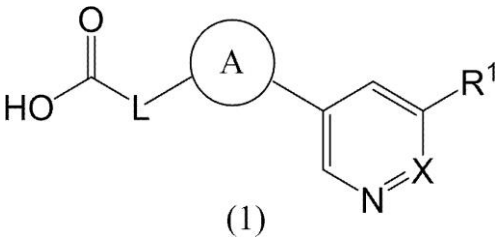
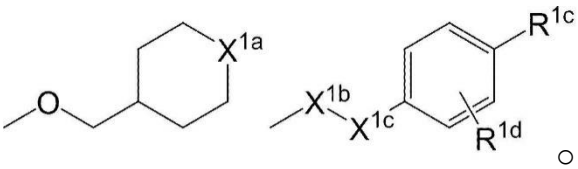
CLAIMS

1. A carboxylic acid compound represented by the following formula (1) or a pharmacologically acceptable salt thereof

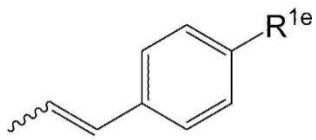


(1)

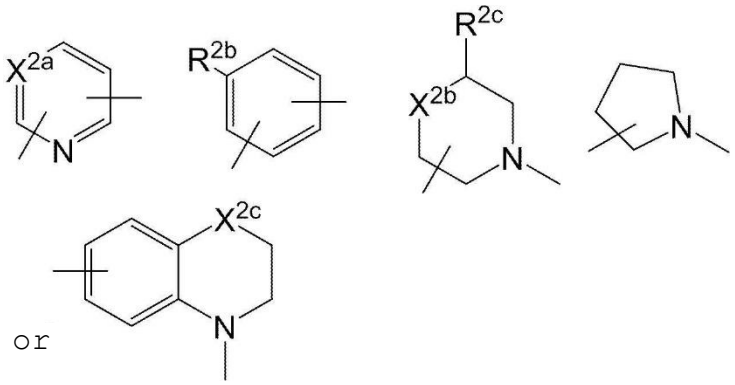
wherein, R^1 is



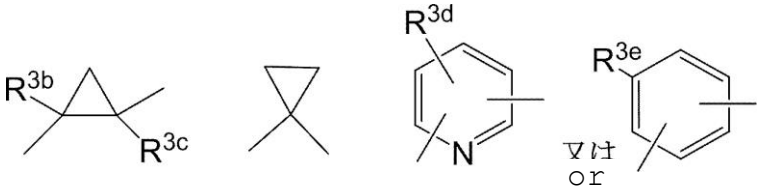
or



wherein X^{1a} is $-C(R^{1a})_2-$ wherein plural symbols R^{1a} are the same or different and each is a hydrogen atom, a halogen atom, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy or C_1-C_6 alkyl, or plural symbols R^{1a} are bonded to form 1,1-C_3-C_6 cycloalkylene or $-NR^{1b}-$
wherein R^{1b} is a hydrogen atom or C_1-C_2 perfluoroalkyl,
X^{1b} and X^{1c} are the same or different and each is -O- or $-CH_2-$
provided X^{1b} and X^{1c} are not simultaneously -O-,
R^{1c} is a hydrogen atom, a halogen atom, C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy, C_1-C_6 alkyl or C_1-C_2 perfluoroalkylthio,
R^{1d} is a hydrogen atom, a halogen atom or C_1-C_6 alkyl, and
R^{1e} is a hydrogen atom, C_1-C_2 perfluoroalkyl or C_1-C_2 perfluoroalkoxy,
X is -N= or -CH=,
ring A is

