Description
Title of Invention: BENZAZEPINE DERIVATIVES

Technical Field

[0001]

The present invention relates to benzazepine derivatives and salts thereof. The present invention also relates to medicines, comprising a benzazepine derivative and a salt thereof as an active ingredient, useful for diagnosing, preventing, and/or treating diseases associated with vasopressin receptors.

Background Art

[0002]

Vasopressin is an antidiuretic hormone and is known to function to increase blood pressure. Vasopressin V_{1a} receptor and vasopressin V_2 receptor are known as a subgroup of vasopressin receptors, each of which is associated with vascular constriction and reabsorption of water in the collecting duct.

[0003]

Tolvaptan has a benzo-heterocyclic structure and is used for treating various diseases, especially as a vasopressin V_2 receptor antagonist. It has been known to be metabolized primarily by a hepatic metabolizing enzyme, CYP3A4 (NPL 1 to 3). Various compounds have been known to have a benzo-heterocyclic structure (PTL 1 to 9), but no compounds having difluorine and hydroxy on positions 4 and 5, respectively, of a benzazepine ring among benzo-heterocycles have been known to have vasopressin antagonisms as both vasopressin V_{1a} and V_2 antagonists.

Citation List

Patent Literature

[0004]

[PTL 1] WO 2011/052519
[PTL 2] JP 10-120592 A
[PTL 3] JP 9-221476 A
[PTL 4] WO 1994/04525
[PTL 5] WO 1994/01113
[PTL 6] JP 4-321669 A
[PTL 7] WO 1991/05549
[PTL 8] WO 1995/34540
[PTL 9] WO 1994/08582

Non Patent Literature

[0005]

[NPL 1] Shoaf S.E. et al. Br J Clin Pharmacol. 2011, 73:579-87
[NPL 2] Sorbera L.A. et al. Drugs of the Future. 2002, 27(4):350–357
[NPL 3] Furukawa M. et al. Arch. Pharm. Res. 2014 37:1578-87

Summary of Invention

Technical Problem

unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms and at least one nitrogen atom, or a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms and at least one nitrogen atom,

Ring A^2 is a saturated or unsaturated 3- to 8-membered monocyclic hydrocarbon ring, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 to 4 nitrogen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms, a saturated or unsaturated 7- to 12-membered heterobicycle comprising as the ring heteroatom 1 to 3 oxygen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms, a saturated or unsaturated 7- to 15-membered heterobicycle comprising as the ring heteroatom 1 to 5 nitrogen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms and at least one nitrogen atom, or a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms and at least one nitrogen atom, and

each of Rings A^1 and A^2 may have at least one substituent.

[0030]

Item 4. The compound according to any one of Items 1 to 3, wherein Ring A^1 is benzene, pyridine, pyrazine, or tetrahydroisoquinoline and Ring A^1 may have 1 to 4 substituents independently selected from the group consisting of optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{1\text{-}6}$ alkyl-O-, halogen, and oxo;

Ring A^2 is benzene, pyridine, furan, thiophene, or tetrahydroisoquinoline and Ring A^2 may have 1 to 4 substituents independently selected from the group consisting of optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{1\text{-}6}$ alkyl-O-, optionally substituted $C_{3\text{-}6}$ cycloalkyl, halogen, oxo, optionally substituted phenyl, and optionally substituted pyridyl,

provided that when Ring A^2 has multiple substituents on its ring carbon atoms, then the substituents may combine together with the carbon atoms to form $C_{3\text{-}6}$ cycloalkyl;

or a salt thereof.

[0031]

Item 5. The compound according to Item 4, wherein, in Ring A^1, a substituent of the optionally substituted $C_{1\text{-}6}$ alkyl or optionally substituted $C_{1\text{-}6}$ alkyl-O- is each independently the same or different 1 to 3 groups selected from the group consisting of halogen and $C_{1\text{-}6}$ alkyl-O-,

in Ring A^2, a substituent of the optionally substituted $C_{1\text{-}6}$ alkyl or optionally substituted $C_{1\text{-}6}$ alkyl-O- is each independently the same or different 1 to 3 halogen, a substituent of the optionally substituted $C_{3\text{-}6}$ cycloalkyl is the same or different 1 to 3 halogen, a substituent of the optionally substituted phenyl is 1 to 3 groups independently selected from the group consisting of halogen, $C_{1\text{-}6}$ alkyl, and $C_{1\text{-}6}$ alkyl-O-,

equation.
Binding rate (%) = (B-NSB)/(TB-NSB) x 100
(B: Binding amount of ^{3}H-AVP in the presence of each compound,
NSB: Binding amount of ^{3}H-AVP in the presence of 1 μM of unlabeled AVP, TB: Binding amount of ^{3}H-AVP in the absence of 1 μM of unlabeled AVP)
The concentration (IC_{50}) where each compound inhibits 50% of ^{3}H-AVP binding amounts was calculated using ^{3}H-AVP binding rates and compound concentrations.
Results are shown below.

