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(54) Benævnelse: **PIPERIDINDERIVATER SOM GPR119-AGONISTER**

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WO-A1-02/06196
WO-A1-02/34739
WO-A1-2008/025798
WO-A1-2009/106561
WO-A1-2010/006191
WO-A1-2011/008663
WO-A2-2008/070692
DE-A1-102004 037 515

Fortsættes ...

DESCRIPTION

Technical Field

[0001] The present invention relates to novel compounds that are useful in the treatment of metabolic disorders, including diabetes mellitus (types I and II) and related disorders, pharmaceutical compositions comprising the compounds, and therapeutic uses for the compounds.

Background Art

[0002] Diabetes mellitus is a severe disorder that affects more and more human in the world. The forecast of International Diabetes Federation alludes that the total worldwide number of human with diabetes mellitus will be 380,000,000 (three hundred eighty million) until 2025. The attack rate of diabetes mellitus is increasing along with a growing tendency of obesity in many countries. The severe effect of diabetes mellitus includes the increased risk of stroke, heart disease, kidney failure, blindness and amputation. Cardiovascular disorders are more than 70% leading cause of all death in human with Type II diabetes (T2DM) [B. Pourcet et al. Expert Opin. Emerging Drugs 2006, 11, 379-401].

[0003] Diabetes mellitus is characterized in the insulin secretion and/or the disturbance of insulin signal reaction in peripheral tissues. There are two types' diabetes mellitus, that is, insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus. Most of the patients with diabetes mellitus are suffering from non-insulin-dependent diabetes mellitus, which is known as Type II diabetes or NIDDM. Because of the severe consequence of diabetes mellitus, the control of diabetes mellitus is necessary desperately.

[0004] The treatment of NIDDM generally begins weight loss, healthy diet and exercise program. Although these factors are important especially to dissolve the increased risk of cardiovascular disorders related to diabetes mellitus, they are not effective generally for the control of diabetes mellitus itself. There are many drugs useful for the treatment of diabetes mellitus, including insulin, metformin, sulfonylureas, acarbose, thiazolidinedione, GLP-1 analogue and DPP IV inhibitor. However, some of such treatment agents have a problem including more than one disadvantage of hypoglycemic episodes, weight gain, gastrointestinal problems and loss in responsiveness to therapy over time.

[0005] Although many medicines for the treatment of diabetes mellitus through the various mechanisms are approved, lots of medicines still are under clinical appraisal, and there still is need to develop novel compound for the treatment of diabetes mellitus. Recently, the research result showing the observation that beta-cell function of diabetes patient declines over time regardless of success or failure of treatment with diet, sulfonylureas, metformin or insulin has been published [R. R. Holman Metabolism 2006, 55, S2-S5].

[0006] GPR119 is a protein consisted of 335 amino acids expressed in beta-cell of pancreatic islet

[Z.-L. Chu et al., Endocrinol. 2007, J 48, 2601-2609] and gastro-intestinal tract [Z.-L. Chu et. al. Endocrinol. 2008, 149, 2038-2047]. Said protein belongs to the receptor family coupled to G-protein, and some candidates including oleoylethanolamide (OEA), N-oleoyldopamine and olvanil are suggested as intrinsic ligand [H. A. Overton et al. Brit. J. Pharmacol. 2008, 513, S76-81].

[0007] It is supported from many research using cell line and animal that GPR119 may perform a certain function in glucose-dependent secretion of insulin, and targeting to GPR119 receptor may be effective to the treatment of diabetes mellitus. Activation of GPR119 receptor by lisophosphatidilcholine forces up the glucose-dependent secretion in the pancreas beta-cell line of mice, and the insulin secretion can be blocked by GPR119-specific siRNA [T. Soga et al. Biochem. Biophys. Res. Commun. 2005, 326]

[0008] Therefore, GPR119 receptor activator is needed for the treatment of disorders, such as diabetes mellitus.

[0009] WO 2011/008663 A1 discloses GPR119 agonist compounds, comprising a 1,2,3,6-tetrahydropyridine ring.

[0010] WO 2009/106561 A1 discloses GPR119 agonist compounds, comprising different substituents at the piperidyl moiety.

Disclosure

Technical Problem

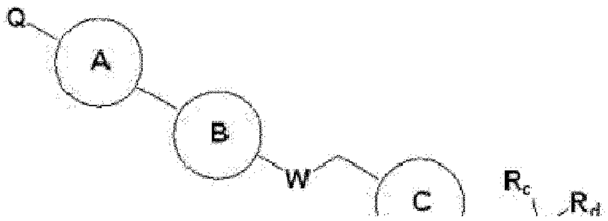
[0011] The object of this invention is to provide a novel piperidine derivative, stereoisomers thereof, pharmaceutically acceptable salts thereof, and a preparing method thereof.

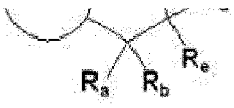
[0012] The other object of this invention is to provide a novel piperidine derivative being able to control GPR119 activity with low adverse effect, stereoisomers thereof, pharmaceutically acceptable salts thereof, and a preparing method thereof.

Technical Solution

[0013] To achieve the above objects, the present invention provides a novel piperidine derivative of the following formula 1, stereoisomers thereof, and pharmaceutically acceptable salts thereof:

[Formula 1]





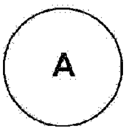
wherein

W is O;

R_a and R_b are each independently H;

R_c is -F or -CF_3;

R_d and R_e are each independently selected from the group consisting of -CH_3 and - CH_2CH_3.



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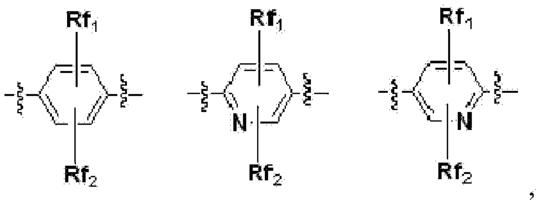
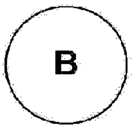


wherein Rf_1 and Rf_2 are each independently H, -F or -CN;



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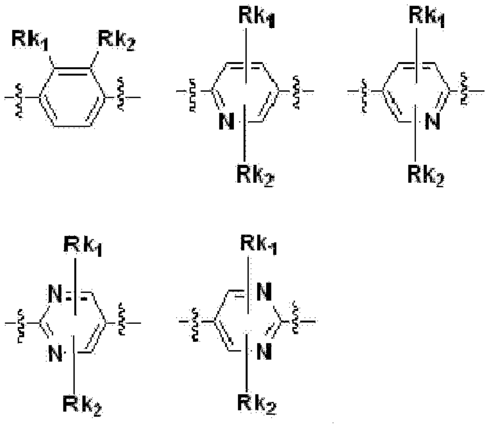
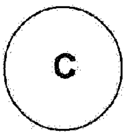


wherein Rk_1 and Rk_2 are each independently H, -F or -CN;



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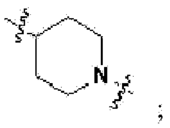

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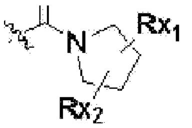
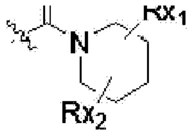
 

,

wherein Rx_1 is -C(O)NH_2 and Rx_2 is H, OH, -F, -CN, -CF_3, -CH_2OH or -C(O)NH_2.

[0014] The compound of formula 1 may be used generally as a form of pharmaceutically acceptable salt thereof. The pharmaceutically acceptable salts thereof include pharmaceutically acceptable base addition salts and acid addition salts, for example, metal salts, such as alkali and alkaline earth metal salts, ammonium salt, organic amine addition salt, amino acid addition salt and sulfonate salt. Acid addition salts include inorganic acid addition salts, such as hydrogen chloride salt, sulfonic acid salt and phosphoric acid salt; and organic acid addition salts, such as alkyl sulfonate, aryl sulfonate, acetate, malate, fumarate, tartrate, citrate and lactate. Examples of metal salts include alkali metal salt, such as lithium salt, sodium salt and potassium salt; alkaline earth metal salts, such as magnesium salt, calcium salt, aluminium salt and zinc salt. Examples of ammonium salt include ammonium salt and tetramethylammonium salt. Examples of organic amine addition salts include salts with morpholine and piperidine. Examples of amino acid addition salts include salts with glycine, phenylalanine, glutamic acid and lysine. Examples of sulfonate salt include mesylate, tosylate and benzenesulfonic acid salts.

[0015] The term of "stereoisomer" means the isomer molecules that have the same molecular formula and bonds, but differ by their three-dimensional orientation.

[0016] Specific examples of preferred compounds of formula 1 according to the present invention include:

Compound 565: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 581: (S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 586: (S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 635: (S)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 644: (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 653: (S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 658: (S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 671: (R)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-

yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 682: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 691: (S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 696: (S)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 705: (2S)-1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 706: (S)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 710: (S)-1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 717: (S)-1-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 722: (S)-1-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 730: (S)-1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 750: (S)-1-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 753: (S)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 755: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 756: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 757: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 760: (S)-1-(4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 770: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 774: (S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidin-2-carboxamide

Compound 778: (S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamide

Compound 782: (S)-1-(5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

Compound 792: 1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 798: 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 799: 1-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 800: 1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 801: 1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 802: 1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 803: 1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 804: 1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-4-carboxamide

Compound 805: 1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-4-carboxamide

Compound 806: (R)-1-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 807: (S)-1-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 813: 1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-4-carboxamide

Compound 814: 1 -(4'-((1 -(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3 -fluorobiphenylcarbonyl)piperidine-4-carboxamide

Compound 816: (R)-1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 817: (S)-1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 818: 1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide

Compound 819: (R)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 820: (S)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 821: (R)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-2-carboxamide

Compound 822: (R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-2-carboxamide

Compound 823: (R)-1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 824: (S)-1-(2-fluoro-4-(5 -((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidine-2-carboxamide

Compound 825: (2R)-1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 828: (S)-1-(4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 831: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 832: (S)-1-(4'-((1 -(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 833: (S)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 837: (S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 843: (S)-1-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 847: (S)-1-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 854: (R)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 855: (S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 856: 1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-

yl)benzoyl)piperidine-4-carboxamide

Compound 860: (2S)-1-(2,6'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 861: (S)-1-(3,6'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 862: (R)-1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 863: (S)-1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 864: 1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-4-carboxamide

Compound 866: (S)-1-(4'-((1 -(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 872: (R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 873: (R)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 874: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 875: (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 876: (S)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 877: (R)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 878: (S)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 879: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 880: (R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 881: (R)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 882: (R)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 884: (S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 885: (R)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxamide

Compound 886: (R)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 887: (S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 891: (S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 895: (S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 896: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 898: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorobenzoyl)pyrrolidine-2-carboxamide

Compound 901: (S)-1-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 906: (S)-1-(5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

Compound 909: (2S)-1-(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 913: (S)-1-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 918: (S)-1-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 922: (S)-1-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 933: (2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 934: (2S,4R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxamide

Compound 935: (S)-1-(5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

Compound 937: (S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 938: (S)-1-(3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 965: (S)-1-(3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 969: (S)-1-(3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 973: (S)-1-(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 977: (S)-1-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 981: (S)-1-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1000: (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1004: (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1015: (R)-1-(3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 1028: (S)-1-(2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1030: (R)-1-(2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide

Compound 1031: (S)-1-(2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1032: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1036: (S)-1-(5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

Compound 1037: (R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidine-2-carboxamide

Compound 1051: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1053: (R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-

yl)benzoyl)piperidine-2-carboxamide

Compound 1054: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoyl)pyrrolidine-2-carboxamide

Compound 1055: (R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoyl)piperidine-2-carboxamide

Compound 1057: (R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoyl)piperidine-2-carboxamide

Compound 1067: (2S,4R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxamide

Compound 1076: (R)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 1079: (S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidine-2-carboxamide

Compound 1082: (S)-1-(5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxamide

Compound 1099: (2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1100: (2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxamide

Compound 1119: (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1120: (R)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)piperidine-2-carboxamide

Compound 1124: (S)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide; and

Compound 1125: (R)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide.

[0017] Specific examples of more preferred compounds of formula 1 according to the present invention include:

Compound 770: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

Compound 896: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

Compound 938: (S)-1-(3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide;

Compound 1028: (S)-1-(2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide; and

Compound 1032: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxamide.

[0018] The present invention also provides pharmaceutical composition comprising the piperidine derivative of the formula 1, stereoisomers thereof, or pharmaceutically acceptable salts thereof; and pharmaceutically acceptable carriers thereof.

[0019] Preferably, the composition is used for treatment of a disease associated with GPR119 agonist.

[0020] Preferably, said disease associated with GPR119 agonist is diabetes mellitus, and more preferably, Type II diabetes mellitus.

Advantageous Effects

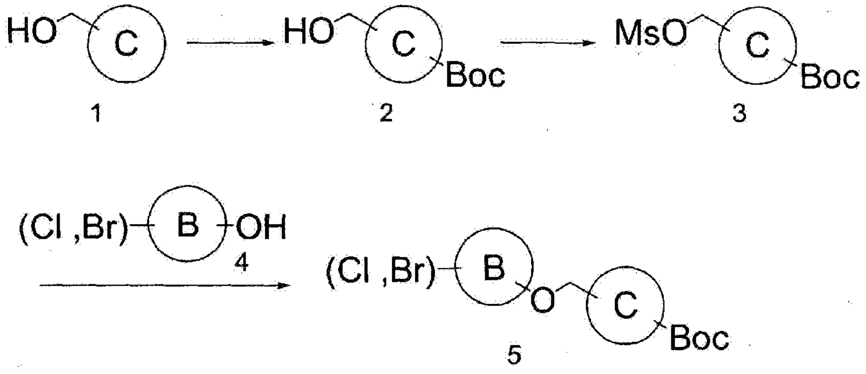
[0021] The present invention can provide a novel piperidine derivative, stereoisomers thereof, and pharmaceutically acceptable salts thereof.

[0022] In addition, the present invention can provide a novel piperidine derivative being able to control GPR119 activity with low adverse effect, stereoisomers thereof, and pharmaceutically acceptable salts thereof.

Synthetic Schemes

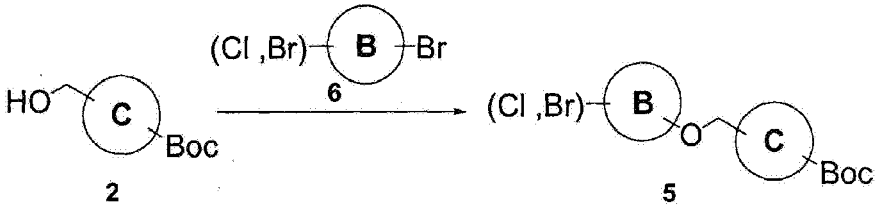
[0023] The intermediate 5 can be synthesized according to the following reaction schemes 1 and 2.

[Reaction Scheme 1]



[0024] As shown in the reaction scheme 1, Boc protecting group is introduced into the amine of compound 1. Hydroxyl group is activated with MsCl, and substituted with aryl alcohol of formula 4 to synthesize the desired compound of formula 5.

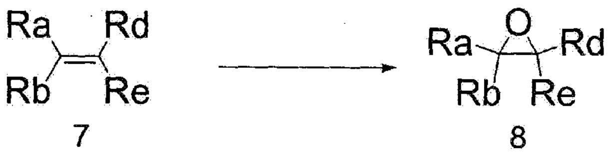
[Reaction Scheme 2]



[0025] As shown in the reaction scheme 2, bromo or chloro compound 6 is substituted with compound 2 to prepare compound 5.

[0026] The intermediate 8 can be synthesized according to the following reaction scheme 3.

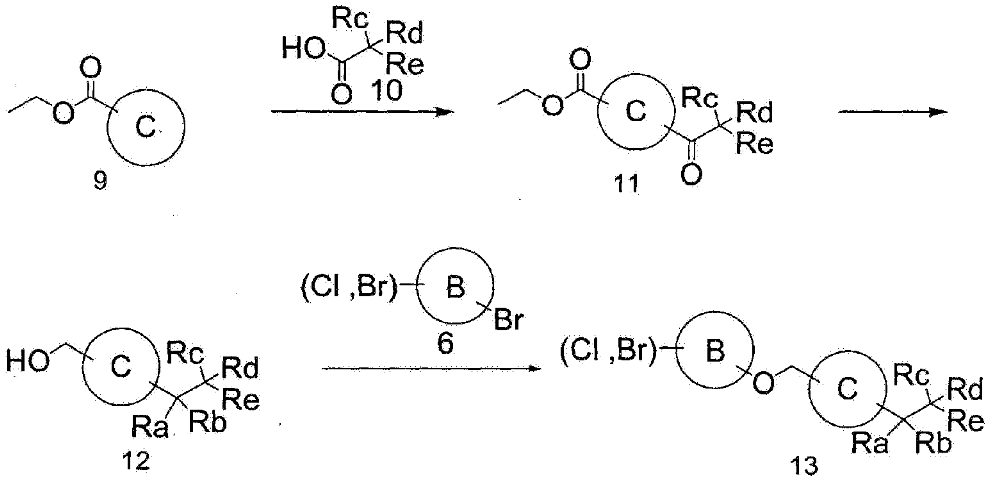
[Reaction Scheme 3]



[0027] As shown in the reaction scheme 3, compound 8 is prepared through the oxidation reaction of compound 7.

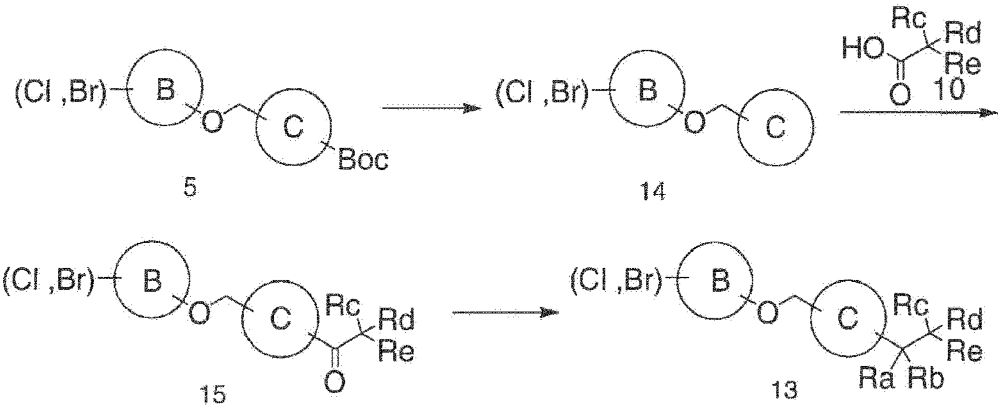
[0028] The intermediate 13 can be synthesized according to the following reaction schemes 4, 5 and 6.

[Reaction Scheme 4]



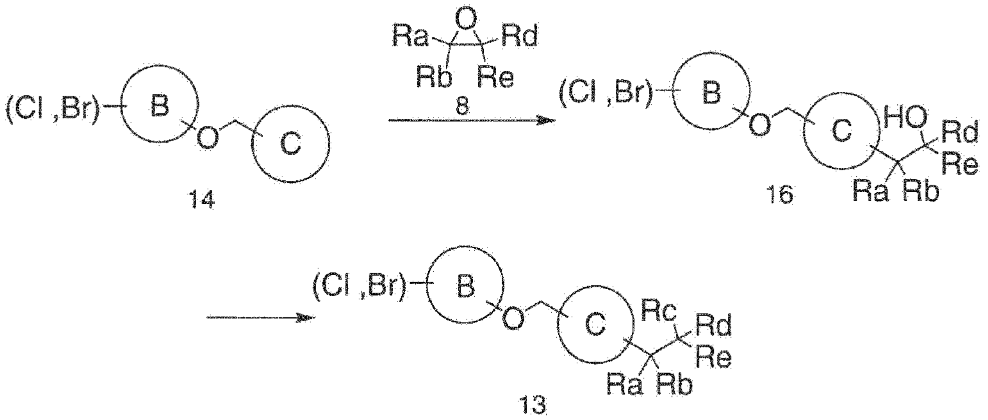
[0029] As shown in the reaction scheme 4, compound 11 is prepared by amide bond formation of compound 9 with compound 10, and then subjected to reduction thereby to obtain compound 12. Finally, the intermediate 13 is prepared through the substitution reaction of compound 12.

[Reaction Scheme 5]



[0030] As shown in the reaction scheme 5, the protecting group of compound 5 is removed, and subjected to the formation of amide bond with compound 10 to prepare compound 15. Finally, compound 13 is prepared through reduction.

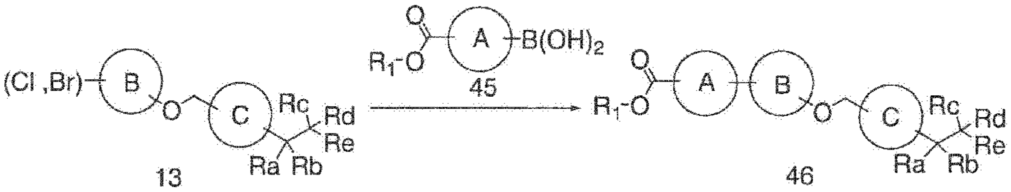
[Reaction Scheme 6]



[0031] As shown in the reaction scheme 6, compound 16 is prepared using compound 14 and oxirane compound 8, and then hydroxyl group of compound 16 is substituted with fluoride to prepare compound 13.

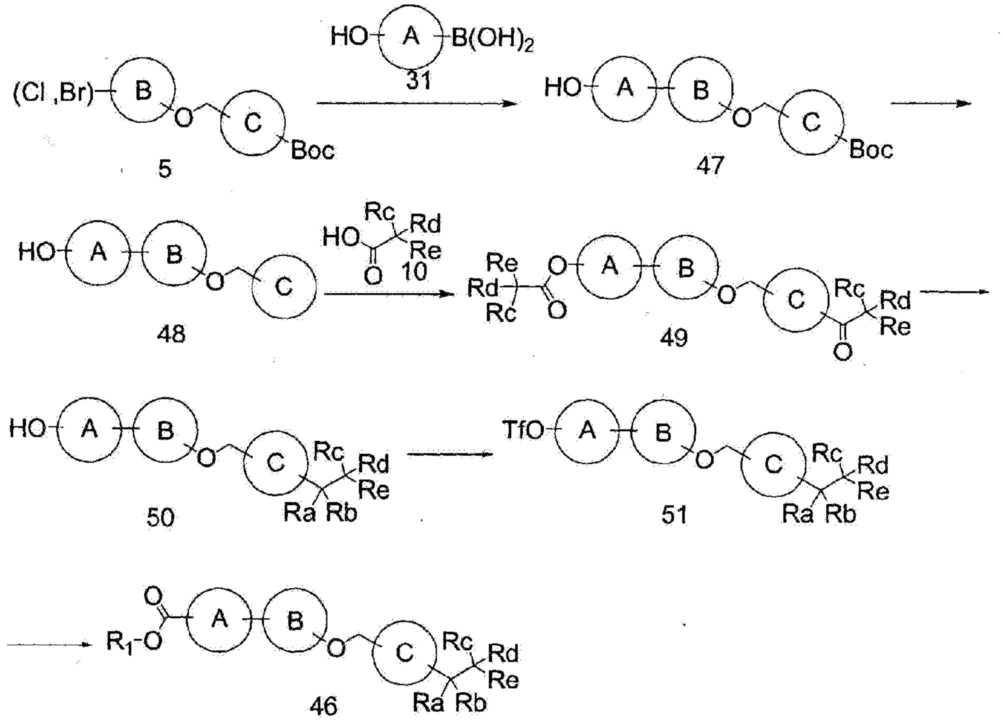
[0032] The intermediate 46 can be synthesized according to the following reaction schemes 17, 18, 19 and 20.

[Reaction Scheme 17]



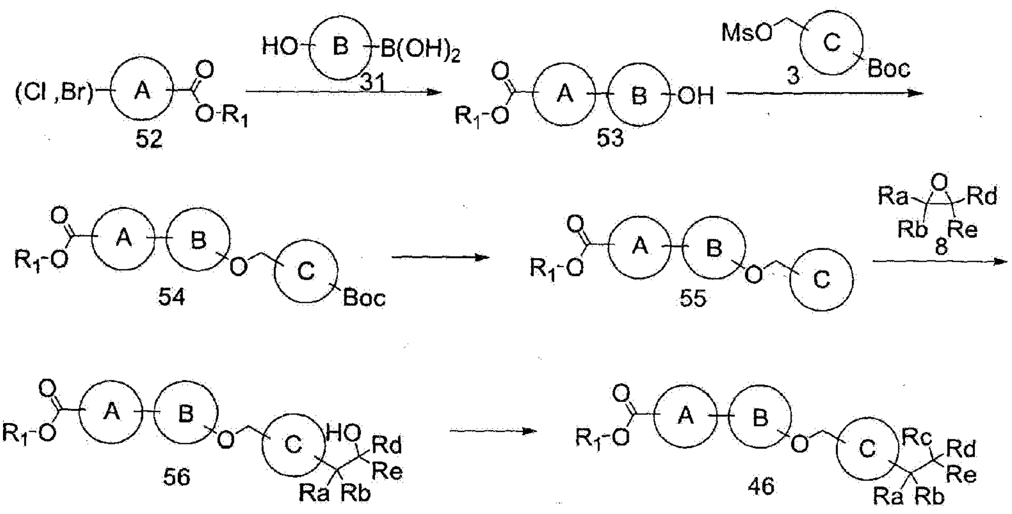
[0033] As shown in the reaction scheme 17, compound 13 is subjected to Suzuki coupling reaction with boronic acid compound 45 to prepare compound 46.

[Reaction Scheme 18]



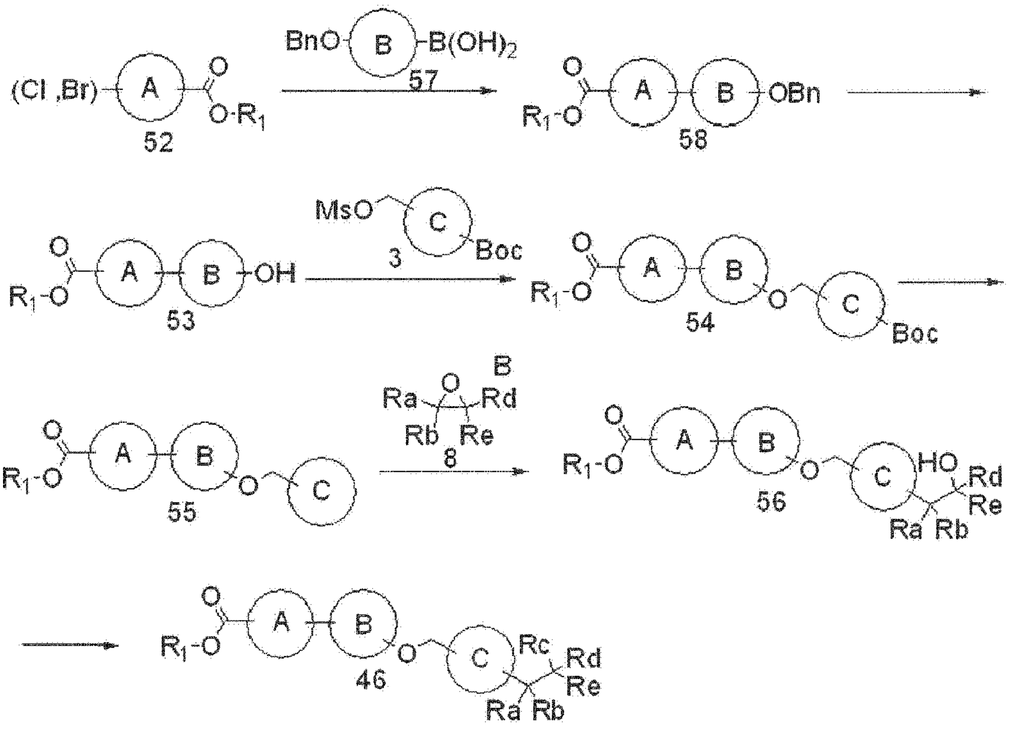
[0034] As shown in the reaction scheme 18, compound 5 is subjected to Suzuki coupling reaction with boronic acid compound 31 to prepare compound 47. The protecting group is removed using acid, following with the formation of amide bond with compound 10 to prepare compound 49. Through the reduction, the removal of carbonyl group from amide and the reduction of ester group proceeds at the same time, and then the formed hydroxyl group is activated with triflate group to prepare compound 51. Finally, compound 46 is synthesized using palladium catalyst and CO gas.

[Reaction Scheme 19]



[0035] As shown in the reaction scheme 19, compound 52 is subjected to Suzuki coupling reaction with boronic acid compound 31 to prepare compound 53. Compound 53 is subjected to the substitution reaction with compound 3 to prepare compound 54. The protecting group of compound 54 is removed. The obtained compound 55 is reacted with oxirane compound 8 to prepare compound 56. Hydroxyl group of compound 56 is substituted with fluoride to obtained compound 46.

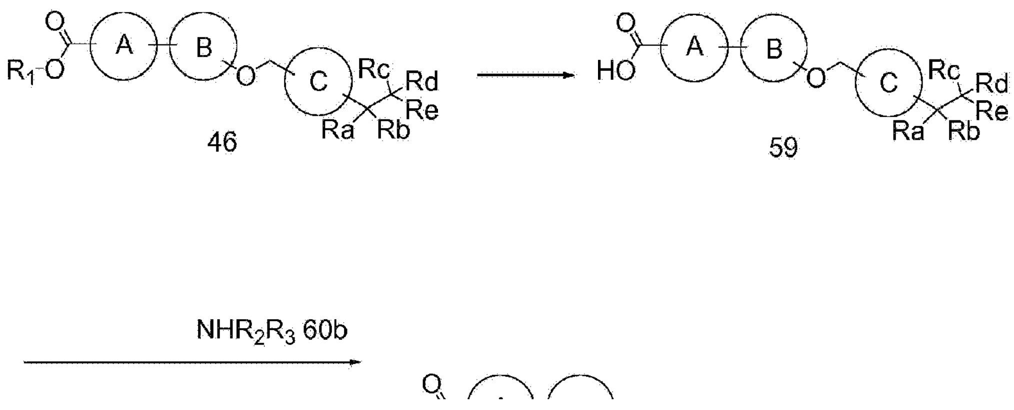
[Reaction Scheme 20]

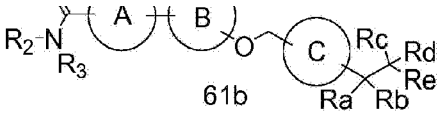


[0036] As shown in the reaction scheme 20, compound 52 is subjected to Suzuki coupling reaction with boronic acid compound 57 to prepare compound 58. Using palladium and hydrogen, compound 53 is synthesized, and then subjected to the substitution reaction with compound 3 to prepare compound 54. After removal of the protecting group from compound 54, compound 55 is reacted with oxirane compound 8 to prepare compound 56. Hydroxyl group of compound 56 is substituted with fluoride to obtain compound 46.

[0037] The compound 61 that Q is $-C(O)NR_2R_3$ in formula 1 can be synthesized according to the following reaction scheme 21.

[Reaction Scheme 21]



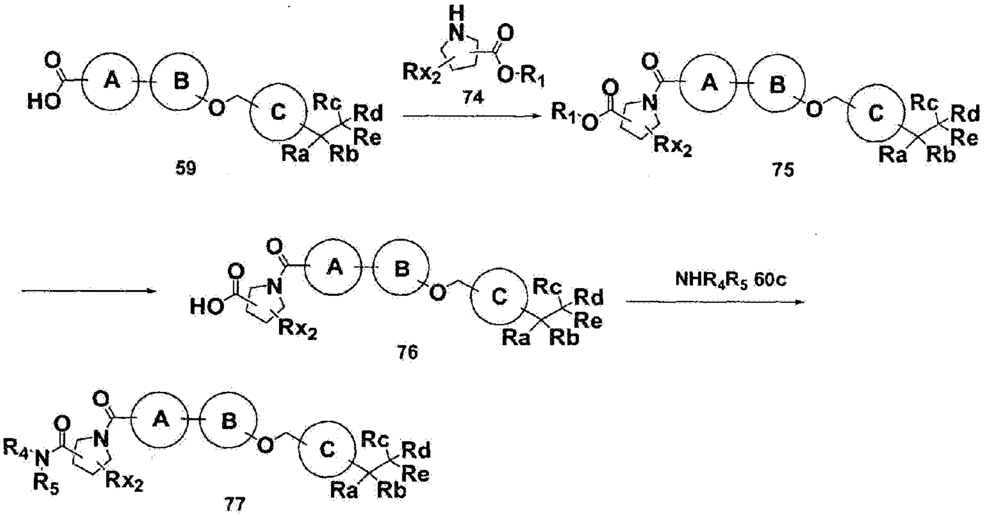


61b

[0038] As shown in the reaction scheme 21, compound 46 is hydrolyzed to prepare compound 59. Finally, compound 59 is subjected to the formation of amide bond with amine compound 60 to prepare compound 61b.

[0039] The compound 77 that Q or -C(O)NR$_2$R$_3$ in formula 1 can be synthesized according to the following reaction scheme 26

[Reaction Scheme 26]



[0040] As shown in the reaction scheme 26, compound 59 is subjected to the formation of amide bond with amine compound 74 to prepare compound 75. Compound 75 is hydrolyzed to prepare compound 76. And compound 76 is subjected to the formation of amide bond with amine compound 60 to prepare compound 77.

Abbreviations

[0041] The following abbreviations and terms have the indicated meanings throughout:

Ac

= acetyl

Boc

= t-butoxycarbonyl

BOP

= benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate

Bu

= butyl

DAST

= diethylaminosulfur trifluoride
DCM
= dichloromethane = methylene chloride = MC = CH_2Cl_2
DIPEA
= N,N-diisopropylethylamine
DME
= dimethoxyethane
DMF
= N,N-dimethylformamide
DMSO
= dimethyl sulfoxide
dppp
= 1,3-Bis(diphenylphosphino)propane
EDC
= 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide = EDCI
Et
= ethyl
EtOAc
= ethyl acetate = EA
EtOH
= ethanol
HOBt
= 1-hydroxybenzotriazole
HX
= hexane
LAH
= lithium aluminium hydride
m-CPBA
= meta-chloroperoxybenzoic acid
Me
= methyl
MeCN
= methyl cyanide = acetonitrile = ACN
MeOH
= methanol
MsCl
= methanesulfonyl chloride
$Pd(dbpf)Cl_2$
= [1,1'-Bis(di-tert-butylphosphino)ferrocene]dichloropalladium(II)
$Pd(dppf)Cl_2$
= [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
PyBOP
= benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate
t- or *tert-*
= tertiary
TEA

= triethylamine

TFA

= trifluoroacetic acid

THF

= tetrahydrofuran

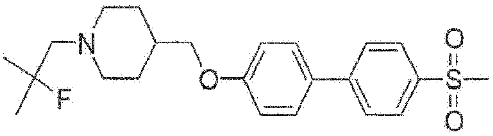
Best Mode for Carrying out the Invention

Preparation of Compounds and Preparing Method of Compounds

[0042] The compound of formula 1 can be prepared by the method known from various references. Hereinafter, the preparing method for compound of formula 1 and comparative compounds will be described in further detail with reaction scheme.

