1.77-1.93 (1H, m), 2.12-2.46 (4H, m), 2.55-2.68 (1H, m), 2.76-2.93 (1H, m), 4.60-4.98 (1H, m), 5.40-6.43 (3H, m), 6.88-7.04 (3H, m), 7.24-7.37 (2H, m), 7.51 (1H, s), 7.76 (1H, br s), 8.44 (1H, s), 8.54 (1H, br s), 9.57 (1H, br).

[0602]

Example 19-34LP

40 *N*-[(*R*)-Carbamoyl(5-trifluoromethylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 3.266

MS(ESI, *m/z*) : 506.0909 (M-H)⁺45 ¹H-NMR(CDCl₃)δppm: 1.71-1.87 (1H, m), 2.10-2.43 (1H, m), 2.59-2.72 (1H, m), 2.81-2.94 (1H, m), 4.79-5.00 (1H, m), 5.51-6.58 (3H, m), 6.89-6.98 (2H, m), 6.99-7.04 (1H, m), 7.27-7.35 (2H, m), 7.45 (1H, s), 8.20 (1H, s), 8.75-8.98 (3H, m).

[0603]

Example 19-35LP

50 *N*-[(*R*)-Carbamoyl(6-trifluoromethylpyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 3.395

MS(ESI, m/z) : 506.0911 (M-H)⁻

¹H-NMR(DMSO-d₆)δppm: 1.21-1.79 (1H, m), 2.00-2.17 (1H, m), 2.45-2.92 (2H, m), 4.89-5.62 (2H, m), 6.69-8.22 (10H, m), 8.65-8.87 (1H, m), 10.14-10.43 (1H, m).

[0604]

5 Example 19-36LP

N-[(*R*)-Carbamoyl(5-chloropyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 3.077

MS(ESI, m/z) : 472.0647 (M-H)⁻

10 ¹H-NMR(CDCl₃)δppm: 1.72-1.89 (1H, m), 2.16-2.38 (1H, m), 2.58-2.70 (1H, m), 2.81-2.94 (1H, m), 4.65-4.96 (1H, m), 5.47-6.45 (3H, m), 6.91-6.96 (2H, m), 6.98-7.03 (1H, m), 7.28-7.35 (2H, m), 7.48 (1H, s), 8.00 (1H, br s), 8.55-8.59 (2H, m), 9.00 (1H, br).

[0605]

15 Example 19-37LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*S*)-5-chloro-7-fluoro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide

RT(min.): 1.942

MS(ESI, m/z) : 440.0827 (M-H)⁻

20 ¹H-NMR(CDCl₃)δppm: 4.32-5.01 (3H, m), 5.56-6.60 (3H, m), 6.92-7.00 (2H, m), 7.04-7.11 (1H, m), 7.26-7.37 (3H, m), 7.43 (1H, dd, J=4.8, 8.0Hz), 7.89-8.02 (1H, m), 8.61-8.65 (1H, m), 8.84 (1H, br s), 10.25 (1H, br).

[0606]

25 Example 19-38LP

N-[(*R*)-Carbamoyl(5-hydroxypyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.133

MS(ESI, m/z) : 454.0983 (M-H)⁻

30 ¹H-NMR(DMSO-d₆)δppm: 1.21-1.39 (1H, m), 2.02-2.17 (1H, m), 2.42-2.93 (2H, m), 4.97-5.44 (2H, m), 6.83-6.96 (2H, m), 7.05-7.70 (7H, m), 7.96-8.15 (2H, m), 10.12 (1H, br).

[0607]

35 Example 19-39LP

N-[(*R*)-Carbamoyl(5-cyanopyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.915

MS(ESI, m/z) : 463.0988 (M-H)⁻

40 ¹H-NMR(CDCl₃)δppm: 1.70-1.86 (1H, m), 2.21-2.45 (1H, m), 2.61-2.73 (1H, m), 2.81-2.94 (1H, m), 4.71-4.90 (1H, m), 5.47-5.64 (1H, m), 5.71-6.70 (2H, m), 6.88 (1H, d, J=8.2Hz), 6.94-7.06 (2H, m), 7.27-7.35 (2H, m), 7.41 (1H, s), 8.28 (1H, br s), 8.52-8.96 (3H, m).

[0608]

45 Example 19-40LP

N-[(*S*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*S*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.176

MS(ESI, m/z) : 438.1033 (M-H)⁻

50 ¹H-NMR(CDCl₃) δ: 1.70-2.40 (2H, m), 2.54-2.94 (2H, m), 4.48-5.03 (1H, m), 5.40-6.53 (3H, m), 6.88-7.04 (3H, m), 7.28-7.35 (2H, m), 7.39 (1H, dd, J=4.8, 7.9Hz), 7.50-7.55 (1H, m), 7.88-8.05 (1H, m), 8.62 (1H, dd, J=1.5, 4.8Hz), 8.69-8.78 (1H, m), 9.38 (1H, br).