[0241]
[Table 5]

Table 1. Binding affinities for vasopressin V_{1a} and V_2 receptors (IC_{50}: nM)

Compound (EX)	rV_{1a}	rV_2
2	3.4	2.1
3	9.5	2.1
15	2.9	1.0
23	2.6	1.0
24	2.7	1.5
51	16.1	1.7
52	8.8	3.0
58	9.3	1.3
63	1.4	1.1
66	21.1	3.5
96	2.0	5.0
97	5.4	1.4
127	7.2	1.8
132	5.2	2.3
153	3.6	4.5
157	12.0	3.2
165	1.7	3.4
168	2.2	4.7
169	1.6	3.3
187	2.6	0.4

[0242]
[Test Example 2: Metabolic stability test]
Reaction system and incubation
According to methods of Obach and Jones, et al. (methods described in R. S. Obach, Drug Metab. Dispos. 1999 (27): 1350-1359 and H. Jones and J. B. Houston, Drug Metab. Dispos. 2004 (32): 973-982), the reaction system shown below was prepared and metabolic stabilities of test compounds (the present compounds and, tolvaptan) were evaluated using the reaction system shown below. Human liver microsomes purchased from Corning Inc. were used. Test compounds were dissolved in DMSO at the concentration of 10 mmol/L and then diluted with acetonitrile to prepare a 100

μmol/L solution for use in the test. The 100 μmol/L solutions were used in the experiment.

<Reaction system>
Test compound 1 μmol/L
Human liver microsome 1 mg/mL
Co-factor (NADPH and NADH) 1 mmol/L each
Magnesium chloride 5 mmol/L
100 mmol/L Potassium phosphate buffer (pH 7.4)
Number of samples: n = 4

<Reaction condition>
The reaction mixture without co-factors was pre-incubated at 37°C for 5 minutes, and then the reaction was initiated by the addition of the co-factors. The mixture was incubated for 0, 5, 10, 20, 30, and 60 minutes after the addition of the co-factors. An aliquot of the reaction mixture was removed and added to a methanol solution containing an internal standard (IS) and mixed to terminate the reaction at each predetermined time.

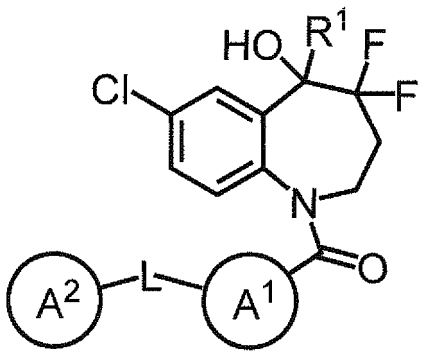
Analytic method
After the reaction was terminated, the mixture was separated by centrifugation and the supernatant was injected into a liquid chromatograph-tandem mass specrometer (LC-MS/MS) to measure unchanged substances remained in the reaction system. The mass spectrometer was operated in a positive ion mode of the electrospray ionization (ESI) method. Unchanged substances and the IS were detected by multiple reaction monitoring (MRM) transitions using selected precursor and product ions set.

Data analysis
The remaining ratios of test compounds were calculated by the following equation.
Remaining ratio = (Peak area ratio of a test compound to IS at t minutes after incubation) ÷ (Peak area ratio of a test compound to IS at 0 minute)
The slope of X-axis (the incubation time) and Y-axis (logarithm of the remaining ratio) was caluculated by a non–linear least square method. Hepatic intrinsic clearance (CL_{int}) was caluculated by the following equation.
CL_{int} (μL/min/mg) = -(Slope (min^{-1})) ÷ 1 (mg/mL) x 1000
Results are shown below.