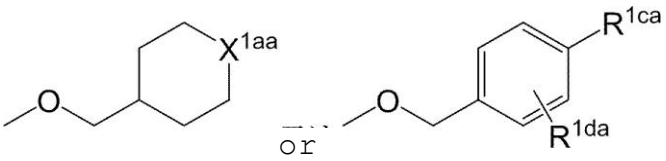


wherein X^{2a} is -N= or $-CR^{2a}$= wherein R^{2a} is a hydrogen atom, a halogen atom, C_1-C_6 alkyl or C_1-C_6 alkoxy,
R^{2b} is a hydrogen atom, a halogen atom, C_1-C_6 alkyl or C_1-C_6 alkoxy,
R^{2c} is a hydrogen atom or C_1-C_6 alkyl,
X^{2b} is -O-, $-NR^{2d}$- wherein R^{2d} is a hydrogen atom or C_1-C_2 perfluoroalkyl or $-CHR^{2e}$- wherein R^{2e} is a hydrogen atom or C_1-C_6 alkyl,
X^{2c} is $-(CH_2)_{n'}$- wherein n' is 0 or 1 or -O-,
L is $-(CHR^{3a})_n$- wherein n is 0, 1, 2 or 3, plural symbols R^{3a} are the same or different and each is a hydrogen atom or a C_1-C_6 alkyl, $-(CH_2)_m$-O-$(CH_2)_{m'}$- wherein m and m' are the same or different and each is 0, 1 or 2, C_2-C_3 alkenylene,



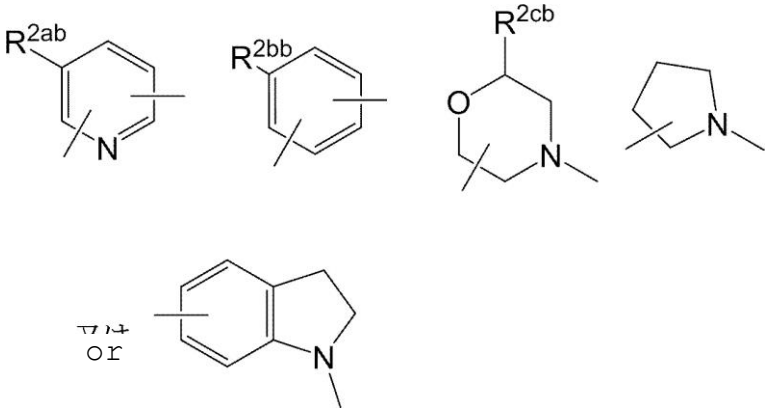
wherein R^{3b} and R^{3c} are the same or different and each is a hydrogen atom or C_1-C_6 alkyl, R^{3d} is a hydrogen atom, C_1-C_6 alkoxy, C_1-C_6 alkyl or C_1-C_2 perfluoroalkyl, R^{3e} is a hydrogen atom, C_1-C_6 alkoxy, C_1-C_6 alkyl or C_1-C_2 perfluoroalkyl.

2. The carboxylic acid compound according to claim 1 wherein R^1 is



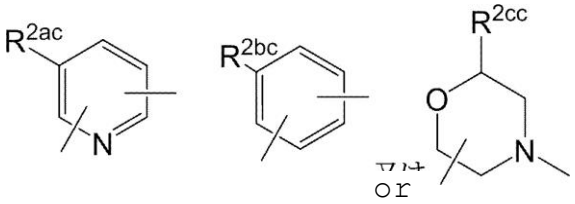
wherein X^{1aa} is $-C(R^{1aa})_2-$ wherein plural symbols R^{1aa} are the same or different and each is a hydrogen atom, C_1-C_2 perfluoroalkyl or C_1-C_6 alkyl, or plural symbols R^{1aa} are bonded to form 1,1-C_3-C_6 cycloalkylene, or $-NR^{1ba}-$ wherein R^{1ba} is a hydrogen atom or C_1-C_2 perfluoroalkyl, R^{1ca} is C_1-C_2 perfluoroalkyl, C_1-C_2 perfluoroalkoxy or C_1-C_2 perfluoroalkylthio, and R^{1da} is a halogen atom or C_1-C_6 alkyl, or a pharmacologically acceptable salt thereof.

3. The carboxylic acid compound according to claim 1 or 2 wherein ring A is



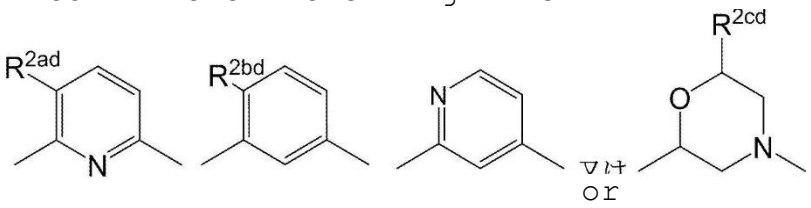
wherein R^{2ab} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, R^{2bb} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, and R^{2cb} is a hydrogen atom or C_1-C_6 alkyl, or a pharmacologically acceptable salt thereof.