[0609]

50 Example 19-41LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide

RT(min.): 2.536

MS(ESI, *m/z*) : 452.1197 (M-H)⁺

- 5 ¹H-NMR(CDCl₃)δppm: 1.69-1.87 (1H, m), 1.98-2.36 (4H, m), 2.54-2.66 (1H, m), 2.73-2.93 (1H, m), 4.58-4.97 (1H, m), 5.46-5.98 (3H, m), 6.80-6.87 (1H, m), 6.97-7.04 (1H, m), 7.15-7.24 (2H, m), 7.34-7.40 (1H, m), 7.61 (1H, br s), 7.98 (1H, br s), 8.59-8.75 (3H, m).

[0610]

Example 20-1

- 10 *N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,4-dihydroxybenzamide

4-{*N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}-3-hydroxyphenyl acetate

[0611]

- 15 To a solution of (*R*)-6-chloro-4-fluoroindan-1-ylamine hydrochloride (0.11g) in methanol (4mL) were added triethylamine (68μL) and 3-formylpyridine (0.054g), and the mixture was stirred for 2hours at 60°C. The reaction mixture was allowed to cool to room temperature, and to the mixture were added 2,4-diacetoxybenzoic acid (0.097g) and 4-phenylcyclohexen-1-ylisocyanide (0.092g). The mixture was stirred overnight at 60°C,
20 then allowed to cool to room temperature, and concentrated under reduced pressure. To the obtained residue were added 1,4-dioxane (5mL), water (0.5mL) and a solution of 4mol/L hydrogen chloride in 1,4-dioxane (0.5mL), and the mixture was stirred for 3hours at room temperature. To the reaction mixture was added a saturated aqueous solution of sodium bicarbonate, and the mixture was purified by preparative reverse phase liquid
25 chromatography (Capcell Pak C18 UG80, eluent: acetonitrile / water = 1/9 to 7/3) to afford *N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,4-dihydroxybenzamide (Example 20-1-1LP, 3mg) and 4-{*N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}-3-hydroxyphenyl acetate (Example 20-1-2LP, 17mg). The structural formulae are shown in Table 43.

- 30 [0612]

Example 20-1-1LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,4-dihydroxybenzamide

RT(min.): 1.798

- 35 MS(ESI, *m/z*) : 454.0987 (M-H)⁺

¹H-NMR(CD₃OD)δppm: 1.10-2.10 (2H, m), 2.54-2.69 (1H, m), 2.80-3.00 (1H, m), 5.12-5.90 (2H, m), 6.37-6.42 (2H, m), 6.89-7.00 (1H, m), 7.06-7.14 (1H, m), 7.45-7.52 (1H, m), 7.60 (1H, s), 7.89-7.97 (1H, m), 8.50-8.56 (1H, m), 8.60 (1H, br s).

[0613]

- 40 Example 20-1-2LP

4-{*N*-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]carbamoyl}-3-hydroxyphenyl acetate

RT(min.): 2.215

MS(ESI, *m/z*) : 496.1094 (M-H)⁺

- 45 ¹H-NMR(CD₃OD)δppm: 1.30-2.36 (5H, m), 2.55-3.08 (2H, m), 5.14-5.80 (2H, m), 6.67-6.77 (2H, m), 6.85-7.11 (1H, m), 7.21-7.56 (2H, m), 7.61 (1H, s), 7.87-8.08 (1H, m), 8.48-8.72 (2H, m).

[0614]

Example 20-2LP

N-[(*R*)-Carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydroxybenzamide

The title compound was synthesized in a manner similar to that of Example 20-1 by using the corresponding starting material. The spectrum data of the title compound is shown as follows, and the structural formula is shown in Table 43.

[0615]

RT(min.): 1.885

MS(ESI, *m/z*) : 454.0985 (M-H)⁺

¹H-NMR(CD₃OD)δppm: 1.22-3.08 (4H, m), 5.06-5.80 (2H, m), 6.59-7.14 (4H, m), 7.40-7.55 (1H, m), 7.64 (1H, s), 7.90-8.13 (1H, m), 8.45-8.72 (2H, m).

[0616]

Example 21-1

N-[(*R*)-(3-Aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

[0617]

A suspension of Raney catalyst was prepared as follows. A mixture of Raney (registered trademark) 2800 nickel, slurry in water, active catalyst (Sigma-Aldrich) (200μL) and ethanol was stirred, and the solvent was removed by decantation. The catalyst was washed 3 times with ethanol, and ethanol (1mL) was added to form a suspension. To a solution of *N*-[(*R*)-carbamoyl-(3-nitrophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 18-12LP, 55mg) in ethanol (5mL) was added the suspension of Raney catalyst at room temperature, and the mixture was stirred for 2 hours under hydrogen atmosphere. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to afford the title compound (36mg). The structural formula is shown in Table 43.

[0618]

RT(min.): 1.959

MS(ESI, *m/z*) : 451.1350 (M-H)⁺

¹H-NMR(DMSO-*d*₆)δppm: 1.40-1.58 (1H, m), 2.03-2.16 (1H, m), 2.29-2.95 (5H, m), 4.93-5.34 (4H, m), 6.34-6.60 (3H, m), 7.00-7.85 (7H, m), 8.48-8.56 (1H, m).

[0619]

Example 21-2 to 21-3

Examples 21-2 to 21-3 were synthesized in a manner similar to that of Example 21-1 by using the corresponding starting materials. The spectrum data of examples 21-2 to 21-3 are shown as follows, and the structural formulae are shown in Table 43.