[0243]

CLAIMS

[Claim 1]
A benzazepine compound of Formula (1):
[Chem. 1]



(1)

wherein R^1 is deuterium, OH, COOH, optionally substituted C_{1-6} alkyl, optionally substituted C_{1-6} alkyl-O-CO-, or optionally substituted C_{2-6} alkenyl;
L is a direct bond or -C(=O)-NH-;
Ring A^1 is a hydrocarbon ring or heterocycle;
Ring A^2 is a hydrocarbon ring or heterocycle; and
each of Rings A^1 and A^2 may have at least one substituent, or a salt thereof.

[Claim 2]
The compound according to claim 1, wherein Ring A^1 is a saturated or unsaturated 3- to 8-membered monocyclic hydrocarbon ring, or a saturated or unsaturated 3- to 15-membered monocyclic, bicyclic, or tricyclic heterocycle comprising as the ring member 1 to 5 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur,
Ring A^2 is a saturated or unsaturated 3- to 8-membered monocyclic hydrocarbon ring, or a saturated or unsaturated 3- to 15-membered monocyclic, bicyclic, or tricyclic heterocycle comprising as the ring member 1 to 5 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and
each of Rings A^1 and A^2 may have at least one substituent, or a salt thereof.

[Claim 3]
The compound according to either claim 1 or 2, or a salt thereof, wherein Ring A^1 is a saturated or unsaturated 3- to 8-membered monocyclic hydrocarbon ring, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 to 4 nitrogen atoms, a saturated or unsaturated 7- to 15-membered heterobicycle comprising as the ring heteroatom 1 to 5 nitrogen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms and at least one nitrogen atom, or a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms and at least one nitrogen atom,

Ring A^2 is a saturated or unsaturated 3- to 8-membered monocyclic hydrocarbon ring, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 to 4 nitrogen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms, a saturated or unsaturated 7- to 12-membered heterobicycle comprising as the ring heteroatom 1 to 3 oxygen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms, a saturated or unsaturated 7- to 15-membered heterobicycle comprising as the ring heteroatom 1 to 5 nitrogen atoms, a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 oxygen atoms and at least one nitrogen atom, or a saturated or unsaturated 5- or 6-membered heteromonocycle comprising as the ring heteroatom 1 or 2 sulfur atoms and at least one nitrogen atom, and
each of Rings A^1 and A^2 may have at least one substituent.

[Claim 4]
The compound according to any one of claims 1 to 3, wherein Ring A^1 is benzene, pyridine, pyrazine, or tetrahydroisoquinoline and Ring A^1 may have 1 to 4 substituents independently selected from the group consisting of optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{1\text{-}6}$ alkyl-O-, halogen, and oxo;
Ring A^2 is benzene, pyridine, furan, thiophene, or tetrahydroisoquinoline and Ring A^2 may have 1 to 4 substituents independently selected from the group consisting of optionally substituted $C_{1\text{-}6}$ alkyl, optionally substituted $C_{1\text{-}6}$ alkyl-O-, optionally substituted $C_{3\text{-}6}$ cycloalkyl, halogen, oxo, optionally substituted phenyl, and optionally substituted pyridyl,
provided that when Ring A^2 has multiple substituents on its ring carbon atoms, then the substituents may combine together with the carbon atoms to form $C_{3\text{-}6}$ cycloalkyl; or a salt thereof.

[Claim 5]
The compound according to claim 4, wherein, in Ring A^1, a substituent of the optionally substituted $C_{1\text{-}6}$ alkyl or optionally substituted $C_{1\text{-}6}$ alkyl-O- is each independently the same or different 1 to 3 groups selected from the group consisting of halogen and $C_{1\text{-}6}$ alkyl-O-,
in Ring A^2, a substituent of the optionally substituted $C_{1\text{-}6}$ alkyl or optionally substituted $C_{1\text{-}6}$ alkyl-O- is each independently the same or different 1 to 3 halogen, a substituent of the optionally substituted $C_{3\text{-}6}$ cycloalkyl is the same or different 1 to 3 halogen, a substituent of the optionally substituted phenyl is 1 to 3 groups independently selected from the group consisting of halogen, $C_{1\text{-}6}$ alkyl, and $C_{1\text{-}6}$ alkyl-O-, and a substituent of the optionally substituted pyridyl is the same or different 1 to 3 halogen, or a salt thereof.