Example 1. Comparative compound 431: 1-(2-fluoro-2-methylpropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

[0043]



Step 1. t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate: 4-Piperidinemethanol (10.00 g, 86.83 mmol) was dissolved in CH_2Cl_2 200 mL, and then cooled with ice bath. Di-t-butyl dicarbonate was added thereto, following with increasing temperature slowly to room temperature and stirring for 3 hours. The obtained reaction mixture was washed in order with water, saturated NH_4Cl aqueous solution and saturated aqueous brine solution. The washed reaction mixture was dried over $MgSO_4$ and filtered. After removing solid material, organic solvent was removed from the filtrate under reduced pressure to yield the title compound as white solid (18.35 g, 98%)

Step 2. t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate: t-Butyl 4-(hydroxymethyl)piperidin-1-carboxylate (18.35 g, 85.24 mmol) was dissolved in CH_2Cl_2 200 mL. Et_3N (35.45 mL, 255.71 mmol) was added thereto, and then the mixture was cooled with ice bath. MsCl (9.83 mL, 127.86 mmol) was added dropwise slowly thereto, following with increasing temperature slowly to room temperature and stirring for 15 hours. The obtained reaction mixture was washed in order with 1 N HCl, saturated $NaHCO_3$ aqueous solution and saturated aqueous brine solution. The washed reaction mixture was dried over $MgSO_4$ and filtered. After removing solid material, organic solvent was removed from the filtrate under reduced pressure to yield the title compound as yellow solid (24.80 g, 99%).

Step 3. t-butyl 4-((4-bromophenoxy)methyl)piperidin-1-carboxylate: t-Butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (13.63 g, 46.46 mmol) and 4-bromophenol (8.34 g, 46.46 mmol) were dissolved in DMF 100 mL, and then K_2CO_3 (19.26 g, 139.38 mmol) was added thereto, following with stirring at 80 °C for 15 hours. Sufficient amount of water was added thereto, following with filtering to obtain a solid. The obtained solid was recrystallized with MeOH to yield the title compound as white solid (11.31 g, 66%). The obtained filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10 % EtOAc/hexane) further to yield the title compound as white solid (2.38 g, 14%).

Step 4. t-butyl 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-carboxylate: t-Butyl 4-((4-bromophenoxy)methyl)piperidin-1-carboxylate (3.00 g, 8.10 mmol) and 4-(methylsulfonyl)phenylboronic acid (1.78 g, 8.91 mmol) were dissolved in DME 15 mL, and then water 5 mL was added thereto. $Pd(dbpf)Cl_2$ (528 mg, 0.81 mmol) and Cs_2CO_3 (3.96 g, 12.15 mmol) were added thereto, and refluxed with heating at 80 °C for a day. The reaction mixture was diluted with water, and extracted with EtOAc three times. The obtained organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (50 % EtOAc/hexane) to yield the title compound as yellow solid (2.50 g, 69%).

Step 5. 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate: t-Butyl 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-carboxylate (2.50 g, 5.61 mmol) was dissolved in CH_2Cl_2 8 mL, and then TFA 644 μL was added thereto, following with stirring at room temperature for 3 hours. The obtained reaction mixture was filtered to yield the title compound as white solid (2.40 g, 96%). Alternatively, 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate (3.78 g, 8.48 mmol) was dissolved in dioxane 20 mL, and then 4 M HCl solution (14.85 mL, 59.39 mmol) was added thereto, following with stirring at room temperature for 1 hour. The reaction mixture was suspended in EtOAc, and then filtered to yield the title compound as white solid (3.15 g, 97%).

Step 6. 2-methyl-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-ol: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate (100 mg, 0.22 mmol) and K_2CO_3 (15 mg, 0.11 mmol) were suspended in EtOH 1 mL. Water 0.5 mL was added thereto, and then suspended with warming. 2,2-Dimethyl oxirane (0.19 mL, 2.18 mmol) was added thereto, and then the reaction was performed at 110 °C for 20 minutes with the radiation of micro-wave ray. A little of water was added thereto, and filtered to yield the title compound as white solid (90 mg, 99%).

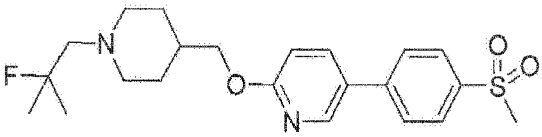
Step 7. Comparative compound 431: 2-Methyl-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-ol (50 mg, 0.12 mmol) was dissolved in CH_2Cl_2 2 mL, and then Deoxo-Fluor (24 μL, 0.13 mmol) was added thereto. After stirring at room temperature for 3 hours, a saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and then filtered to remove the solid materials. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to yield the title compound as white solid (40 mg, 79%).

1H NMR (400 MHz, $CDCl_3$) δ 8.02 - 7.96 (m, 2 H), 7.78 - 7.71 (m, 2 H), 7.59 - 7.54 (m, 2 H), 7.04 -

6.98 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.10 (s, 3 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.23 - 2.13 (m, 2 H), 1.88 - 1.75 (m, 3 H), 1.48 - 1.40 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 420 (M+ + H).

Example 2. Comparative compound 596: 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)phenyl)pyridine

[0044]



Step 1. t-butyl 4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-carboxylate: *N*-Boc-4-piperidinemethanol (500 mg, 2.32 mmol) was dissolved in DMF 10 mL. 2,5-bromopyridine (600 mg, 2.55 mmol) and 95 % NaH (83 mg, 3.48 mmol) were added thereto slowly at 0 °C, following with increasing the temperature and stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was extracted with EtOAc. The obtained organic layer was washed three times with saturated NH_4Cl aqueous solution and saturated aqueous brine solution. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-20 % EtOAc/hexane) to yield the title compound as white solid (67 mg, 78%).

Step 2. t-butyl 4-((5-(4-(methylsulfonyl)phenyl)pyridine-2-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-carboxylate (0.65 g, 1.80 mmol) was dissolved in dioxane 20 mL and H_2O 5 mL. 4-methylsulfonylphenylboronic acid (0.36 g, 1.80 mmol), Pd(dbpf)Cl_2 (59 mg, 0.09 mmol) and Cs_2CO_3 (1.17 g, 3.61 mmol) was added thereto, and refluxed with stirring for 2 hours. After the completion of the reaction, the reaction mixture was filtered through Celite. The obtained filtrate was concentrated under reduced pressure. The obtained concentrate was dissolved in CH_2Cl_2, washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-50 % EtOAc/hexane) to yield the title compound as white solid (0.67 g, 83%).

Step 3. 5-(4-(methylsulfonyl)phenyl)-2-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((5-(4-(methylsulfonyl)phenyl)pyridine-2-yloxy)methyl)piperidin-1-carboxylate (0.2 g, 0.45 mmol) was dissolved in MeOH. 1.25 M HCl in MeOH (2.24 mmol, 1.8 mL) was added thereto. The solvent was removed completely and the residue was washed with ether to yield the title compound as white solid (0.15 g, 88%). The product was used without further purification.

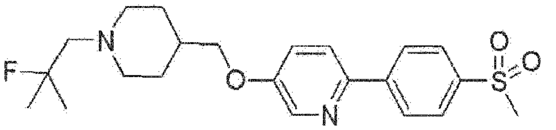
Step 4. 2-methyl-1-(4-((5-(4-(methylsulfonyl)phenyl)pyridine-2-yloxy)methyl)piperidin-1-yl)propan-2-ol: 5-(4-(methylsulfonyl)phenyl)-2-(piperidin-4-ylmethoxy)pyridine hydrochloride (0.20 g, 0.58 mmol) was dissolved in EtOH 3 mL and H_2O 3 mL. Isobutylene oxide (0.42 g, 5.77 mmol) and K_2CO_3 (0.40 g, 2.89 mmol) were added slowly thereto. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The concentrate was dissolved in CH_2Cl_2 , and washed with water three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-5 % $MeOH/CH_2Cl_2$) to yield the title compound as white solid (0.15 g, 62%).

Step 5. Comparative compound 596: 2-methyl-1-(4-((5-(4-(methylsulfonyl)phenyl)pyridine-2-yloxy)methyl)piperidin-1-yl)propan-2-ol (0.15 g, 0.36 mmol) was dissolved in CH_2Cl_2 2 mL, and then Deoxo-Fluor (0.34 mL, 1.80 mmol) was added slowly thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the obtained CH_2Cl_2 layer was washed several times with water. The organic layer was concentrated under reduced pressure. The organic layer was distilled under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-30 % EtOAc/hexane) to yield the title compound as white solid (0.1 g, 66%).

1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1 H, J = 2.5 Hz), 8.02 (d, 2 H, J = 12.0 Hz), 7.82 (dd, 1 H, J = 8.6, 2.6 Hz), 7.72 (d, 2 H, J = 8.4 Hz), 6.86 (d, 1 H, J = 8.6 Hz), 4.22 - 4.20 (m, 2 H), 3.10 (s, 3 H), 3.0 (brs, 2 H), 2.45 (d, 2 H, J = 24.0 Hz), 2.17 (brs, 2 H), 1.81 (brs, 3 H), 1.40 - 1.25 (m, 8 H); MS (ESI) m/z 421 (M+ + H).

Example 3. Comparative compound 597: 5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-2-(4-(methylsulfonyl)phenyl)pyridine

[0045]



Step 1. t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate: *N*-Boc-4-piperidinemethanol (0.50 g, 2.32 mmol) was dissolved in CH_2Cl_2 5 mL, and then Et_3N (0.48 mL, 3.48 mmol) and MsCl (0.32 g, 2.79 mmol) was added dropwise slowly thereto at 0 °C. The mixture was stirred for 30 minutes, following with increasing the temperature and stirring at room temperature for 12 hours. After the completion of the reaction, the reaction mixture was washed with excess water three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (0.68 g, 100%). The product was dissolved in DMF 10 mL. K_2CO_3 (1.13 g, 3.48 mmol) and 2-chloro-5-hydroxypyridine (0.3 g, 2.32 mmol) were added thereto slowly. After increasing the temperature, the mixture was stirred with heating at 100 °C for 3 hours. After the completion of the reaction, the reaction mixture was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-30 % EtOAc/hexane) to yield the title compound as white solid (0.45 g, 59%).

Step 2. t-butyl 4-((6-(4-(methylsulfonyl)phenyl)pyridine-3-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate (0.45 g, 1.37 mmol) was dissolved in dioxane 20 mL and H_2O 5 mL. 4-Methylsulfonylphenylboronic acid (0.28 g, 1.38 mmol) and Pd(dbpf)Cl_2 (45 mg, 0.07 mmol), Cs_2CO_3 (0.89 g, 2.75 mmol) was added thereto, and refluxed with stirring for 2 hours. After the completion of the reaction, the reaction mixture was filtered through Celite. The obtained filtrate was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-50 % EtOAc/hexane) to yield the title compound as white solid (0.45 g, 73%).

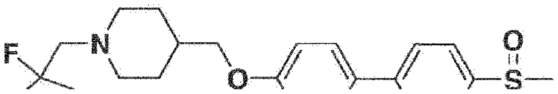
Step 3. 2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((6-(4-(methylsulfonyl)phenyl)pyridine-3-yloxy)methyl)piperidin-1-carboxylate (0.45 g, 1.0mmol) was dissolved in dioxane 10 mL. 4M HCl in MeOH (1.26 mL, 5.0 mmol) was added thereto. The solvent was removed completely and the residue was washed with ether to yield the title compound as white solid (0.36 g, 93%). The product was used without further purification.

Step 4. 2-methyl-1-(4-((6-(4-(methylsulfbnyl)phcnyl)pyridine-3-yloxy)methyl)piperidin-1-yl)propan-2-ol: 2-(4-(methylsulfonyl)phenyl)-5-(piperidin-4-ylmethoxy)pyridine hydrochloride (0.15 g, 0.39 mmol) was dissolved in EtOH 5 mL and H_2O 5 mL. Isobutylene oxide (0.28 g, 3.92 mmol) and K_2CO_3 (0.27 g, 1.96 mmol) were added slowly thereto. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The concentrate was dissolved in CH_2Cl_2, and washed with water three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-5 % MeOH/CH_2Cl_2) to yield the title compound as white solid (0.15 g, 92%).

Step 5. Comparative compound 597: 2-methyl-1-(4-((6-(4-(methylsulfonyl)phenyl)pyridine-3-yloxy)methyl)piperidin-1-yl)propan-2-ol (0.15 g, 0.36 mmol) was dissolved in CH_2Cl_2 10 mL. Deoxo-Fluor (0.34 mL, 1.79 mmol) was added slowly thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the obtained CH_2Cl_2 layer was washed several times with water. The organic layer was distilled under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-30 % EtOAc/hexane) to yield the title compound as white solid (0.1 g, 66%).
1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1 H, J = 12.0 Hz), 8.16 (d, 2 H, J = 1.6 Hz), 8.02 (d, 2 H, J = 8.5 Hz), 7.74 (d, 1 H, J = 8.7 Hz), 7.30 (s, 1 H), 3.91 (d, 2 H, J = 5.5 Hz), 3.09 (s, 3 H), 3.0 (brs, 2 H), 2.48 - 2.42 (m, 2 H), 2.25 - 2.15 (m, 2 H), 1.93 - 1.78 (m, 3 H), 1.47 - 1.35 (m, 8 H); MS (ESI) m/z 421 (M+ + H).

Example 4. Comparative compound 789: 1-((1-fluorocyclohexyl)methyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

[0046]



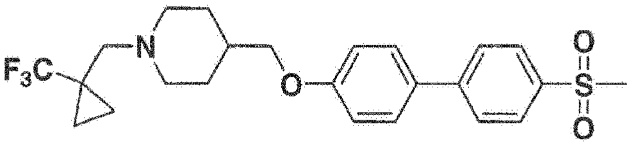
Step 1. 1-((4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)methyl)cyclohexanol: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (0.04 g, 0.11 mmol) and K_2CO_3 (0.01 g, 0.06mmol) were suspended in EtOH (1 mL). Water (0.5 mL) was added thereto, and the mixture was suspended with a little heating. 1-oxaspiro[2,5]octane (0.13 g, 1.18 mmol) was added thereto. The reaction was performed in a microwave at 110 °C for 20 minutes. A little of water was added thereto, and filtered to yield the title compound as white solid (0.05 g, 87%).

Step 2. Comparative compound 789: 1-((4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)methyl)cyclohexanol (0.05 g, 0.10 mmol) was dissolved in CH_2Cl_2 (2 mL), and then the temperature was lowered with dry ice / acetone. DAST (0.02 mL, 0.10 mmol)was added thereto little by little, and stirred for 4 hours, and then further stirred at room temperature for 1 hour. A saturated $NaHCO_3$ aqueous solution was added thereto, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g, ISU silica gel cartridge, 10 % $MeOH/CH_2Cl_2$) to yield the title compound as brown solid (0.01 g, 27%).

1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, 2 H, J = 8.5 Hz), 7.72 (d, 2 H, J = 8.5 Hz), 7.55 (d, 2 H, J = 8.8 Hz), 6.99 (d, 2 H, J = 8.8 Hz), 3.85 (d, 2 H, J = 5.8 Hz), 3.08 (s, 3 H), 2.98 (d, 2 H, J = 10.0 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.16 (t, 2 H, J = 11.3 Hz), 1.92 - 1.74 (m, 5 H), 1.68 - 1.55 (m, 4 H), 1.55 - 1.35 (m, 6 H); MS (ESI) m/z 460 (M+ + H).

Example 5. Comparative compound 500: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine

[0047]



Step 1. (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclopropyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride [the product of synthesis step 5 of compound 431; 74 mg, 0.20 mmol], 1-(trifluoromethyl)cyclopropan-1-carboxylic acid (30 mg, 0.20 mmol), and EDC (74 mg, 0.39 mmol) and HOBt (52 mg, 0.39 mmol) were dissolved in DMF 3 mL, and then DIPEA (173 µL, 0.97 mmol) was added thereto. At 80 °C, the reaction was performed for 16 hours. The reaction mixture was added with CH_2Cl_2, and washed with saturated NH_4Cl aqueous solution. The obtained organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (30 mg, 32%).

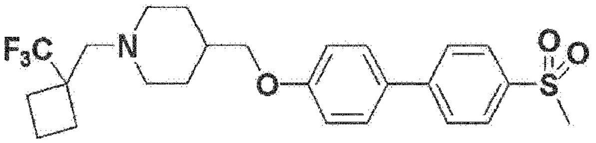
Step 2. Comparative compound 500: (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)

(1-(trifluoromethyl)cyclopropyl)methanone (50 mg, 0.10 mmol) was dissolved in dry THF 2 mL, and then cooled with ice bath. LAH (1 M in THF, 0.21 mL, 0.21 mmol) was added dropwise slowly thereto, following with increasing the temperature to room temperature slowly and stirring for 4 hours. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (20-40 % EtOAc/hexane) to yield the title compound as white solid (26 mg, 54%).

1H NMR (400 MHz, $CDCl_3$) δ 7.99 - 7.96 (m, 2 H), 7.74 - 7.71 (m, 2 H), 7.56 - 7.52 (m, 2 H), 7.01 - 6.98 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.09 (s, 3 H), 3.06 - 2.96 (m, 4 H), 2.41 (t, 2 H, J = 10.9 Hz), 1.87 - 1.81 (m, 3 H), 1.56 (s, 2 H), 1.52 - 1.43 (m, 2 H); MS (ESI) m/z 468 (M+ + H).

Example 6. Comparative compound 542: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine

[0048]



Step 1. (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclobutyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate [the product of synthesis step 5 of comparative compound 431; 140 mg, 0.37 mmol], 1-(trifluoromethyl)cyclobutanecarboxylic acid (92 mg, 0.55 mmol), EDC (141 mg, 0.73 mmol) and HOBt (99 mg, 0.73 mmol) were dissolved in DMF 2 mL, and then DIPEA (95 mg, 0.73 mmol) was added thereto. At 60 °C, the reaction was performed for 10 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (50-60 % EtOAc/hexane) to yield the title compound as white solid (105 mg, 57%).

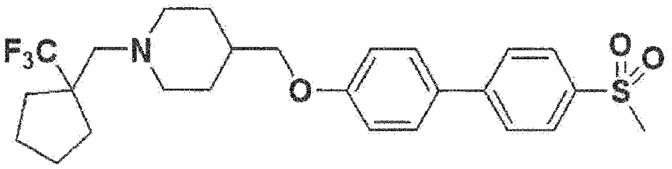
Step 2. Comparative compound 542: (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl) (1-(trifluoromethyl)cyclobutyl)methanone (80 mg, 0.16 mmol) was dissolved in dry THF 6 mL, and then cooled with ice bath. LAH (1 M in THF, 0.18 mL, 0.18 mmol) was added dropwise slowly thereto, following with increasing the temperature to room temperature slowly and stirring for 1 hour. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (50 % EtOAc/hexane) to yield the title compound as white solid (9 mg, 11%).

1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 2 H, J = 6.7, 1.9 Hz), 7.73 (dd, 1 H, J = 6.7, 1.8 Hz), 7.55 (dd, 2 H, J = 6.8, 2.0 Hz), 7.00 (dd, 2 H, J = 6.3, 2.0 Hz), 3.85 (d, 2 H, J = 6.1 Hz), 3.08 (s, 3 H), 2.09 (m, 2 H), 2.53 (s, 2 H), 2.23 (m, 4 H), 1.92 (m, 7 H), 1.45 (m, 2 H).; MS (ESI) m/z 482 (M+ +

H).

Example 7. Comparative compound 546: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidine

[0049]

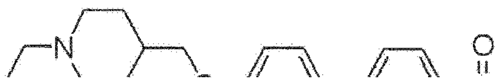


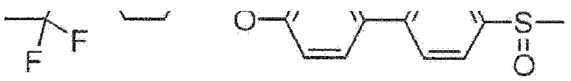
<u>Step 1.</u> (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopentyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate [the product of synthesis step 5 of comparative compound 431; 150 mg, 0.39 mmol], 1-(trifluoromethyl)cyclopentanecarboxylic acid (107 mg, 0.59 mmol), EDC (151 mg, 0.79 mmol) and HOBt (106 mg, 0.79 mmol) were dissolved in DMF 2 mL, and then DIPEA (101 mg, 0.79 mmol) was added thereto. At 60 °C, the reaction was performed for 10 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (50-60 % EtOAc / hexane) to yield the title compound as white solid (90 mg, 45%).

<u>Step 2.</u> Comparative compound 546: (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopentyl)methanone (35 mg, 0.07 mmol) was dissolved in dry THF 4 mL, and then cooled with ice bath. LAH (1 M in THF, 0.18 mL, 0.18 mmol) was added dropwise slowly thereto, following with increasing the temperature to 60 °C slowly and stirring for a day. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by Prep. TLC (40 % EtOAc/hexane) to yield the title compound as white solid (5 mg, 14%). 1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, 2 H, J = 6.8, 1.9 Hz), 7.72 (dd, 2 H, J = 6.8, 1.9 Hz), 7.54 (dd, 2 H, J = 6.8, 2.0 Hz), 6.99 (dd, 2 H, J = 6.8, 2.0 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.08 (s, 3 H), 2.46 (s, 2 H), 2.26 (m, 2 H), 2.17 (s, 4 H), 1.81 (m, 4 H), 1.67 (m, 5 H), 1.40 (m, 2 H); MS (ESI) m/z 496 (M+ + H).

Example 8. Comparative compound 547: 1-(2,2-difluoropropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

[0050]



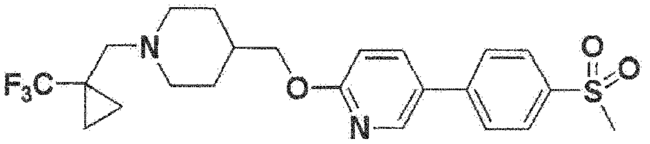


Step 1. 1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-one 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate (the product of synthesis step 5 of comparative compound 431; 50 mg, 0.11 mmol) and 1-chloropropan-2-one (13 μL, 0.16 mmol) were dissolved in MeCN 2 mL. K_2CO_3 (53 mg, 0.38 mmol) was added thereto, following with stirring at room temperature for 15 hours. The reaction mixture was diluted with water, and extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-5 % MeOH/CH_2Cl_2) to yield the title compound as pale gray solid (30 mg, 68%).

Step 2. Comparative compound 547: 1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-one (32 mg, 0.08 mmol) was dissolved in CH_2Cl_2 0.5 mL, and then Deoxo-Fluor (29 μL, 0.16 mmol) was added thereto. EtOH (1 μL, 0.02 mmol) was added thereto, following with increasing the temperature to room temperature and stirring for 15 hours. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-5 % MeOH/CH_2Cl_2) to yield the title compound as yellow solid. The obtained product was purified again by silica gel column chromatography (0-50 % EtOAc/Hexane) to yield the title compound as white solid (7 mg, 20%).
1H NMR (400 MHz, $CDCl_3$) δ 7.95 - 8.01 (m, 2 H), 7.77 - 7.69 (m, 2 H), 7.59 - 7.53 (m, 2 H), 7.03 - 6.97 (m, 2 H), 3.85 (d, 2 H, J = 5.8 Hz), 3.09 (s, 3 H), 3.00 (d, 2 H, J = 11.8 Hz), 2.68 (t, 2 H, J = 13.8 Hz), 2.26 (td, 2 H, J = 11.7, 1.9 Hz), 1.88 - 1.77 (m, 3 H), 1.65 (t, 3 H, J = 18.7 Hz), 1.46 - 1.42 (m, 2 H); MS (ESI) m/z 424 (M+ + H).

Example 9. Comparative compound 589: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine

[0051]



Step 1. ethyl 1-(1-(trifluoromethyl)cyclopropanecarbonyl)piperidin-4-carboxylate: 1-(trifluoromethyl)cyclopropanecarboxylic acid(500 mg, 3.25 mmol), ethyl piperidin-4-carboxylate (561 mg, 3.57 mmol), EDC (1.24 g, 6.49 mmol) and HOBt (877 mg, 6.49 mmol) were dissolved in CH_2Cl_2 10 mL, and then DIPEA (114 μL, 6.49 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered.

The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as colorless oil (800 mg, 84%).

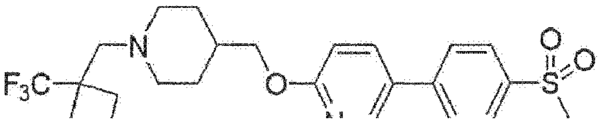
Step 2. (1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methanol: ethyl 1-(1-(trifluoromethyl)cyclopropanecarbonyl)piperidin-4-carboxylate (818 mg, 2.79 mmol) was dissolved in dry THF 20 mL. At 0°C, LAH (1 M in THF, 13.94 mL, 13.94 mmol) was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. The reaction was quenched by slow addition of MeOH at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (577 mg, 87%).

Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine: (1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methanol (577 mg, 2.43 mmol) was dissolved in THF 10 mL. At 0 °C, NaH (87 mg, 3.65 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine (0.57 g, 2.43 mmol) in THF 5 mL was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (500 mg, 52%).

Step 4. Comparative compound 589: 5-bromo-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine (100 mg, 0.25 mmol), 4-(methylsulfonyl)phenylboronic acid(76 mg, 0.38 mmol), Pd(dbpf)Cl_2 (5 mg, 0.01 mmol), Cs_2CO_3 (247 mg, 0.76 mmol) were added into a microwave reactor, and then dioxane 6 mL and water 3 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (10-50 % EtOAc/hexane) to yield the title compound as white solid (38 mg, 32%).
1H NMR (400 MHz, $CDCl_3$) δ 8.40 (m, 1 H), 8.02 (dd, 2 H, J = 5.2, 3.4 Hz), 7.83 (dd, 1 H, J = 8.6, 2.6 Hz), 7.72 (dt, 2 H, J = 8.6, 1.9 Hz), 6.86 (dd, 1 H, J = 8.6, 0.6 Hz), 4.21 (d, 2 H, J = 6.0 Hz), 3.10 (s, 3 H), 2.98 (d, 2 H, J = 10.1 Hz), 2.54 (s, 2 H), 1.99 (m, 2 H), 1.81 (d, 2 H, J = 10.0 Hz), 1.41 (m, 2 H), 0.98 (s, 2 H), 0.65 (s, 2 H); MS (ESI) m/z 469 (M+ + H).

Example 10. Comparative compound 676: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine

[0052]



Step 1. ethyl 1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-carboxylate: 1-(trifluoromethyl)cyclobutanecarboxylic acid (500 mg, 2.97 mmol), ethyl piperidin-4-carboxylate (514 mg, 3.27 mmol), EDC (1.14 g, 5.94 mmol) and HOBt (803 mg, 5.95 mmol) was dissolved in CH_2Cl_2 10 mL. DIPEA (1.05 mL, 5.95 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and then filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as colorless oil (750 mg, 82%).

Step 2. (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol: ethyl 1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-carboxylate (759 mg, 2.47 mmol) was dissolved in dry THF 20 mL. At 0 °C, LAH (1 M in THF, 12.34 mL, 12.34 mmol) was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. The reaction was quenched by slow addition of MeOH at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (581 mg, 94%).

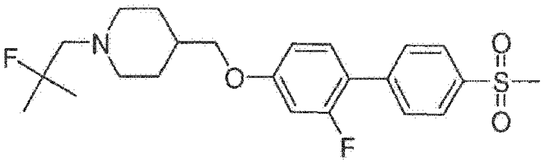
Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyridine: (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol (581 mg, 2.31 mmol) were dissolved in THF 10 mL. At 0 °C, NaH (83 mg, 3.47 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine (547 mg, 2.31 mmol) in THF 5 mL was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (500 mg, 53%).

Step 4. Comparative compound 676: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine (500 mg, 0.12 mmol), 4-(methylsulfonyl)phenylboronic acid (27 mg, 0.13 mmol), Pd(dbpf)Cl_2 (2 mg, 0.01 mmol), Cs_2CO_3 (119 mg, 0.37 mmol) were added into a microwave reactor, and then dioxane 2 mL and water 1 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (10-50 % EtOAc/hexane) to yield the title compound as white solid (20 mg, 34%).
1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1 H, J = 2.6 Hz), 8.02 (dd, 2 H, J = 8.5, 1.8 Hz), 7.83 (dd, 1 H, J = 8.7, 2.6 Hz), 7.72 (dd, 2 H, J = 6.6, 1.7 Hz), 6.87 (d, 1 H, J = 8.6 Hz), 4.22 (d, 2 H, J = 6.2 Hz), 3.10 (s, 3 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.53 (s, 2 H), 2.24 - 2.18 (m, 4 H), 2.10 - 1.79 (m, 7 H), 1.47 - 1.43 (m, 2 H); MS (ESI) m/z 483 (M+ + H).

Example 11. Comparative compound 714: 1-(2-fluoro-2-methylpropyl)-4-((2-fluoro-4'-

(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

[0053]

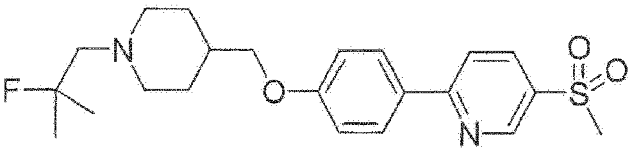


[0054] 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of comparative compound 704; 850 mg, 2.35 mmol), 4-(methylsulfonyl)phenylboronic acid (563 mg, 2.82 mmol), Pd(dbpf)Cl_2 (77 mg, 0.12 mmol) and Cs_2CO_3 (1.53 g, 4.69 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. Water was poured thereto, and the reaction mixture was extracted with EtOAc, The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as yellow solid (390 mg, 38%).

1H NMR (400 MHz, $CDCl_3$) δ 8.01 - 7.98 (m, 2 H), 7.73 - 7.70 (m, 2 H), 7.39 - 7.27 (m, 1 H), 6.82 - 6.72 (m, 2 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.10 (s, 3 H), 3.02 (brs, 2 H), 2.49 - 2.44 (m, 2 H), 2.19 (brs, 2 H), 1.82 - 1.79 (m, 3 H), 1.45 - 1.36 (m, 8 H); MS (ESI) m/z 438 (M+ + H).

Example 12. Comparative compound 617: 2-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-5-(methylsulfonyl)pyridine

[0055]



Step 1. 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid: 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 3 of comparative compound 498; 0.54 g, 1.57 mmol) was dissolved in dry THF 10 mL. At -78 °C, n-BuLi (1.6 M in hexane, 1.17 mL, 1.88 mmol) was added slowly thereto. The reaction was performed at -78 °C for 30 minutes. At -78 °C, triisopropyl borate (0.47 mL, 2.04 mmol) was added thereto. The reaction was performed at room temperature for 4 hours. At 0 °C, 1 M HCl 5 mL was added thereto, and the reaction was performed for 1 hour. The reaction mixture was added with EtOAc, and stirred. The resulting precipitate was filtered to yield the title compound as white solid (0.40 g, 83%).

Step 2. Comparative compound 617: 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid (50 mg, 0.16 mmol), 2-bromo-5-(methylsulfonyl)pyridine (42 mg, 0.18 mmol), Pd(dbpf)Cl_2 (3 mg, 0.01 mmol), Cs_2CO_3 (104 mg, 0.32 mmol) were added into a microwave reactor, and then dioxane 2 mL and water 1 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-50 % EtOAc/hexane) to yield the title compound as white solid (30 mg, 44%).

1H NMR (400 MHz, $CDCl_3$) δ 9.14 (m, 1 H), 8.21 (dd, 1 H, J = 8.5, 2.4 Hz), 8.05 (dt, 2 H, J = 9.0, 2.5 Hz), 7.85 (dd, 1 H, J = 8.5, 0.8 Hz), 7.02 (dt, 2 H, J = 8.9, 2.4 Hz), 3.88 (d, 2 H, J = 5.9 Hz), 3.14 (s, 3 H), 3.07 (m, 2 H), 2.60 - 2.40 (m, 2 H), 2.22 (m, 2 H), 1.85 - 1.82 (m, 3 H), 1.47 - 1.37 (m, 8 H); MS (ESI) m/z 421 (M+ + H).

[0056] According to the above-described synthesis process of comparative compound 617 (Step 2), the compounds of Table 2 were synthesized using 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid and the reactant of Table 1.