[0620]

Example 21-2

N-[(*R*)-(3-Aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 2.395

MS(ESI, *m/z*) : 452.1190 (M-H)⁺

¹H-NMR(DMSO-*d*₆)δppm: 1.27-1.41 (1H, m), 2.07-2.21 (1H, m), 2.46-2.61 (1H, m), 2.79-2.91 (1H, m), 5.03-5.13 (1H, m), 5.18 (2H, br s), 5.25 (1H, br s), 6.45-6.57 (3H, m), 6.81-6.93 (2H, m), 6.99-7.29 (5H, m), 7.41 (1H, br s), 7.58 (1H, br s), 10.00 (1H, br s).

[0621]

Example 21-3

4-Amino-*N*-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide

RT(min.): 1.611

MS(ESI, *m/z*) : 453.1149 (M-H)⁺

¹H-NMR(CD₃OD)δppm: 1.45-2.09 (2H, m), 2.54-2.67 (1H, m), 2.83-2.97 (1H, m), 5.22-5.84 (2H, m), 6.23 (1H, d, J=2.0Hz), 6.28 (1H, dd, J=2.0, 8.3Hz), 6.91-6.97 (1H, m), 7.02 (1H, d, J=8.3Hz), 7.48 (1H, dd, J=5.0, 7.8Hz), 7.57 (1H, s), 7.88-7.94 (1H, m), 8.50-8.54 (1H, m), 8.56-8.60 (1H, m).

5 [0622]

Example 22

N-[(*R*)-(3-Acetylamino-phenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

[0623]

10 To a mixture of *N*-[(*R*)-(3-aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 21-1, 80mg), *N,N*-diisopropylethylamine (0.03mL) and dichloromethane (3mL) was added acetyl chloride (14mg) at room temperature, and the mixture was stirred for 2hours. To the reaction mixture was added water, and the crude product was extracted with ethyl acetate. The
15 organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 5/1 to ethyl acetate / methanol = 10/1) to afford the title compound (75mg). The structural formula is shown in Table 43.

20 [0624]

RT(min.): 2.267

MS(ESI, m/z) : 539.1513 (M+HCO₂)⁻

¹H-NMR(DMSO-d₆)δppm: 1.29-1.53 (1H, m), 1.99-2.15 (4H, m), 2.34-2.70 (4H, m), 2.84-2.97 (1H, m), 4.90-5.38 (2H, m), 6.88-7.94 (10H, m), 8.51-8.59 (1H, m), 10.07 (1H, s).

25 [0625]

Example 23

N-[(*R*)-Carbamoyl-(3-methanesulfonylamino-phenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide

[0626]

30 To a mixture of *N*-[(*R*)-(3-aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide (Example 21-1, 80mg), *N,N*-diisopropylethylamine (0.03mL) and dichloromethane (3mL) was added methanesulfonyl chloride (18mg) at room temperature, and the mixture was stirred for 2hours. To the reaction mixture was added water, and the crude product was extracted with ethyl acetate.
35 The organic layer was washed with water and brine, and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: ethyl acetate / *n*-hexane = 5/1 to ethyl acetate / methanol = 10/1) to afford the title compound (34mg). The structural formula is shown in Table 43.

40 [0627]

RT(min.): 2.397

MS(ESI, m/z) : 529.1127 (M-H)⁻

¹H-NMR(DMSO-d₆)δppm: 1.28-1.53 (1H, m), 1.98-2.15 (1H, m), 2.35-2.70 (4H, m), 2.84-3.05 (4H, m), 4.93-5.37 (2H, m), 6.97-7.87 (10H, m), 8.51-8.60 (1H, m), 9.93 (1H, br s).

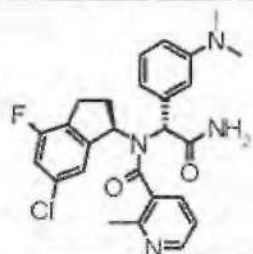
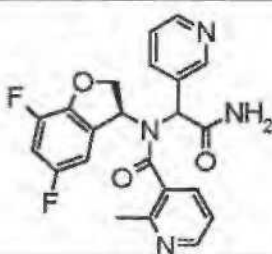
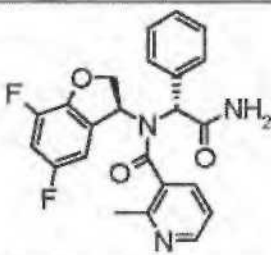
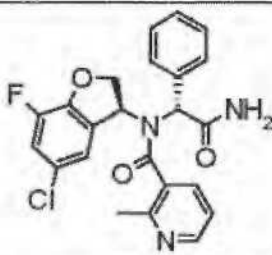
45 [0628]

[Table 37]

Ex.No.	Strc.	Ex.No.	Strc.
18-1LP		18-7LP	
18-2LP		18-8LP	
18-3LP		18-9LP	
18-4LP		18-10LP	
18-5LP		18-11LP	
18-6LP		18-12LP	