[Claim 6]
The compound according to any one of claims 1 to 5, wherein R^1 is deuterium; OH; COOH; $C_{1\text{-}6}$ alkyl optionally substituted with 1 to 3 groups independently selected from the group consisting of optionally substituted amino, optionally substituted $C_{1\text{-}6}$ alkyl-O-, optionally substituted $C_{1\text{-}6}$ alkyl-SO_2-O-, optionally substituted silyl-O-, OH, optionally substituted $C_{1\text{-}6}$ alkyl-COO-, tetrahydropyranyl-O-, thiazolyl, and pyridyl; optionally substituted $C_{1\text{-}6}$ alkyl-O-CO-; or optionally substituted $C_{2\text{-}6}$ alkenyl,
the optionally substituted amino is amino optionally substituted with 1 or 2 groups

independently selected from the group consisting of C_{1-6} alkyl optionally substituted with OH, optionally substituted C_{1-6} alkyl-SO_2-, optionally substituted C_{1-6} alkyl-O-CO-, and benzyl-O-CO-,
the optionally substituted C_{1-6} alkyl in the optionally substituted C_{1-6} alkyl-O-, optionally substituted C_{1-6} alkyl-SO_2-, optionally substituted C_{1-6} alkyl-SO_2-O-, optionally substituted C_{1-6} alkyl-COO-, and optionally substituted C_{1-6} alkyl-O-CO- is C_{1-6} alkyl optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl-O-, optionally substituted phenyl, optionally substituted phenyl-SO_2-NH-, and naphthalenyl-SO_2-NH-, the optionally substituted phenyl being phenyl optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl, and NO_2,
the optionally substituted silyl-O- is silyl-O- optionally substituted with the same or different 1 to 3 C_{1-6} alkyl, and
the optionally substituted C_{2-6} alkenyl is C_{2-6} alkenyl optionally substituted with the same or different 1 to 3 halogen, or a salt thereof.

[Claim 7]
The compound according to any one of claims 1 to 6, wherein R^1 is deuterium; OH; or C_{1-6} alkyl optionally substituted with optionally substituted amino, optionally substituted C_{1-6} alkyl-O-, or OH,
the optionally substituted amino is amino optionally substituted with C_{1-6} alkyl optionally substituted with OH, and
the optionally substituted C_{1-6} alkyl-O- is C_{1-6} alkyl-O- optionally substituted with the same or different 1 to 3 halogen, or a salt thereof.

[Claim 8]
The compound according to any one of claims 1 to 7, wherein R^1 is C_{1-6} alkyl substituted with OH, or a salt thereof.

[Claim 9]
The compound according to any one of claims 1 to 8, wherein Ring A^1 is benzene optionally substituted with halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkyl-O-, halo-C_{1-6} alkyl-O-, C_{1-6} alkyl-O-C_{1-6} alkyl-O-, halo-C_{1-6} alkyl-O-C_{1-6} alkyl-O-, C_{1-6} alkyl-O-halo-C_{1-6} alkyl-O-, or halo-C_{1-6} alkyl-O-halo-C_{1-6} alkyl-O-; pyridine optionally substituted with halogen; pyrazine; or tetrahydroisoquinoline optionally substituted with oxo; and
Ring A^2 is benzene optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkyl-O-, halo-C_{1-6} alkyl-O-, C_{3-6} cycloalkyl, optionally substituted phenyl, and pyridyl, the optionally substituted phenyl being phenyl optionally substituted with halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkyl-O-, or halo-C_{1-6} alkyl-O-; pyridine optionally substituted with C_{1-6} alkyl, halo-C_{1-6} alkyl, or phenyl; furan optionally substituted with C_{1-6} alkyl; thiophene optionally substituted with C_{1-6} alkyl; or tetrahydroisoquinoline optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl, and oxo, provided that when tetrahydroisoquinoline has multiple C_{1-6} alkyl groups on its ring carbon atoms, then the C_{1-6} alkyl groups may combine together with the carbon atoms to form C_{3-6} cycloalkyl, or a salt thereof.