4. The carboxylic acid compound according to any one of claims 1 to 3 wherein the ring A is



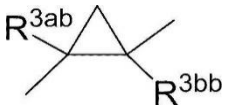
wherein R^{2ac} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, R^{2bc} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, and R^{2cc} is a hydrogen atom or C_1-C_6 alkyl, or a pharmacologically acceptable salt thereof.

5. The carboxylic acid compound according to any one of claims 1 to 4 wherein the ring A is



wherein R^{2ad} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, R^{2bd} is a hydrogen atom, C_1-C_6 alkoxy or C_1-C_6 alkyl, and R^{2cd} is a hydrogen atom or C_1-C_6 alkyl, or a pharmacologically acceptable salt thereof.

6. The carboxylic acid compound according to any one of claims 1 to 5, wherein L is $-(CH_2)_n-$ wherein n is 1 or 2 or



wherein R^{3ab} and R^{3bb} are the same or different and each is a hydrogen atom or C_1-C_6 alkyl, or a pharmacologically acceptable salt thereof.

7. The carboxylic acid compound according to any one of claims 1 to 6, wherein X is -N=, or a pharmacologically acceptable salt thereof.

8. The carboxylic acid compound according to claim 1, wherein the compound represented by the formula (1) is any of the following, or a pharmacologically acceptable salt thereof:
trans-2-[2-methoxy-5-(5-{[4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)phenyl]cyclopropanecarboxylic acid,
trans-2-[2-methoxy-5-(6-{[4-(trifluoromethoxy)benzyl]oxy}pyridazin-4-yl)phenyl]cyclopropanecarboxylic acid,
(1S,2S)-2-[2-methoxy-5-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)phenyl]cyclopropanecarboxylic acid,
(1R,2R)-2-[2-methoxy-5-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)phenyl]cyclopropanecarboxylic acid,
(1S,2S)-2-(5-methoxy-5’-{[4-(trifluoromethoxy)benzyl]oxy}-2,3’-bipyridin-6-yl)cyclopropanecarboxylic acid,
(1S,2S)-2-[3-methoxy-6-(6-{[4-(trifluoromethoxy)benzyl]oxy}pyridazin-4-yl)pyridin-2-yl]cyclopropanecarboxylic acid,
(1S,2S)-2-[3-methoxy-6-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)pyridin-2-yl]cyclopropanecarboxylic acid,
(1S,2S)-2-(5-{[4-(trifluoromethoxy)benzyl]oxy}-3,4’-bipyridin-2’-yl)cyclopropanecarboxylic acid,
(1R,2R)-2-(5-{[4-(trifluoromethoxy)benzyl]oxy}-3,4’-bipyridin-2’-yl)cyclopropanecarboxylic acid,
(1S,2S)-2-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}-3,4’-bipyridin-2’-yl)cyclopropanecarboxylic acid,
(1R,2R)-2-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}-3,4’-bipyridin-2’-yl)cyclopropanecarboxylic acid,
(1S,2S)-2-[4-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)pyridin-2-yl]cyclopropanecarboxylic acid,
(1R,2R)-2-[4-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)pyridin-2-

yl]cyclopropanecarboxylic acid,
(1S,2S)-2-(5′-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}-2,3′-bipyridin-6-yl)cyclopropanecarboxylic acid,
(1R,2R)-2-(5′-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}-2,3′-bipyridin-6-yl)cyclopropanecarboxylic acid,
(1S,2S)-2-[3-methoxy-6-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)pyridin-2-yl]-1-methylcyclopropanecarboxylic acid,
(1R,2R)-2-[3-methoxy-6-(6-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridazin-4-yl)pyridin-2-yl]-1-methylcyclopropanecarboxylic acid,
(1S,2S)-2-[2-ethoxy-5-(6-{[1-(2,2,2-trifluoroethyl)piperidin-4-yl]methoxy}pyridazin-4-yl)phenyl]cyclopropanecarboxylic acid,
3-[(2S)-4-(5-{[4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S)-4-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S)-4-(5-{[3-fluoro-4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S)-4-(5-{[2-fluoro-4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S)-4-(5-{[2-methyl-4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S)-4-(5-{[3-chloro-4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
3-[(2S,6R)-6-methyl-4-(5-{[4-(trifluoromethoxy)benzyl]oxy}pyridin-3-yl)morpholin-2-yl]propanoic acid,
(1S,2S)-2-[(2S)-4-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridin-3-yl)morpholin-2-yl]cyclopropanecarboxylic acid,
(1R,2R)-2-[(2S)-4-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridin-3-yl)morpholin-2-yl]cyclopropanecarboxylic acid,
(1R,2R)-2-[(2R)-4-(5-{[trans-4-