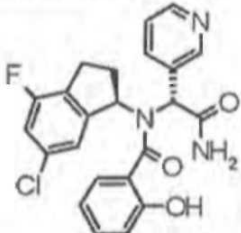
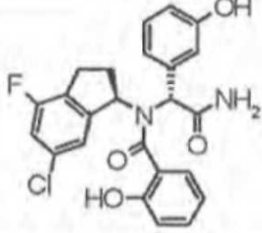
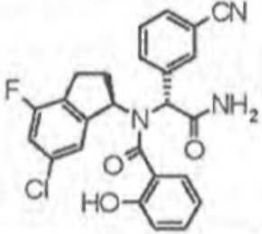
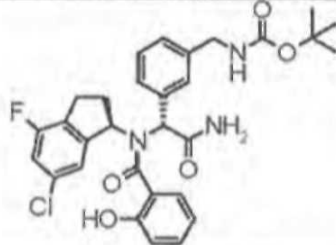
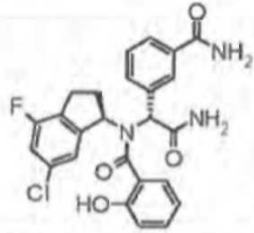
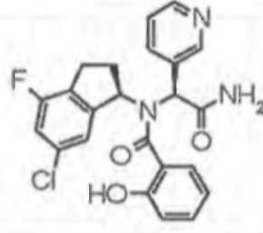
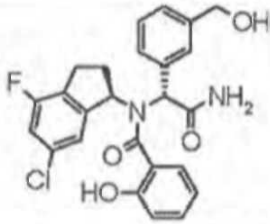
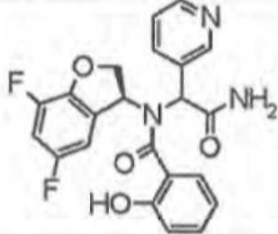
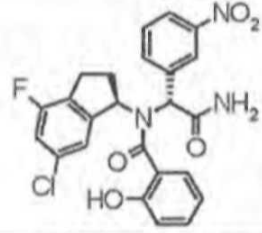
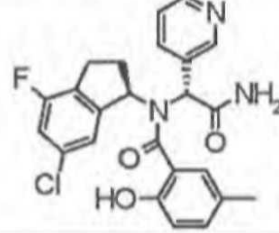
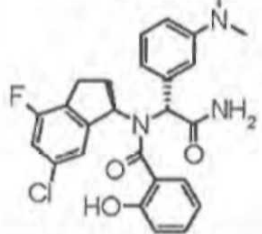
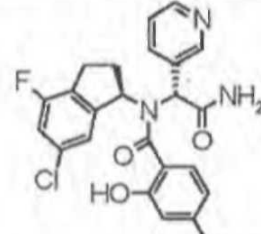
[0629]

[Table 38]

Ex.No.	Strc.	Ex.No.	Strc.
18-13LP		18-15M	
18-14LP		18-16LP	

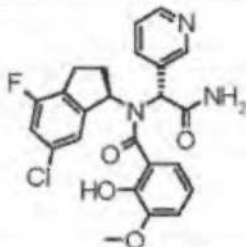
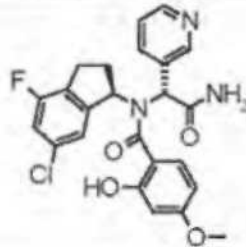
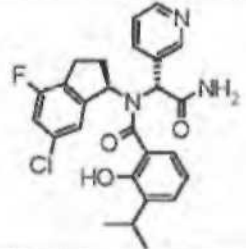
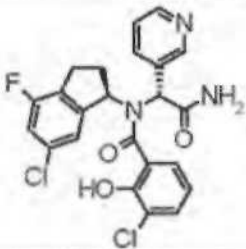
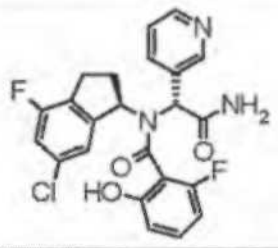
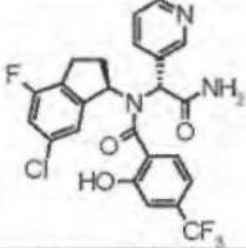
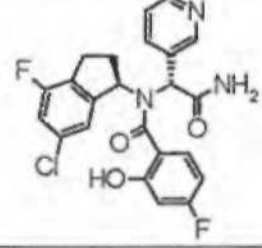
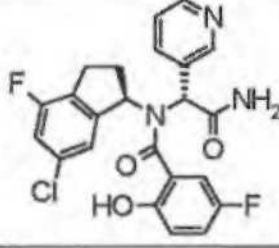
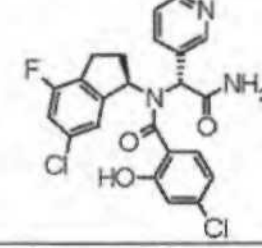
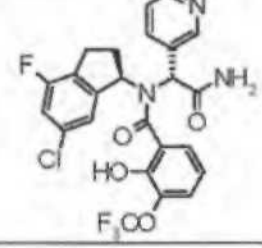
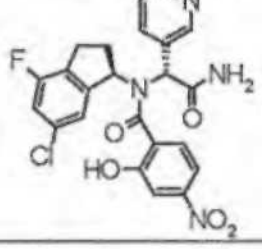
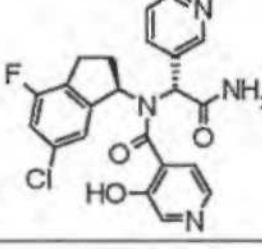
[0630]