Table 1. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
618*	5-bromo-2-(methylsulfonyl)pyridine	47
614*	4-bromo-N,N-dimethylbenzenesulfonamide	43
615*	1-(4-bromophenylsulfonyl)pyrrolidine	35
616*	1-(4-bromophenylsulfonyl)piperidine	35
666*	(S)-1-(4-bromophenylsulfonyl)pyrrolidine-3-ol	27
667*	(R)-(1-(4-bromophenylsulfonyl)pyrrolidine-2-yl)methanol	30
668*	(S)-1-(4-bromophenylsulfonyl)pyrrolidine-2-carboxamide	34
669*	(R)-1-(4-bromophenylsulfonyl)piperidin-3-ol	33
670*	(S)-1-(4-bromophenylsulfonyl)piperidin-3-ol	31
674*	4-bromobenzenesulfonamide	34
675*	4-bromo-N-methylbenzenesulfonamide	37

Table 2. (* marks comparative compound)

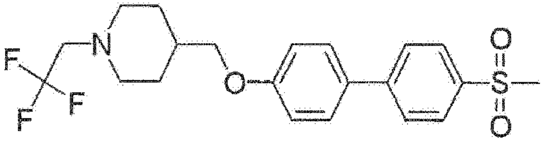
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
618*	5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2-(methylsulfonyl)pyridine
	1H NMR (400 MHz, $CDCl_3$) δ 8.90 (m, 1 H), 8.13 (dd, 1 H, J = 8.2, 0.8 Hz), 8.08 (dd, 1 H, J = 8.2, 2.2 Hz), 7.56 (dt, 2 H, J = 9.0, 2.5 Hz), 7.05 (dt, 2 H, J = 8.9, 2.4 Hz), 3.88 (d, 2 H, J = 5.9 Hz), 3.26 (s, 3 H), 3.07 (m, 2 H), 2.60 - 2.40 (m, 2 H), 2.22 (m, 2 H), 1.88 - 1.82 (m, 3 H), 1.47 - 1.37 (m, 8 H); MS (ESI) m/z 421 (M+ + H).
614*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-sulfonamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, 2 H, J = 8.6, 3.8 Hz), 7.71 (dd, 2 H, J = 8.6, 3.8 Hz), 7.56 (dd, 2 H, J = 9.7, 5.1 Hz), 7.01 (dd, 2 H, J =

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	9.7, 5.1 Hz), 3.86 (d, 2 H, J = 5.9 Hz), 3.00 (m, 2 H), 2.75 (s, 6 H), 2.49 - 2.42 (m, 2 H), 2.18 (m, 2 H), 1.82 (m, 3 H), 1.41 - 1.26 (m, 8 H); MS (ESI) m/z 449.1 (M+ + H).
615*	1-(2-fluoro-2-methylpropyl)-4-((4'-(pyrrolidine-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine
	1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2 H, J = 8.6, 3.8 Hz), 7.69 (dd, 2 H, J = 8.6, 3.8 Hz), 7.56 (dd, 2 H, J = 9.7, 5.1 Hz), 7.00 (dd, 2 H, J = 9.7, 5.1 Hz), 3.86 (d, 2 H, J = 5.9 Hz), 3.28 (m, 4 H), 3.00 (m, 2 H), 2.50 - 2.44 (m, 2 H), 2.19 (m, 2 H), 1.83 - 1.75 (m, 7 H), 1.41 - 1.26 (m, 8 H); MS (ESI) m/z 475 (M+ + H).
616*	1-(2-fluoro-2-methylpropyl)-4-((4'-(piperidin-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine
	1H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, 2 H, J = 8.6, 3.8 Hz), 7.68 (dd, 2 H, J = 8.6, 3.8 Hz), 7.56 (dd, 2 H, J = 9.7, 5.1 Hz), 7.00 (dd, 2 H, J = 9.7, 5.1 Hz), 3.86 (d, 2 H, J = 5.9 Hz), 3.03 (m, 6 H), 2.49 - 2.44 (m, 2 H), 2.19 (m, 2 H), 1.83 - 1.81 (m, 3 H), 1.68 (m, 4 H), 1.47 - 1.36 (m, 10 H); MS (ESI) m/z 489 (M+ + H).
666*	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidine-3-ol
	1H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, 2 H, J = 8.6, 1.9 Hz), 7.69 (dd, 2 H, J = 8.6, 1.9 Hz), 7.55 (dd, 2 H, J = 8.6, 1.9 Hz), 6.99 (dd, 2 H, J = 8.6, 1.9 Hz), 4.41 (m, 1 H), 3.86 (d, 2 H, J = 5.9 Hz), 3.44 (m, 3 H), 3.31 (m, 1 H), 3.20 - 3.02 (m, 2 H), 2.61 - 2.45 (m, 2 H), 2.38 - 2.20 (m, 2 H), 1.97 (m, 1 H), 1.88 - 1.83 (m, 4 H), 1.61 - 1.38 (m, 9 H); MS (ESI) m/z 491 (M+ + H).
667*	(R)-(1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidine-2-yl)methanol
	1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 2 H, J = 8.6, 1.9 Hz), 7.71 (dd, 2 H, J = 8.6, 1.9 Hz), 7.56 (dd, 2 H, J = 8.6, 1.9 Hz), 6.99 (dd, 2 H, J = 8.6, 1.9 Hz), 3.86 (d, 2 H, J = 5.9 Hz), 3.71 (m, 3 H), 3.52 (m, 1 H), 3.31 (m, 1 H), 3.08 - 2.90 (m, 2 H), 2.84 (m, 1 H), 2.60 - 2.40 (m, 2 H), 2.30 - 2.10 (m, 2 H), 1.84 - 1.70 (m, 6 H), 1.52 - 1.36 (m, 9 H); MS (ESI) m/z 505 (M+ + H).
668*	(S)-1-(4'-((1 -(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, 2 H, J = 8.6, 1.9 Hz), 7.73 (dd, 2 H, J = 8.6, 1.9 Hz), 7.56 (dd, 2 H, J = 8.6, 1.9 Hz), 7.00 (dd, 2 H, J = 8.6, 1.9 Hz), 6.93 (m, 1 H), 5.59 (m, 1 H), 4.13 (m, 1 H), 3.87 (d, 2 H, J = 5.9 Hz), 3.62 (m, 1 H), 3.23 (m, 1 H), 3.02 (m, 2 H), 2.55 - 2.40 (m, 2 H), 2.30 - 2.12 (m, 2 H), 1.82 (m, 4 H), 1.65 (m, 3 H), 1.45 - 1.37 (m, 7 H); MS (ESI) m/z 518 (M+ + H).
	(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol
	1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, 2 H, J = 8.6, 1.9 Hz), 7.70 (dd,

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
669*	2 H, J = 8.6, 1.9 Hz), 7.55 (dd, 2 H, J = 8.6, 1.9 Hz), 7.00 (dd, 2 H, J = 8.6, 1.9 Hz), 3.90 - 3.85 (m, 3 H), 3.37 (m, 1 H), 3.17 (m, 1 H), 3.02 (m, 2 H), 2.85 (m, 1 H), 2.77 (m, 1 H), 2.60 - 2.40 (m, 2 H), 2.30 - 2.18 (m, 2 H), 2.09 (m, 1 H), 1.85 - 1.60 (m, 6 H), 1.48 - 1.37 (m, 9 H); MS (ESI) m/z 505 (M+ + H).
670*	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol
	1H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, 2 H, J = 8.6, 1.9 Hz), 7.70 (dd, 2 H, J = 8.6, 1.9 Hz), 7.54 (dd, 2 H, J = 8.6, 1.9 Hz), 7.00 (dd, 2 H, J = 8.6, 1.9 Hz), 3.91 - 3.85 (m, 3 H), 3.36 (m, 1 H), 3.19 (m, 1 H), 3.01 (m, 2 H), 2.85 (m, 1 H), 2.77 (m, 1 H), 2.49 - 2.43 (m, 2 H), 2.18 (m, 2 H), 2.09 (m, 1 H), 1.86 - 1.60 (m, 6 H), 1.48 - 1.37 (m, 9 H); MS (ESI) m/z 505 (M+ + H).
674*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-sulfonamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, 2 H, J = 8.6, 1.9 Hz), 7.70 (dd, 2 H, J = 8.6, 1.9 Hz), 7.54 (dd, 2 H, J = 8.6, 1.9 Hz), 7.00 (dd, 2 H, J = 8.6, 1.9 Hz), 4.83 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.00 (d, 2 H, J = 9.7 Hz), 2.46 (d, 2 H, J = 23.2 Hz), 2.18 (m, 2 H), 1.82 (m, 3 H), 1.45 - 1.35 (m, 8 H); MS (ESI) m/z 421 (M+ + H).
675*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-sulfonamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, 2 H, J = 8.6, 1.9 Hz), 7.70 (dd, 2 H, J = 8.6, 1.9 Hz), 7.55 (dd, 2 H, J = 8.6, 1.9 Hz), 7.00 (dd, 2 H, J = 8.6, 1.9 Hz), 4.36 (m, 1 H), 3.86 (d, 2 H, J = 5.8 Hz), 3.00 (d, 2 H, J = 11.5 Hz), 2.72 (d, 3 H, J = 5.4 Hz), 2.46 (d, 2 H, J = 22.8 Hz), 2.18 (m, 2 H), 1.82 (d, 3 H, J = 10.8 Hz), 1.45 - 1.35 (m, 8 H); MS (ESI) m/z 435 (M+ + H).

Example 13. Comparative compound 499: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(2,2,2-trifluoroethyl)piperidine

[0057]

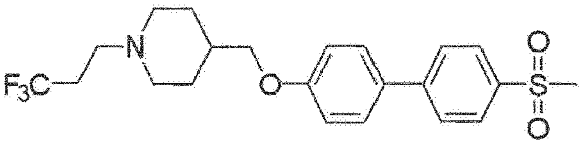


[0058] 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (the product of synthesis step 5 of comparative compound 431; 50 mg, 0.13 mmol) was dissolved in DMSO 2 mL. 2,2,2-trifluoroethyl trifluoromethanesulfonate (30 mg, 0.13 mmol) and K_2CO_3 (91 mg, 0.66 mmol) were added thereto, following with stirring at room temperature for 15 hours. The reaction mixture was added with EtOAc, and washed with water three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-40 % EtOAc/hexane) to yield the title compound as white solid (23 mg, 41%).

1H NMR (400 MHz, $CDCl_3$) δ 7.99 - 7.96 (m, 2 H), 7.74 - 7.71 (m, 2 H), 7.56 - 7.52 (m, 2 H), 7.01 - 6.98 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.09 (s, 3 H), 3.06 - 2.96 (m, 4 H), 2.41 (t, 2 H, J = 10.9 Hz), 1.87 - 1.81 (m, 3 H), 1.56 (s, 2 H), 1.52 - 1.43 (m, 2 H); MS (ESI) m/z 428 (M+ + H).

Example 14. Comparative compound 524: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(3,3,3-trifluoropropyl)piperidine

[0059]

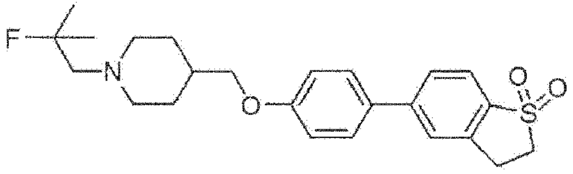


Step 1. 3,3,3-trifluoro-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-1-one: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (the product of synthesis step 5 of comparative compound 431; 40 mg, 0.11 mol) and CF_3CH_2COCl (16 μL, 0.16 mmol) were dissolved in CH_2Cl_2 2 mL. Et_3N (44 μL, 0.31 mmol) was added thereto, following with stirring for 5 hours at room temperature. The reaction mixture was added with water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered to remove solid, and then concentrated under reduced pressure The obtained concentrate was purified by silica gel column chromatography (20 % EtOAc/hexane) to yield the title compound as white solid (54 mg, 113%).

Step 2. Comparative compound 524: 3,3,3-trifluoro-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl) piperidin-1-yl)propan-1-one (46 mg, 0.10 mmol) was dissolved in dry THF 2 mL, and then cooled with ice bath. 1 M LAH in THF (0.20 mL, 0.20 mmol) was added dropwise slowly thereto, following with increasing the temperature to room temperature slowly and stirring for 4 hours. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-40 % EtOAc/hexane) to yield the title compound as white solid (9 mg, 19%). 1H NMR (400 MHz, $CDCl_3$) δ 8.00 - 7.93 (m, 2 H), 7.77 - 7.69 (m, 2 H), 7.59 - 7.52 (m, 2 H), 7.03 - 6.95 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.08 (s, 3 H), 2.95 (d, 2 H, J = 11.5 Hz), 2.66 - 2.57 (m, 2 H), 2.41 - 2.26 (m, 2 H), 2.11 - 2.01 (m, 2 H), 1.93 - 1.81 (m, 3 H), 1.50 - 1.36 (m, 2 H); MS (ESI) m/z 468 (M+ + H).

Example 15. Comparative compound 470: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide

[0060]



Step 1. 4-(benzo[b]thiophen-5-yl)phenol: 5-bromobenzo[b]thiophene (3.0 g, 14.08 mmol) and 4-hydroxyphenylboronic acid (2.91 g, 21.11 mmol) were dissolved in DME 40 mL. Water 10 mL was added thereto. Pd(dbpf)Cl_2 (459 mg, 0.70 mmol) and CS_2CO_3 (13.68 g, 42.24 mmol) were added thereto, and refluxed with heating at 90 °C for a day. The reaction mixture was filtered through Celite. The obtained filtrate was extracted with EtOAc three times, dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (15-20 % EtOAc/hexane) to yield the title compound as white solid (2.30 g, 72%).

Step 2. t-butyl 4-((4-(benzo[b]thiophen-5-yl)phenoxy)methyl)piperidin-1-carboxylate: 4-(benzo[b]thiophen-5-yl)phenol (1.30 g, 5.74 mmol) and t-butyl 4-((methylsulfonyloxy) methyl)piperidin-1-carboxylate (the product of synthesis step 2 of compound 431; 2.02 g, 6.89 mmol) were dissolved in ACN 10 mL. CS_2CO_3 (3.74 g, 11.49 mmol) was added thereto, and refluxed with heating for a day. The reaction mixture was diluted with water, and extracted with EtOAc. The organic layer was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-30 % EtOAc/hexane) to yield the title compound as white solid (1.81 g, 74%).

Step 3. t-butyl 4-((4-(1,1-dioxidobenzo[b]thiophen-5-yl)phenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((4-(benzo[b]thiophen-5-yl)phenoxy)methyl)piperidin-1-carboxylate (1.8 g, 4.28 mmol) was dissolved in $CHCl_3$ 30 mL. m-CPBA (1.85 g, 10.70 mmol) was added thereto, following with stirring for 1 hour. A saturated $NaHCO_3$ aqueous solution was added thereto, and then, and extracted with CH_2Cl_2. The obtained concentrate was purified by silica gel column chromatography (10-20 % EtOAc/CH_2Cl_2) to yield the title compound as white solid (1.50 g, 77%).

Step 4. t-butyl 4-((4-(1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)phenoxy)methyl) piperidin-1-carboxylate: t-butyl 4-((4-(1,1-dioxidobenzo[b]thiophen-5-yl)phenoxy)methyl) piperidin-1-carboxylate (700 mg, 1.54 mmol) was dissolved in THF 10 mL and EtOH 10 mL. 10% wt Pd/C (70 mg) was added thereto, following with hydrogen gas flowing and stirring at room temperature for two days. The reaction mixture was filtered through Celite to remove a solid. The obtained filtrate was concentrated. The obtained concentrate was purified by silica gel column chromatography (20-30 % EtOAc/CH_2Cl_2) to yield the title compound as white solid (680 mg, 96%).

Step 5. 5-(4-(piperidin-4-ylmethoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide 2,2,2-trifluoroacetate: t-butyl 4-((4-(1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)phenoxy) methyl)piperidin-1-carboxylate (800 mg, 1.75 mmol) was dissolved in CH_2Cl_2 6 mL. TFA 161 µL was added thereto, following with stirring at room temperature for 2 hours. The reaction mixture was filtered, and a recrystallization was performed with ether to yield the title compound as white solid (740 mg, 93%).

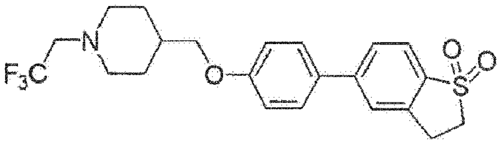
Step 6. 5-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide: 5-(4-(piperidin-4-ylmethoxy)phenyl)-2,3-

dihydrobenzo[b]thiophene 1,1-dioxide 2,2,2-trifluoroacetate (50 mg, 0.13 mmol) and K_2CO_3 (35 mg, 0.25 mmol) were suspended in EtOH 0.5 mL. Water 0.5 mL was added thereto, and the mixture was suspended with a little heating. 2,2-dimethyl oxirane (35 mg, 1.27 mmol) was added thereto. With a microwave radiation, the reaction was performed at 110 °C for 20 minutes. The reaction mixture was diluted with water, and extracted with EtOAc. The obtained concentrate was purified by silica gel column chromatography (50-60 % EtOAc/Hexane) to yield the title compound as white solid (31 mg, 57%).

Step 7. Comparative compound 470: 5-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy) phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide (14 mg, 0.03 mmol) was dissolved in CH_2Cl_2 1 mL. Deoxo-Fluor (8 mg, 0.04 mmol) was added thereto at 0 °C, following with stirring at room temperature for 3 hours. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered to remove solid, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (50-60 % EtOAc/Hexane) to yield the title compound as white solid (11 mg, 78%).
1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, 1 H, J = 8.2 Hz), 7.63 (d, 1 H, J = 8.7 Hz), 7.49 (m, 3 H), 6.98 (dd, 2 H, J = 9.2, 2.4 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.53 (m, 2 H), 3.42 (m, 2 H), 2.98 (m, 2 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (td, 2 H, J = 11.7, 1.6 Hz), 1.80 (m, 3 H), 1.40 (m, 5 H), 1.33 (s, 3 H); MS (ESI) m/z 432 (M+ + H).

Example 16. Comparative compound 540: 5-(4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy) phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide

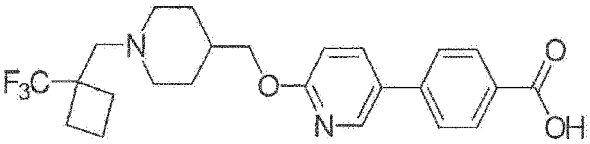
[0061]



[0062] 5-(4-(piperidin-4-ylmethoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide 2,2,2-trifluoroacetate (the product of synthesis step 5 of comparative compound 470; 50 mg, 0.11 mmol) was dissolved in DMSO 1 mL. 2,2,2-trifluoroethyl trifluoromethanesulfonate (26 mg, 0.11 mmol) and K_2CO_3 (76 mg, 0.55 mmol) were added thereto, and stirred at room temperature for 20 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove solid, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (40-60 % EtOAc/Hexane) to yield the title compound as white solid (9 mg, 18%).
1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, 1 H, J = 8.2 Hz), 7.64 (m, 1 H), 7.51 (m, 3 H), 6.98 (dd, 2 H, J = 6.8, 2.0 Hz), 3.85 (d, 2 H, J = 5.9 Hz), 3.53 (m, 2 H), 3.42 (m, 2 H), 3.00 (m, 4 H), 2.40 (m, 2 H), 1.85 (m, 3 H), 1.31 (m, 2 H); MS (ESI) m/z 440 (M+ + H).

Example 17. Comparative compound 574: 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid

[0063]

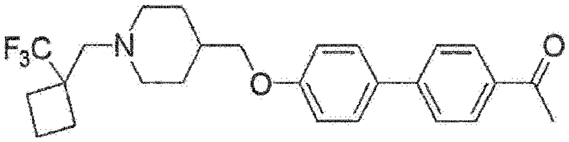


Step 1. methyl 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine (the product of synthesis step 3 of comparative compound 676; 0.34 g, 0.85 mmol), 4-(methoxycarbonyl)phenylboronic acid (306 mg, 1.70 mmol), Pd(dbpf)Cl_2 (55 mg, 0.09 mmol), Cs_2CO_3 (1.19 g, 3.68 mmol) were added into a microwave reactor, and then dioxane 5 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (15-20 % EtOAc/hexane) to yield the title compound as white solid (80 mg, 20%).

Step 2. Comparative compound 574: methyl 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (135 mg, 0.29 mmol) was dissolved in the mixed solvents of THF 2 mL / MeOH 1 mL / water 0.5 mL. LiOH·H_2O (24 mg, 0.58 mmol) was added thereto, and refluxed with heating and stirring for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl 5 mL thereto, the resulting precipitate was filtered. The obtained solid was purified by silica gel column chromatography (30-80 % EtOAc/hexane) to yield the title compound as white solid (80 mg, 62%).
1H NMR (400 MHz, DMSO) δ 8.53 (s, 1 H), 8.07 (d, 1 H, J = 7.8 Hz), 7.99 (d, 2 H, J = 7.6 Hz), 7.78 (d, 2 H, J = 7.7 Hz), 6.92 (d, 1 H, J = 8.5 Hz), 4.15 (m, 2 H), 2.94 (m, 2 H), 2.51 (m, 2 H), 2.12 (m, 7 H), 1.90 (m, 2 H), 1.71 (m, 2 H), 1.28 (m, 2 H); MS (ESI) m/z 449 (M+ + H).

Example 18. Comparative compound 575: 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanone

[0064]



Step 1. t-butyl 4-((4'-acetylbiphenyl-4-yloxy)methyl)piperidin-1-carboxylate: *t*-butyl 4-((4-bromophenoxy)methyl)piperidin-1-carboxylate (the product of synthesis step 3 of comparative

compound 431; 500 mg, 1.35 mmol) and 4-acetylphenylboronic acid(244 mg, 1.49 mmol) were dissolved in dioxane 4 mL. water 1.5 mL was added thereto. Pd(dbpf)Cl_2 (88 mg, 0.14 mmol) and CS_2CO_3 (660 mg, 2.03 mmol) were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was filtered through Celite, and the filtrate was dissolved in EtOAc. The solution was washed with saturated $NaHCO_3$ aqueous solution and water, dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (30-40 % EtOAc/hexane) to yield the title compound as yellow solid (400 mg, 72%).

Step 2. 1-(4'-(piperidin-4-ylmethoxy)biphenyl-4-yl)ethanone hydrochloride: t-butyl 4-((4'-acetylbiphenyl-4-yloxy)methyl)piperidin-1-carboxylate (400 mg, 0.98 mmol) was dissolved in CH_2Cl_2 4 mL. 4 M HCl 488 µL was added thereto, following with stirring at room temperature for 2 hours. The obtained reaction mixture was filtered to yield the title compound as white solid (330 mg, 97%).

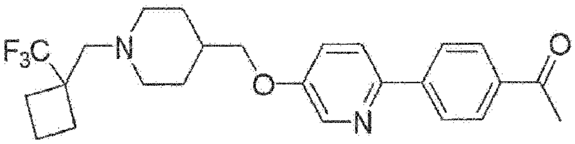
Step 3. 1-(4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanone: 1-(4'-(piperidin-4-ylmethoxy)biphenyl-4-yl)ethanone hydrochloride (380 mg, 1.10 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (185 mg, 1.10 mmol), EDC (421 mg, 2.20 mmol) and HOBt (270 mg, 2.20 mmol) were dissolved in DMF 6 mL. DIPEA (284 mg, 2.20 mmol) was added thereto, and the reaction was performed at 60 °C for 3 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (40 - 50 % EtOAc / hexane) to yield the title compound as yellow solid (350 mg, 69%).

Step 4. 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanol: 1-(4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy) biphenyl-4-yl)ethanone (193 mg, 0.42 mmol) was dissolved in dry THF 10 mL, and then cooled with ice bath. LAH (1 M in THF, 0.13 mL, 0.13 mmol) was added dropwise slowly thereto, following with increasing the temperature to 50 °C and stirring for a day.. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (90 mg, 48%).

Step 5. Comparative compound 575: 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanol (27 mg, 0.06 mmol) was dissolved in CH_2Cl_2 mL. Dess-Martin periodinane (38 mg, 0.09 mmol) was added thereto. The reaction was performed at room temperature for 3 hours. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc / hexane) to yield the title compound as white solid (16 mg, 59%).
1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 2 H, J = 8.4 Hz), 7.66 (d, 2 H, J = 8.3 Hz), 7.58 (d, 2 H, J = 8.7 Hz), 7.00 (d, 2 H, J = 8.7 Hz), 3.86 (d, 2 H, J = 6.0 Hz), 2.91 (d, 2 H, J = 11.3 Hz), 2.64 (s, 3 H), 2.54 (s, 2 H), 2.22 (m, 4 H), 2.01 (m, 4 H), 1.82 (m, 3 H), 1.43 (m, 2 H); MS (ESI) m/z 446 (M+ + H).

Example 19. Comparative compound 593: 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanone

[0065]



__Step 1.__ t-butyl 4-((6-(4-acetylphenyl)pyridine-3-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 597; 500 mg, 1.53 mmol) and 4-acetylphenylboronic acid(276 mg, 1.68 mmol) were dissolved in dioxane 4 mL water 1 mL was added thereto. Pd(dppf)Cl_2 (63 mg, 0.08 mmol) and Na_2CO_3 (660 mg, 2.03 mmol) were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was filtered through Celite, and the obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution and water, dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (30-40 % EtOAc/CH_2Cl_2) to yield the title compound as white solid (300 mg, 47%).

__Step 2.__ 1-(4-(5-(piperidin-4-ylmethoxy)pyridine-2-yl)phenyl)ethanone hydrochloride: t-butyl 4-((6-(4-acetylphenyl)pyridine-3-yloxy)methyl)piperidin-1-carboxylate (300 mg, 0.73 mmol) was dissolved in CH_2Cl_2 3 mL. 4 M HCl 201 mL was added thereto, following with stirring at room temperature for 2 hours. The obtained reaction mixture was filtered to yield the title compound as white solid (250 mg, 98%).

__Step 3.__ 1-(4-(5-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanone: 1-(4-(5-(piperidin-4-ylmethoxy)pyridine-2-yl)phenyl)ethanone hydrochloride (250 mg, 0.72 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (145 mg, 0.87 mmol), EDC (276 mg, 1.44 mmol) and HOBt (195 mg, 1.44 mmol) were dissolved in DMF 2 mL. DIPEA (186 mg, 1.44 mmol) was added thereto. At 50 °C, the reaction was performed for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (40-50 % EtOAc/hexane) to yield the title compound as white solid (158 mg, 47%).

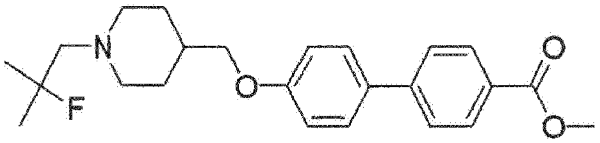
__Step 4.__ 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanol: 1-(4-(5-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanone (148 mg, 0.32 mmol) was dissolved in dry THF 7 mL, and then cooled with ice bath. LAH (1 M in THF, 0.96 mL, 0.96 mmol) was added dropwise slowly thereto, following with increasing the temperature to 50 °C and stirring for 6 hours. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (110 mg, 76%).

Step 5. Comparative compound 593: 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanol (96 mg, 0.21 mmol) was dissolved in CH_2Cl_2 2 mL. DMP (118 mg, 0.28 mmol) was added thereto. The reaction was performed at room temperature for 3 hours. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane) to yield the title compound as white solid (78 mg, 81%).

1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1 H, J = 2.9 Hz), 8.02 (s, 4 H), 7.74 (d, 1 H, J = 8.7 Hz), 7.29 (dd, 1 H, J = 8.8, 3.0 Hz), 3.91 (d, 2 H, J = 6.0 Hz), 2.94 (d, 2 H, J = 11.4 Hz), 2.65 (s, 3 H), 2.57 (s, 2 H), 2.21 (m, 4 H), 2.08 (m, 2 H), 1.99 (m, 1 H), 1.94 (m, 1 H), 1.89 (m, 3 H), 1.49 (m, 2 H); MS (ESI) m/z 447 (M+ + H).

Example 20. Comparative compound 498: methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate

[0066]



Step 1. 4-((4-bromophenoxy)methyl)piperidine hydrochloride: t-butyl 4-((4-bromophenoxyl) methyl)piperidin-1-carboxylate (the product of synthesis step 3 of compound 431; 5.00 g, 13.50 mmol) was dissolved in EtOAc 10 mL. 1 M HCl 30 mL was added thereto, following with stirring at room temperature for 15 hours and refluxing with heating and stirring for 2 hours. The reaction mixture was cooled to room temperature, and filtered to yield the title compound as white solid (4.01 g, 97%).

Step 2. 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (1.00 g, 3.26 mmol) and K_2CO_3 (0.23 g, 1.63 mmol) were suspended in EtOH 10 mL. Water 5 mL was added thereto to make a solution. 2,2-dimethyl oxirane (2.90 mL, 32.61 mmol) was added thereto. With a microwave radiation, the reaction was performed at 110 °C for 20 minutes. A little of water was added thereto, following with removing EtOH under reduced pressure, and extracting with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (1.10 g, 98%).

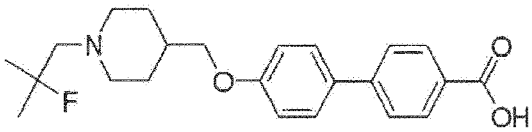
Step 3. 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine: 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol(1.10 g, 3.21 mmol) was dissolved in CH_2Cl_2 10 mL. DAST (0.43 mL, 3.21 mmol) was added thereto, following with stirring with at room temperature for 1 hour. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid.

The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-5 % MeOH/CH_2Cl_2) to yield the title compound as white solid (0.77 g, 70%).

Step 4. Comparative compound 498: 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (770 mg, 2.24 mmol) and 4-(methoxycarbonyl)phenylboronic acid (483 mg, 2.68 mmol) were dissolved in dioxane 3 mL. water 1 mL was added thereto. Pd(dbpf)Cl_2 (44 mg, 0.07 mmol) and CS_2CO_3 (2.18 g, 6.71 mmol) were added thereto. With a microwave radiation, the reaction was performed at 140°C for 15 minutes. The reaction mixture was diluted with water, and extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (20 % EtOAc/hexane) to yield the title compound as white solid (682 mg, 76%).
1H NMR (400 MHz, $CDCl_3$) δ 8.11 - 8.04 (m, 2 H), 7.66 - 7.60 (m, 2 H), 7.59 - 7.53 (m, 2 H), 7.02 - 6.94 (m, 2 H), 3.93 (s, 3 H), 3.84 (d, 2 H, J = 6.0 Hz), 2.99 (d, 2 H, J = 11.0 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.82 - 1.79 (m, 3 H), 1.49 - 1.37 (m, 1 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 400 (M+ + H).

Example 21. Comparative compound 548: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid

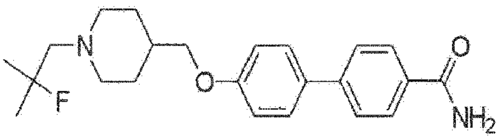
[0067]



[0068] Methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (Comparative compound 498; 682 mg, 1.71 mmol) was dissolved in THF 6 mL. MeOH 2 mL and H_2O 2 mL were added thereto. LiOH (358 mg, 8.53 mmol) was added thereto, following with stirring at room temperature and refluxing with heating and stirring for 15 hours. After acidification with 1 N HCl, the resulting precipitate was filtered. The obtained solid was dissolved in MeOH, following with filtering to remove insoluble material and concentrating under reduced pressure to yield the title compound as pale gray solid (625 mg, 95.1%).
1H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, 2 H, J = 8.3 Hz), 7.72 (d, 2 H, J = 8.3 Hz), 7.65 (d, 2 H, J = 8.7 Hz), 7.02 (d, 2 H, J = 8.7 Hz), 3.85 (d, 2 H, J = 5.8 Hz), 2.90 (d, 2 H, J = 11.2 Hz), 2.42 (s, 1 H), 2.36 (s, 1 H), 2.06 (t, 2 H, J = 11.4 Hz), 1.72 - 1.69 (m, 3 H), 1.30 (m, 2 H), 1.30 (s, 3 H), 1.25 (s, 3 H); MS (ESI) m/z 486 (M+ + H).

Example 22. Comparative compound 515: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

[0069]

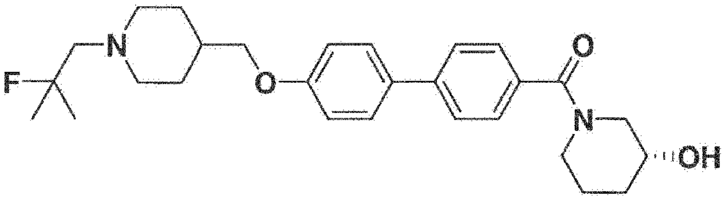


[0070] 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (compound 548, 15 mg, 0.04 mmol) and NH_4Cl (4 mg, 0.08 mmol) were dissolved in DMF 1 mL. EDC (15 mg, 0.08 mmol) and HOBt (11 mg, 0.08 mmol) were added thereto. Lastly, DIPEA (34 µL, 0.20 mmol) was added thereto, following with stirring at room temperature for 15 hours. The solvent was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10 % $MeOH/CH_2Cl_2$) to yield the title compound as white solid (7 mg, 48%).

1H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.87 (m, 2 H), 7.64 - 7.58 (m, 2 H), 7.56 - 7.50 (m, 2 H), 6.99 - 6.93 (m, 2 H), 3.82 (d, 2 H, J = 6.0 Hz), 2.97 (d, 2 H, J = 11.8 Hz), 2.46 (s, 1 H), 2.40 (s, 1 H), 2.20 - 2.04 (m, 6 H), 1.84 - 1.72 (m, 3 H), 1.49 - 1.35 (m, 2 H), 1.38 (s, 3 H), 1.32 (s, 3 H); MS (ESI) m/z 385 (M+ + H).

Example 23. Comparative compound 612: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0071]



[0072] 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (comparative compound 548, 50 mg, 0.13 mmol) was suspended in CH_2Cl_2 1 mL, and then added with EDC (50 mg, 0.26 mmol), HOBt (35 mg, 0.26 mmol) and DIPEA (113 µl, 0.65 mmol), thereby being dissolved completely. Lastly, (R)-hydroxypiperidine hydrochloride (36 mg, 0.26 mmol) was added thereto, following with stirring at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, dissolved in a little of MeOH, and then added with water. The resulting precipitate was filtered to obtain a solid. The obtained solid was purified by silica gel column chromatography (0-10 % $MeOH/CH_2Cl_2$) to yield the title compound as white solid (45 mg, 73%).

1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.56 - 7.50 (m, 2 H), 7.50 - 7.46 (m, 2 H), 7.02 - 6.95 (m, 2 H), 3.94 (brs, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.47 (br, 4 H), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.2 Hz), 1.97 (br, 2 H), 1.83 - 1.80 (m, 3 H), 1.67 (br, 2 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 469 (M+ + H).

[0073] According to the above-described synthesis process of comparative compound 515, the compounds of Table 4 were synthesized using 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-

yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 3.