(trifluoromethyl)cyclohexyl]methoxy}pyridin-3-yl)morpholin-2-yl]cyclopropanecarboxylic acid, or
(1S,2S)-2-[(2R)-4-(5-{[trans-4-(trifluoromethyl)cyclohexyl]methoxy}pyridin-3-yl)morpholin-2-yl]cyclopropanecarboxylic acid.

9. A pharmaceutical composition comprising the carboxylic acid compound according to any one of claims 1 to 8, or a pharmacologically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. The pharmaceutical composition according to claim 9, which is used as an autotaxin inhibitor.

11. The pharmaceutical composition according to claim 9, which is used for the treatment or prophylaxis of a disease involving autotaxin.

12. The pharmaceutical composition according to claim 11, wherein the disease involving autotaxin is cancer or tumor, a fibrotic disease, an inflammatory disease, an ophthalmic disease, a urological disease, type II diabetes-related obesity or an acute coronary syndrome.

13. The pharmaceutical composition according to claim 12, wherein the cancer or tumor is malignant melanoma, brain tumor, neuroblastoma, glioblastoma multiforme, EBV positive Hodgkin lymphoma, glioblastoma, non-small cell lung cancer, lung tumor, breast tumor, ovary tumor, pancreas tumor, prostate intraepithelial tumor, prostate tumor, thyroid gland tumor, follicular lymphoma, liver tumor or renal cell carcinoma.

14. The pharmaceutical composition according to claim 12, wherein the fibrotic disease is lung fibrosis, scleroderma, hepatic fibrosis, renal fibrosis, diabetic nephropathy or atherosclerosis.

15. The pharmaceutical composition according to claim 14, wherein the fibrotic disease is lung fibrosis, scleroderma, hepatic fibrosis or renal fibrosis.

16. The pharmaceutical composition according to claim 12, wherein the inflammatory disease is asthma, COPD, rheumatoid arthritis, arthritis deformans, NASH, NAFLD, inflammatory bowel disease, Crohn’s disease, ulcerative colitis, neuropathic pain or pruritus.

17. The pharmaceutical composition according to claim 16, wherein the inflammatory disease is asthma or COPD.

18. The pharmaceutical composition according to claim 16, wherein the inflammatory disease is rheumatoid arthritis or arthritis deformans.

19. The pharmaceutical composition according to claim 16, wherein the inflammatory disease is NASH or NAFLD.

20. The pharmaceutical composition according to claim 16, wherein the inflammatory disease is an inflammatory bowel disease, a Crohn’s disease or ulcerative colitis.

21. The pharmaceutical composition according to claim 16, wherein the inflammatory disease is neuropathic pain or pruritus.

22. The pharmaceutical composition according to claim 12, wherein the acute coronary syndrome is angina pectoris or myocardial infarction.

23. The pharmaceutical composition according to claim 12, wherein the ophthalmic disease is glaucoma.

24. The pharmaceutical composition according to claim 12, wherein the urological disease is prostatomegaly.

~~25. A method for treating or preventing a disease involving autotaxin in a test subject comprising administering an effective amount of the carboxylic acid compound according to any one of claims 1 to 8 or a pharmacologically acceptable salt thereof to the test subject.~~

~~26. The method according to claim 25, wherein the disease involving autotaxin is cancer or tumor, a fibrotic disease, an inflammatory disease, an ophthalmic disease, a urological disease, type II diabetes-related obesity or an acute coronary syndrome.~~

25~~7~~. Use of the carboxylic acid compound according to any one of claims 1 to 8 or a pharmacologically acceptable salt thereof ~~in the production of an agent~~in the manufacture of medicament for treating or preventing a disease involving autotaxin.

26~~8~~. The use according to claim 25~~7~~, wherein the disease involving autotaxin is cancer or tumor, a fibrotic disease, an inflammatory disease, an ophthalmic disease, a urological disease, type II diabetes-related obesity or acute coronary syndrome.