[Table 39]

Ex.No.	Strc.	Ex.No.	Strc.
19-1LP		19-7LP	
19-2LP		19-8LP	
19-3LP		19-9HP	
19-4LP		19-10M	
19-5LP		19-11LP	
19-6LP		19-12LP	

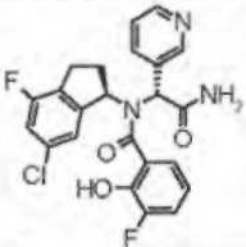
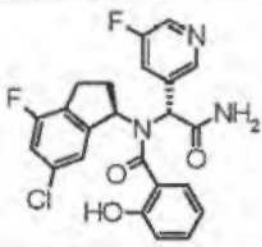
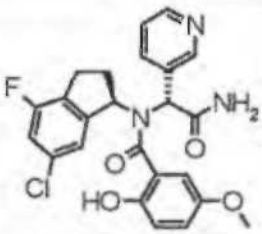
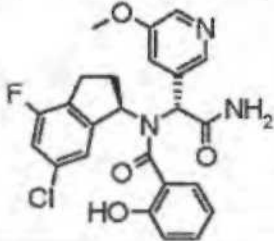
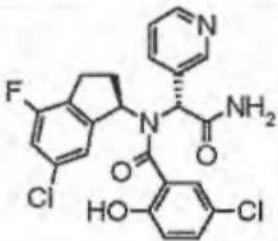
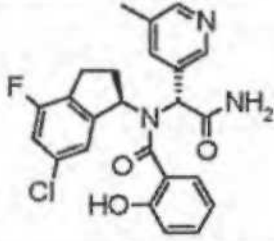
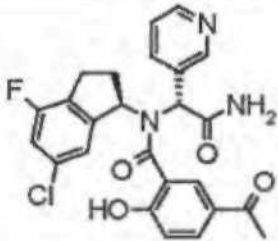
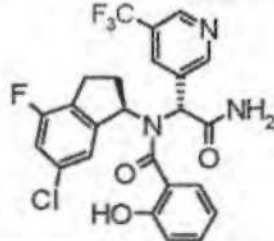
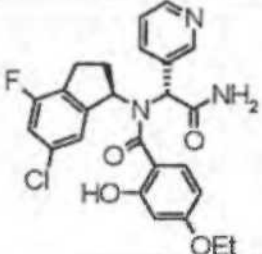
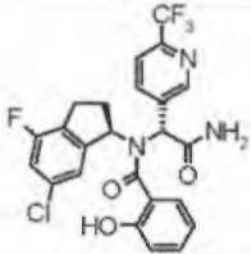
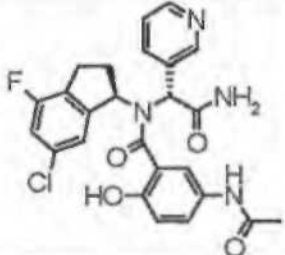
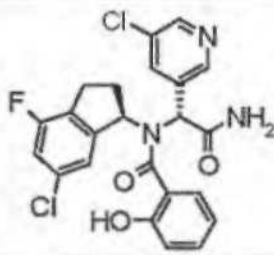
[0631]

[Table 40]

Ex.No.	Strc.	Ex.No.	Strc.
19-13LP		19-19LP	
19-14LP		19-20LP	
19-15LP		19-21LP	
19-16LP		19-22LP	
19-17LP		19-23LP	
19-18LP		19-24LP	

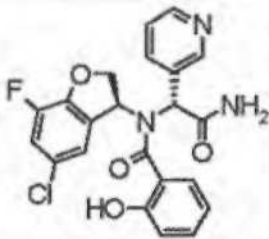
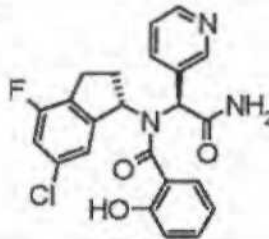
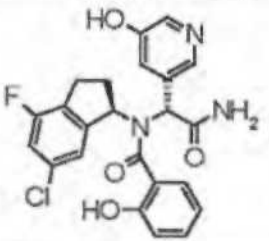
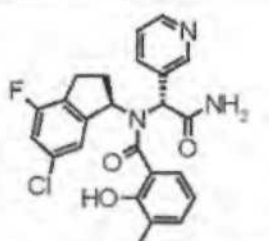
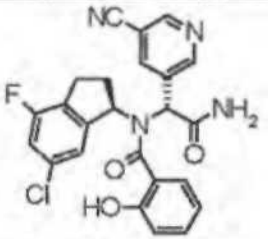
[0632]

[Table 41]

Ex.No.	Strc.	Ex.No.	Strc.
19-25LP		19-31LP	
19-26LP		19-32LP	
19-27LP		19-33LP	
19-28LP		19-34LP	
19-29LP		19-35LP	
19-30LP		19-36LP	

[0633]

[Table 42]