Table 3. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
516*	dimethylamine hydrochloride	73
517*	morpholine	53
526*	cyclopropylamine	69
527*	cyclobutylamine	67
528*	cyclopentylamine	73
529*	cyclohexylamine	68
530*	pyrrolidine	80
531*	piperidine	66
533*	4-aminobutan-1-ol	64
534*	methylamine	67
549*	2-aminoethanol	77
550*	3-aminopropan-1-ol	74
551*	2-(methylamino)ethanol	71
553*	(R)-3-pyrrolidinol	72
554*	(S)-3-pyrrolidinol	76
555*	(R)-prolinol	77
556*	(S)-prolinol	66
557*	(R)-2-(methoxymethyl)pyrrolidine	80
558*	(S)-2-(methoxymethyl)pyrrolidine	69
559*	2-(butylamino)ethanol	66
560*	furfurylamine	78
561*	propylamine	70
562*	benzylamine	74
563*	N-ethylbenzylamine	80
564*	(S)-2-trifluoromethylpyrrolidine	71
565	L-prolinamide	67
566*	3-fluoropyrrolidine hydrochloride	76
567*	4-piperidinemethanol	69
568*	4-hydroxypiperidine	73
569*	3-hydroxypiperidine hydrochloride	55
570*	(R)-3-fluoropyrrolidine hydrochloride	76
571*	(S)-3-fluoropyrrolidine hydrochloride	72
594*	3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine	52
598*	N-methylethanamine	76

Compound No.	Reactant	Yield (%)
599*	N-methylpropan-2-amine	74
600*	azetidin-3-ol	73
601*	3,3-difluoroazetidine	67
602*	t-butylamine	79
603*	isopropylamine	98
604*	diethylamine	89
605*	2-amino-2-methyl-1-propanol	81
606*	(S)-2-amino-1-propanol	83
607*	(R)-2-amino-1-butanol	75
608*	D-valinol	84
609*	L-valinol	78
610*	serinol	62
611*	3-amino-1,2-propanediol	65
613*	(S)-3-hydroxypiperidine hydrochloride	79
619*	(R)-methyl pyrrolidine-2-carboxylate	48
622*	(S)-methyl pyrrolidine-2-carboxylate	42
623*	cyclopropyl(piperazin-1-yl)methanone	83
624*	1-(methylsulfonyl)piperazine	87
625*	(S)-methyl pyrrolidine-2-carboxylate	23
626*	t-butyl piperazin-1-carboxylate	62
627*	1-benzylpiperazine	51
628*	1-(piperazin-1-yl)ethanone	17
629*	3,3-difluoro pyrrolidine	40
645*	glycine methyl ester hydrochloride	82
646*	3-oxetaneamine	77
647*	β-alanine methyl ester	78
648*	D-serine methyl ester hydrochloride	71
649*	L-serine methyl ester hydrochloride	57
650*	ethyl 4-amino-1-piperidinecarboxylate	83
651*	amylamine	81
677*	ethyl piperidin-2-carboxylate	72
678*	ethyl piperidin-4-carboxylate	83
679*	ethyl piperidin-3-carboxylate	85
680*	1-ethylpiperazine	48
681*	1-isopropylpiperazine	42
685*	1-methylpiperazine	47

Compound No.	Reactant	Yield (%)
686*	2,6-dimethylpiperazine	17
687*	2,6-dimethylmorpholine	58
790*	piperazin-2-one	82
791*	piperidin-4-carbonitrile	77
830*	4-(2-aminoethyl)benzene-1,2-diol	25
831	(R)-piperidin-2-carboxamide hydrochloride	65
832	(S)-piperidin-2-carboxamide hydrochloride	71
874	(S)-piperidin-3-carboxamide hydrochloride	64
879	(R)-piperidin-3-carboxamide hydrochloride	79

Table 4. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
516*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.50 - 7.45 (m, 2 H), 7.01 - 6.94 (m, 2 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.13 (br, 3 H), 3.05 (br, 3 H), 2.99 (d, 2 H, J = 11.0 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.85 - 1.75 (m, 3 H), 1.50 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 413 (M+ + H).
517*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl) (morpholino)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.62 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.49 - 7.44 (m, 2 H), 7.00 - 6.95 (m, 2 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.81 - 3.45 (m, 8 H), 2.99 (d, 2 H, J = 11.8 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.21 - 2.12 (m, 2 H), 1.85 - 1.76 (m, 3 H), 1.49 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 455 (M+ + H).
526*	N-cyclopropyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.81 - 7.75 (m, 2 H), 7.62 - 7.57 (m, 2 H), 7.56 - 7.50 (m, 2 H), 7.00 - 6.94 (m, 2 H), 6.25 (s, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.95 - 2.89 (m, 1 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.19 - 2.14 (m, 2 H), 1.85 - 1.75 (m, 3 H), 1.47 - 1.39 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 0.93 - 0.85 (m, 2 H), 0.67 - 0.60 (m, 2 H); MS (ESI) m/z 425 (M+ + H).
527*	N-cyclobutyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.77 (m, 2 H), 7.63 - 7.58 (m, 2 H), 7.57 - 7.51 (m, 2 H), 7.01 - 6.95 (m, 2 H), 6.24 (d, 1 H, J = 8.0 Hz), 4.65 - 4.59 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.51 - 2.40 (m, 4 H), 2.17 (t, 2 H, J = 10.8 Hz), 2.04 - 1.91 (m, 2 H), 1.85 - 1.75 (m, 5 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3H), 1.34 (s, 3 H); MS (ESI) m/z 439 (M+ + H).
	N-cyclopentyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
528*	yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2 H, J = 8.5 Hz), 7.59 (d, 2 H, J = 8.3 Hz), 7.56 - 7.50 (m, 2 H), 7.00 - 6.94 (m, 2 H), 6.12 (d, 1 H, J = 7.3 Hz), 4.48 - 4.37 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.21 - 2.05 (m, 4 H), 1.86 - 1.60 (m, 7 H), 1.56 - 1.37 (m, 4 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 453 (M+ + H).
529*	N-cyclohexyl-4'-((1-(2-fluoro-2-methylpropyl)pipendin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2 H, J = 8.5 Hz), 7.60 (d, 2 H, J = 8.5 Hz), 7.56 - 7.51 (m, 2 H), 6.98 (d, 2 H, J = 8.8 Hz), 6.00 - 5.94 (m, 1 H), 4.07 - 3.94 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.03 - 2.95 (m, 2 H), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.19 - 2.14 (m, 2 H), 2.10 - 2.00 (m, 2 H), 1.82 - 1.75 (m, 5 H), 1.51 - 1.37 (m, 4 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.31 - 1.20 (m, 4 H); MS (ESI) m/z 467 (M+ + H).
530*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 4 H), 7.55 - 7.51 (m, 2 H), 7.00 - 6.95 (m, 2 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.67 (t, 2 H, J = 7.0 Hz), 3.50 (t, 2 H, J = 6.5 Hz), 2.98 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.21 - 2.11 (m, 2 H), 2.02 - 1.93 (m, 2 H), 1.92 - 1.87 (m, 2 H), 1.84 - 1.74 (m, 3 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 439 (M+ + H).
531*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.55 (m, 2 H), 7.54 - 7.49 (m, 2 H), 7.47 - 7.41 (m, 2 H), 7.00 - 6.94 (m, 2 H), 3.84 (d, 2 H, J = 5.8 Hz), 3.72 (br, 2 H), 3.41 (br, 2 H), 2.98 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (td, 2 H, J = 11.7, 2.0 Hz), 1.86 - 1.74 (m, 3 H), 1.74 - 1.50 (m, 6 H), 1.48 - 1.36 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 453 (M+ + H).
533*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(4-hydroxybutyl)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.78 (m, 2 H), 7.64 - 7.58 (m, 2 H), 7.57 - 7.50 (m, 2 H), 7.01 - 6.94 (m, 2 H), 6.50 (t, 1 H, J = 5.6 Hz), 3.84 (d, 2 H, J = 5.8 Hz), 3.75 (t, 2 H, J = 6.0 Hz), 3.53 (q, 2 H, J = 6.5 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.8 Hz), 1.86 - 1.60 (m, 7 H), 1.49 - 1.37 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
534*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.78 (m, 2 H), 7.64 - 7.58 (m, 2 H), 7.57 - 7.52 (m, 2 H), 7.01 - 6.94 (m, 2 H), 6.16 (d, 1 H, J = 4.3 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.04 (d, 3 H, J = 4.8 Hz), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.85 - 1.75 (m, 3 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 399 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
549*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide
	1 H NMR (400 MHz, CDCl$_3$) δ 7.85 - 7.79 (m, 2 H), 7.62 - 7.56 (m, 2 H), 7.55 - 7.49 (m, 2 H), 7.00 - 6.93 (m, 2 H), 6.75 (t, 1 H, J = 5.4 Hz), 3.89 - 3.80 (m, 4 H), 3.69 - 3.61 (m, 2 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.86 - 1.74 (m, 3 H), 1.49 - 1.37 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 429 (M+ + H).
550*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(3-hydroxypropyl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.85 - 7.79 (m, 2 H), 7.63 - 7.57 (m, 2 H), 7.56 - 7.49 (m, 2 H), 7.00 - 6.93 (m, 2 H), 6.78 (br, 1 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.73 (t, 2 H, J = 5.5 Hz), 3.65 (q, 2 H, J = 6.1 Hz), 2.99 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.85 - 1.73 (m, 5 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 443 (M+ + H).
551*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)-N-methylbiphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.63 - 7.45 (m, 6 H), 6.97 (d, 2 H, J = 8.8 Hz), 3.92 (br, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.75 (br, 2 H), 3.51 (br, 1H), 3.11 (br, 3 H) 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 1.86 - 1.73 (m, 3 H), 1.50 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 443 (M+ + H).
553*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.61 - 7.47 (m, 6 H), 6.96 (d, 2 H, J = 8.8 Hz), 3.83 (d, 2 H, J = 5.8), 3.80 - 3.47 (m, 4 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 2.10 - 1.91 (m, 3 H), 1.86 - 1.73 (m, 3 H), 1.50 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 455 (M+ + H).
554*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.60 - 7.46 (m, 6 H), 6.99 - 6.93 (m, 2 H), 3.83 (d, 2 H, J = 5.8 Hz), 3.80 - 3.45 (m, 4 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.22 - 2.11 (m, 2 H), 2.11 - 1.91 (d, 3 H, J = 3.5 Hz), 1.85 - 1.73 (m, 3 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 455 (M+ + H).
555*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.62 - 7.55 (m, 4 H), 7.54 - 7.50 (m, 2 H), 7.00 - ! 6.94 (m, 2 H), 4.43 (d, 1 H, J = 6.0 Hz), 3.87 - 3.71 (m, 4 H), 3.66 - 3.49 (m, 2 H), 2.98 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.20 - 2.13 (m, 3 H), 1.95 - 1.58 (m, 6 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 469 (M+ + H).
	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
556*	1H NMR (400 MHz, CDCl$_3$) δ 7.61 - 7.55 (m, 4 H), 7.54 - 7.50 (m, 2 H), 7.00 - 6.94 (m, 2 H), 4.48 - 4.38 (m, 1 H), 3.87 - 3.71 (m, 4 H), 3.66 - 3.48 (m, 2 H), 2.98 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.16 (m, 3 H), 1.94 - 1.58 (m, 6 H), 1.49 - 1.36 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 469 (M+ + H).
557*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 4 H), 7.55 - 7.50 (m, 2 H), 7.00 - 6.94 (m, 2 H), 4.46 (br, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.74 - 3.47 (m, 4 H), 3.41 (s, 3 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.22 - 2.12 (m, 2 H), 2.12 - 1.90 (m, 3 H), 1.86 - 1.69 (m, 4 H), 1.50 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 483 (M+ + H).
558*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.57 (s, 3 H), 7.55 - 7.49 (m, 2 H), 7.01 - 6.93 (m, 2 H), 4.46 (br, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.74 - 3.47 (m, 4 H), 3.41 (s, 3 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.22 - 2.12 (m, 2 H), 2.11 - 1.89 (m, 3 H), 1.85 - 1.72 (m, 4 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 483 (M+ + H).
559*	N-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.58 (d, 2 H, J = 8.0 Hz), 7.53 (d, 2 H, J = 8.8 Hz), 7.47 - 7.42 (m, 2 H), 7.01 - 6.94 (m, 2 H), 3.90 (br, 2 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.72 (br, 2 H), 3.33 (br, 2 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.9 Hz), 1.86 - 1.73 (m, 3 H), 1.58 (br, 2 H), 1.50 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.28 - 1.14 (m, 2 H), 0.83 (br, 3 H); MS (ESI) m/z 485 (M+ + H).
560*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(furan-2-ylmethyl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.86 - 7.80 (m, 2 H), 7.63 - 7.57 (m, 2 H), 7.56 - 7.50 (m, 2 H), 7.38 (dd, 1 H, J = 1.8, 0.8 Hz), 7.01 - 6.93 (m, 2 H), 6.49 (t, 1 H, J = 5.1 Hz), 6.37 - 6.29 (m, 2 H), 4.66 (d, 2 H, J = 5.5 Hz), 3.83 (d, 2 H, J = 6.0 Hz), 2.98 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.21 - 2.11 (m, 2 H), 1.86 - 1.70, (m, 3 H) 1.51 - 1.36, (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 465 (M+ + H).
561*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.88 - 7.78 (m, 2 H), 7.66 - 7.59 (m, 2 H), 7.59 - 7.49 (m, 2 H), 7.05 - 6.93 (m, 2 H), 6.17 (t, 1 H, J = 5.8 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.52 - 3.41 (m, 2 H), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1H), 2.43 (s, 1H), 2.18 (t, 2 H, J = 10.8 Hz), 1.88 - 1.73 (m, 3 H), 1.72 - 1.63 (m, 2 H), 1.52 - 1.41 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 1.02 (t, 3 H, J = 7.4 Hz); MS (ESI) m/z 427 (M+ + H).
	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
562*	1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2 H, J = 8.5 Hz), 7.62 (d, 2 H, J = 8.5 Hz), 7.59 - 7.50 (m, 2 H), 7.44 - 7.29 (m, 5 H), 7.04 - 6.93 (m, 2 H), 6.44 (t, 1 H, J = 5.5 Hz), 4.69 (d, 2 H, J = 5.5 Hz), 3.85 (d, 2 H, J = 5.8 Hz), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1H), 2.43 (s, 1H), 2.18 (t, 2 H, J = 10.9 Hz), 1.83 - 1.82 (d, 3 H), 1.48 - 1.41 (m, 2 H), 1.41 (s 3H), 1.35 (s, 3H); MS (ESI) m/z 475 (M+ + H).
563*	N-benzyl-N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.45 (m, 6 H), 7.43 - 7.17 (m, 5 H), 6.98 (d, 2 H, J = 7.8 Hz), 4.81 (br, 1 H), 4.59 (br, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.55 - 3.53 (m, 1 H), 3.29 (br, 1 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1H), 2.43 (s, 1H), 2.18 (t, 2 H, J = 11.2 Hz), 1.83 - 1.80 (m, 3 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.29 - 1.12 (m, 3H); MS (ESI) m/z 503 (M+ + H).
564*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(trifluoromethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.58 (m, 4 H), 7.57 - 7.52 (m, 2 H), 7.02 - 6.96 (m, 2 H), 5.18 (br, 1H), 3.85 (d, 2 H, J = 6.0 Hz), 3.73 - 3.55 (m, 2 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (m, 1 H), 2.26 - 2.03 (m, 5 H), 1.96 - 1.74 (m, 4 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 507 (M+ + H).
565	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 4 H) 7.53 (d, 2 H, J = 8.8 Hz) 7.07 (br, 1 H) 6.98 (d, 2 H, J = 8.5 Hz) 5.71 (br, 1 H) 4.82 (dd, 1 H, J = 7.4, 5.4 Hz) 3.84 (d, 2 H, J = 6.0 Hz) 3.70 - 3.53 (m, 2 H) 3.00 (d, 2 H, J = 11.5 Hz) 2.48 (s, 1 H), 2.46 - 2.39 (m, 1 H), 2.42 (s, 1 H) 2.23 - 1.96 (m, 4 H) 1.93 - 1.72 (m, 4 H) 1.52 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 482 (M+ + H).
566*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.50 (m, 6 H) 7.03 - 6.95 (m, 2 H) 5.30 (t, 1 H, 51.3 Hz) 4.04 - 3.61 (m, 6 H) 3.00 (d, 2 H, J = 11.5 Hz) 2.48 (s, 1 H), 2.43 (s, 1 H) 2.43 - 2.18 (m, 1 H) 2.18 (t, 2 H, J = 10.8 Hz) 2.13 - 1.91 (m, 1 H) 1.88 - 1.74 (m, 3 H) 1.53 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
567*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.47 - 7.42 (m, 2 H), 7.01 - 6.95 (m, 2 H), 4.76 (br, 1 H), 3.89 (br, 1H), 3.84 (d, 2 H, J = 6.0 Hz), 3.53 (d, 2 H, J = 3.8 Hz), 3.03 (br, 1 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.80 (br, 1 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.23 - 2.12 (m, 2 H), 1.95 - 1.67 (m, 7 H), 1.52 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.29 -1.19 (m, 2 H); MS (ESI) m/z 483 (M+ + H).
	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
568*	hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) 8 7.61 - 7.56 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.45 (d, 2 H, J = 8.5 Hz), 7.01 - 6.95 (m, 2 H), 4.23 (br, 1 H), 4.01 - 3.95 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.76 (br, 1 H), 3.48 - 3.15 (m, 2 H), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.0 Hz), 2.07 - 1.74 (m, 6 H), 1.71 - 1.38 (m, 4 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 469 (M+ + H).
569*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.55 - 7.51 (m, 2 H), 7.48 (d, 2 H, J = 8.3 Hz,), 7.02 - 6.95 (m, 2 H), 3.94 (br, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.80 -3.16 (br, 3 H), 3.01 (d, 2 H, J = 10.8 Hz), 2.49 (s, 1 H), 2.44 (s, 1 H), 2.19 (t, 2 H, J = 11.0 Hz), 2.08 - 1.52 (m, 9 H), 1.51 - 1.39 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 469 (M+ + H).
570*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.57 (m, 4 H), 7.54 (d, 2 H, J = 8.5 Hz), 7.02 - 6.96 (m, 2 H), 5.45 - 5.14 (m, 1 H), 4.02 - 3.87 (m, 2 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.82 - 3.62 (m, 2 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.39 - 2.22 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.13 - 1.91 (m, 1 H), 1.87 - 1.74 (m, 3 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
571*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.57 (m, 4 H), 7.54 (d, 2 H, J = 8.5 Hz), 7.02 - 6.95 (m, 2 H), 5.45 - 5.14 (m, 1 H), 4.04 - 3.87 (m, 2 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.82 - 3.61 (m, 5 H), 3.00 (d, 5 H, J = 11.3 Hz), 2.48 (s, 3 H), 2.43 (s, 3 H), 2.40 - 2.23 (m, 1 H), 2.22 - 2.13 (m, 2 H), 2.12 - 1.92 (m, 1 H), 1.87 - 1.74 (m, 3 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3H), 1.35 (s, 8 H); MS (ESI) m/z 457 (M+ + H).
594*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 6.7 Hz), 7.54 (d, 4 H, J = 8.6 Hz), 7.00 (d, 2 H, J = 8.8 Hz), 5.10 (s, 2 H), 4.27 (m, 2 H), 4.13 (m, 2 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.01 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.3 Hz), 1.82 (m, 2 H), 1.47 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 560 (M+ + H)
598*	N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 2 H, *J* = 8.0 Hz), 7.46 (m, 2 H), 6.98 (d, 2 H, *J* = 8.5 Hz), 3.86 (d, 2 H, *J* = 5.6 Hz), 3.62 (brs, 1 H), 3.38 (brs, 1 H), 3.05 (m, 5 H), 2.47 - 2.38 (m, 4 H), 1.85 - 1.82 (m, 2 H), 1.53-1.37 (m, 10 H), 1.28 - 1.15 (m, 3 H); MS (ESI) m/z 427 (M++ H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
599*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropyl-N-methylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.0 Hz), 7.53 (d, 2 H, J = 8.6 Hz), 7.43 - 7.42 (m, 2 H), 6.98 (d, 2 H, J = 8.6 Hz), 4.16 (brs, 1H), 3.86 (d, 2 H, J = 5.8 Hz), 3.02 - 2.85 (m, 5H), 2.32 (brs, 2 H), 2.20 (brs, 2 H), 1.82 - 1.68 (m, 3 H), 1.53 - 1.37 (m, 8 H), 1.19 (s, 6 H); MS (ESI) m/z 441 (M+ + H).
600*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxyazetidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 7.8 Hz), 7.54 (dd, 4 H, J = 20.0, 8.0 Hz), 6.97 (d, 2 H, J = 8.1 Hz), 4.71 (brs, 1 H), 4.49 (brs, 2 H), 4.22 (brs, 2H), 3.84 (d, 2 H, J = 4.9 Hz), 3.53 (d, 1 H, J = 5.4 Hz), 3.03 (brs, 2 H), 2.49 (d, 2 H, J = 21.4 Hz), 2.21 (brs, 2 H), 1.84 - 1.82 (m, 3 H), 1.42 - 1.36 (m, 8 H); MS (ESI) m/z 441 (M+ + H)
601*	(3,3-difluoroazetidin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2 H, *J* = 8.2 Hz), 7.63 (d, 2 H, *J* = 8.2 Hz), 7.55 (d, 2 H, *J* = 8.6 Hz), 6.99 (d, 2 H, *J* = 8.6 Hz), 4.58 (t, 4 H, *J* = 11.5 Hz), 3.86 (d, 2 H, *J* = 5.8 Hz), 3.03 (brs, 2 H), 2.52 - 2.45 (m, 2 H), 2.21 (brs, 2 H), 1.83 (d, 3 H, *J* = 10.0 Hz), 1.48 - 1.36 (m, 8 H); **MS** (ESI) m/z 461 (M+ + H).
602*	N-t-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.74 (m, 2 H), 7.62 - 7.57 (m, 2 H), 7.56 - 7.51 (m, 2 H), 7.01 - 6.95 (m, 2 H), 5.96 (s, 1 H), 3.84 (d, 2 H, J = 5.8 Hz), 2.98 (d, 2 H, J = 11.8 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.19 - 2.14 (m, 2 H), 1.81 (d, 3 H, J = 11.5 Hz), 1.49 (s, 9 H), 1.38 - 1.46 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 441 (M+ + H).
603*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.83 - 7.77 (m, 2 H), 7.63 - 7.58 (m, 2 H), 7.57 - 7.51 (m, 2 H), 7.01 - 6.95 (m, 2 H), 5.93 (d, 1 H, J = 8.0 Hz), 4.34 - 4.29 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 2.99 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.21 - 2.12 (m, 2 H), 1.82 - 1.79 (m, 3 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.28 (d, 6 H, J = 6.5 Hz); MS (ESI) m/z 427 (M+ + H).
604*	N,N-diethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.55 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.46 - 7.40 (m, 2 H), 7.01 - 6.94 (m, 2 H), 3.84 (d, 2 H, J = 5.8 Hz), 3.57 (br, 2 H), 3.32 (br, 2 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.9 Hz), 1.87 - 1.74 (m, 3 H), 1.52 - 1.37 (m, 2 H), 1.41 (s, 3 H), 1.34 (s, 3 H), 1.31 - 1.07 (m, 6 H); MS (ESI) m/z 441 (M+ + H).
	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
605*	1H NMR (400 MHz, CDCl$_3$) δ 7.81 - 7.74 (m, 2 H), 7.63 - 7.58 (m, 2 H), 7.57 - 7.50 (m, 2 H), 7.01 - 6.94 (m, 2 H), 6.26 (s, 1 H), 3.84 (d, 2 H, J = 5.8 Hz), 3.71 (s, 2 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.8 Hz), 1.81 (dd, 3 H, J = 8.8, 2.8 Hz), 1.45 - 1.39 (m, 2 H), 1.44 (s, 6 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
606*	(S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxypropan-2-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.82 (d, 2 H, J = 8.5 Hz), 7.64 - 7.59 (m, 2 H), 7.57 - 7.51 (m, 2 H), 7.01 - 6.95 (m, 2 H), 6.34 (d, 1 H, J = 7.3 Hz), 4.37 - 4.27 (m, 1 H), 3.88 - 3.78 (m, 3 H), 3.68 (m, 1 H), 2.99 (d, 2 H, J = 11.0 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 11.8 Hz), 1.82 - 1.79 (m, 3 H), 1.51 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.32 (d, 3 H, J = 6.8 Hz); MS (ESI) m/z 443 (M+ + H).
607*	(R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxybutan-2-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.85 - 7.79 (m, 2 H), 7.62 - 7.57 (m, 2 H), 7.56 - 7.50 (m, 2 H), 7.00 - 6.94 (m, 2 H), 6.39 (d, 1 H, J = 7.8 Hz), 4.14 - 4.16 (m, 1 H), 3.87 - 3.79 (m, 3 H), 3.76 - 3.69 (m, 1 H), 2.99 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.9 Hz), 1.86 - 1.58 (m, 5 H), 1.51 - 1.37 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.04 (t, 3 H, J = 6.0 Hz); MS (ESI) m/z 457 (M+ + H).
608*	(R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.86 - 7.80 (m, 2 H), 7.65 - 7.59 (m, 2 H), 7.57 - 7.51 (m, 2 H), 7.02 - 6.95 (m, 2 H), 6.36 (d, 1 H, J = 8.3 Hz), 4.01 - 3.94 (m, 1 H), 3.88 - 3.77 (m, 4 H), 2.99 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.8 Hz), 2.10 - 1.99 (m, 1 H), 1.86 - 1.75 (m, 3 H), 1.50 - 1.37 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.05 (t, 6 H, J = 6.4 Hz); MS (ESI) m/z 471 (M+ + H).
609*	(S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.86 - 7.81 (m, 2 H), 7.66 - 7.60 (m, 2 H), 7.57 - 7.51 (m, 2 H), 7.02 - 6.95 (m, 2 H), 6.35 (d, 1 H, J = 8.5 Hz), 4.03 - 3.93 (m, 1 H), 3.89 - 3.78 (m, 4 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.22 - 2.12 (m, 2 H), 2.09 - 2.00 (m, 1 H), 1.83 - 1.80 (m, 3 H), 1.51 - 1.38 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.05 (t, 6 H, J = 6.4 Hz); MS (ESI) m/z 471 (M+ + H).
610*	N-(1,3-dihydroxypropan-2-yl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.85 (d, 2 H, J = 8.5 Hz), 7.60 (d, 2 H, J = 8.5 Hz), 7.49 - 7.55 (m, 2 H), 7.21 (s, 1 H), 6.99 - 6.92 (m, 2 H), 4.12 - 4.03 (m, 1 H), 3.91 - 3.71 (m, 6 H), 2.97 (d, 2 H, J = 11.5 Hz), 2.46 (s, 1 H), 2.40 (s, 1 H), 2.15 (t, 2 H, J = 8.0 Hz), 1.80 - 1.77 (m, 3 H), 1.49 - 1.35 (m, 2 H), 1.38 (s, 3 H), 1.32 (s, 3 H); MS (ESI) m/z 459 (M+ + H).
	N-(2,3-dihydroxypropyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
611*	yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, 2 H, J = 8.3 Hz), 7.62 (d, 2 H, J = 8.5 Hz), 7.57 - 7.51 (m, 2 H), 7.27 (t, 1 H, J = 4.0 Hz), 7.01 - 6.95 (m, 2 H), 3.90 - 3.82 (m, 3 H), 3.68 - 3.53 (m, 4 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.17 (t, 2 H, J = 11.3 Hz), 1.82 - 1.80 (m, 3 H), 1.37 - 1.51 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 459 (M+ + H).
613*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.55 - 7.51 (m, 2 H), 7.50 - 7.46 (m, 2 H), 7.02 - 6.95 (m, 2 H), 4.07 - 3.89 (m, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.81 - 3.17 (m, 4 H), 3.00 (d, 2 H, J = 11.0 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.3 Hz), 1.96 (br, 2 H), 1.83 - 1.80 (m, 3 H), 1.67 (br, 2 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 469 (M+ + H).
619*	(R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.63 - 7.50 (m, 6 H), 6.95 (d, 2 H, *J* = 6.1 Hz), 4.64 (m, 1 H), 3.82 (d, 2 H, *J* = 5.8 Hz), 3.77 (s, 3 H), 3.68 - 3.46 (m. 4 H), 2.99 (d, 2 H, *J* = 10.2 Hz), 2.48 - 2.41 (m, 2 H), 2.32 (m, 1 H), 2.18 -2.14 (m, 2 H), 2.02 - 2.00 (m, 2 H), 1.96 (brs, 1 H), 1.79 (d, 3 H, *J* = 10.5 Hz), 1.38 - 1.33 (m, 8 H); MS (ESI) m/z 497 (M+ + H).
622*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)thiazolidin-3-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.52 (m, 6 H), 6.98 (d, 2 H, *J* = 8.4 Hz), 4.65 (brs, 2H), 3.98 (brs, 2 H), 3.02 (brs, 4 H), 2.51 - 2.48 (m, 2 H), 2.20 (t, 2 H, *J* = 12.0 Hz), 1.82 (d, 3 H, *J* = 8.0 Hz), 1.48 - 1.45 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
623*	(4-(cyclopropanecarbonyl)piperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2 H, *J* = 6.1 Hz), 7.53 (d, 2 H, *J* = 6.5 Hz), 7.48 (d, 2 H, *J* = 6.1 Hz), 6.99 (d, 2 H, *J* = 6.5 Hz), 3.86 (d, 2 H, *J* = 4.4 Hz), 3.76 - 3.69 (m, 8 H), 3.13 (brs, 2 H), 2.61 - 2.54 (m, 2 H), 2.29 (brs, 2 H), 1.87 - 1.84 (m, 3 H), 1.78 (brs, 1 H), 1.58 - 1.56 (brs, 2 H), 1.44 (s, 3 H), 1.39 (s, 3 H), 1.05 - 1.01 (m, 2 H), 0.82 - 0.81 (m, 2 H); MS (ESI) m/z 522 (M+ + H).
624*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2 H, J = 6.2 Hz), 7.53 (d, 2 H, J = 6.6 Hz), 7.48 (d, 2 H, J = 6.2 Hz), 6.99 (d, 2 H, J = 6.5 Hz), 3.87 - 3.85 (m, 6 H), 3.28 (brs, 4 H), 3.13 (brs, 2 H), 2.82 (s, 3 H), 2.55 (brs, 2 H), 2.21 (brs, 2 H), 1.87 - 1.84 (m, 3 H), 1.42 - 1.37 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
	(S)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
625*	1H NMR (400 MHz, $CDCl_3$) δ 7.66 - 7.52 (m, 6 H), 6.98 (d, 2 H, *J* = 12.0 Hz), 3.85 (d, 2 H, *J* = 5.9 Hz), 3.79 (s, 3 H), 3.83 - 3.62 (m, 2 H), 3.01 (d, 2 H, *J* = 11.9 Hz), 2.47 (d, 2 H, *J* = 24.0 Hz), 2.38 (m, 1 H), 2.51 - 2.44 (m, 2 H), 2.02 - 1.87 (m, 3 H), 1.82 (d, 3 H, *J* = 12.0 Hz), 1.47 - 1.36 (m, 8 H); MS (ESI) m/z 497 (M+ + H).
626*	t-butyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2 H, *J* = 8.3 Hz), 7.54 (d, 2 H, *J* = 1.8 Hz), 7.46 (d, 2 H, *J* = 8.3 Hz), 6.98 (d, 2 H, *J* = 9.9 Hz), 3.86 (d, 2 H, *J* = 5.1 Hz), 3.83 - 3.49 (m, 8 H), 3.01 (brs, 2 H), 2.47 - 2.41 (m, 2 H), 2.19 (brs, 2 H), 1.83 (brs, 3 H). 1.48 (s, 9 H), 1.42 - 1.37 (m, 8 H); MS (ESI) m/z 554 (M+ + H).
627*	(4-benzylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) 8.19 (d, 2 H, J = 9.3 Hz), 7.63 (d, 2 H, J = 5.1 Hz), 7.57 (d, 2 H, J = 4.5 Hz), 6.99 (d, 2 H, J = 6.9 Hz), 3.86 (m, 4 H), 3.56 (m, 4 H), 2.96 (brs, 2 H), 2.54 - 2.43 (m, 6 H), 2.18 (brs, 2 H), 1.82 (brs, 3 H), 1.59 - 1.26 (m, 8 H); MS (ESI) m/z 544 (M+ + H).
628*	1-(4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone
	1H NMR (400 MHz, $CDCl_3$) 7.59 (d, 2 H, J = 8.1 Hz), 7.51 (d, 2 H, J = 8.6 Hz), 7.45 (d, 2 H, J = 9.9 Hz), 6.96 (d, 2 H, J = 8.7 Hz), 3.83 (d, 2 H, J = 5.8 Hz), 3.63 (brs, 4 H), 3.52 (brs, 4 H), 2.98 (brs, 2 H), 2.47 (d, 2 H, J = 22.5 Hz), 2.19 -2.12 (m, 5 H), 1.80 (m, 3 H), 1.39 - 1.33 (m, 8 H); MS (ESI) m/z 496 (M+ + H).
629*	(3,3-difluoropyrrolidine-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.52 (m, 6 H), 6.99 (d, 2 H, *J* = 6.5 Hz), 4.03 - 3.80 (m, 6 H), 3.10 - 3.01 (m, 2 H), 2.65 - 2.43 (m, 4 H), 2.19 - 2.05 (m, 2 H), 1.97 - 1.82 (m, 2 H), 1.59 - 1.41 (m, 2 H), 1.36 (s, 3 H), 1.27 (s, 3 H); MS (ESI) m/z 475 (M+ + H).
645*	methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)acetate
	1H NMR (400 MHz, $CDCl_3$) δ 7.91 - 7.85 (m, 2 H), 7.67 - 7.62 (m, 2 H), 7.59 - 7.53 (m, 2 H), 7.02 - 6.96 (m, 2 H), 6.68 (t, 1 H, J = 5.0 Hz), 4.29 (d, 2 H, J = 5.0 Hz), 3.86 (d, 2 H, J = 6.0 Hz), 3.83 (s, 3 H), 3.00 (d, 2 H, J = 11.0 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.2 Hz), 1.83 - 1.81 (m, 3 H), 1.38 - 1.51 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 457 (M+ + H).
646*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(oxetane-3-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2 H, J = 8.5 Hz), 7.67 - 7.62 (m, 2 H), 7.59 - 7.53 (m, 2 H), 7.03 - 6.96 (m, 2 H), 6.65 (d, 1 H, J = 7.5 Hz), 5.35 - 5.24 (m, 1 H), 5.06 (t, 2 H, J = 7.2 Hz), 4.64 (t, 2 H, J = 6.5 Hz), 3.86 (d, 2 H, J = 5.8 Hz), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(t, 2 H, J = 10.8 Hz), 1.82 (d, 3 H, J = 11.5 Hz), 1.38 - 1.51 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 441 (M+ + H).
647*	methyl 3-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)propanoate
	1H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.79 (m, 2 H), 7.65 - 7.59 (m, 2 H), 7.58 - 7.52 (m, 2 H), 7.02 - 6.96 (m, 2 H), 6.87 (t, 1 H, J = 5.9 Hz), 3.85 (d, 2 H, J = 5.8 Hz), 3.80 - 3.75 (m, 2 H), 3.74 (s, 3 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.69 (t, 2 H, J = 5.9 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 10.8 Hz), 1.83 - 1.80 (m, 3 H), 1.38 - 1.52 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 471 (M+ + H).
648*	(R)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydrox ypropanoate
	1H NMR (400 MHz, $CDCl_3$) δ 7.86 - 7.93 (m, 2 H), 7.61 - 7.67 (m, 2 H), 7.52 - 7.59 (m, 2 H), 7.14 (d, J = 6.8 Hz, 1 H), 6.95 - 7.02 (m, 2 H), 4.88 - 4.95 (m, 1 H), 4.11 (dd, J=3.5, 1.8 Hz, 2 H), 3.82 - 3.90 (m, 5 H), 3.00 (d, J=11.3 Hz, 2 H), 2.57 - 2.69 (m, 1 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, J=11.3 Hz, 2 H), 1.82 (d, J=11.8 Hz, 3 H), 1.38 - 1.53 (m, 5 H), 1.35 (s, 3 H); MS (ESI) m/z 487 (M+ + H).
649*	(S)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydroxypropanoate
	1H NMR (400 MHz, $CDCl_3$) δ 7.92 - 7.87 (m, 2 H), 7.67 - 7.61 (m, 2 H), 7.59 - 7.53 (m, 2 H), 7.15 (d, 1 H, J = 7.0 Hz), 6.99 (d, 2 H, J = 8.8 Hz), 4.94 - 4.89 (m, 1 H), 4.11 - 4.10 (m, 2 H), 3.89 - 3.83 (m, 5 H), 3.00 (d, 2 H, J = 11.0 Hz), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.0 Hz), 1.82 (d, 3 H, J = 11.8 Hz), 1.38 - 1.52 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 487 (M+ + H).
650*	ethyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)piperidin-1-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.78 (m, 2 H), 7.65 - 7.60 (m, 2 H), 7.58 - 7.52 (m, 2 H), 7.02 - 6.96 (m, 2 H), 6.02 (d, 1 H, J = 7.5 Hz), 4.27 - 4.10 (m, 5 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.01 - 2.98 (m, 4 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.4 Hz), 2.08 (d, 2 H, J = 10.3 Hz), 1.83 - 1.80 (m, 3 H), 1.52 - 1.38 (m, 4 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.28 (t, 3 H, J = 7.2 Hz); MS (ESI) m/z 540 (M+ + H).
651*	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-pentylbiphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.79 (m, 2 H), 7.65 - 7.59 (m, 2 H), 7.58 - 7.52 (m, 2 H), 7.02 - 6.96 (m, 2 H), 6.15 (t, 1 H, J = 5.6 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.52 - 3.44 (m, 2 H), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.0 Hz), 1.83 - 1.80 (m, 3 H), 1.70 - 1.60 (m, 3 H), 1.50 - 1.37 (m, 9 H), 1.35 (s, 3 H), 0.93 (t, 3 H, J = 7.1 Hz); MS (ESI) m/z 455 (M+ + H).
	ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.3 Hz), 7.53 (d, 2 H, J = 8.8