[Claim 10]

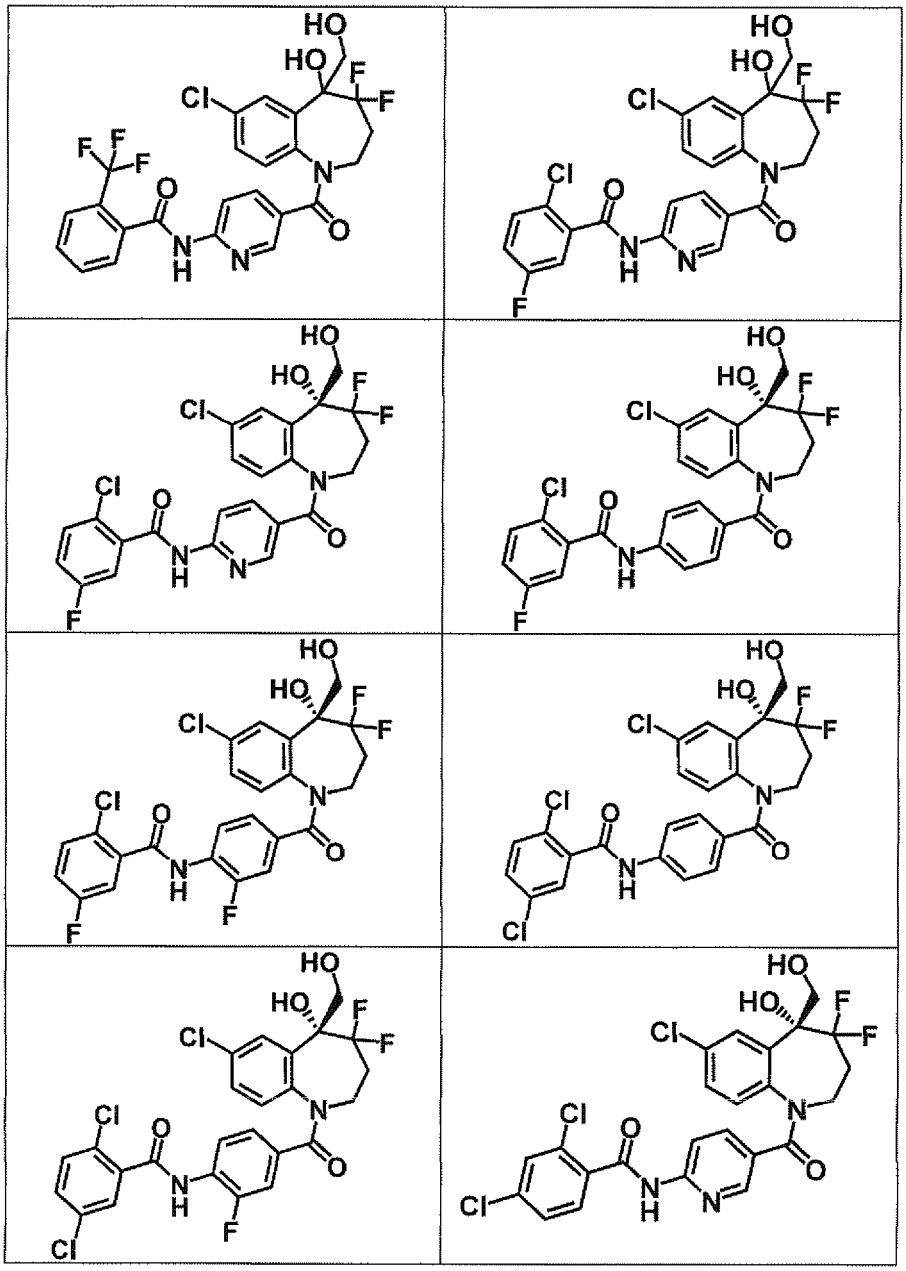
The compound according to any one of claims 1 to 9, wherein R^1 is C_{1-6} alkyl substituted with OH,
Ring A^1 is benzene optionally substituted with halogen, C_{1-6} alkyl, C_{1-6} alkyl-O-, or C_{1-6} alkyl-O-C_{1-6} alkyl-O-; or pyridine optionally substituted with halogen, and
Ring A^2 is benzene optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkyl-O-, halo-C_{1-6} alkyl-O-, C_{3-6} cycloalkyl, optionally substituted phenyl, and pyridyl, the optionally substituted phenyl being phenyl optionally substituted with halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkyl-O-, or halo-C_{1-6} alkyl-O-, or a salt thereof.

[Claim 11]
The compound according to any one of claims 1 to 9, wherein R^1 is C_{1-6} alkyl substituted with OH,
Ring A^1 is benzene optionally substituted with halogen, C_{1-6} alkyl-O-, or halo-C_{1-6} alkyl-O-; or pyridine, and
Ring A^2 is benzene optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, and phenyl optionally substituted with halogen;
pyridine optionally substituted with phenyl or halo-C_{1-6} alkyl; or tetrahydroisoquinoline optionally substituted with 1 to 3 groups independently selected from the group consisting of halogen and oxo, or a salt thereof.