Ex.No.	Strc.	Ex.No.	Strc.
19-37LP		19-40LP	
19-38LP		19-41LP	
19-39LP			

[0634]

[Table 43]

Ex.No.	Strc.	Ex.No.	Strc.
20-1-1 LP		21-2	
20-1-2 LP		21-3	
20-2 LP		22	
21-1		23	

Test example 1

Confirmation Test of Inhibitory Effects on Icilin-induced wet-dog Shakes

5 [0635]

Test compounds were dissolved in dimethylacetamide (wako), and 0.5 % methylcellulose solution (wako) was added to make the solution or suspension containing 5% of dimethylacetamide. At a dose of 3 or 10 mg/kg/5mL of test compounds were orally administered to female SD rats. After 1 hour, wet-dog shakes were induced by the intraperitoneal injection of icilin (1 mg/kg) which was dissolved in polyethylene glycol 400 (wako). From 5 minutes after the administration of icilin, wet-dog shakes were counted for 5 minutes. For control example, vehicle (a mixture of dimethylacetamide (wako) : 0.5% methylcellulose (wako) = 5:95) was administrated similarly, and the number of wet-dog shakes was counted in the same manner. A percent inhibition of wet-dog shakes by test compound was calculated from the following formula: $[1 - (\text{test compound wet-dog shake count} / \text{vehicle wet-dog shake count})] \times 100$. Results are shown in Tables 44 and 45.

15 [0636]

[Table 44]

Ex. No.	Dose (mg/kg)	% inhibition of Wet-Dog Shake	Ex. No.	Dose (mg/kg)	% inhibition of Wet-Dog Shake
1-1	10	95	2-97LP	3	35
1-6	10	64	2-100LP	3	47
2-2LP	10	100	2-107LP	3	68
2-4LP	10	79	2-111LP	3	91
2-5LP	10	89	2-118LP	3	62
2-11LP	10	85	2-125LP	3	37
2-26LP	10	83	2-128LP	3	65
2-27LP	10	95	2-131LP	3	100
2-31LP	10	87	2-132LP	3	49
2-33LP	10	98	2-133LP	3	55
2-39LP	10	98	2-137LP	3	53
2-40LP	10	95	2-147LP	3	91
2-56LP	10	50	2-150LP	3	49
2-66LP	10	100	2-152LP	3	44
2-71LP	10	83	2-154LP	3	36
2-76LP	10	95	2-161LP	3	42
2-86LP	10	73	2-167LP	3	64
2-221LP	10	100	2-168LP	3	36
3-2	10	73	2-172LP	3	43
4-2	10	86	2-173LP	3	99
6-1	10	89	2-175LP	3	40
12	10	93	2-179LP	3	32
1-3	3	69	2-180LP	3	32
2-6LP	3	69	2-252M	3	31
2-23LP	3	56	4-5	3	76
2-36LP	3	74	4-8	3	37
2-46LP	3	79	4-9	3	36
2-87LP	3	36	11	3	100
2-88LP	3	46	13	3	93
2-89LP	3	100	14LP	3	100
2-93LP	3	100	15LP	3	100

[0637]

[Table 45]

Ex. No.	Dose (mg/kg)	% inhibition of Wet-Dog Shake	Ex. No.	Dose (mg/kg)	% inhibition of Wet-Dog Shake
18-13LP	10	86	19-25LP	10	86
19-6LP	10	99	19-41LP	10	92
19-12LP	10	82	21-1	10	99
19-15LP	10	72	21-2	10	94
19-16LP	10	63	19-31LP	3	71
19-17LP	10	66			

[0638]

Test example 2

- 5 Confirmation test of elongation action of micturition interval of overactive bladder induced by acetic acid

[0639]

- 10 Urethane (sigma) was dissolved into pure water by 25% w/v, and female SD rats were anesthetized with 1.25 g/kg urethane by subcutaneous administration. Cannulae were placed in femoral vein and bladder, and the bladder cannula was connected to both a syringe pump and a pressure transducer. Detrusor overactivity was induced by intravesical infusion of 0.25% acetic acid in saline at a rate of 3.6mL/h, and intravesical pressure was monitored via pressure transducer concurrently. Test compounds were dissolved into a mixture of dimethylacetamide and saline (20:80), and were administered via the femoral vein.
- 15 When an average of the three micturition interval before administration was taken as 100%, an average of the three micturition interval after administration was calculated as Elongation of micturition interval (%) Dose and results are shown in tables 46 and 47.

[0640]

[Table 46]

Ex.No.	Dose / Volume	Elongation of micturition interval(%)
1-1	1 mg/kg/ml	209
1-3	1 mg/kg/ml	206
2-2LP	1 mg/kg/2 ml	221
2-4LP	1 mg/kg/2 ml	156
2-5LP	1 mg/kg/2 ml	177
2-6LP	0.3 mg/kg/ml	184
2-23LP	1 mg/kg/ml	205
2-31LP	1 mg/kg/ml	176
2-40LP	1 mg/kg/ml	186
2-66LP	1 mg/kg/ml	173
2-86LP	1 mg/kg/2 ml	145
2-89LP	1 mg/kg/2 ml	196
2-111LP	0.3 mg/kg/2 ml	135
2-131LP	1 mg/kg/ml	192
2-137LP	1 mg/kg/2 ml	146
2-221LP	1 mg/kg/2 ml	154
6-1	1 mg/kg/2 ml	194
11	1 mg/kg/ml	162
12	1 mg/kg/ml	142
13	1 mg/kg/ml	193
14LP	1 mg/kg/ml	181
15LP	1 mg/kg/ml	188