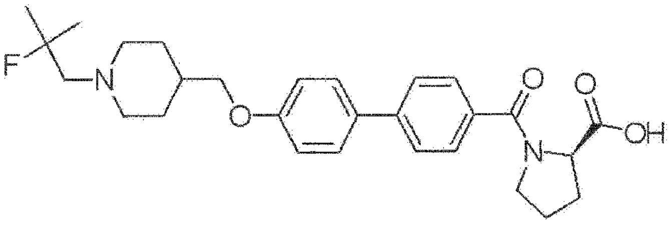
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
677*	Hz), 7.46 (d, 2 H, J = 8.3 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 4.22 - 4.07 (m, 2 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.13 - 3.05 (m, 1 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.24 - 2.10 (m, 3 H), 1.88 - 1.70 (m, 5 H), 1.50 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.31 - 1.17 (m, 3 H); MS (ESI) m/z 525 (M++ H).
678*	ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.53 (d, 2 H, J = 9.0 Hz), 7.46 (d, 2 H, J = 8.5 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 4.65 - 4.48 (m, 1 H), 4.18 (q, 2 H, J = 7.2 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.04 - 3.19 (m, 2 H), 3.00 (d, 2 H, J = 11.0 Hz), 2.64 - 2.54 (m, 1 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 11.3 Hz), 2.10 - 1.89 (m, 2 H), 1.76 - 1.64 (m, 5 H), 1.38 - 1.52 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H), 1.28 (t, 3 H, J = 7.0 Hz); MS (ESI) m/z 525 (M+ + H).
679*	ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxylate
	1H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.39 (m, 6 H), 6.98 (d, 2 H, J = 8.8 Hz), 4.31 - 4.22 (m, 2 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.76 (d, 1 H, J = 13.6 Hz), 3.34 - 3.27 (m, 1 H), 3.00 (d, 2 H, J = 11.3 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.38 (d, 1 H, J = 13.3 Hz), 2.24 - 2.12 (m, 2 H), 1.88 - 1.72 (m, 5 H), 1.68 - 1.59 (m, 2 H), 1.53 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.37 - 1.26 (m, 2 H), 1.35 (s, 3 H); MS (ESI) m/z 525 (M+ + H).
680*	(4-ethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.1 Hz), 7.53 (d, 2 H, J = 8.6 Hz), 7.46 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 9.1 Hz), 3.85 - 3.84 (m, 4 H), 3.58 (brs, 2 H), 3.02 (d, 2 H, J = 10.0 Hz), 2.55 - 2.44 (m, 8 H), 2.20 (t, 2 H, J = 11.5 Hz), 1.82 (d, 3 H, J = 11.0 Hz), 1.47 - 1.40 (m, 2 H), 1.35 (s, 3 H), 1.26 (s, 3 H), 1.13 (t, 3 H, J = 8.0 Hz); MS (ESI) m/z 482 (M+ + H).
681*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-isopropylpiperazin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.0 Hz), 7.52 (d, 2 H, J = 8.0 Hz), 7.47 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.0 Hz), 3.85 - 3.84 (m, 4 H), 3.58 (brs, 2 H), 3.03 (d, 2 H, J = 11.1 Hz), 3.03 (d, 2 H, J = 11.1 Hz), 2.67 (m, 1 H), 2.56 - 2.45 (m, 6 H), 2.20 (t, 2 H, J = 12.0 Hz), 1.82 (d, 3 H, J = 7.2 Hz), 1.48 - 1.41 (m, 2 H), 1.36 (s, 3 H), 1.26 (s, 3 H), 1.11 (d, 6 H, J = 6.4 Hz); MS (ESI) m/z 496 (M+ + H).
685*	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-methylpiperazin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 6.0 Hz), 7.52 (d, 2 H, J = 8.0 Hz), 7.47 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.5 Hz), 3.85 - 3.84 (m, 4 H), 3.55 (brs, 2 H), 3.02 (d, 2 H, J = 10.2 Hz), 2.50 - 2.45 (m, 6 H), 2.35 (s, 3 H), 2.20 (t, 2 H, J = 11.3 Hz), 1.82 (d, 3 H, J = 12.0 Hz), 1.47 - 1.44 (m, 2 H). 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 468 (M+ + H).
	(3,5-dimethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
686*	1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2 H, J = 8.0 Hz), 7.54 (d, 2 H, J = 8.4 Hz), 7.46 (d, 2 H, J = 8.0 Hz), 6.99 (d, 2 H, J = 8.5 Hz), 4.64 (brs, 1 H), 3.85 (d, 2 H, J = 5.6 Hz), 3.01 - 3.00 (m, 2 H), 2.46 - 2.45 (m, 2 H), 2.19 (t, 2 H, J = 11.6 Hz), 1.82 (d, 3 H, J = 10.6 Hz), 1.48 - 1.35 (m, 8 H), 1.26 - 1.04 (m, 6 H); MS (ESI) m/z 482 (M+ + H)
687*	(2,6-dimethylmorpholino)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2 H, J = 6.8 Hz), 7.53 (d, 2 H, J = 7.1 Hz), 7.45 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 7.2 Hz), 3.85 (d, 2 H, J = 5.6 Hz), 3.64 (brs, 2 H), 3.02 (d, 2 H, J = 10.7 Hz), 2.48 - 2.47 (m, 2 H), 2.21 (t, 2 H, J = 7.5 Hz), 1.82 (d, 3 H, J = 10.5 Hz), 1.47 - 1.12 (m, 14 H); MS (ESI) m/z 483 (M+ + H)
790*	4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-2-one
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.0 Hz), 7.51 (d, 2 H, J = 8.8 Hz), 7.47 (d, 2 H, J = 8.0 Hz), 6.97 (d, 2 H, J = 8.8 Hz), 4.28 (s, 2 H), 3.84 (s, 2 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.44 (s, 2 H), 2.98 (d, 2 H, J = 11.5 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.16 (t, 2 H, J = 10.9 Hz), 1.85 - 1.72 (m, 3 H), 1.49 - 1.36 (m, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 468 (M+ + H).
791*	1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.5 Hz), 7.51 (d, 2 H, J = 8.8 Hz), 7.44 (d, 2 H, J = 8.5 Hz), 6.97 (d, 2 H, J = 8.8 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.74 (s, 4 H), 2.89 - 3.03 (m, 3 H), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.17 (t, 2 H, J = 10.9 Hz), 1.92 (s, 4 H), 1.74 - 1.84 (m, 3 H), 1.37 - 1.50 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 478 (M+ + H).
830*	N-(3,4-dihydroxyphenethyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2 H, J = 8.0 Hz), 7.54 (d, 2 H, J = 7.5 Hz), 7.48 (d, 2 H, J = 8.0 Hz), 6.92 (d, 2 H, J = 7.5 Hz), 6.75 (d, 1 H, J = 7.5 Hz), 6.71 (s, 1 H), 6.56 (d, 1 H, J = 7.5 Hz), 3.80 (d, 2 H, J = 5.8 Hz), 3.59 (d, 2 H, J = 5.8 Hz), 2.98 (d, 2 H, J = 10.0 Hz), 2.76 (t, 2 H, J = 6.9 Hz), 2.52 - 2.37 (m, 2 H), 2.22 - 2.09 (m, 2 H), 1.78 (d, 3 H, J = 10.8 Hz), 1.53 - 1.34 (m, 2 H), 1.36 (s, 3 H), 1.31 (s, 3 H); MS (ESI) m/z 521 (M+ + H).
831	(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.41 (m, 6 H), 6.97 (d, 2 H, J = 8.5 Hz), 3.84 (d, 2 H, J = 5.8 Hz), 3.80 (s, 1 H), 3.11 (t, 1 H, J = 12.8 Hz), 3.00 (d, 2 H, J = 10.8 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.34 (d, 1 H, J = 12.5 Hz), 2.18 (t, 2 H, J = 11.5 Hz), 1.91 - 1.73 (m, 6 H), 1.71 - 1.50 (m, 4 H), 1.49 - 1.37 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H).
	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
832	1H NMR (400 MHz, $CDCl_3$) δ 7.65 - 7.41 (m, 6 H), 6.97 (d, 2 H, J = 8.5 Hz), 3.84 (d, 2 H, J = 5.8 Hz), 3.80 (s, 1 H), 3.11 (t, 1 H, J = 13.3 Hz), 3.00 (d, 2 H, J = 10.3 Hz), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.34 (d, 1 H, J = 12.3 Hz), 2.18 (t, 2 H, J = 11.2 Hz), 1.91 - 1.73 (m, 6 H), 1.72 - 1.51 (m, 3 H), 1.51 - 1.37 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 496 (M+ + H).
874	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.0 Hz), 7.53 (d, 2 H, J = 8.8 Hz), 7.45 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 4.15 - 4.01 (m, 1 H), 3.85 (d, 3 H, J = 6.0 Hz), 3.02 (d, 2 H, J = 10.8 Hz), 2.60 (s, 1 H), 2.51 (s, 1 H), 2.45 (s, 1 H), 2.20 (t, 2 H, J = 11.4 Hz), 2.06 - 1.87 (m, 3 H), 1.86 - 1.76 (m, 4 H), 1.62 (s, 1 H), 1.55 - 1.43 (m, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 496 (M+ + H).
879	(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, J = 8.0 Hz), 7.53 (d, 2 H, J = 8.8 Hz), 7.45 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 4.01 - 4.10 (m, 1 H), 3.86 (d, 3 H, J = 6.0 Hz), 3.63 - 3.39 (m, 2 H), 2.65 - 2.40 (m, 3 H), 2.29 - 2.11 (m, 3 H), 1.98 - 1.79 (m, 5 H), 1.76 - 1.58 (m, 3 H), 1.56 - 1.46 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 496 (M+ + H).

Example 24. Comparative compound 620: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid

[0074]



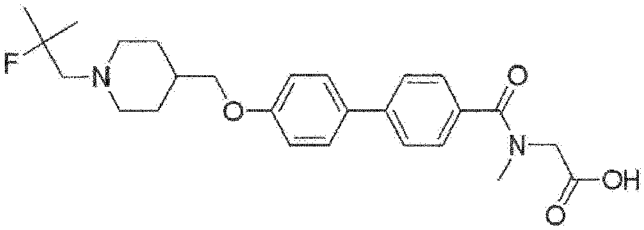
[0075] (R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl) pyrrolidine-2-carboxylate (comparative compound 619, 53 mg, 0.11 mmol) was dissolved in THF 1.5 mL, H_2O 0.5 mL and MeOH 0.5 mL. $LiOH{\cdot}H_2O$ (25 mg, 0.53 mmol) was added slowly thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was acidified to pH 5 by addition of 1 N HCl, following with adding excess amount of water. The resulting precipitate was filtered to yield the title compound as white solid (41 mg, 80%).

1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2 H, J = 10.2 Hz), 7.37 - 7.23 (m, 4 H), 6.65 (d, 2 H, J = 7.6 Hz), 3.82 (d, 2 H, J = 5.8 Hz), 3.72 - 3.50 (m, 6 H), 3.32 - 3.16 (m, 2 H), 2.70 (brs, 2 H), 2.32 (m, 1 H), 2.18 -2.14 (m, 2 H), 2.02 - 2.00 (m, 2 H), 1.96 (brs, 1 H), 1.79 (d, 3 H, J = 10.5 Hz), 1.38 - 1.33

(m, 8 H); MS (ESI) m/z 483 (M+ + H).

Example 25. Comparative compound 621: 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-ylcarboxamido)acetic acid

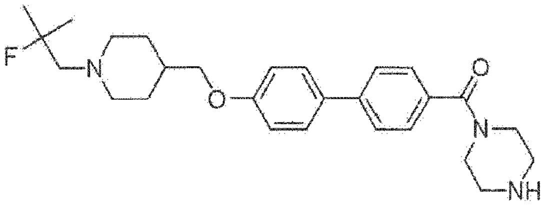
[0076]



[0077] 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (comparative compound 548, 0.12 g, 0.31 mmol) and methyl 2-(methylamino)acetate (29 mg, 0.28 mmol) were dissolved in DMF 1 mL. EDC (0.12 g, 0.62 mmol) and HOBt (84 mg, 0.62 mmol) were added thereto. Lastly, DIPEA (0.27 mL, 1.56 mmol) was added thereto, following with stirring at room temperature for 15 hours. The reaction mixture was added with EtOAc, and washed three times with water. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (10 % MeOH/CH_2Cl_2) to yield the title compound as white solid (0.12 g, 82%). The obtained product (90 mg, 0.19 mmol) was dissolved in THF 1.5 mL, H_2O 0.5 mL and MeOH 0.5 mL. $LiOH \cdot H_2O$ (40 mg, 0.96 mmol) was added slowly thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was acidified to pH 5 by addition of 1 N HCl. Excess amount of water was added thereto. The resulting precipitate was filtered to yield the title compound as white solid (16 mg, 18%).
1H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.42 (m, 6 H), 6.92 - 6.89 (m, 2 H), 4.03 - 3.85 (m, 2 H), 3.80 - 3.79 (m, 2 H), 2.83 (brs, 5 H), 2.51 - 2.44 (m, 2 H), 2.20 - 2.18 (m, 2 H), 1.80 - 1.78 (m, 3 H), 1.45 - 1.42 (m, 2 H), 1.38 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 457 (M+ + H).

Example 26. Comparative compound 630: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperazin-1-yl)methanone

[0078]



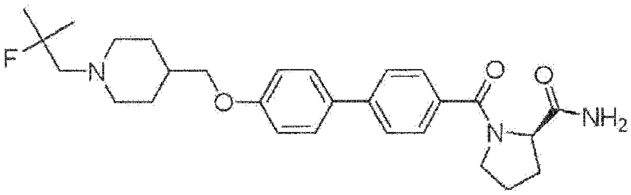
[0079] t-butyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-

1-carboxylate (comparative compound 626, 20 mg, 0.04 mmol) was dissolved in MeOH. Trifluoroacetic acid (8 µL, 0.11 mmol) was added slowly thereto, following with stirring at room temperature for 1 hour. After the completion of the reaction, the obtained reaction mixture was alkalinized with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2, The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over $MgSO_4$ to yield the title compound as white solid (5 mg, 31 %).

1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2 H, *J* = 6.0 Hz), 7.53 (d, 2 H, *J* = 6.5 Hz), 7.46 (d, 2 H, *J* = 6.2 Hz), 6.98 (d, 2 H, *J* = 6.5 Hz), 3.85 (d, 2 H, *J* = 4.2 Hz), 3.79 (brs, 4 H), 3.01 (d, 2 H, *J* = 8.5 Hz), 2.93 (brs, 4 H), 2.50 - 2.44 (m, 2 H), 2.19 (t, 2 H, *J* = 8.3 Hz), 1.83 - 1.80 (m, 3 H). 1.49 - 1.40 (m, 2 H), 1.35 (s, 3 H), 1.26 (s, 3 H); MS (ESI) m/z 454 (M+ + H).

Example 27. Compound 682: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0080]



[0081] (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid (comparative compound 620, 40 mg, 0.084 mmol) and NH_4Cl (6 mg, 0.12 mmol) were dissolved in DMF 1 mL. EDC (31 mg, 0.17 mmol) and HOBt (22 mg, 0.17 mmol) were added thereto. Lastly, DIPEA (72 uL, 0.42 mmol) was added thereto, following with stirring at room temperature for 15 hours. The reaction mixture was added with EtOAc, and washed three times with water. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10 % $MeOH/CH_2Cl_2$) to yield the title compound as white solid (15 mg, 37%).

1H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 4 H), 7.53 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.0 Hz), 5.53 (s, 1 H), 4.83 (t, 1 H, J = 6.0 Hz), 3.85 (d, 2 H, J = 8.0 Hz), 3.66 - 3.58 (m, 2 H), 2.50 - 2.47 (m, 2 H), 2.20 - 2.06 (m, 4 H), 1.88 - 1.81 (m, 5 H), 1.42 - 1.26 (m, 8 H); MS (ESI) m/z 482 (M+ + H).

[0082] According to the above-described synthesis process of compound 682, the compounds of Table 6 were synthesized using 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 5.

Table 5. (* marks comparative compound)

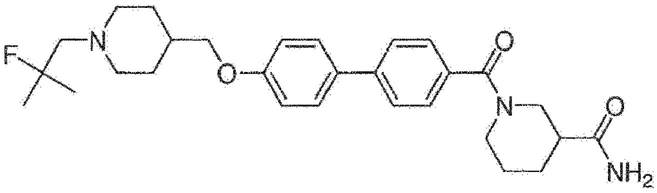
Compound No.	Reactant	Yield (%)
683*	dimethylamine hydrochloride	21
684*	methylamine	55

Table 6. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
683*	(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N,N-dimethylpyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 2 H, *J* = 8.0 Hz), 7.58 - 7.53 (m, 4 H), 6.97 (d, 2 H, *J* = 8.6 Hz), 5.10 (q, 1 H, *J* = 4.6 Hz), 3.86 - 3.63 (m, 4 H), 3.23 (s, 3 H), 3.02 (s, 3 H), 2.83 - 2.61 (m, 2 H), 2.28 - 1.84 (m, 9 H), 1.42 - 1.26 (m, 8 H); MS (ESI) m/z 510 (M+ + H).
684*	(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N-methylpyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 3 H), 7.53 (d, 2 H, *J* = 8.0 Hz), 7.10 (brs, 1 H), 6.98 (d, 2 H, *J* = 8.5 Hz), 4.80 - 4.79 (m, 1 H), 3.85 (d, 2 H, *J* = 5.8 Hz), 3.62 - 3.58 (m, 2 H), 3.01 (brs, 2 H), 2.96 - 2.88 (m, 2 H), 2.83 (d, 2 H, *J* = 4.8 Hz), 2.52 - 2.44 (m, 2 H), 2.20 (t, 2 H, *J* = 10.8 Hz), 2.07 - 2.05 (m, 2 H), 1.83 - 1.80 (m, 3 H), 1.46 - 1.43 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 496 (M+ + H).

Example 28. Compound 755: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide

[0083]



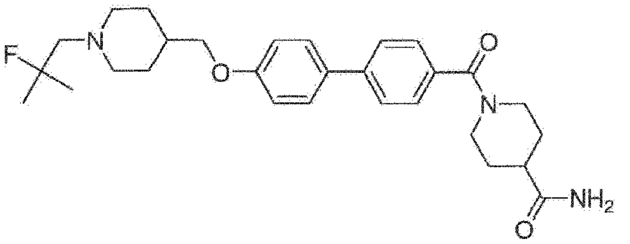
Step 1. 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-3-carboxylate (comparative compound 677, 0.07 g, 0.14 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and H_2O (0.5 mL) were poured thereto. LiOH·(0.3 g, 0.70 mmol) was added thereto, and refluxed with heating and stirring for 4 hours. The reaction mixture was acidified with 1 N HCl, and extracted with EtOAc and CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as yellow solid (0.070 g, 100%).

Step 2. Compound 755: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidin-3-carboxylic acid (0.07 g, 0.14 mmol), EDC (0.05 g, 0.28 mmol), HOBt (0.05 g, 0.28 mmol) and DIPEA (0.12 mL, 0.70 mmol) were dissolved in DMF (21 mL) completely. Lastly, NH_4Cl (0.02 g, 0.28 mmol) was added thereto, following with stirring at room temperature for 15 hours . Water (10 mL) was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g, ISCO silica gel cartridge, 0 - 10% MeOH/CH_2Cl_2) to yield the title compound

as yellow solid (0.03 g, 51%).
1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2 H, J = 8.3 Hz), 7.51 (d, 2 H, J = 8.8 Hz), 7.43 (d, 2 H, J = 8.5 Hz), 6.96 (d, 2 H, J = 8.8 Hz), 6.84 - 6.67 (m, 1 H), 5.65 (s, 1 H), 4.09 (s, 1 H), 3.83 (d, 2 H, J = 5.8 Hz), 3.69 - 3.80 (m, 1 H), 3.49 - 3.63 (m, 1 H), 3.47 - 3.32 (m, 1 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.57 (s, 1 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (t, 2 H, J = 11.0 Hz), 2.11 - 2.05 (m, 1 H), 1.92 (s, 1 H), 1.85 - 1.72 (m, 1 H), 1.61 (s, 1 H), 1.50 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 496 (M+ + H).

Example 29. Compound 756: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide

[0084]

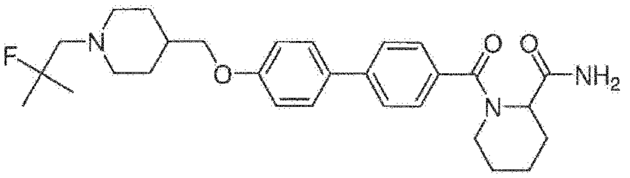


Step 1. 1 -(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-4-carboxylate (comparative compound 678, 0.09 g, 0.17 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and H_2O (0.5 mL) were poured thereto. LiOH ·(0.4 g, 0.87 mmol) was added thereto, and refluxed with heating and stirring for 4 hours. The reaction mixture was acidified with 1 N HCl, and extracted with EtOAc and CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as yellow solid (0.087 g, 100%).

Step 2. Compound 756: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidin-4-carboxylic acid (0.08 g, 0.17 mmol), EDC (0.06 g, 0.35 mmol), HOBt (0.05 g, 0.35 mmol) and DIPEA (0.11 mL, 0.87 mmol) were dissolved in DMF (21 mL) completely. Lastly, NH_4Cl (0.02 g, 0.35 mmol) was added thereto, following with stirring at room temperature for 15 hours . Water (10 mL) was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g, ISCO silica gel cartridge, 0 - 10% MeOH/CH_2Cl_2) to yield the title compound as yellow solid (0.06 g, 70%).
1H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.54 (m, 2 H), 7.50 (d, 2 H, J = 8.8 Hz), 7.42 (d, 2 H, J = 8.5 Hz), 6.96 (d, 2 H, J = 8.8 Hz), 5.82 (d, 2 H, J = 15.6 Hz), 4.78 - 4.55 (m, 1 H), 3.99 - 3.85 (m, 1 H), 3.83 (d, 2 H, J = 5.8 Hz), 3.11 - 2.83 (m, 2 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.48 - 2.40 (m, 1 H), 2.49 - 2.37 (m, 1 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.16 (t, 2 H, J = 11.0 Hz), 2.05 - 1.84 (m, 2 H), 1.84 - 1.65 (m, 6 H), 1.50 - 1.36 (m, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 496 (M+ + H).

Example 30. Compound 757: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide

[0085]

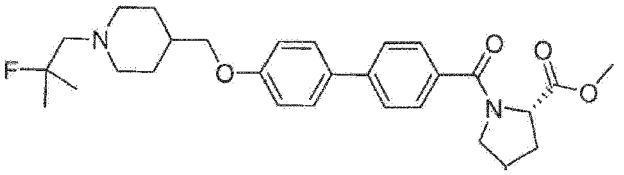


Step 1. 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-2-carboxylate (comparative compound 679, 0.09 g, 0.16 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and H_2O (0.5 mL) were poured thereto. LiOH·(0.3 g, 0.83 mmol) was added thereto, and refluxed with heating and stirring for 4 hours. The reaction mixture was acidified with 1 N HCl, and extracted with EtOAc and CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as yellow solid (0.082 g, 100%).

Step 2. Compound 757: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidin-2-carboxylic acid (0.08 g, 0.17 mmol), EDC (0.06 g, 0.33 mmol), HOBt (0.05 g, 0.33 mmol) and DIPEA (0.11 mL, 0.83 mmol) were dissolved in DMF (21 mL) completely. Lastly, NH_4Cl (0.02 g, 0.33 mmol) was added thereto, following with stirring at room temperature for 15 hours . Water (10 mL) was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g, ISCO silica gel cartridge, 0 - 10% MeOH/CH_2Cl_2) to yield the title compound as yellow solid (0.04 g, 46%).
1H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.40 (m, 6 H), 6.97 (d, 2 H, J = 8.5 Hz), 6.54 (s, 1 H), 3.84 (d, 2 H, J = 5.8 Hz), 3.79 (s, 1 H), 3.12 (t, 1 H, J = 13.8 Hz), 2.99 (d, 2 H, J = 11.0 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.33 (d, 1 H, J = 12.3 Hz), 2.17 (t, 2 H, J = 11.2 Hz), 1.89 - 1.72 (m, 5 H), 1.64 (s, 2 H), 1.61 - 1.51 (m, 2 H), 1.49 - 1.37 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 496 (M+ + H).

Example 31. Comparative compound 932: (2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate

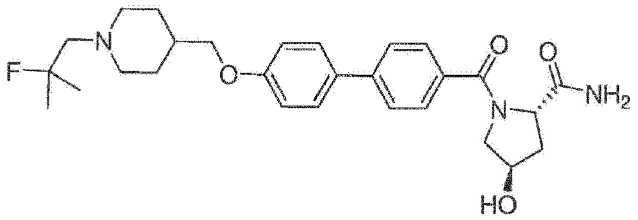
[0086]



[0087] 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (comparative compound 548; 300 mg, 0.78 mmol), (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (212 mg, 1.17 mmol), EDC (298 mg, 1.56 mmol), HOBt (210 mg, 1.56 mmol) and DIPEA (0.28 mL, 1.56 mmol) were dissolved in DMF (5 mL) at room temperature. After stirring at 80 °C for 12 hours, the reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 5 % to 80 %), and concentrated to yield the title compound as white solid (240 mg, 60%).
1H NMR (400 MHz, $CDCl_3$) δ 7.63 - 7.50 (m, 6 H), 6.97 (m, 2 H), 4.87 (m, 1 H), 4.53 (m, 1 H), 3.89 - 3.79 (m, 5 H), 3.62 (m, 1 H), 3.11 (m, 2 H), 2.59 - 2.13 (m, 7 H), 1.86 (m, 4 H), 1.58 (m, 2 H), 1.41 (m, 6 H); MS (ESI) m/z 513 (M++H).

Example 32. Compound 934: (2S,4R)-1-(4'-((10-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxamide

[0088]



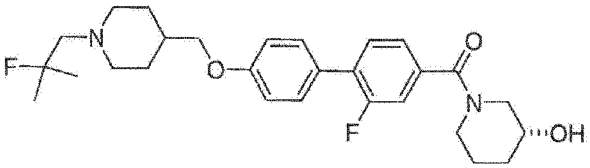
Step 1. (2S,4R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid: (2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate (comparative compound 932; 400 mg, 0.78 mmol) and $LiOH \cdot H_2O$ (65 mg, 1.56 mmol) were dissolved in THF (10 mL) / H_2O (5 mL) at room temperature. The solution was stirred at 60 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent. The obtained concentrate was added with 1 M-HCl aqueous solution, and concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 2. Compound 934: (2S,4R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (400 mg, 0.80 mmol), ammonium chloride (64 mg, 1.20 mmol), EDC (231 mg, 1.20 mmol), HOBt (163 mg, 1.20 mmol) and DIPEA (21 mg, 1.61 mmol) were dissolved in DMF (10 mL) at room temperature. The solution was stirred at 60 °C for 10 hours, the reaction mixture was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as brown solid (100 mg, 25%).
1H NMR (400 MHz, $CDCl_3$ + MeOD) δ 7.58 - 7.46 (m, 6 H), 7.22 (brs, 1 H), 6.91 (m, 2 H), 6.07 (br,

1 H), 4.76 (m, 1 H), 4.37 (m, 1 H), 3.81 - 3.73 (m, 3 H), 3.51 (m, 1 H), 3.95 (m, 2 H), 2.49 - 2.11 (m, 6 H), 1.76 (m, 3 H), 1.41 - 1.31 (m, 8 H); MS (ESI) m/z 498 (M+ + H).

Example 33. Comparative compound 749: (R)-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0089]



<u>**Step 1.**</u> methyl 2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 3 of compound 498; 180 mg, 0.52 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (124 mg, 0.63 mmol), Pd(dppf)Cl_2 (43 mg, 0.05 mmol) and CS_2CO_3 (341 mg, 1.05 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (30 % EtOAc/hexane) to yield the title compound as white solid (114 mg, 52%).

<u>**Step 2.**</u> 2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (114 mg, 0.27 mmol) was dissolved in THF (10 mL)/water (5 mL). At room temperature, $LiOH \cdot H_2O$ (57 mg, 1.36 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was acidified by the addition of IN HCl. The resulting precipitate was filtered, and dried to yield the title compound as white solid (90 mg, 81%).

<u>**Step 3.**</u> Comparative compound 749: 2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (45 mg, 0.11 mmol), (R)-piperidin-3-ol hydrochloride (13 mg, 0.13 mmol), BOP (94 mg, 0.21 mmol) and Et_3N (30 µL, 0.21 mmol) were dissolved in DMF (1 mL). At 60 °C, the reaction was performed for a day. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (10 % MeOH/CH_2Cl_2) to yield the title compound as yellow solid (18 mg, 33%).
1H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.43 (m, 3 H), 7.27 - 7.22 (m, 2 H), 7.00 - 6.96 (m, 2 H), 3.96 (brs, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.68 - 3.39 (m, 3 H), 3.04 - 3.02 (m, 2 H), 2.52 - 2.46 (m, 2 H), 2.35 - 2.21 (m, 2 H), 2.20 - 1.95 (m, 2 H), 1.84 - 1.82 (m, 4 H), 1.69 (brs, 2 H), 1.42 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 487 (M+ + H).

[0090] According to the above-described synthesis process of comparative compound 749, the compounds of Table 8 were synthesized using 2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 7.

Table 7.

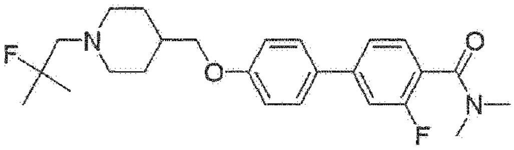
Compound No.	Reactant	Yield (%)
750	(S)-pyrrolidine-2-carboxamide	28

Table 8.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
750	(S)-1-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	MS (ESI) m/z 500 (M+ + H).

Example 34. Comparative compound 638: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide

[0091]



Step 1. ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 3 of compound 498; 450 mg, 1.31 mmol) and 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (305 mg, 1.44 mmol) were dissolved in dioxane 6 mL. Water 2 mL was added thereto. Pd(dbpf)Cl_2 (43 mg, 0.07 mmol) and CS_2CO_3 (851 mg, 2.61 mmol) were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was filtered through Celite. The filtrate was added with a saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (MeOH/CH_2Cl_2) to yield the title compound as white solid (350 mg, 62%).

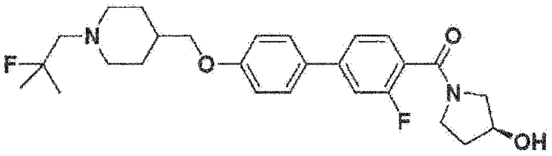
Step 2. 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (350 mg, 0.84 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 0.5 mL were added thereto. LiOH·(70 mg, 1.68 mmol) was added thereto, and refluxed with heating and stirring for 5 hours. After acidification with 1 N HCl, the resulting precipitate was filtered to yield the title compound as white solid (300 mg, 88%).

Step 3. Comparative compound 638: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), dimethylamine hydrochloride (9 mg, 0.11 mmol) and PyBOP (58 mg, 0.11 mmol) were dissolved in CH_2Cl_2 1 mL. DIPEA (19 mg, 0.15 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) to yield the title compound as white solid (15 mg, 47%).

1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2 H, J = 8.8 Hz), 7.39 (m, 2 H), 7.27 (s, 1 H), 6.97 (d, 2 H, J = 8.8 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.15 (m, 3 H), 2.99 (m, 5 H), 2.52 (s, 1 H), 2.47 (s, 1 H), 2.22 (m, 2 H), 1.82 (m, 3 H), 1.44 (m, 5 H), 1.27 (m, 3 H); MS (ESI) m/z 431 (M+ + H).

Example 35. Comparative compound 640: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone

[0092]



[0093] 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), (S)-3-pyrrolidinol (10 mg, 0.11 mmol) and PyBOP (58 mg, 0.11 mmol) were dissolved in CH_2Cl_2 1 mL, following with stirring for 10 minutes. DIPEA (19 mg, 0.15 mmol) was added thereto, following with stirring at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove a solid, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) to yield the title compound as white solid (18 mg, 51%).

1H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 3 H), 7.35 (m, 1 H), 7.24 (m, 1 H), 6.96 (d, 2 H, J = 8.6 Hz), 4.57 (m, 0.5 H), 4.44 (m, 0.5 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.78 (m, 1 H), 3.75 (m, 2 H), 3.53 (m, 2 H), 3.13 (m, 2 H), 3.01 (m, 2 H), 2.50 (s, 1 H), 2.44 (s, 1 H), 2.20 (m, 2 H), 1.98 (m, 1 H), 1.40 (m, 5 H), 1.25 (s, 3 H); MS (ESI) m/z 473 (M+ + H).

[0094] According to the above-described synthesis process of comparative compound 638 (Step 3), the compounds of Table 10 were synthesized using 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 9.