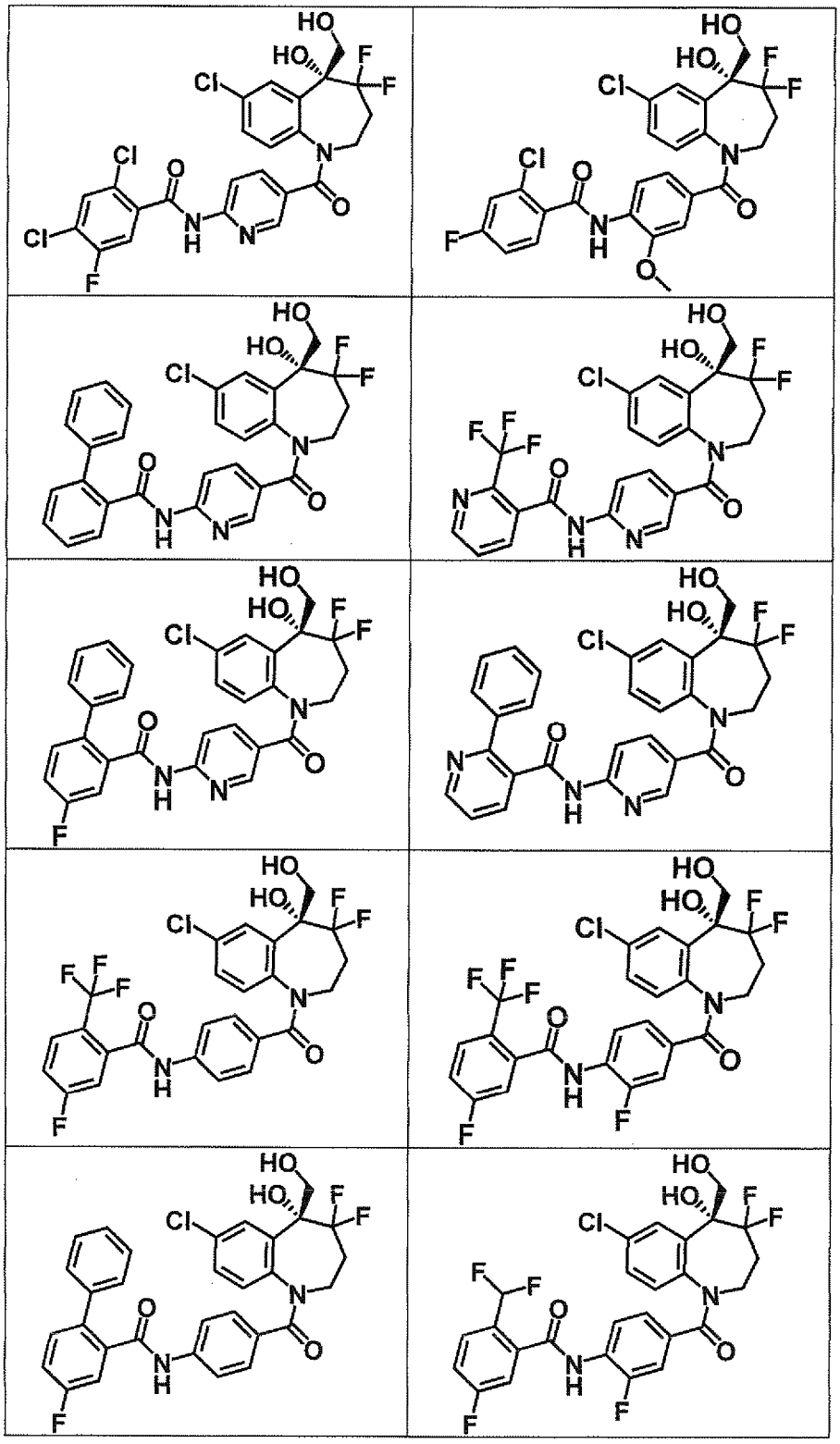
[Claim 12]
The compound according to any one of claims 1 to 11, wherein L is -C(=O)-NH-, or a salt thereof.

[Claim 13]
A compound, or a salt thereof, selected from the following compound group

[Chem. 2-1]



[Chem. 2-2]



5

[Chem. 2-3]