[0641]

[Table 47]

Ex.No.	Dose / Volume	Elongation of micturition interval(%)
19-1LP	1 mg/kg/ml	178

[0642]

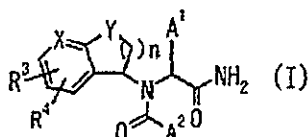
As shown in Tables 44 and 45, the compounds of the present invention exhibited potent TRPM8 inhibitory effects. Further, as shown in Tables 46 and 47, the compounds of the present invention have the elongation action against micturition interval and were proved to be effective for suppression of detrusor overactivity.

[INDUSTRIAL APPLICABILITY]

[0643]

The compounds of the present invention exhibit potent TRPM8 inhibitory activity and thus are useful as an agent for treating or preventing of diseases or symptoms caused by the activation of TRPM8, in particular the symptoms of lower urinary tract symptoms (LUTS), especially, overactive bladder syndrome (OAB).

[Chem.1]



A^1 is a group selected from the group consisting of the following a)

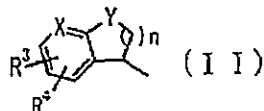
R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆

alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, C₂₋₆ alkenyl or cyano with the proviso that when X is CH, and R¹ and R² are hydrogen atoms, R³ and R⁴ are not hydrogen atoms at the same time; and
n is 1 or 2.

[Claim 2] The compound according to claim 1 or a pharmaceutically acceptable salt thereof, wherein X is CH; and n is 1.

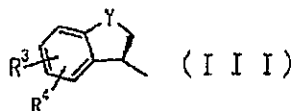
[Claim 3] The compound according to claim 2 or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[Chem.2]



is a group represented by the following general formula:

[Chem.3]

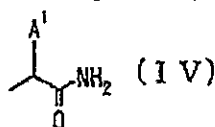


wherein R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₃₋₆ cycloalkoxy, C₂₋₆ alkenyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[Claim 4] The compound according to claim 3 or a pharmaceutically acceptable salt thereof, wherein Y is -CR¹R².

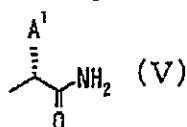
[Claim 5] The compound according to claim 4 or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:

[Chem.4]



is a group represented by the following general formula:

[Chem.5]



wherein A¹ is a group selected from the group consisting of the following a1), b) and c);

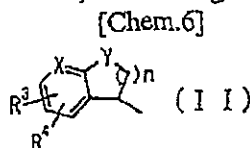
a1) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen

atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, C₁₋₆ alkoxy-carbonyl, cyano, hydroxy-C₁₋₆ alkyl, carbamoyl, nitro, amino, C₁₋₆ alkoxy-carbonylamino-C₁₋₆ alkyl, mono(di)C₁₋₆ alkylamino, (C₁₋₆ alkyl)carbonylamino, C₁₋₆ alkylsulfonylamino and C₁₋₆ alkylsulfonyl,

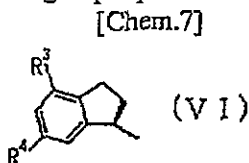
b) 5-membered aromatic heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, cyano and halo-C₁₋₆ alkoxy, and

c) 6-membered aromatic heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, cyano and halo-C₁₋₆ alkoxy.

[Claim 6] The compound according to claim 5 or a pharmaceutically acceptable salt thereof, wherein a group represented by the general formula:



is a group represented by the following general formula:



wherein R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl, C₂₋₆ alkenyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[Claim 7] The compound according to claim 6 or a pharmaceutically acceptable salt thereof, wherein A² is a group selected from the group consisting of the following d1) and e):

d1) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, amino, nitro, carboxy, (C₁₋₆ alkyl)carbonylamino, (C₁₋₆ alkyl)carbonyloxy, (C₁₋₆ alkyl)carbonyl and (C₇₋₁₀ aralkyloxy)carbonyl, and

e) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfonyl, amino, (C₇₋₁₀ aralkyloxy)carbonyl, hydroxy-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkoxy, C₂₋₆ alkenyl, morpholino and (C₁₋₆ alkyl)carbonyl.

[Claim 8] The compound according to claim 7 or a pharmaceutically acceptable salt thereof, wherein A¹ is a group selected from the group consisting of the following a2), b1) and c1):

a2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, hydroxy-C₁₋₆ alkyl, cyano, amino, mono(di)C₁₋₆ alkylamino and C₁₋₆ alkoxy,

b1) thiazolyl, and

c1) a group selected from the group consisting of pyridyl, pyrimidinyl and pyrazinyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy and cyano;

A² is a group selected from the group consisting of the following d2) and e1):

d2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, (C₁₋₆ alkyl)carbonyloxy and amino, and

e1) heterocycle, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, hydroxy-C₁₋₆ alkyl and C₂₋₆ alkenyl; and

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[Claim 9] The compound according to claim 8 or a pharmaceutically acceptable salt thereof, wherein A² is a group selected from the group consisting of the following d2) and e2):

d2) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₆ alkoxy, halo-C₁₋₆ alkyl, halo-C₁₋₆ alkoxy, cyano, (C₁₋₆ alkyl)carbonyloxy and amino, and

e2) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thienyl, thiazolyl, isothiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, imidazolyl, isoxazolyl, oxazolyl, furazanyl and benzo[1, 3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, cyano, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, amino, hydroxy-C₁₋₆ alkyl and C₂₋₆ alkenyl.