Table 9. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
639*	dimethylamine hydrochloride	44
641*	(R)-prolinol	55
642*	3-hydroxypiperidine	38

Compound No.	Reactant	Yield (%)
643*	2-amino-2-methyl-1-propanol	53
644	L-prolinamide	45
700*	(R)-piperidin-3-ol hydrochloride	46
701*	(S)-piperidin-3-ol hydrochloride	30
702*	(R)-pyrrolidine-3-ol	45
703*	(S)-pyrrolidine-2-ylmethanol	41
792	piperidin-4-carboxamide hydrochloride	39
793*	3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine	29
872	(R)-piperidin-2-carboxamide hydrochloride	63
875	(S)-piperidin-2-carboxamide hydrochloride	65
880	(R)-piperidin-3-carboxamide hydrochloride	63
1097*	(2S,4S)-4-fluoropyrrolidine-2-carbonitrile hydrochloride	49
1098*	(2S,4R)-4-hydroxypyrrolidine-2-carbonitrile hydrochloride	49

Table 10. (* marks comparative compound)

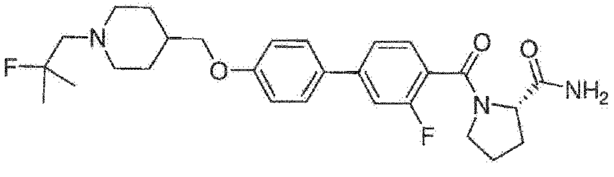
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
639*	N,N-diethyl-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, 2 H, J = 8.8 Hz), 7.37 (m, 2 H), 7.27 (m, 1 H), 6.97 (d, 2 H, J = 8.8 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.61 (m, 2 H), 3.27 (m, 2 H), 3.01 (m, 2 H), 2.51 (s, 1 H), 2.45 (s, 1 H), 2.20 (m, 2 H), 1.45 (m, 5 H), 1.35 (s, 3 H), 1.28 (t, 4 H, J = 7.1 Hz), 1.12 (t, 3 H, J = 7.1 Hz); MS (ESI) m/z 459 (M+ + H).
641*	(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 3 H), 7.39 (m, 1 H), 7.29 (d, 1 H, J = 9.8 Hz), 6.98 (d, 2 H, J = 8.8 Hz), 4.40 (m, 1 H), 3.75 (m, 4 H), 3.47 (m, 2 H), 3.01 (d, 2 H, J = 11.5 Hz), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.18 (m, 3 H), 1.76 (m, 6 H), 1.46 (m, 5 H), 1.40 (s, 3 H); MS (ESI) m/z 487 (M+ + H).
642*	(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-l-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, 2 H, J = 8.8, 2.3 Hz), 7.39 (m, 2 H), 7.27 (m, 1 H), 6.98 (d, 2 H, J = 6.8 Hz), 4.41 (m, 1 H), 3.93 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.38 (m, 2 H), 3.14 (m, 2 H), 3.01 (d, 2 H, J = 11.5 Hz), 2.49 (s, 1 H), 2.44 (s, 1 H), 2.19 (m, 2 H), 1.82 (m, 5 H), 1.61 (m, 1 H), 1.43 (m, 5 H), 1.35 (s, 3 H); MS (ESI) m/z 487 (M+ + H).
643*	3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.09 (t, 1 H, J = 8.4 Hz), 7.54 (dd, 2 H, J = 6.9, 1.9 Hz), 7.46 (dd, 1 H, J = 8.2, 1.7 Hz), 7.30 (dd, 1 H, J = 13.9, 1.6 Hz), 6.99 (dd, 2 H, J = 6.9, 1.9 Hz), 6.88 (d, 1 H, J = 15.2 Hz), 4.73 (s, 1

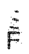
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	H), 3.85 (d, 2 H, J = 6.0 Hz), 3.72 (s, 2 H), 3.00 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.18 (td, 2 H, J = 11.7, 1.7 Hz), 1.80 (m, 3 H), 1.43 (s, 6 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 475 (M + H).
644	(S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide 1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.47 (m, 1 H), 7.40 (m, 1 H), 7.29 (m, 1 H), 6.99 (d, 2 H, J = 8.7 Hz), 5.46 (s, 1 H), 4.83 (m, 1 H), 3.85 (d, 2 H, J = 5.9 Hz), 3.53 (m, 1 H), 3.43 (m, 1 H), 2.99 (m, 2 H), 2.48 (m, 3 H), 2.10 (m, 5 H), 1.95 (m, 4 H), 1.26 (m, 5 H), 1.20 (s, 3 H); MS (ESI) m/z 450 (M+ + H).
700*	(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone MS (ESI) m/z 487 (M+ + H).
701*	(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone MS (ESI) m/z 487 (M+ + H).
702*	(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone MS (ESI) m/z 473 (M+ + H).
703*	(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone 1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.40 (m, 3 H), 7.39 - 7.30 (m, 1 H), 7.30 - 7.27 (m, 1 H), 6.98 - 6.95 (m, 2 H), 4.41 - 4.12 (m, 1 H), 3.88 - 3.82 (m, 2 H), 3.80 - 3.75 (m, 1 H), 3.49 - 3.45 (m, 2 H), 3.30 - 3.21 (m, 2 H), 2.78 - 2.73 (m, 2 H), 2.50 - 2.38 (m, 1 H), 2.23 - 2.19 (m, 1 H), 1.92 - 1.81 (m, 3 H), 1.79 - 1.70 (m, 4 H), 1.51 (s, 3 H), 1.43 (s, 3 H), 1.28 - 1.22 (m, 3 H); MS (ESI) m/z 487 (M+ + H).
792	1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide 1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.36 (m, 2 H), 7.24 (m, 1 H), 6.91 (m, 2 H), 5.50 (m, 2 H), 4.74 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.71 (m, 2 H), 3.01 (m, 4 H), 2.41 (m, 3 H), 2.22 (m, 2 H), 2.02 (m, 1 H), 1.80 (m, 6 H), 1.55 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 514 (M + H).
793*	(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(811)-yl)methanone 1H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4 H), 7.33 (d, 1 H, J = 11.3 Hz), 7.00 (d, 2 H, J = 8.5 Hz), 5.22 (s, 1 H), 4.94 (s, 1 H), 4.28 (m, 2 H), 3.87 (m, 2 H), 3.04 (m, 2 H), 2.87 (d, 1 H, J = 10.2 Hz), 2.50 (s, 1 H), 2.44 (s, 1 H), 2.19 (m, 2 H), 1.82 (m, 4 H), 1.40 (m, 5 H), 1.19 (s, 3 H).
	(R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide 1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.55 (m, 4 H), 7.32 - 7.28 (m, 1 H),

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
872	6.99 (d, 2 H, J = 8.8 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.62 (d, 1 H, J = 12.0 Hz), 3.22 (t, 1 H, J = 12.5 Hz), 3.02 (d, 2 H, J = 9.8 Hz), 2.55 - 2.35 (m, 3 H), 2.20 (t, 2 H, J = 11.2 Hz), 1.88 - 1.70 (m, 6 H), 1.64 (d, 3 H, J = 12.5 Hz), 1.53 - 1.39 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 514 (M+ + H).
875	(S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.37 (m, 4 H), 7.32 - 7.28 (m, 1 H), 6.99 (d, 1 H, J = 9.0 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.62 (d, 1 H, J = 12.3 Hz), 3.22 (t, 1 H, J = 13.2 Hz), 3.02 (d, 2 H, J = 11.0 Hz), 2.50 (s, 1 H), 2.45 (s, 1 H), 2.42 - 2.35 (m, 1 H), 2.20 (t, 2 H, J = 11.3 Hz), 1.88 - 1.71 (m, 6 H), 1.70 - 1.54 (m, 3 H), 1.53 - 1.43 (m, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 514 (M+ + H).
880	(R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2 H, J = 8.5 Hz), 7.40 (d, 2 H, J = 3.5 Hz), 7.31 - 7.24 (m, 1 H), 6.98 (d, 2 H, J = 8.8 Hz), 3.86 (d, 2 H, J = 5.8 Hz), 3.82 - 3.74 (m, 1 H), 3.49 - 3.43 (m, 1 H), 3.37 - 3.31 (m, 1 H), 3.03 (s, 2 H), 2.62 - 2.56 (m, 1 H), 2.54 - 2.43 (m, 2 H), 2.28 - 2.04 (m, 3 H), 1.97 - 1.77 (m, 5 H), 1.74 - 1.60 (m, 4 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 514 (M+ + H).
1097*	(2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.45 (m, 4 H), 7.33 - 7.28 (m, 1 H), 7.00 (m, 2 H), 5.45 - 5.32 (m, 1 H), 5.13 (m, 1 H), 3.88 - 3.77 (m, 4 H), 3.16 - 3.01 (m, 3 H), 2.82 - 2.42 (m, 6 H), 1.98 - 1.80 (m, 4 H), 1.47 - 1.29 (m, 6 H); MS (ESI) m/z 500.2 (M+ + H).
1098*	(2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.49 (m, 3 H), 7.41 - 7.38 (m, 1 H), 7.30 - 7.27 (m, 1 H), 6.98 (m, 2 H), 5.04 (t, 1 H, J = 8.2 Hz), 4.58 (m, 1 H), 3.86 (m, 2 H), 3.80 - 3.76 (m, 1 H), 3.49 - 3.46 (m, 1 H), 3.15 (s, 2 H), 2.58 - 2.47 (m, 4 H), 2.38 (s, 2 H), 1.87 - 1.85 (m, 3 H), 1.49 - 1.27 (m, 9 H); MS (ESI) m/z 498.2 (M+ + H).

Example 36. Compound 1099: (2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0095]





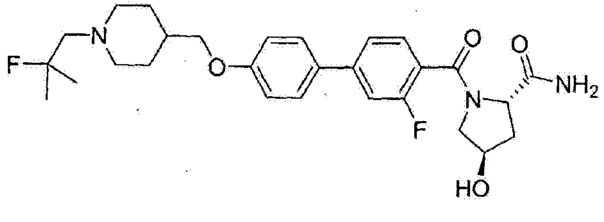
<u>Step 1.</u> (2S,4S)-methyl 4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (150 mg, 0.37 mmol), (2S,4S)-methyl 4-fluoropyrrolidine-2-carboxylate (55 mg, 0.37 mmol), EDC (107 mg, 0.56 mmol), HOBt (75 mg, 0.56 mmol) and DIPEA (0.13 mL, 0.74 mmol) were dissolved in DMF (4 mL) at room temperature. The solution was stirred at 80 °C for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_3, 4 g cartridge; ethyl acetate / hexane = 10 % to 50 %), and concentrated to yield the title compound as colorless oil (0.12 g, 61 %).

<u>Step 2.</u> (2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)pyrrolidine-2-carboxylic acid: (2S,4S)-methyl 4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate (120 mg, 0.23 mmol) and $LiOH \cdot H_2O$ (19 mg, 0.45 mmol) were dissolved in THF (10 mL) / H_2O (5 mL) at room temperature. The solution was stirred at 60 °C for 4 hours. The reaction mixture was concentrated under reduced pressure. The obtained material was used without further purifying process.

<u>Step 3.</u> Compound 1099: (2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid (200 mg, 0.39 mmol), ammonium chloride (31 mg, 0.58 mmol), EDC (111 mg, 0.58 mmol), HOBt (78 mg, 0.58 mmol) and DIPEA (0.14 mL, 0.77 mmol) were dissolved in DMF (6 mL) at room temperature. The solution was stirred at 80 °C for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; ethyl acetate / hexane = 10 % to 90 %), and concentrated to yield the title compound as light-red solid (30 mg, 15%).
1H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.28 (m, 5 H), 7.00 - 6.96 (m, 2 H), 6.68 (s, 0.78 H), 6.35 (s, 0.16 H), 5.70 (m, 1 H), 5.33 - 5.20 (m, 1 H), 5.00 (m, 1 H), 3.92 - 3.83 (m, 3 H), 3.74 - 3.62 (m, 1 H), 3.18 - 2.89 (m, 3 H), 2.58 - 2.18 (m, 5 H), 1.85 (m, 3 H), 1.43 - 1.27 (m, 8 H); MS (ESI) m/z 518.2 (M+ + H).

Example 37. Compound 1100: (2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxamide

[0096]



<u>Step 1.</u> (2S,4R)-methyl 1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (100 mg, 0.25 mmol), (2S,4R)-

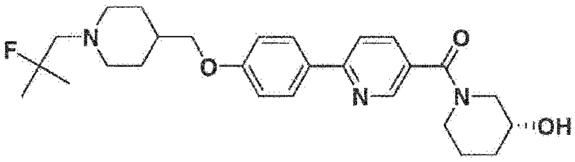
methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (45 mg, 0.25 mmol), EDC (71 mg, 0.37 mmol), HOBt (50 mg, 0.37 mmol) and DIPEA (0.09 mL, 0.50 mmol) were dissolved in DMF (4 mL) at room temperature. The solution was stirred at 80 °C for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; ethyl acetate / hexane = 10 % to 80 %), and concentrated to yield the title compound as colorless oil (70 mg, 53%).

Step 2. (2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid: (2S,4R)-methyl 1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate (70 mg, 0.13 mmol) and $LiOH{\cdot}H_2O$ (11 mg, 0.26 mmol) were dissolved in THF (6 mL) / H_2O (3 mL) at room temperature. The solution was stirred at 60 °C for 4 hours. The reaction mixture was concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 3. Compound 1100: (2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid (100 mg, 0.19 mmol), ammonium chloride (16 mg, 0.29 mmol), EDC (56 mg, 0.29 mmol), HOBt (39 mg, 0.29 mmol) and DIPEA (0.07 mL, 0.39 mmol) were dissolved in DMF (5 mL) at room temperature. The solution was stirred at 80 °C for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as light-red solid (15 mg, 15%).
1H NMR (400 MHz, $CDCl_3$+MeOD) δ 7.57 - 7.44 (m, 3 H), 7.38 - 7.31 (m, 1 H), 7.28 - 7.27 (m, 1 H), 6.93 (m, 2 H), 4.79 (t, 1 H, J = 8.2 Hz), 4.41 (m, 1 H), 3.86 (m, 2 H), 3.72 - 3.68 (m, 2 H), 3.41 - 3.37 (m, 2H), 2.34 - 2.25 (m, 3 H), 2.01 - 1.90 (m, 4 H), 1.47 - 1.38 (m, 6 H), 1.37 - 1.21 (m, 4 H); MS (ESI) m/z 516.2 (M+ + H).

Example 38. Comparative compound 758: (R)-(6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridine-3-yl)(3-hydroxypiperidin-1-yl)methanone

[0097]



Step 1. methyl 6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)nicotinate: Methyl 6-bromonicotinate (0.07 g, 46%) was dissolved in 1,4-dioxane 2 mL and H_2O 1 mL. 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid (the product of synthesis step 1 of comparative compound 617; 0.1 g, 0.32 mmol), $Pd(dbpf)Cl_2$ (0.01g, 0.02 mmol) and CS_2CO_3 (0.21 g, 0.65 mmol) were added thereto. The mixture was stirred in a microwave at 110 °C for 30 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The

filtrate was added with water, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 0 - 20 % EtOAc/Hexane) to yield the title compound as yellow solid (0.06 g, 46%).

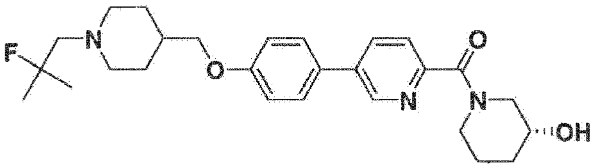
Step 2. 6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)nicotinic acid: Methyl 6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)nicotinate (0.06 g, 0.15 mmol) were dissolved in THF 10 mL, H_2O 3 mL and MeOH 3 mL. $LiOH \cdot H_2O$ (0.03 g, 0.75 mmol) was added thereto, following with increasing the temperature slowly. The mixture was refluxed with stirring for 3 hours. After the completion of the reaction, HCl was added thereto to acidify to pH 5. The resulting precipitate was filtered to yield the title compound as light-yellow solid (0.03 g, 55%).

Step 3. Comparative compound 758: 6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) nicotinic acid (0.03 g, 0.08 mmol) and (R)-piperidin-3-ol (0.02 g, 0.15 mmol) were dissolved in DMF 2 mL. DIPEA (0.05 g, 0.38 mmol), EDCI (0.03 g, 0.15 mmol) and HOBt (0.02 g, 0.15 mmol) were added thereto slowly, following with stirring at room temperature for 3 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as brown solid (0.02 g, 61%).

1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 1 H), 7.96 (d, 2 H, J = 8.4 Hz), 7.82 (d, 1 H, J = 6.8 Hz), 7.71 (d, 1 H, J = 8.4 Hz), 7.00 (d, 2 H, J = 8.8 Hz), 3.99 - 3.57 (m, 7 H), 3.00 (d, 2 H, J = 10.4 Hz), 2.48 - 2.43 (m, 2 H), 2.19 (t, 2 H, J = 11.2 Hz), 2.05 - 1.67 (m, 7 H), 1.55 - 1.35 (m, 8 H).

Example 39. Comparative compound 759: (R)-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridine-2-yl)(3-hydroxypiperidin-1-yl)methanone

[0098]



Step 1. methyl 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinate: Methyl 5-bromopicolinate (0.10 g, 0.46 mmol) was dissolved in 1,4-dioxane 2 mL and H_2O 1 mL. 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid (Synthesis step 1 of comparative compound 617, 0.13 g, 0.42 mmol), Pd(dbpf)Cl_2 (0.01 g, 0.02 mmol) and CS_2CO_3 (0.27 g, 0.84 mmol) were added thereto. The mixture was stirred in a microwave at 110 °C for 30 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 0 - 20 % EtOAc/Hex) to yield the title compound as light-yellow solid (0.03 g, 18%).

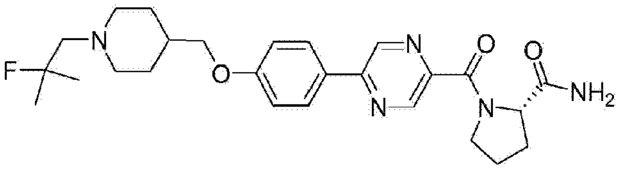
Step 2. 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid: methyl 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinate (0.03 g, 0.08 mmol) was dissolved in THF 10 mL, H_2O 3 mL, MeOH 3 mL. $LiOH \cdot H_2O$ (0.02 g, 0.38 mmol) was added thereto, following with increasing the temperature slowly and then refluxing with stirring for 3 hours. After the completion of the reaction, the reaction mixture was acidified to pH 5 by the addition of HCl. The resulting precipitate was filtered to yield the title compound as white solid (0.03 g, 97%).

Step 3. Comparative compound 759: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinic acid (0.03 g, 0.07 mmol) and (R)-piperidin-3-ol (0.01 g, 0.08 mmol) were dissolved in DMF. DIPEA (0.05 g, 0.36 mmol), EDCI (0.03 g, 0.15 mmol) and HOBt (0.02 g, 0.15 mmol) were added thereto slowly, following with stirring at room temperature for 3 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated NH_4Cl aqueous solution, dried over $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (0.01 g, 38%).

1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1 H), 8.00 (d, 1 H, J = 6.1 Hz), 7.84 (d, 1 H, J = 8.4 Hz), 7.53 (d, 2 H, J = 7.7 Hz), 7.02 (d, 2 H, J = 7.6 Hz), 5.84 (s, 1 H), 4.61 (d, 1 H, J = 12.8 Hz), 4.10 - 4.03 (m, 2 H), 3.86 (d, 2 H, J = 5.4 Hz), 3.27 (d, 1 H, J = 14.0 Hz), 3.01 - 2.91 (m, 3 H), 2.48 - 2.43 (m, 2 H), 2.21 - 1.98 (m, 4 H), 1.82 - 1.48 (m, 5 H), 1.46 - 1.26 (m, 8 H); MS (ESI) m/z 470 (M+ + H).

Example 40. Comparative Compound 1038:(S)-1-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxamide

[0099]



Step 1. methyl 5-(4-hydroxymethyl)pyrazine-2-carboxylate: methyl 5-bromopyrazine-2-carboxylate (500 mg, 2.30 mmol), 4-hydroxyphenylboronic acid (381 mg, 2.77 mmol), methyl 5-bromopyrazine-2-carboxylate, Pd(dppf)Cl_2 (188 mg, 0.23 mmol) and CS_2CO_3 (1.50 g, 4.61 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (30 % EtOAc/hexane) to yield the title compound as brown solid (210 mg, 40%).

Step 2. methyl 5-(4-((1-(t-butoxycarbonyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: methyl 5-(4-hydroxymethyl)pyrazine-2-carboxylate (150 mg, 0.65 mmol) was dissolved in DMF(10 mL). At room temperature, K_2CO_3 (318 mg, 0.98 mmol) was added thereto. After 5 minutes, t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (229 mg, 0.78 mmol) was added thereto, following with stirring at 80 °C for 5 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material was,used without further purifying process. (170 mg, 61 %).

Step 3. methyl 5-(4-(piperidin-4-ylmethoxy)phenyl)pyrazine-2-carboxylate hydrochloride: Methyl 5-(4-((1-(t-butoxycarbonyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate (170 mg, 0.39 mmol) was dissolved in CH_2Cl_2 (10 mL). At room temperature, 4 M HCl in 1,4-dioxane (1.99 mL, 7.95 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The resulting precipitate was filtered, and dried to yield the title compound as white solid (142 mg, 98%).

Step 4. methyl 5-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: Methyl 5-(4-(piperidin-4-ylmethoxy)phenyl)pyrazine-2-carboxylate hydrochloride (142 mg, 0.39 mmol), 2,2-dimethyloxirane (352 μL, 0.28 mmol) and K_2CO_3 (27 mg, 0.19 mmol) were dissolved in ethanol(10 mL), With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material was used without further purifying process (117 mg, 100%).

Step 5. methyl 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: methyl 5-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) pyrazine-2-carboxylate (117 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (15 mL). At room temperature, DAST (39 μL, 0.29 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material was used without further purifying process (100 mg, 85%).

Step 6. 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylic acid: methyl 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) pyrazine-2-carboxylate (100 mg, 0.24 mmol) was dissolved in THF (10 mL)/water (5 mL). At room temperature, $LiOH \cdot H_2O$ (52 mg, 1.24 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The obtained solid was filtered, and dried to yield the title compound as white solid (75 mg, 78%).

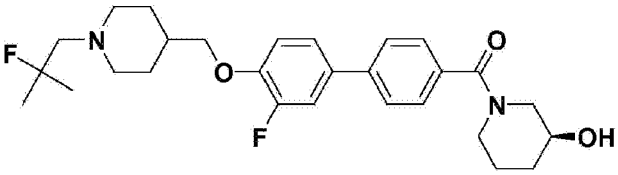
Step 7. Comparative Compound 1038: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) phenyl)pyrazine-2-carboxylic acid (35 mg, 0.09 mmol), (S)-pyrrolidine-2-carboxamide (21 mg, 0.18 mmol), EDC (35 mg, 0.18 mmol), HOBt (24 mg, 0.18 mmol) and DIPEA (32 μL, 0.18 mmol) were dissolved in CH_2Cl_2 (1 mL), following with stirring at room temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (10 % $MeOH/CH_2Cl_2$) to yield the title compound as white solid (19 mg, 44%).

1H NMR (400 MHz, $CDCl_3$) δ 9.25 - 9.15 (m, 1 H), 8.93 - 8.87 (m, 1 H), 8.05 - 7.99 (m, 2 H), 7.05 - 6.99 (m, 2 H), 5.48 (brs, 1 H), 5.04 - 4.85 (m, 1 H), 4.12 - 4.06 (m, 1 H), 3.95 - 3.84 (m, 3 H), 3.04

(brs, 2 H), 2.50 - 2.41 (m, 3 H), 2.39 - 2.20 (m, 3 H), 2.18 - 1.97 (m, 3 H), 1.83 (brs, 3 H), 1.61 - 1.22 (m, 8 H); MS (ESI) m/z 484 (M+ + H).

Example 41. Comparative compound 725: (S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0100]



Step 1. t-butyl 4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 2 of compound 431; 4.50 g, 15.34 mmol) was dissolved in DMF. K_2CO_3 (4.24 g, 30.67 mmol) and 2-fluoro-4-bromo phenol (1.85 mL, 16.87 mmol) were added thereto slowly, following with increasing the temperature and stirring at 60 °C for 3 hours. After the completion of the reaction, the reaction mixture was extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution three times, dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g ISCO silica gel cartridge, 0 - 20 % EtOAc/Hex) to yield the title compound as white solid (5.10 g, 86%).

Step 2. 4-((4-bromo-2-fluorophenoxy)methyl)piperidine hydrochloride: t-butyl 4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-carboxylate (5.60 g, 14.42 mmol) was dissolved in MeOH. And 1.25 M HCl in MeOH (57.69 mL, 72.12 mmol) was added thereto. After the solvent was distilled out completely, the residue was washed with ether to yield the title compound as white solid (4.1 g, 99%).

Step 3. 1-(4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 4-((4-bromo-2-fluorophenoxy)methyl)piperidine hydrochloride (2.30 g, 7.98 mmol) was dissolved in EtOH 50 mL and H_2O 50 mL. And 1,2-epoxy-2-methylpropane (5.76 g, 79.82 mmol) and K_2CO_3 (5.52 g, 39.91 mmol) were added slowly thereto. The mixture was stirred in a microwave at 120 °C for 20 minutes. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. Excess amount of H_2O was added thereto, and then a little of MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as white solid (2.4 g, 86%).

Step 4. 4-((4-bromo-2-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine: 1-(4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (4.88 g, 13.55 mmol) was dissolved in CH_2Cl_2. At 0 °C, DAST (1.97 mL, 14.90 mmol) was added slowly thereto, following with stirring with at 0 °C for 2 hours. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution to pH 7, and then washed with saturated aqueous brine solution three times. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 ~ 40 % EtOAc/Hex) to yield the title compound as light-yellow solid (3.3 g, 67%).

Step 5. methyl 3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-2-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (0.62 g, 1.71 mmol) was dissolved in 1,4-dioxane 12 mL and H_2O 3 mL. And then, 4-(methoxycarbonyl)phenylboronic acid (0.31 g, 1.71 mmol), Pd(dbpf)Cl_2 (0.056 g, 0.086 mmol) and CS_2CO_3 (1.12 g, 3.42 mmol) were added thereto, following with increasing the temperature slowly and stirring at 120 °C for 3 hours. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as white solid (0.23 g, 32%).

Step 6. 3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)bipheny1-4-carboxylic acid: methyl 3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylate (0.32 g, 0.77 mmol) was dissolved in THF 10 mL, H_2O 3 mL and MeOH 3 mL. LiOH·H_2O (0.26 g, 6.13 mmol) was added thereto, following with stirring at room temperature for 12 hours. After the completion of the reaction, The reaction mixture was acidified to pH 5 by the addition of HCl. The reaction mixture was extracted with CH_2Cl_2, The organic layer was washed with saturated aqueous brine solution three times, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (0.12 g, 39%).

Step 7. Comparative compound 725: 3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylic acid (0.04 g, 0.10 mmol) and (S)-piperidin-3-ol (0.02 g, 0.20 mmol) were dissolved in DMF 2 mL. DIPEA (0.06 g, 0.50 mmol), EDCI (0.04 g, 0.20 mmol) and HOBt (0.03 g, 0.20 mmol) were added thereto slowly, following with stirring at room temperature for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered, and then dissolved in CH_2Cl_2. The solution was concentrated under reduced pressure. The obtained concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (0.032 g, 68%).
1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 4 H), 7.32 - 7.24 (m, 2 H), 7.00 (t, 1 H, J = 8.5 Hz), 3.89 (d, 2 H, J = 6.0 Hz), 3.44 - 2.98 (m, 6 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 - 1.65 (m, 9 H), 1.38 - 1.23 (m, 8 H); MS (ESI) m/z 487 (M+ + H).

[0101] According to the above-described synthesis process of comparative compound 725, the compounds of Table 12 were synthesized using 3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 11.

Table 11. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
726*	(R)-piperidin-3-ol	85
727*	(R)-pyrrolidine-2-ylmethanol	3

Compound No.	Reactant	Yield (%)
728*	(S)-pyrrolidine-2-ylmethanol	27
729*	(R)-pyrrolidine-3-ol	28
799	piperidin-4-carboxamide	47
806	(R)-piperidin-2-carboxamide	47
807	(S)-piperidin-2-carboxamide	16

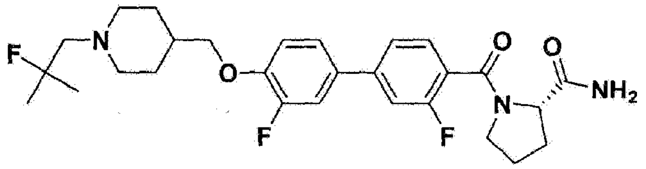
Table 12. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
726*	(R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.53 - 7.44 (m, 4 H), 7.32 - 7.24 (m, 2 H), 7.00 (t, 1 H, J = 8.5 Hz), 3.89 - 3.44 (m, 6 H), 2.98 (d, 2 H, J = 9.6 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (t, 2 H, J = 11.1 Hz), 1.91 - 1.38 (m, 9 H), 1.32 (s, 3H), 1.23 (s, 3 H); MS (ESI) m/z 487 (M+ + H)
727*	(R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.66 - 7.19 (m, 5 H), 7.01 (t, 1 H, J = 8.5 Hz), 4.98 (brs, 1 H), 3.90 (d, 2 H, J = 5.9 Hz), 3.80 - 3.74 (m, 2 H), 3.58 - 3.50 (m, 3 H), 3.01 - 2.48 (m, 4 H), 2.19 - 1.60 (m, 9 H), 1.40 - 1.34 (m, 8 H); MS (ESI) m/z 487 (M+ + H).
728*	(S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.55 (brs, 4 H), 7.33 - 7.24 (m, 2 H), 7.01 (t, 1 H, J = 8.5 Hz), 4.98 (brs, 1 H), 3.90 (d, 2 H, J = 5.9 Hz), 3.80 - 3.74 (m, 2 H), 3.58 - 3.50 (m, 3 H), 3.01 - 2.48 (m, 4 H), 2.19 - 1.60 (m, 9 H), 1.40 - 1.34 (m, 8 H); MS (ESI) m/z 487 (M+ + H).
729*	(R)-(3'-fluoro-4'-((1(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.60 - 7.50 (m, 4 H), 7.33 - 7.24 (m, 2 H), 7.00 (t, 1 H, J = 8.5 Hz), 4.60 (s, 0.5 H), 4.47 (s, 0.5 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.83 - 3.76 (m, 2 H), 3.68 - 3.45 (m, 2 H), 3.00 (brs, 2 H), 2.47 - 1.85 (m, 7 H), 1.44 - 0.83 (m, 8 H); MS (ESI) m/z 473 (M+ + H).
799	1-(3'-fluoro-4'-((1(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, 2 H, J = 8.0 Hz), 7.46 (d, 2 H, J = 8.0 Hz), 7.34 - 7.27 (m, 2 H), 7.03 (t, 1 H, J = 8.4 Hz), 5.58 (d, 2 H, J = 12.9 Hz), 3.91 - 3.90 (m, 4 H), 3.01 - 2.98 (m, 4 H), 2.48 - 2.42 (m, 3 H), 2.19 (t, 2 H, J = 11.4 Hz), 1.85 - 1.82 (m, 7 H), 1.47 - 1.26 (m, 8 H); MS (ESI) m/z 514 (M++ H).
	(R)-1-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.55 (dd, 4 H, J = 28.0, 7.2 Hz), 7.35 - 7.27

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
806	(m, 2 H), 7.03 (t, 1 H, J = 8.5 Hz), 6.53 (brs, 1 H), 5.70 (brs, 1 H), 5.29 (brs, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.79 (d, 1 H, J = 13.2 Hz), 3.14 (t, 1 H, J = 12.6 Hz), 2.99 (d, 2 H, J = 11.2 Hz), 2.47 (s, 1 H), 2.42 (s, 1 H), 2.34 (d, 1 H, J = 12.4 Hz), 2.18 (t, 2 H, J = 11.1 Hz), 1.88 - 1.53 (m, 8 H), 1.49 - 1.25 (m, 8 H); MS (ESI) m/z 514 (M+ + H).
807	(S)-1(3'-fluoro-4'-(((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.50 (m, 4 H), 7.35 - 7.27 (m, 1 H), 7.03 (t, 1 H, J = 8.4 Hz), 6.49 (brs, 1 H), 5.48 (brs, 1 H), 5.29 (brs, 1 H), 3.91 (d, 2 H, J = 5.2 Hz), 3.80 (d, 1 H, J = 13.2 Hz), 3.13 (t, 1 H, J = 12.2 Hz), 3.00 (d, 2 H, J = 11.2 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.35 (d, 1 H, J = 12.8 Hz), 2.19 (t, 2 H, J = 11.0 Hz), 1.89 - 1.44 (m, 8 H), 1.41 - 1.26 (m, 8 H); MS (ESI) m/z 514 (M+ + H).

Example 42. Compound 730: (S)-1(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0102]



<u>Step 1.</u> methyl 3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-2-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl) piperidine (the product of synthesis step 4 of compound 725; 0.6 g, 1.66 mmol) was dissolved in 1,4-dioxane 12 mL and H_2O 3 mL. 4-(ethoxycarbonyl)-3-fluorophenylboronic acid, Pd(dbpf)Cl_2 (0.05 g, 0.08 mmol) and CS_2CO_3 (1.07 g, 3.13 mmol) were added thereto, following with increasing the temperature, slowly and stirring at 120 °C for hours. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as brown solid (0.5 g, 69%).

<u>Step 2.</u> 3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.5 g, 1.15 mmol) was dissolved in THF 10 mL, H_2O 3 mL and MeOH 3 mL. $LiOH \cdot H_2O$ (0.24 g, 5.74 mmol) was added thereto, following with stirring at room temperature for 12 hours. After the completion of the reaction, The reaction mixture was acidified to pH 5 by the addition of HCl. The reaction mixture was extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times, dried over Na_2SO_4, and filtered. The filtrate was

concentrated under reduced pressure to yield the title compound as white solid (0.37 g, 77%).

Step 3. Compound 730: 3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.10 mmol) and (S)-pyrrolidine-2-carboxamide (0.02 g, 0.19 mmol) were dissolved in DMF 1 mL. DIPEA (0.08 mL, 0.47 mmol), EDCI (0.04 g, 0.19 mmol) and HOBt (0.03 g, 0.19 mmol) were added thereto slowly, following with stirring at 60 °C for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered to yield the title compound as brown solid (0.04 g, 75%).
1H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.21 (m, 5 H), 7.00 (t, 1 H, J = 8.4 Hz), 6.89 (brs, 1 H), 5.41 (brs, 1 H), 4.81 - 4.80 (m, 1 H), 3.91 (brs, 2 H), 3.53 - 3.41 (m, 2 H), 3.13 - 2.43 (m, 4 H), 2.21 - 1.86 (m, 3 H), 1.71 - 1.23 (m, 10 H); MS (ESI) m/z 518 (M+ + H).

[0103] According to the above-described synthesis process of compound 730, the compounds of Table 14 were synthesized using 3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 13.

Table 13. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
731*	(S)-piperidin-3-ol	48
732*	(S)-pyrrolidine-3-ol	22
733*	(R)-pyrrolidine-3-ol	28
734*	(R)-piperidin-3-ol	65
800	piperidin-4-carboxamide	53
816	(R)-piperidin-2-carboxamide	51
817	(S)-piperidin-2-carboxamide	42

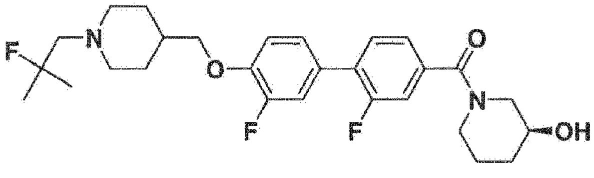
Table 14. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
731*	(S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.02 (m, 5 H), 6.99 (t, 1 H, J = 10.2 Hz), 3.89 (d, 2 H, J = 6.4 Hz), 3.56 - 3.08 (m, 4 H), 3.06 (brs, 2 H), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.28 - 1.54 (m, 9 H), 1.38 - 0.86 (m, 8 H); MS (ESI) m/z 505 (M+ + H).
732*	(S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.46 (m, 1 H), 7.37 - 7.10 (m, 4 H), 7.04 - 7.00 (m, 1 H) 4.62 (s, 1 H), 4.50 (s, 1 H), 3.92 (d, 2 H, J = 4.6 Hz), 3.85 - 3.33 (m, 4 H), 3.02 (brs, 2 H), 2.49 (d, 2 H, J = 16.1 Hz), 2.30 - 1.84 (m, 7 H), 1.66 - 1.26 (m, 8 H); MS (ESI) m/z 491 (M+ + H).
	(R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
733*	1H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.46 (m, 1 H), 7.41 - 7.25 (m, 4 H), 7.03 (t, 1 H, J = 6.3 Hz), 4.62 (s, 0.5 H), 4.49 (s, 0.5 H), 3.92 (d, 2 H, J = 4.5 Hz), 3.85 - 3.03 (m, 4 H), 3.03 (brs, 2 H), 2.51 (s, 1 H), 2.47 (s, 1 H), 2.31 - 1.84 (m, 7 H), 1.69 - 1.36 (m, 8 H); MS (ESI) m/z 491 (M+ + H).
734*	(R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, 1 H, J = 5.3 Hz), 7.34 - 7.20 (m, 4 H), 7.00 (t, 1 H, J = 6.3 Hz), 3.88 (d, 2 H, J = 4.6 Hz), 3.56 - 3.08 (m, 4 H), 2.98 (d, 2 H, J = 8.1 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (t, 2 H, J = 8.5 Hz), 1.98 - 1.59 (m, 7 H), 1.43 - 1.23 (m, 8 H); MS (ESI) m/z 505 (M+ + H).
800	1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.27 (m, 5 H), 7.07 (t, 1 H, J = 8.3 Hz), 5.70 (brs, 2 H), 4.78 (d, 1 H, J = 12.9 Hz), 3.95 (d, 2 H, J = 5.9 Hz), 3.75 (d, 1 H, J = 12.8 Hz), 3.16 - 2.95 (m, 4 H), 2.51 - 2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.2 Hz), 2.06 - 1.59 (m, 7 H), 1.48 - 0.92 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
816	(R)-1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, 1 H, J = 7.4 Hz), 7.42 - 7.25 (m, 4 H), 7.03 (t, 1 H, J = 8.4 Hz), 6.32 (brs, 1 H), 5.68 (brs, 1 H), 5.44 (brs, 1 H), 3.91 (d, 2 H, J = 6.4 Hz), 3.60 (d, 1 H, J = 12.7 Hz), 3.22 (t, 1 H, J = 12.0 Hz), 2.99 (d, 2 H, J = 8.0 Hz), 2.48 - 2.42 (m, 3 H), 2.15 - 1.39 (m, 8 H), 1.34 - 1.26 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
817	(S)-1-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, J = 6.0 Hz), 7.42 - 7.27 (m, 5 H), 7.03 (t, 1 H, J = 7.0 Hz), 6.31 (brs, 1 H), 5.52 (brs, 1 H), 5.45 (brs, 1 H), 3.92 (d, 2 H, J = 5.8 Hz), 3.61 (d, 1 H, J = 13.9 Hz), 3.21 (brs, 1 H), 3.00 (d, 2 H, J = 11.1 Hz), 2.48 - 2.42 (m, 3 H), 2.19 (t, 2 H, J = 11.6 Hz), 2.05 - 1.45 (m, 8 H), 1.40 - 1.25 (m, 8 H); MS (ESI) m/z 532 (M+ + H).

Example 43. Comparative compound 735: (S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0104]



Step 1. methyl 2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-2-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of compound 725; 0.60 g, 1.66 mmol) was dissolved in 1,4-dioxane 12 mL and H_2O 3 mL. 2-Fluoro-4-(methoxycarbonyl)phenylboronic acid (0.33 g, 1.66 mmol), $Pd(dbpf)Cl_2$ (0.05 g, 0.08 mmol) and CS_2CO_3 (1.07 g, 3.31 mmol) was added thereto. The mixture was stirred in a microwave at 120 °C for 30 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as light-yellow solid (0.35 g, 49%).

Step 2. 2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.35 g, 0.80 mmol) was dissolved in THF 10 mL, H_2O 3 mL and MeOH 3 mL. $LiOH{\cdot}H_2O$ (0.17 g, 4.02 mmol) was added thereto, following with increasing the temperature slowly and then refluxing with stirring for 3 hours. After the completion of the reaction, The reaction mixture was acidified to pH 5 by the addition of HCl. The reaction mixture was extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (0.33 g, 97%).

Step 3. Compound 735: 2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.10 mmol) and (S)-piperidin-3-ol (0.02 g, 0.19 mmol) were dissolved in DMF 2 mL. DIPEA (0.08 mL, 0.48 mmol), EDCI (0.04 g, 0.19 mmol) and HOBt (0.03 g, 0.19 mmol) were added thereto slowly, following with stirring at 60 °C for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered, and dissolved in CH_2Cl_2. The solution was concentrated under reduced pressure. The obtained concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (0.02 g, 42%).

1H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, 1 H, J = 5.8 Hz), 7.29 - 7.21 (m, 4 H), 6.99 (t, 1 H, J = 6.4 Hz), 3.88 (d, 2 H, J = 4.6 Hz), 3.78 - 3.27 (m, 4 H), 2.97 (d, 2 H, J = 8.2 Hz), 2.45 (s, 1 H), 2.40 (s, 1 H), 2.16 (t, 2 H, J = 8.5 Hz), 1.91 - 1.65 (m, 7 H), 1.45 ~ 1.23 (m, 8 H); MS (ESI) m/z 505 (M+ + H).

[0105] According to the above-described synthesis process of compound 735, the compounds of Table 16 were synthesized using 2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 15.

Table 15. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
736*	(R)-pyrrolidine-3-ol	43
737*	(S)-pyrrolidine-3-ol	21

Compound No.	Reactant	Yield (%)
751*	(R)-pyrrolidine-2-ylmethanol	10
752*	(S)-pyrrolidine-2-ylmethanol	6
753	(S)-pyrrolidine-2-carboxamide	71
754*	(R)-piperidin-3-ol	31
818	piperidin-4-carboxamide	41
819	(R)-piperidin-2-carboxamide	43
820	(S)-piperidin-2-carboxamide	40

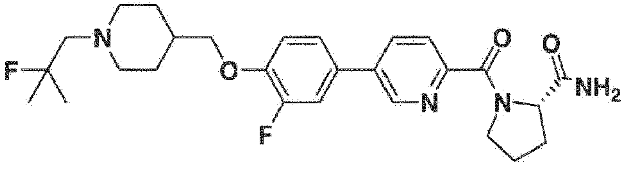
Table 16. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
736*	(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.22 (m, 5 H), 6.99 (t, 1 H, J = 8.5 Hz), 4.57 (brs, 0.5 H), 4.46 (brs, 0.5 H), 3.88 (d, 2 H, J = 6.1 Hz), 3.80 - 3.45 (m, 4 H), 2.98 (d, 2 H, J = 11.2 Hz), 2.46 (s, 1 H), 2.41 (s, 1 H), 2.17 (t, 2 H, J = 11.3 Hz), 2.07 - 1.98 (m, 2 H), 1.82 - 1.80 (m, 3 H), 1.43 - 1.23 (m, 8 H); MS (ESI) m/z 491(M+ + H).
737*	(S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.22 (m, 5 H), 6.99 (t, 1 H, J = 8.7 Hz), 4.52 (d, 1 H, J = 46.7 Hz), 3.88 (d, 2 H, J = 8.0 Hz), 3.82 - 3.45 (m, 4 H), 2.98 (d, 2 H, J = 12.0 Hz), 2.44 (d, 2 H, J = 22.3 Hz), 2.17 (t, 2 H, J = 11.2 Hz), 2.11 - 1.80 (m, 5 H), 1.42 - 1.23 (m. 8 H); MS (ESI) m/z 491(M+ + H).
751*	(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.02 - 7.22 (m, 5 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.73 (d, 1 H, J = 8.0 Hz), 4.44 - 4.40 (m, 1 H), 3.93 (d, 2 H, J = 6.0 Hz), 3.86 - 3.42 (m, 4 H), 3.01 (brs, 2 H), 2.50 (s, 1 H), 2.45 (s, 1 H), 2.22 - 1.42 (m, 9 H), 1.36 - 1.15 (m, 8 H); MS (ESI) m/z 505 (M+ + H).
752*	(S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.27 (m, 5 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.73 (brs, 1 H), 4.43 - 4.41 (m, 1 H), 3.92 (d, 2 H, J = 5.9 Hz), 3.85 - 3.50 (m, 4 H), 3.02 - 2.71 (m, 2 H), 2.52 - 2.46 (d, 2 H), 2.22 - 1.41 (m, 11 H), 1.36 - 1.13 (m, 6 H); MS (ESI) m/z 505 (M+ + H).
753	(S)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.25 (m, 5 H), 7.02 (t, 1 H, J = 8.0 Hz), 6.96 (brs, 1 H), 5.81 (brs, 1 H), 4.76 - 4.75 (m, 1 H), 3.91 (d, 2 H, J = 5.6 Hz), 3.66 - 3.57 (m, 2 H), 3.00 (d, 2 H, J = 12.0 Hz), 2.48 - 2.37

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(m, 2 H), 2.21 - 1.81 (m, 9 H), 1.44 - 1.25 (m, 8 H); MS (ESI) m/z 518 (M+ + H).
754*	(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, 1 H, J = 8.8 Hz), 7.31 - 7.23 (m, 4 H), 7.02 (t, 1 H, J = 8.6 Hz), 3.91 - 3.35 (m, 7 H), 3.00 (d, 2 H, J = 11.2 Hz), 2.48 - 2.42 (m, 2 H), 2.18 (t, 2 H, J = 11.4 Hz), 1.93 - 1.41 (m, 7 H), 1.39 - 1.25 (m, 8 H); MS (ESI) m/z 505 (M+ + H).
818	1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ3.00 (d, 2 H, J = 11.1 Hz), 7.32 - 7.19 (m, 4 H), 7.03 (t, 1 H, J = 8.4 Hz), 5.59 (brs, 2 H), 4.73 (brs, 1 H), 3.92 - 3.90 (m, 3 H), 3.00 - 2.97 (m, 4 H), 2.49 - 2.42 (m, 3 H), 2.18 (t, 2 H, J = 11.0 Hz), 1.88 - 1.81 (m, 7 H), 1.47 - 1.26 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
819	(R)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.44 (m, 1 H), 7.33 - 7.25 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 6.45 (brs, 1 H), 5.56 (brs, 1 H), 5.27 (brs, 1 H), 3.92 (d, 2 H, J = 6.2 Hz), 3.78 - 3.73 (m, 1 H), 3.16 - 3.18 (m, 1 H), 3.01 (d, 2 H, J = 11.2 Hz), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.34 (d, 1 H, J = 12.0 Hz), 2.19 (t, 2 H, J = 11.2 Hz), 2.05 - 1.40 (m, 8 H), 1.34 - 1.24 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
820	(S)-1-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) 67.47 (t, 1 H, J = 7.6 Hz), 7.33 - 7.25 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 6.41 (brs, 1 H), 5.56 (brs, 1 H), 5.26 (brs, 1 H), 3.92 (d, 2 H, J = 6.0 Hz), 3.78 (d, 1 H, J = 13.6 Hz), 3.17 (m, 1 H), 3.00 (d, 2 H, J = 11.2 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.34 (d, 1 H, J = 12.4 Hz), 2.19 (t, 2 H, J = 11.1 Hz), 2.05 - 1.43 (m, 8 H), 1.40 - 1.24 (m, 8 H); MS (ESI) m/z 532 (M+ + H).

Example 44. Compound 782: (S)-1-(5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

[0106]



Step 1. methyl 5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinate: 4-((4-bromo-2-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of

synthesis step 4 of compound 725; 1.0 g, 2.76 mmol) was dissolved in 1,4-dioxane 8 mL and H_2O 2 mL. 6-(Methoxycarbonyl)pyridine-3-ylboronic acid (0.50 g, 2.76 mmol), Pd(dbpf)Cl_2 (0.22 g, 0.28 mmol) and CS_2CO_3 (1.80 g, 5.52 mmol) were added thereto. The mixture was stirred in a microwave at 110 °C for 30 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer was washed three times with saturated aqueous brine solution, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as dark brown solid (0.1 g, 9%).

Step 2. 5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid: methyl 5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinate (0.12 g, 0.29 mmol) was dissolved in THF 10 mL, H_2O 3 mL and MeOH 3 mL. LiOH·H_2O (0.06 g, 1.43 mmol) was added thereto, following with increasing the temperature slowly and then refluxing with stirring for 3 hours. After the completion of the reaction, The reaction mixture was acidified to pH 5 by the addition of HCl, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution three times, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as dark brown solid (0.08 g, 69%).

Step 3. Compound 782: 5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid (0.03 g, 0.07 mmol) and (S)-pyrrolidine-2-carboxamide (0.02 g, 0.15 mmol) was dissolved in DMF 1 mL. DIPEA (0.05 g, 0.37 mmol, EDCI (0.03 g, 0.15 mmol) and HOBt (0.02 g, 0.15 mmol) were added thereto slowly, following with stirring at 60 °C for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered, and dissolved in CH_2Cl_2 again. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (0.01 g, 38%).
1H NMR (400 MHz, $CDCl_3$) δ 8.77 (brs, 1 H), 8.14 - 7.93 (m, 2 H), 7.37 - 7.29 (m, 2 H), 7.07 - 7.05 (m, 1 H), 5.50 (brs, 1 H), 5.16 - 4.82 (m, 1 H), 3.93-3.89 (m, 5 H), 3.02 (d, 2 H, J = 12.5 Hz), 2.50 - 1.78 (m, 11 H), 1.47 - 1.26 (m, 8 H); MS (ESI) m/z 501 (M+ + H).

[0107] According to the above-described synthesis process of compound 782, the compounds of Table 18 were synthesized using 5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid and the reactant of Table 17.

Table 17. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
783*	(R)-piperidin-3-ol	44

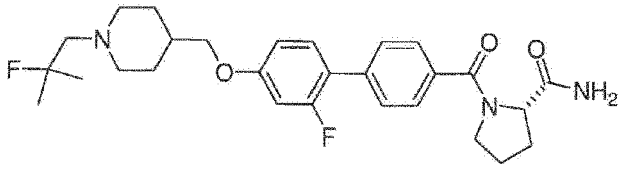
Table 18. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
783*	(R)-(5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridine-2-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, CDCl3) δ 8.70 (s, 1 H), 7.99 (d, 1 H, J = 2.4 Hz), 7.85 (d, 1 H, J = 8.4 Hz), 7.36 - 7.27 (m, 2 H), 7.07 (t, 1 H, J = 8.3 Hz),

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	5.69 (s, 1 H), 4.61 (d, 1 H, J = 12.8 Hz), 4.08 - 4.04 (m, 2 H), 3.92 (d, 2 H, J = 8.0 Hz), 3.29 - 2.92 (m, 4 H), 2.49 - 2.43 (m, 2 H), 2.26 - 1.56 (m, 9 H), 1.46 - 1.35 (m, 8 H); MS (ESI) m/z 488 (M+ + H).

Example 45. Compound 706: (S)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0108]



__Step 1.__ methyl 2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of comparative compound 704; 500 mg, 1.38 mmol), 4-(methoxycarbonyl) phenylboronic acid (298 mg, 1.57 mmol), $Pd(dppf)Cl_2$ (56 mg, 0.07 mmol) and Cs_2CO_3 (341 mg, 1.05 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as white solid (210 mg, 36%).

__Step 2.__ 2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (210 mg, 0.50 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH{\cdot}H_2O$ (106 mg, 2.52 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified by the addition of IN HCl. The resulting precipitate was filtered to yield the title compound as white solid (200 mg, 98%).

__Step 3.__ Compound 706: 2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (50 mg, 0.12 mmol), (S)-pyrrolidine-2-carboxamide (17 mg, 0.15 mmol), Bop (110 mg, 0.248 mmol) and Et_3N (34 μL, 0.25 mmol) were dissolved in DMF. The reaction was performed at 60 °C for a day. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_3Cl_3 /MeOH = 10/1) to yield the title compound as yellow solid (23 mg, 37%).
1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.53 (m, 4 H), 7.37 - 7.27 (m, 1 H), 7.04 (brs, 1 H), 6.79 - 6.70 (m, 2 H), 5.53 (brs, 1 H), 4.85 - 4.82 (m, 1 H), 3.83 (d, 2 H, J = 5.8 Hz), 3.67 - 3.56 (m, 2 H), 3.01 (brs, 1 H), 2.50 - 2.39 (m, 2 H), 2.20 - 2.12 (m, 2 H), 2.10 - 2.06 (m, 2 H), 1.89 - 1.80 (m, 4 H), 1.42

- 1.37 (m, 8 H), 1.29 - 1.21 (m, 2 H); MS (ESI) m/z 500 (M+ + H).

[0109] According to the above-described synthesis process of compound 706, the compounds of Table 20 were synthesized using 2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 19.

Table 19. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
707*	(R)-pyrrolidine-2-ylmethanol	21
708*	(R)-pyrrolidine-3-ol	22
709*	(R)-piperidin-3-ol hydrochloride	34
738*	(S)-piperidin-3-ol hydrochloride	29
739*	(S)-pyrrolidine-3-ol	35
740*	(S)-pyrrolidine-2-ylmethanol	29
801	piperidin-4-carboxamide	62
873	(R)-piperidin-2-carboxamide hydrochloride	77
876	(S)-piperidin-2-carboxamide hydrochloride	64
881	(R)-piperidin-3-carboxamide hydrochloride	80

Table 20. (* marks comparative compound

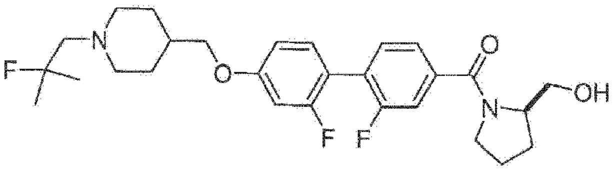
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
707*	(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.57 - 7.53 (m, 4 H), 7.37 - 7.33 (m, 1 H), 6.79 - 6.69 (m, 2 H), 5.00 (brs, 1 H), 4.47 - 4.42 (m, 1 H), 3.84 - 3.61 (m, 3 H), 3.57-3.51 (m, 2 H), 3.04 - 3.02 (m, 2 H), 2.51 - 2.46 (m, 2 H), 2.28 - 2.18 (m, 3 H), 1.91 - 1.60 (m, 6 H), 1.42 - 1.27 (m, 8 H); MS (ESI) m/z 487 (M+ + H).
708*	(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.62 - 7.54 (m, 4 H), 7.37 - 7.27 (m, 1 H), 6.79 - 6.69 (m, 2 H), 4.62 - 4.49 (m, 1 H), 3.90 - 3.77 (m, 4 H), 3.71 - 3.68 (m, 1 H), 3.66 - 3.49 (m, 1 H), 3.03 (brs, 1 H), 2.57 (brs, 2 H), 2.26 (brs, 2 H), 2.16 - 2.06 (m, 2 H), 1.99 - 1.73 (m, 3 H), 1.55 - 1.44 (m, 6 H), 1.33 (s, 2 H), 0.91 - 0.86 (m, 1 H); MS (ESI) m/z 487 (M+ + H).
709*	(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	MS (ESI) m/z 487 (M+ + H).
738*	(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.56 - 7.52 (m, 4 H), 7.49 - 7.32 (m, 1 H), 6.79 - 6.70 (m, 2 H), 3.99 (brs, 1 H), 3.83 (d, 2 H, J = 5.9 Hz), 3.51

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(brs, 2 H), 3.03 (brs, 2 H), 2.51 - 2.46 (m, 2 H), 2.20 (brs, 2 H), 2.05 - 2.03 (m, 2 H), 1.97 - 1.67 (m, 4 H), 1.55 (brs, 2 H), 1.42 - 1.32 (m, 8 H), 1.26 - 1.20 (m, 1 H); MS (ESI) m/z 487 (M+ + H).
739*	(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.62 - 7.54 (m, 4 H), 7.34 (t, 1 H, J = 8.7 Hz), 6.78 - 6.69 (m, 2 H), 4.60 - 4.48 (m, 1 H), 3.87 - 3.81 (m, 4 H), 3.79 - 3.71 (m, 1 H), 3.69 - 3.49 (m, 1 H), 3.03 (brs, 2 H), 2.52 - 2.46 (m, 2 H), 2.21 - 2.18 (m, 2 H), 2.15 - 2.13 (m, 1 H), 2.12 - 2.00 (m, 2 H), 1.99 - 1.71 (m, 3 H), 1.57 - 1.54 (m, 1 H), 1.47 (s, 3 H), 1.42 (s, 3 H); MS (ESI) m/z 473 (M+ + H).
740*	(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 7.60 - 7.55 (m, 4 H), 7.35 (t, 1 H, J = 8.8 Hz), 6.77 6.69 (m, 2 H), 4.97 - 4.95 (m, 1 H), 4.46 - 4.44 (m, 1 H), 3.87 - 3.75 (m, 4 H), 3.65 - 3.46 (m, 3 H), 2.24 - 2.22 (m, 1 H), 2.20 - 2.00 (m, 1 H), 1.97 - 1.92 (m, 2 H), 1.90 - 1.81 (m, 2 H), 1.70 - 1.32 (m, 10 H), 1.29 - 1.26 (m, 3 H); MS (ESI) m/z 487 (M+ + H).
801	1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, 2 H, J = 7.6 Hz), 7.49 (d, 2 H, J = 7.7 Hz), 7.38 (t, 1 H, J = 8.6 Hz), 6.81 (d, 1 H, J = 8.4 Hz), 6.75 (d, 1 H, J = 12.7 Hz), 5.73 (d, 2 H, J = 19.0 Hz), 4.73 (brs, 1 H), 3.95 (brs, 1 H), 3.86 (d, 2 H, J = 5.6 Hz), 3.04 - 3.01 (m, 4 H), 2.51 - 2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.4 Hz), 1.84 - 1.48 (m, 7 H), 1.44 - 0.89 (m, 8 H); MS (ESI) m/z 514 (M+ + H).
873	(R)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.64 - 7.43 (m, 4 H), 7.35 (t, 1 H, J = 8.8 Hz), 6.82 - 6.67 (m, 2 H), 3.83 (d, 3 H, J = 6.0 Hz), 3.13 (t, 1 H, J = 13.3 Hz), 3.01 (d, 2 H, J = 11.3 Hz), 2.50 (s, 1 H), 2.44 (s, 1 H), 2.34 (d, 1 H, J = 12.5 Hz), 2.19 (t, 2 H, J = 11.2 Hz), 1.93 - 1.74 (m, 6 H), 1.72 - 1.52 (m, 3 H), 1.52 - 1.38 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 514 (M+ + H).
876	(S)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.63 - 7.43 (m, 4 H), 7.35 (t, 1 H, J = 8.9 Hz), 6.82 - 6.67 (m, 2 H), 3.83 (d, 3 H, J = 5.8 Hz), 3.13 (t, 1 H, J = 12.8 Hz), 3.01 (d, 2 H, J = 11.3 Hz), 2.50 (s, 1 H), 2.44 (s, 1 H), 2.34 (d, 1 H, J = 12.3 Hz), 2.19 (t, 2 H, J = 11.5 Hz), 1.95 - 1.73 (m, 6 H), 1.73 - 1.52 (m, 3 H), 1.52 - 1.42 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 514 (M+ + H).
881	(R)-1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 7.56 (d, 2 H, J = 7.0 Hz), 7.45 (d, 2 H, J = 8.3 Hz), 7.34 (t, 1 H, J = 8.8 Hz), 6.81 - 6.67 (m, 2 H), 3.84 (d, 3 H, J

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	= 5.8 Hz), 3.57 (s, 1 H), 3.47 (s, 1 H), 3.03 (s, 2 H), 2.66 - 2.40 (m, 3 H), 2.21 (s, 2 H), 1.99 - 1.47 (m, 10 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 514 (M+ + H).

Example 46. Comparative compound 704: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0110]



Step 1. t-butyl 4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 2 of compound 431; 6.0 g, 20.45 mmol) was dissolved in DMF (60 mL). 4-Bromo-3-fluorophenol (3.91 g, 20.45 mmol) and K_2CO_3 (8.48 g, 61.35 mmol) were added thereto slowly, following with stirring at 80 °C for 5 hours. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane 1/10) to yield the title compound as white solid (6.27g, 79%).

Step 2. 4-((4-bromo-3-fluorophenoxy)methyl)piperidine hydrochloride: t-butyl 4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-carboxylate (6.27 g, 16.15 mmol) was dissolved in CH_2Cl_2 (70 mL). 4 M HCl in 1,4-dioxane (80.74 mL, 322.97 mmol) was added thereto, following with stirring for 1 hour. The resulting precipitate was filtered to yield the title compound as white solid (5.03 g, 96%).

Step 3. 1-(4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 4-((4-bromo-3-fluorophenoxy)methyl)piperidine hydrochloride (5.32 g, 16.39 mmol) was dissolved in EtOH (5 mL) and H_2O (5 mL). 2,2-Dimethyloxirane (14.59 mL, 163.88 mmol) and K_2CO_3 (1.13 g, 8.19 mmol) were added thereto slowly. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/4) to yield the title compound as white solid (5.2 g, 88%).

Step 4. 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine: 1-(4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (5.2 g, 14.43 mmol) was dissolved in CH_2Cl_2 (15 mL). At 0 °C, DAST (1.91 mL, 14.43 mmol) was added slowly thereto. After stirring for 1 hour at room temperature, the reaction mixture was added with a saturated NH_4Cl

aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as yellow solid (2.50 g, 48%).

Step 5. methyl 2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (200 mg, 0.55 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (131 mg, 0.06 mmol), $Pd(dppf)Cl_2$ (22 mg, 0.03 mmol) and Cs_2CO_3 (360 mg, 1.10 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as white solid (81 mg, 34%).

Step 6. 2,2'-difluoro-4'-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (81 mg, 0.19 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (39 mg, 0.93 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified by the addition of 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (60 mg, 77%).

Step 7. Comparative compound 704: 2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol),(R)-pyrrolidine-2-ylmethanol (9 mg, 0.09 mmol), Bop (63 mg, 0.14 mmol) and Et_3N (20 µL, 0.14 mmol) were dissolved in DMF, and at 60 °C. The reaction was performed at a day. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 10/1) to yield the title compound as yellow solid (17 mg, 47%).
1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.27 (m, 4 H), 6.77 - 6.70 (m, 2 H), 4.43 - 3.83 (m, 1 H), 4.12 - 3.83 (m, 3 H), 3.78 - 3.47 (m, 4 H), 3.05 - 2.81 (m, 2 H), 2.67 - 2.49 (m, 2 H), 2.22 - 2.21 (m, 1 H), 2.20 (s, 1 H), 2.06 - 1.85 (m, 5 H), 1.57 (s, 3 H), 1.51 (s, 3 H), 1.36 - 1.31 (m, 3 H); MS (ESI) m/z 505 (M+ + H).

[0111] According to the above-described synthesis process of compound 704, the compounds of Table 22 were synthesized using 2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 21.

Table 21. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
705	(S)-pyrrolidine-2-carboxamide	35
741*	(S)-piperidin-3-ol hydrochloride	25
742*	(R)-pyrrolidine-3-ol	30

Compound No.	Reactant	Yield (%)
743*	(S)-pyrrolidine-3-ol	36
744*	(S)-pyrrolidine-2-ylmethanol	33
745*	(R)-piperidin-3-ol hydrochloride	31
803	piperidin-4-carboxamide	61
825	(R)-piperidin-2-carboxamide	48
860	(S)-piperidin-2-carboxamide	41

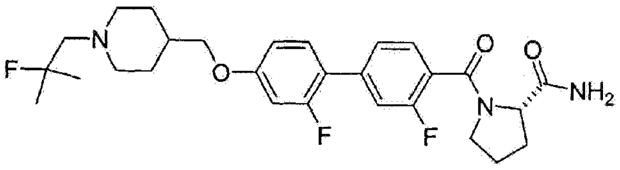
Table 22. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
705	(2S)-1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.27 (m, 4 H), 6.90 (brs, 1 H), 6.79 - 6.70 (m, 2 H), 5.46 (brs, 1 H), 3.87 - 3.85 (m, 2 H), 3.68 - 3.57 (m, 2 H), 2.18 - 2.03 (m, 3 H), 1.91 - 1.87 (m, 4 H), 1.59 - 1.38 (m, 6 H), 1.34 (s, 6 H), 0.89 - 0.76 (m, 3 H); MS (ESI) m/z 518 (M+ + H).
741*	(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, 1 H, J = 7.4 Hz), 7.30 - 7.22 (m, 3 H), 6.79 - 6.70 (m, 2 H), 3.97 - 3.95 (m, 1 H), 3.84 - 3.82 (m, 3 H), 3.57 (brs, 1 H), 3.46 (brs, 1 H), 3.04 - 3.01 (m, 2 H), 2.51 - 2.45 (m, 2 H), 2.20 (t, 2 H, J = 11.5 Hz), 1.94 (brs, 2 H), 1.89 - 1.79 (m, 3 H), 1.68 (brs, 2 H), 1.47 - 1.44 (m, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 505 (M+ + H).
742*	(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.27 (m, 4 H), 6.79 - 6.71 (m, 2 H), 4.63 - 4.51 (m, 1 H), 3.84 - 3.80 (m, 3 H), 3.77 - 3.66 (m, 1 H), 3.65 - 3.49 (m, 1 H), 3.03 (brs, 2 H), 2.52 - 2.46 (m, 2 H), 2.21 - 2.13 (m, 2 H), 2.09 - 2.02 (m, 3 H), 1.97 - 1.70 (m, 3 H), 1.69 - 1.26 (m, 8 H); MS (ESI) m/z 491 (M+ + H).
743*	(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.40 - 7.27 (m, 4 H), 6.79 - 6.71 (m, 2 H), 4.63 - 4.51 (m, 1 H), 3.84 - 3.80 (m, 3 H), 3.77 - 3.66 (m, 1 H), 3.65 - 3.49 (m, 1 H), 3.03 (brs, 2 H), 2.52 - 2.46 (m, 2 H), 2.21 - 2.13 (m, 2 H), 2.09 - 2.02 (m, 3 H), 1.97 - 1.70 (m, 3 H), 1.69 - 1.26 (m, 8 H); MS (ESI) m/z 491 (M+ + H).
744*	(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.27 (m, 4 H), 6.77 - 6.69 (m, 2 H), 4.43 - 4.41 (m, 1 H), 3.85 (d, 2 H ,J = 5.3 Hz), 3.78 - 3.74 (m, 1 H), 3.62 - 3.52 (m, 2 H), 3.24 (brs, 2 H), 2.72 - 2.67 (m, 2 H), 2.36 - 2.33 (brs, 2 H), 2.23 - 2.18 (m, 1 H), 1.94 - 1.81 (m, 5 H), 1.79 - 1.65 (m, 3 H), 1.63 (s, 3 H), 1.48 (s, 3 H), 1.26 - 1.21 (m, 1 H); MS (ESI) m/z 505

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(M+ + H).
745*	(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, 1 H, J = 7.7 Hz), 7.31 - 7.22 (m, 3 H), 6.77 - 6.69 (m, 2 H), 4.14 - 4.12 (m, 1 H), 3.96 - 3.81 (m, 3 H), 3.79 - 3.46 (m, 5 H), 2.91 (brs, 2 H), 2.58 (brs, 2 H), 1.94 - 1.79 (m, 6 H), 1.69 (brs, 2 H), 1.56 (s, 3 H), 1.50 (s, 3 H), 1.31 - 1.23 (m, 1 H); MS (ESI) m/z 505 (M+ + H).
803	1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1 H, J = 7.4 Hz), 7.34 - 7.23 (m, 3 H), 6.83 - 6.75 (m, 2 H), 5.51 (d, 2 H, J = 32.0 Hz), 4.73 (brs, 1 H), 3.96 (brs, 1 H), 3.87 (d, 2 H, J = 5.6 Hz), 3.05 - 3.02 (m, 4 H), 2.52 - 2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.2 Hz), 2.09 - 1.66 (m, 7 H), 1.60 - 0.90 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
825	(2R)-1-(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.25 (m, 4 H), 6.80 - 6.71 (m, 2 H), 6.40 (brs, 1 H), 5.42 (brs, 1 H), 5.28 (brs, 1 H), 3.86 - 3.79 (m, 3 H), 3.16 - 3.13 (m, 1 H), 3.00 (d, 2 H, J = 11.2 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.35 (d, 1 H, J = 13.6 Hz), 2.18 (t, 2 H, J = 11.2 Hz), 1.86 - 1.55 (m, 8 H), 1.50 - 1.26 (m, 8 H); MS (ESI) m/z 532 (M+ + H).
860	(2S)-1-(2,6'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.24 (m, 4 H), 6.78 - 6.71 (m, 2 H), 6.46 (brs, 1 H), 5.69 (brs, 1 H), 5.28 (brs, 1 H), 3.83 - 3.77 (m, 3 H), 3.19 - 3.17 (m, 1 H), 3.00 (d, 2 H, J = 9.6 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.33 (d, 1 H, J = 12.4 Hz), 2.18 (t, 2 H, J = 11.0 Hz), 1.81 - 1.52 (m, 8 H), 1.48 - 1.25 (m, 8 H)

Example 47. Compound 710: (S)-1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0112]



Step 1. ethyl 2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of compound 704; 500 mg, 1.38 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (351 mg, 1.66 mmol), $Pd(dppf)Cl_2$ (56 mg, 0.07 mmol) and Cs_2CO_3 (899

mg, 2.76 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as white solid (287 mg, 46%).

Step 2. 2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: ethyl 2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (287 mg, 0.64 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH{\cdot}H_2O$ (134 mg, 3.19 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified by the addition of 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (220 mg, 82%).

Step 3. Compound 710: 2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (50 mg, 0.12 mmol), (S)-pyrrolidine-2-carboxamide (16 mg, 0.14 mmol), Bop (105 mg, 0.24 mmol) and Et_3N (33 μL, 0.24 mmol) were dissolved in DMF. The reaction was performed at 60 °C for a day. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 10/1) to yield the title compound as yellow solid (19 mg, 31%).
1H NMR (400 MHz, $CDCl_3$) δ 7.49 - 7.45 (m, 1 H), 7.39 - 7.32 (m, 3 H), 6.95 (brs, 1 H), 6.80 - 6.70 (m, 2 H), 5.56 (brs, 1 H), 4.84 - 4.81 (m, 1 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.58 - 3.51 (m, 1 H), 3.47 - 3.52 (m, 1 H), 3.00 (brs, 2 H), 2.51 - 2.43 (m, 3 H), 2.20 (brs, 2 H), 2.18 - 2.04 (m, 2 H), 1.94 - 1.91 (m, 1 H), 1.89 - 1.82 (m, 3 H), 1.80 - 1.42 (m, 8 H); MS (ESI) m/z 518 (M+ + H).

[0113] According to the above-described synthesis process of compound 710, the compounds of Table 24 were synthesized using 2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 23.