[Claim 10] The compound according to claim 9 or a pharmaceutically acceptable salt thereof,

wherein A¹ is phenyl, pyridyl or pyrazinyl, in which the each ring is unsubstituted or substituted with selected from the group consisting of the following: a halogen atom, amino, mono(di)C₁₋₆ alkylamino or hydroxy;

A² is a group selected from the group consisting of the following d3) and e3):

d3) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy and amino, and

e3) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, isoxazolyl and benzo[1, 3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents

independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, and amino, and

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[Claim 11] The compound according to claim 10 or a pharmaceutically acceptable salt thereof, wherein A¹ is phenyl, pyridyl or pyrazinyl, in which the each ring is unsubstituted or substituted with selected from the group consisting of the following: a halogen atom or hydroxy;

A² is a group selected from the group consisting of the following d4) and e3):

d4) phenyl, wherein the ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, hydroxy, C₁₋₆ alkoxy and amino, and

e3) a group selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, thiazolyl, 2,3-dihydrobenzofuranyl, pyrazolyl, isoxazolyl and benzo[1,3]dioxolyl, wherein the each ring is unsubstituted or substituted with 1 to 2 substituents independently selected from the group consisting of the following: a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, mono(di)C₁₋₆ alkylamino, C₁₋₆ alkylsulfanyl, and amino, and

R³ and R⁴ independently represent a hydrogen atom, a halogen atom, C₁₋₆ alkyl, C₁₋₆ alkoxy, halo-C₁₋₆ alkoxy, C₃₋₆ cycloalkyl or cyano with the proviso that R³ and R⁴ are not hydrogen atoms at the same time.

[Claim 12] The compound according to claim 1 selected from the following group or a pharmaceutically acceptable salt thereof:

N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-methoxyindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyclopropylindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide;
2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-difluoromethoxyindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide;
2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methoxyindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoro-6-methylindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4-fluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]thiazole-5-carboxamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-fluoronicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-cyanoindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*S*)-5-chloro-2,3-dihydrobenzofuran-3-yl]-2-hydroxybenzamide;
2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]benzamide;

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;
 2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-methoxynicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methoxynicotinamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-4-methylthiazole-5-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide;
N-[(*R*)-carbamoylphenylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-2-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylnicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylamino)nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2,3-dihydrobenzofuran-7-carboxamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxybenzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-(methylsulfanyl)nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-(methylsulfanyl)nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-4,6-difluoroindan-1-yl]-4-methylthiazole-5-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methyl-2H-pyrazole-3-carboxamide (Example 2-133LP);
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-5-methylthiazole-4-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylisoxazole-5-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyridine-2-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylpyrimidine-5-carboxamide;
N-[(*R*)-carbamoyl-(3-fluorophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylisonicotinamide;
N-[(*R*)-carbamoyl-(3-hydroxyphenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;

N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]benzo[1,3]dioxole-4-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-methylpyrazine-2-carboxamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]pyrazine-2-carboxamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide;
N-[(*RS*)-carbamoylphenylmethyl]-*N*-[(*SR*)-5-chloro-7-fluoro-2,3-dihydrobenzofuran-3-yl]benzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoylpyrazin-2-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methoxynicotinamide;
2-amino-*N*-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]nicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-carbamoylphenylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-methylthiazole-5-carboxamide;
N-[(*R*)-carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-carbamoyl-(3-dimethylaminophenyl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-4-methylbenzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-fluoro-6-hydroxybenzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-4-fluoro-2-hydroxybenzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-4-chloro-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-3-fluoro-2-hydroxybenzamide;
N-[(*R*)-(3-aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-methylnicotinamide;
N-[(*R*)-(3-aminophenyl)carbamoylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide;
N-[(*R*)-carbamoyl(5-fluoropyridin-3-yl)methyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxybenzamide; and
N-[(*R*)-carbamoylpyridin-3-ylmethyl]-*N*-[(*R*)-6-chloro-4-fluoroindan-1-yl]-2-hydroxy-3-methylbenzamide.

[Claim 13] A pharmaceutical composition comprising the compound according to any one of claim 1 to 12 or a pharmaceutically acceptable salt thereof.

[Claim 14] The pharmaceutical composition according to claim 13, for use in the treatment or prevention of a disease or a symptom caused by hyperexcitability or a disorder of afferent neurons.

[Claim 15] Use of the compound according to any one of claim 1 to 12 or a pharmaceutically acceptable salt thereof for the manufacturing of a pharmaceutical composition for preventing or treating anxietas, depression, lower urinary tract symptoms (LUTS), algi, circulatory disorder, itch, pins-and-needles sensation and hives.