Table 23. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
711*	(R)-pyrrolidine-2-ylmethanol	31
712*	(R)-pyrrolidine-3-ol	46
713*	(R)-piperidin-3-ol hydrochloride	30
746*	(S)-piperidin-3-ol hydrochloride	38
747*	(S)-pyrrolidine-3-ol	30
748*	(S)-pyrrolidine-2-ylmethanol	35
802	piperidin-4-carboxamide	59
823	(R)-piperidin-2-carboxamide	52
861	(S)-piperidin-2-carboxamide	49

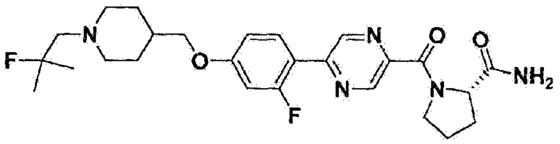
Table 24. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
711*	(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.46 (m, 1 H), 7.38 - 7.27 (m, 3 H), 6.80 - 6.70 (m, 2 H), 4.80 - 4.78 (m, 1 H), 4.43 - 4.38 (m, 1 H), 3.85 - 3.75 (m, 4 H), 3.50 - 3.46 (m, 2 H), 3.16 (brs, 1 H), 2.50 (brs, 1 H), 2.24 -- 2.03 (m, 3 H), 1.94 - 1.80 (m, 5 H), 1.53 - 1.43 (m, 6 H), 1.38 (s, 3 H), 0.90 - 0.88 (m, 1 H); MS (ESI) m/z 505 (M+ + H).
712*	(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.46 (m, 1 H), 7.36 - 7.27 (m, 3 H), 6.79 - 6.69 (m, 2 H), 4.62 - 4.50 (m, 1 H), 3.84 - 3.80 (m, 3 H), 3.79 - 3.61 (m, 1 H), 3.59 - 3.35 (m, 1 H), 3.01 (brs, 2 H), 2.54 (brs, 2 H), 2.32 - 2.21 (m, 2 H), 2.19 - 2.02 (m, 3 H), 1.90 - 1.71 (m, 3 H), 1.69 - 1.31 (m, 7 H), 1.29 - 1.26 (m, 1 H); MS (ESI) m/z 491 (M+ + H).
713*	(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.42 (m, 1 H), 7.37 - 7.26 (m, 3 H), 6.79 - 6.70 (m, 2 H), 4.12 - 3.95 (m, 1 H), 3.83 (d, 2 H, J = 5.8 Hz), 3.68 - 3.59 (m, 1 H), 3.39 - 3.26 (m, 1 H), 3.16 - 3.00 (m, 2 H), 2.50 (brs, 2 H), 2.21 - 2.03 (m, 2 H), 1.99 - 1.91 (m, 2 H), 1.93 - 1.75 (m, 4 H), 1.72 - 1.69 (m, 2 H), 1.68 - 1.43 (m, 8 H), 1.37 - 1.27 (m, 2 H); MS (ESI) m/z 505 (M+ + H).
746*	(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.6 Hz), 7.35 - 7.24 (m, 3 H), 6.76 - 6.67 (m, 2 H), 4.12 (brs, 1 H), 3.95 - 3.89 (m, 3 H), 3.75 - 3.58 (m, 2 H), 3.46 (brs, 1 H), 3.36 (brs, 1 H), 3.16 - 3.00 (m, 3 H), 2.68 (brs, 2 H), 2.10 - 1.89 (m, 7 H), 1.83 - 1.53 (m, 9 H); MS (ESI) m/z 505 (M+ + H).
747*	(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.48 (m, 1 H), 7.46 - 7.27 (m, 3 H), 6.79 - 6.70 (m, 2 H), 3.86 - 3.81 (m, 3 H), 3.79 - 3.60 (m, 2 H), 3.50 - 3.46 (m, 1 H), 3.38 - 3.35 (m, 1 H), 3.04 (brs, 2 H), 2.44 (brs, 2 H), 2.21 - 2.18 (m, 2 H), 2.14 (brs, 2 H), 1.89 - 1.81 (m, 4 H), 1.60 (brs, 1 H), 1.43 - 1.38 (m, 7 H); MS (ESI) m/z 491 (M+ + H).
748*	(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, J = 7.5 Hz), 7.38 - 7.17 (m, 3 H), 6.80 - 6.70 (m, 2 H), 4.83 - 4.81 (m, 1 H), 4.42 - 4.40 (m, 1 H), 3.86 - 3.78 (m, 4 H), 3.50 - 3.46 (m, 2 H), 3.01 (brs, 1 H), 2.48 (brs, 1 H), 2.23 - 2.18 (m, 2 H), 1.92 - 1.88 (m, 1 H), 1.87 - 1.71 (m, 4 H), 1.70 - 1.64 (m, 2 H), 1.42 - 1.24 (m, 8 H), 1.22 (brs, 1 H); MS (ESI) m/z 505 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
802	1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.47 - 7.30 (m, 4 H), 6.82 (d, 1 H, J = 8.4 Hz), 6.76 (d, 1 H, J = 12.6 Hz), 5.62 (d, 2 H, J = 24.5 Hz), 4.79 (d, 1 H, J = 12.9 Hz), 3.87 (d, 2 H, J = 5.5 Hz), 3.78 (d, 1 H, J = 13.0 Hz), 3.17 - 2.95 (m, 4 H), 2.52 - 2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.5 Hz), 2.07 - 1.82 (m, 7 H), 1.48 - 0.92 (m, 6 H); MS (ESI) m/z 532 (M+ + H).
823	(R)-1-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.60 - 7.27 (m, 4 H), 6.80 - 6.68 (m, 2 H), 6.33 (brs, 1 H), 5.64 (brs, 1 H), 5.44 (brs, 1 H), 3.90 (brs, 2 H), 3.63 - 3.59 (m, 1 H), 3.25 - 3.19 (m, 1 H), 2.96 (d, 2 H, J = 26.4 Hz), 2.89 - 2.86 (m, 3 H), 2.73 - 2.70 (m, 2 H), 2.44 - 1.57 (m, 8 H), 1.27 - 1.14 (m, 8 H); MS (ESI) m/z 532 (M+ + H)
861	(S)-1-(3,6'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.24 (m, 4 H), 6.77 - 6.67 (m, 2 H), 6.28 (brs, 1 H), 5.71 (brs, 1 H), 5.42 (brs, 1 H), 3.80 (d, 2 H, J = 6.2 Hz), 3.61 - 3.58 (m, 1 H), 3.23 - 3.19 (m, 1 H), 2.97 (d, 2 H, J = 11.5 Hz), 2.45 - 2.40 (m, 3 H), 2.15 (t, 2 H, J = 11.0 Hz), 1.78 - 1.60 (m, 8 H), 1.42 - 1.32 (m, 8 H)

Example 48. Compound 1082: (S)-1-(5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxamide

[0114]



Step 1. methyl 5-(4-(benzoxy)-2-fluorophenyl)pyrazine-2-carboxylate: DME (8 mL) / H_2O (2 mL) was added to 4-(benzoxy)-2-fluorophenylboronic acid (1.00 g, 4.06 mmol), methyl 5-bromopyrazine-2-carboxylate (0.77 g, 4.47 mmol), Pd(dppf)Cl_2 (0.16 g, 0.20 mmol) and Cs_2CO_3 (2.64 g, 8.12 mmol). With a microwave radiation, the mixture was heated at 110 °C for 25 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated NH_4Cl aqueous solution, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; ethyl acetate / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.75 g, 54%).

Step 2. methyl 5-(2-fluoro-4-hydroxyphenyl)pyrazine-2-carboxylate: methyl 5-(4-(benzoxy)-2-

fluorophenyl)pyrazine-2-carboxylate (0.750 g, 2.21 mmol) was dissolved in MeOH (10 mL) / THF (10 mL) at room temperature. 10 % wt Pd/C (150 mg) was added slowly thereto, and then following with stirring at the same temperature for 1 hour under hydrogen gas balloon. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was concentrated under reduced pressure. To the obtained concentrate, methanol (5 mL) and hexane (20 mL) were added thereto, following with stirring. The resulting precipitate was filtered, and dried to yield the title compound as green solid (0.19 g, 34%).

Step 3. methyl 5-(4-((1-(t-butoxycarbonyl)piperidin-4-yl)methoxy)-2-fluorophenyl)pyrazine-2-carboxylate: methyl 5-(2-fluoro-4-hydroxyphenyl)pyrazine-2-carboxylate (0.19 g, 0.76 mmol), t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (0.22 g, 0.76 mmol) and K_2CO_3 (0.15 g, 1.14 mmol) were dissolved in 70 °C for DMF (10 mL), following with stirring at the same temperature for 18 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.28 g, 82%, white solid).

Step 4. methyl 5-(2-fluoro-4-(piperidin-4-ylmethoxy)phenyl)pyrazine-2-carboxylate hydrochloride: methyl 5-(4-((1-(t-butoxycarbonyl)piperidin-4-yl)methoxy)-2-fluorophenyl)pyrazine-2-carboxylate (0.28 g, 0.62 mmol) was dissolved in DCM (10 mL). At room temperature, HCl (4.00M solution in dioxane, 0.62 mL, 2.51 mmol) was added thereto, following with stirring at the same temperature for 18 hours. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.14 g, 59%).

Step 5. methyl 5-(2-fluoro-4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: EtOH (10 mL) was added to methyl 5-(2-fluoro-4-(piperidin-4-ylmethoxy)phenyl)pyrazine-2-carboxylate hydrochloride (0.14 g, 0.29 mmol), 2,2-dimethyl oxirane (0.26 mL, 2.96 mmol) and K_2CO_3 (0.20 g, 1.48 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.12 g, 96%, red solid).

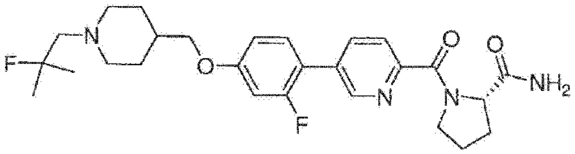
Step 6. methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: methyl 5-(2-fluoro-4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate (0.12 g, 0.28 mmol) and DAST (0.05 mL, 0.34 mmol) were dissolved in DCM (10 mL) at room temperature. The solution was stirred at the same temperature for 4 hours. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.09 g, 73%, yellow solid).

Step 7. 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylic acid: methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate (0.09 g, 0.21 mmol) and $LiOH \cdot H_2O$ (0.04 g, 1.04 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (1mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.06 g, 76%).

Step 8. Compound 1082: 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylic acid (0.06 g, 0.14 mmol), (S)-pyrrolidine-2-carboxamide (0.01 g, 0.17 mmol), HOBt (0.04 g, 0.29 mmol), EDC (0.05 g, 0.29 mmol) and iPr_2NEt (0.05 mL, 0.29 mmol) were dissolved in DCM (2 mL) at room temperature. The solution was stirred at the same temperature for 18 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.02 g, 35%).
1H NMR (400 MHz, $CDCl_3$) δ 9.18 - 9.19 (m, 1 H), 8.95 - 9.02 (m, 1 H), 8.06 (td, 1 H, J = 8.9, 2.5 Hz), 6.85 (td, 1 H, J = 8.4, 2.2 Hz), 6.68 - 6.74 (m, 1 H), 6.19 (s, 1 H), 5.44 (s, 1 H), 5.04 - 4.83 (m, 1 H), 4.83 - 4.86 (m, 1 H), 4.06 - 4.11 (m, 1 H), 3.88 - 3.96 (m, 1 H), 3.83 - 3.86 (m, 2 H), 2.97 - 3.00 (m, 2 H), 2.41 - 2.47 (m, 3 H), 2.13 - 2.21 (m, 3 H), 1.97 - 2.06 (m, 2 H), 1.77 - 1.80 (m, 3 H), 1.41 - 1.47 (m, 2 H), 1.39 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 502.3 (M+ + H).

Example 49. Compound 935: (S)-1-(5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

[0115]



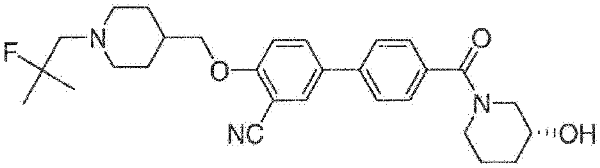
Step 1. methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinate: 4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of comparative compound 704; 1.00 g, 2.76 mmol), 6-(methoxycarbonyl)pyridine-3-ylboronic acid (600 mg, 3.31 mmol), $Pd(dppf)Cl_2$ (113 mg, 0.14 mmol) and Cs_2CO_3 (1.80 g, 5.52 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1/7) to yield the title compound as white solid (200 g, 17%).

Step 2. 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid: methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinate (200 mg, 0.48 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH{\cdot}H_2O$ (100 g, 2.39 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified by the addition of 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (145 mg, 75%).

__Step 3.__ Compound 935: 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid (30 mg, 0.07 mmol), EDC (28 mg, 0.15 mmol) and HOBt (20 mg, 0.15 mmol) was added thereto, DIPEA (26 µL, 0.15 mmol) was dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (17 mg, 0.15 mmol) was added thereto, following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (19 mg, 51%).
1H NMR (400 MHz, $CDCl_3$) δ 8.75 - 8.70 (m, 1 H), 8.10 - 7.91 (m, 2 H), 7.40 - 7.34 (m, 1 H), 6.95 (brs, 0.5 H), 6.84 - 6.73 (m, 2 H), 5.44 (brs, 0.5 H), 5.07 (d, 0.5 H, J = 7.1 Hz), 4.88 - 4.85 (m, 0.5 H), 3.84 (d, 2 H, J = 5.9 Hz), 3.01 (d, 2 H, J = 10.4 Hz), 2.49 - 2.41 (m, 2 H), 2.21 - 1.95 (m, 5 H), 1.82 - 1.61 (m, 7 H), 1.49 - 1.46 (m, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 501 (M+ + H).

Example 50. Comparative compound 963: (R)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile

[0116]



__Step 1.__ methyl 3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)metoxy)biphenyl-4-carboxylate: DME (4 mL) / H_2O (1 mL) was added to 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 938; 0.25 g, 0.67 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.14 g, 0.81 mmol), Pd(dppf)Cl_2 (0.02 g, 0.03 mmol) and Cs_2CO_3 (0.44 g, 1.35 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc.. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.22 g, 78%).

__Step 2.__ 3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)metoxy)biphenyl-4-carboxylate (0.22 g, 0.53 mmol) and LiOH·H_2O (0.11 g, 2.65 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (2 mL) at room temperature. The solution was stirred at the same temperature for 2 hours, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.18 g, 86%).

Step 3. Comparative compound 963: 3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.09 mmol), (R)-piperidin-3-ol (0.01 g, 0.11 mmol), HOBt (0.02 g, 0.19 mmol), EDC (0.03 g, 0.19 mmol) and DIPEA (0.02 g, 0.19 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 10 %), and concentrated to yield the title compound as red solid (0.02 g, 49%).
1H NMR (400 MHz, $CDCl_3$) δ 7.72 - 7.74 (m, 2 H), 7.53 (dd, 4 H, J = 14.7, 8.5 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 3.95 - 4.01 (m, 3 H), 3.43 - 3.94 (m, 4 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.44 (s, 1 H), 2.17 - 2.23 (m, 2 H), 1.86 - 1.95 (m, 6 H), 1.63 - 1.72 (m, 2 H), 1.42 - 1.56 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 494.3 (M+ + H).

[0117] According to the above-described synthesis process of comparative compound 963, the compounds of Table 26 were synthesized using 3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 25.

Table 25. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
964*	(S)-piperidin-3-ol hydrochloride	83
965	L-prolinamide	26
966*	(R)-pyrrolidine-3-ol	49

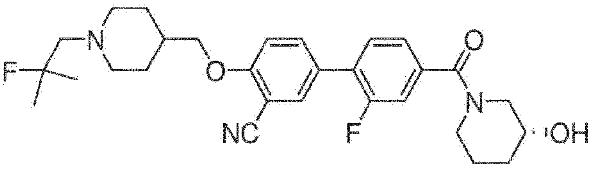
Table 26. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
964*	(S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.71 - 7.73 (m, 2 H), 7.52 (dd, 4 H, J = 14.4, 8.5 Hz), 7.04 (d, 1 H, J = 8.8 Hz), 3.93 - 3.95 (m, 3 H), 3.02 - 3.92 (m, 5 H), 2.99 - 3.02 (m, 2 H), 2.43 - 2.49 (m, 3 H), 2.16 - 2.22 (m, 2 H), 1.85 - 1.93 (m, 5 H), 1.42 - 1.45 (m, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 494.3 (M+ + H).
965	(S)-1-(3'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.79 (m, 2 H), 7.63 (d, 2 H, J = 8.2 Hz), 7.57 (d, 2 H, J = 8.2 Hz), 7.05 (d, 1 H, J = 8.8 Hz), 6.97 (s, 1 H), 5.56 (s, 1 H), 4.82 (dd, 1 H, J = 7.4, 5.0 Hz), 3.95 (d, 2 H, J = 6.4 Hz), 3.53 - 3.67 (m, 2 H), 2.99 - 3.02 (m, 2 H), 2.43 - 2.49 (m, 3 H), 2.10 - 2.22 (m, 2 H), 1.98 - 2.10 (m, 2 H), 1.78 - 1.92 (m, 5 H), 1.35 - 1.49 (m, 7 H); MS (ESI) m/z 507.3 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
966*	(S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1 H, J = 7.9 Hz), 7.71 - 7.78 (m, 2 H), 7.53 - 7.64 (m, 3 H), 7.01 (t, 1 H, J = 8.8 Hz), 4.49 - 4.61 (m, 1 H), 3.96 (d, 2 H, J = 6.0 Hz), 3.51 - 3.83 (m, 2 H), 3.20 - 3.27 (m, 2 H), 2.68 (dd, 2 H, J = 22.7, 15.3 Hz), 2.32 - 2.40 (m, 2 H), 1.92 - 2.08 (m, 5 H), 1.47 - 1.66 (m, 2 H), 1.40 - 1.46 (m, 9 H); MS (ESI) m/z 480.3 (M+ + H).

Example 51. Comparative compound 967: (R)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile

[0118]



Step 1. methyl 3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: DME (4 mL) / H_2O (1 mL) was added to 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 938; 0.25 g, 0.67 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (0.14 g, 0.81 mmol), $Pd(dppf)Cl_2$ (0.02 g, 0.03 mmol) and Cs_2CO_3 (0.44 g, 1.35 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc.. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.14 g, 49%).

Step 2. 3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.14 g, 0.32 mmol) and $LiOH \cdot H_2O$ (0.06 g, 1.63 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (2 mL) at room temperature. The solution was stirred at the same temperature for 2 hours, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.13 g, 95%).

Step 3. Comparative compound 967: 3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.093 mmol), (R)-piperidin-3-ol (0.01 g, 0.11 mmol), HOBt (0.02 g, 0.18 mmol), EDC (0.03 g, 0.18 mmol) and DIPEA (0.03 mL, 0.18 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 10 %), and concentrated to yield the title compound as yellow oil (0.02 g, 46%).

1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.70 (m, 2 H), 7.42 (t, 1 H, J = 7.8 Hz), 7.24 - 7.30 (m, 2 H), 7.04 (d, 1 H, J = 8.8 Hz), 3.95 (d, 2 H, J = 6.4 Hz), 3.38 - 3.78 (m, 4 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.17 - 2.27 (m, 3 H), 1.85 - 1.95 (m, 5 H), 1.63 - 1.71 (m, 1 H), 1.42 - 1.56 (m, 3 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 512.3 (M+ + H).

[0119] According to the above-described synthesis process of comparative compound 967, the compounds of Table 28 were synthesized using 3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 27.

Table 27. (* marks comparative compound)

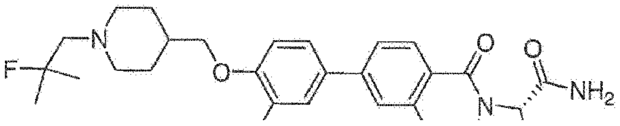
Compound No.	Reactant	Yield (%)
968*	(S)-piperidin-3-ol hydrochloride	52
969	L-prolinamide	42

Table 28. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
968*	(S)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.71 (m, 2 H), 7.42 (t, 1 H, J = 7.8 Hz), 7.24 - 7.30 (m, 2 H), 7.04 (d, 1 H, J = 8.8 Hz), 3.95 (d, 2 H, J = 6.4 Hz), 3.36 - 3.79 (m, 4 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.17 - 2.22 (m, 3 H), 1.91 - 2.11 (m, 6 H), 1.43 - 1.71 (m, 3 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 512.3 (M+ + H).
969	(S)-1-(3'-cyano-2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.70 - 7.75 (m, 2 H), 7.36 - 7.46 (m, 3 H), 7.05 (d, 1 H, J = 8.8 Hz), 6.87 (s, 1 H), 5.66 (s, 1 H), 4.77 - 4.80 (m, 1 H), 3.95 (d, 2 H, J = 6.4 Hz), 3.56 - 3.68 (m, 2 H), 2.99 - 3.02 (m, 2 H), 2.41 - 2.49 (m, 2 H), 2.07 - 2.33 (m, 5 H), 1.85 - 1.92 (m, 4 H), 1.42 - 1.48 (m, 2 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 525.3 (M+ + H).

Example 52. Compound 938: (S)-1-(3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0120]



Step 1. t-butyl 4-((4-bromo-2-cyanophenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate (the product of synthesis step 2 of comparative compound 431; 800 mg, 2.73 mmol) was dissolved in ACN (80 mL). At room temperature, 5-bromo-2-hydroxybenzonitrile (540 mg, 2.73 mmol) was added thereto, and stirred for 5 minutes. Cs_2CO_3 (1.33 g, 4.09 mmol) was added thereto, following with stirring at 80 °C for 5 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 30 % ~ 70 %), and concentrated to yield the title compound as white solid (655 mg, 60%).

Step 2. 5-bromo-2-(piperidin-4-ylmethoxy)benzonitrile hydroxychloride: t-butyl 4-((4-bromo-2-cyanophenoxy)methyl)piperidin-1-carboxylate (655 mg, 1.66 mmol) was dissolved in CH_2Cl_2 (10 mL). 4 M HCl solution in 1,4-dioxane (414 µL, 1.66 mmol) was added thereto at room temperature. The mixture was stirred at the same temperature for 1 hour. The resulting precipitate was filtered, and dried to yield the title compound as white solid (540 mg, 98%).

Step 3. 5-bromo-2-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile: To 5-bromo-2-(piperidin-4-ylmethoxy)benzonitrile hydroxychloride (540 mg, 1.63 mmol), 2,2-dimethyl oxirane (1.45 mL, 16.3 mmol) and K_2CO_3 (112 mg, 0.81 mmol), EtOH (5 mL) / H_2O (5 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material, which is the title compound as white solid (440 mg, 73%), was used without further purification.

Step 4. 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile: 5-bromo-2-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (440 mg, 1.20 mmol) was dissolved in CH_2Cl_2 (10 mL). At 0 °C, DAST (158 µL, 1.20 mmol) was added thereto, following with stirring at room temperature for 1 hour. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 30 % ~ 70 %), and concentrated to yield the title compound as white solid (254 mg, 57%).

Step 5. ethyl 3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) benzonitrile (the product of synthesis step 4 of compound 963; 254 mg, 0.69 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (160 mg, 0.76 mmol), Pd(dppt)Cl_2 (56 mg, 0.07 mmol) and Cs_2CO_3 (448 mg, 1.38 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography

(EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (205 mg, 65%).

Step 6. 3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)pipendin-4-yl)methoxy)biphenyl-4-carboxylic acid: Ethyl 3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (205 mg, 0.45 mmol) was dissolved in THF (10 mL) and water (5 mL). LiOH·H_2O (94 mg, 2.25 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (120 mg, 62%).

Step 7. Compound 938: 3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), EDC (27 mg, 0.14 mmol) and HOBt (19 mg, 0.14 mmol) was added thereto, DIPEA (25 µL, 0.14 mmol) was dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (16 mg, 0.14 mmol) was added thereto, following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5%) to yield the title compound as white solid (21 mg, 57%).
1H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.71 (m, 2 H), 7.52 (t, 1 H, J = 7.5 Hz), 7.44 - 7.39 (m, 1 H), 7.37 - 7.23 (m, 1 H), 7.06 (d, 1 H, J = 8.9 Hz), 6.89 (brs, 1 H), 5.50 (brs, 1 H), 4.83 - 4.80 (m, 1 H), 3.96 (d, 2 H, J = 6.4 Hz), 3.56 - 3.39 (m, 2 H), 3.03 (brs, 2 H), 2.52 - 2.41 (m, 2 H), 2.22 - 2.14 (m, 2 H), 2.12 - 2.01 (m, 2 H), 1.94 - 1.87 (m, 4 H), 1.67 (brs, 2 H), 1.57 - 1.45 (brs, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 525 (M+ + H).

[0121] According to the above-described synthesis process of compound 938, the compounds of Table 30 were synthesized using 3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 29.

Table 29. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
939*	(R)-piperidin-3-ol hydrochloride	53
1015	(S)-piperidin-2-carboxamide hydrochloride	33
1016*	(S)-piperidin-2-ol hydrochloride	50
1017*	(S)-pyrrolidine-3-ol	46

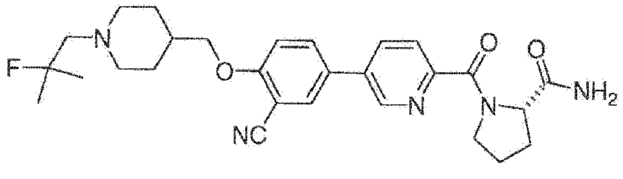
Table 30. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
939*	(R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.70 (m, 2 H), 7.48 (t, 1 H, J = 7.3 Hz), 7.36 - 7.34 (m, 1 H), 7.27 - 7.22 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.14 - 4.07 (m, 1 H), 3.96 (d, 2 H, J = 6.4 Hz), 3.58 - 3.52 (m, 1 H), 3.38 - 3.23 (m, 1 H), 3.16 - 3.13 (m, 2 H), 2.51 - 2.46 (m, 2 H), 2.22 - 2.17 (m, 2 H), 2.05 -

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	1.87 (m, 6 H), 1.76 - 1.71 (m, 3 H), 1.70- 1.48 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 512 (M+ + H).
1015	(R)-1-(3'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.69 - 7.78 (m, 2 H), 7.50 - 7.54 (m, 1 H), 7.40 (dd, 1 H, J = 8.0, 1.5 Hz), 7.22 - 7.32 (m, 1 H), 7.06 (d, 1 H, J = 8.9 Hz), 6.28 (s, 1 H), 5.31 (s, 1 H), 3.96 (d, 2 H, J = 6.4 Hz), 3.58 (d, 1 H, J = 13.0 Hz), 3.18 - 3.25 (m, 1 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.17 - 2.23 (m, 2 H), 1.86 - 1.92 (m, 3 H), 1.73 - 1.76 (m, 2 H), 1.53 - 1.66 (m, 5 H), 1.42 - 1.48 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 539.3 (M+ + H).
1016*	(S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.75 - 7.76 (m, 1 H), 7.70 - 7.73 (m, 1 H), 7.48 (t, 1 H, J = 7.4 Hz), 7.32 - 7.37 (m, 1 H), 7.22 - 7.27 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.06 - 4.10 (m, 1 H), 4.00 (d, 2 H, J = 6.3 Hz), 3.11 - 3.58 (m, 3 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.17 - 2.23 (m, 2 H), 1.81 - 2.05 (m, 5 H), 1.48 - 1.68 (m, 4 H), 1.42 - 1.46 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 512.3 (M+ + H).
1017*	(S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.77 (m, 1 H), 7.72 (dd, 1 H, J = 8.8, 1.6 Hz), 7.53 (dd, 1 H, J = 13.3, 7.4 Hz), 7.22-7.32 (m, 1 H), 7.05 (d, 2 H, J = 8.8 Hz), 4.51 - 4.64 (m, 1 H), 3.95 (d, 2 H, J = 6.3 Hz), 3.33 - 3.85 (m, 4 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 - 2.22 (m, 3 H), 2.02 - 2.08 (m, 1 H), 1.85 - 1.91 (m, 2 H), 1.70 - 1.63 (m, 2 H), 1.42 - 1.49 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 498.3 (M+ + H).

Example 53. Compound 1036: (S)-(5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

[0122]



Step 1. methyl 5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 938; 673 mg, 1.82 mmol), 6-(methoxycarbonyl) pyridine-3-ylboronic acid (330 mg, 1.82 mmol), Pd(dppf)Cl_2 (59 mg, 0.09 mmol) and Cs_2CO_3 (1.19 g, 3.65 mmol) were added to water (2 mL)/1,4-dioxane (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with

water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as brown solid (150 mg, 19%).

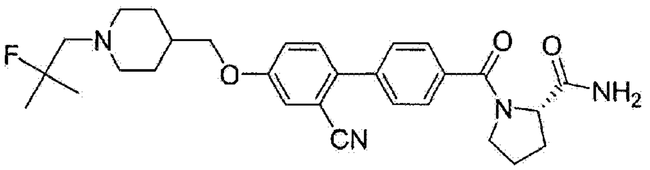
Step 2. 5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid: Methyl 5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinate (150 mg, 0.35 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (74 mg, 1.76 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (41 mg, 28%).

Step 3. Compound 1036: 5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid (30 mg, 0.07 mmol), (S)-pyrrolidine-2-carboxamide (22 mg, 0.19 mmol), EDC (37 mg, 0.19 mmol), HOBt (26 mg, 0.19 mmol) and DIPEA (34 μL, 0.19 mmol) were dissolved in CH_2Cl_2 (1 mL), following with stirring at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (21 mg, 42%).

1H NMR (400 MHz, $CDCl_3$) δ 8.77 - 8.72 (m, 1 H), 8.14 - 8.12 (m, 0.4 H), 7.99 - 7.93 (m, 1.6 H), 7.82 - 7.75 (m, 2 H), 7.11 - 7.08 (m, 1 H), 6.39 (brs, 0.5 H), 6.39 (brs, 0.5 H), 5.43 (brs, 1 H), 4.87 - 4.86 (m, 0.5 H), 4.85 - 4.84 (m, 0.5 H), 4.06 - 3.87 (m, 4 H), 3.05 (brs, 2 H), 2.46 - 2.36 (m, 2 H), 2.21 - 2.15 (m, 2 H), 2.13 - 1.97 (m, 5 H), 1.64 (brs, 2 H), 1.58 - 1.39 (m, 6 H), 1.36 - 1.25 (m, 2 H); MS (ESI) m/z 508 (M+ + H).

Example 54. Compound 1031: (S)-1-(2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0123]



Step 1. methyl 2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: DME (4 mL) / H_2O (1 mL) was added to 2-bromo-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 1028; 0.30 g, 0.81 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.17 g, 0.97 mmol), $Pd(dppf)Cl_2$ (0.03 g, 0.04 mmol) and Cs_2CO_3 (0.52 g, 1.62 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried

over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0% to 40%), and concentrated to yield the title compound as white solid (0.05 g, 14%).

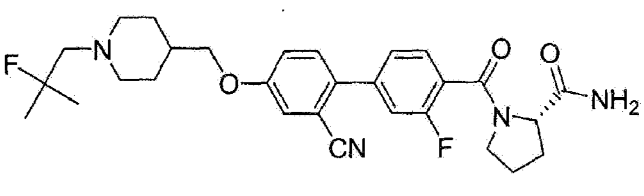
Step 2. 2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.05 g, 0.11 mmol) and $LiOH \cdot H_2O$ (0.02 g, 0.58 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (2 mL) at room temperature. The solution was stirred at the same temperature for 12 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.01 g, 20%).

Step 3. Compound 1031: 2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.03 g, 0.08 mmol), L-prolinamide (0.01 g, 0.10 mmol), HOBt (0.02 g, 0.17 mmol), EDC (0.03 g, 0.17 mmol) and DIPEA (0.02 mL, 0.17 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0% to 15%), and concentrated to yield the title compound as white solid (0.02 g, 64%).

1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2 H, J = 8.2 Hz), 7.59 (d, 2 H, J = 8.3 Hz), 7.42 (d, 1 H, J = 8.7 Hz), 7.25 (d, 1 H, J = 2.6 Hz), 7.19 (dd, 1 H, J = 8.7, 2.6 Hz), 7.01 (s, 1 H), 5.59 (s, 1 H), 4.83 (dd, 1 H, J = 7.4, 5.2 Hz), 3.86 (d, 2 H, J = 6.0 Hz), 3.57 - 3.68 (m, 2 H), 2.99 - 3.02 (m, 2 H), 2.43 - 2.50 (m, 3 H), 2.05 - 2.21 (m, 4 H), 1.78 - 1.92 (m, 4 H), 1.43 - 1.49 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 507.3 (M+ + H).

Example 55. Compound 1028: (S)-1-(2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0124]



Step 1. t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate: Piperidin-4-ylmethanol (10.0 g, 86.8 mmol), $(Boc)_2O$ (21.9 mL, 95.5 mmol) and TEA (14.4 mL, 104.1 mmol) were dissolved in DCM (50 mL) at room temperature. The solution was stirred at the same temperature for 1 hour. The reaction mixture was added with water, and extracted with ethyl acetate. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was recrystallized with ethyl acetate (10 mL) and hexane (150 mL) at 25 °C to yield the title compound as white solid (18.0 g,

96%).

Step 2. t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate: t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (18.0 g, 83.6 mmol), MsCl (7.16 mL, 91.9 mmol) and TEA (13.9 mL, 100.3 mmol) were dissolved in DCM (50 mL) at 0 °C, following with stirring at room temperature for 2 hours. The reaction mixture was added with water, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was recrystallized with ethyl acetate (10 mL) and hexane (150 mL) at 25 °C to yield the title compound as white solid (16.0 g, 65%).

Step 3. t-butyl 4-((4-bromo-3-cyanophenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (2.00 g, 6.81 mmol), 2-bromo-5-hydroxybenzonitrile (1.35 g, 6.87 mmol) and K_2CO_3 (1.88 g, 13.63 mmol) were dissolved in DMF (50 mL) at 80 °C, following with stirring at the same temperature for 5 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (1.90 g, 70%).

Step 4. 2-bromo-5-(piperidin-4-ylmethoxy)benzonitrile hydrochloride: t-butyl 4-((4-bromo-3-cyanophenoxy)methyl)piperidin-1-carboxylate (1.90 g, 4.80 mmol) and 4MHCl solution in 1,4-dioxane (6.00 mL, 24.03 mmol) were dissolved in CH_2Cl_2 (15 mL) at room temperature. The solution was stirred at the same temperature for 2 hours. The resulting precipitate was filtered, and dried to yield the title compound as white solid (1.52 g, 95%).

Step 5. 2-bromo-5-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile: EtOH (8 mL) / H_2O (2 mL) was added to 2-bromo-5-(piperidin-4-ylmethoxy)benzonitrile hydrochloride (1.72 g, 5.18 mmol), 2,2-dimethyl oxirane (4.61 mL, 51.86 mmol) and K_2CO_3 (3.58 g, 25.93 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (1.70 g, 89%, white solid).

Step 6. 2-bromo-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile: 2-bromo-5-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (1.70 g, 4.62 mmol) was dissolved in CH_2Cl_2 (20 mL). At 0 °C, DAST (0.72 mL, 5.55 mmol) was added thereto, following with stirring at the same temperature for 2 hours. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (1.10 g, 64%).

Step 7. ethyl 2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: DME (4 mL) / H_2O (1 mL) was added to 2-bromo-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (0.30 g, 0.81 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.17 g, 0.97 mmol), Pd(dppf)Cl_2 (0.03 g, 0.04 mmol) and Cs_2CO_3 (0.52 g, 1.62 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0 % to 40 %), and concentrated to yield the title compound as white solid (0.16 g, 43%).

Step 8. 2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Ethyl 2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.16 g, 0.35 mmol) and LiOH·H_2O (0.07 g, 1.75 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (2 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (15 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.15 g, 93%).

Step 9. Compound 1028: 2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.10 mmol), L-prolinamide (0.01 g, 0.12 mmol), HOBt (0.02 g, 0.21 mmol), EDC (0.04 g, 0.21 mmol) and DIPEA (0.03 mL, 0.21 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.05 g, 92%).
1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.56 (m, 1 H), 7.41 (dd, 2 H, J = 8.0, 1.7 Hz), 7.30 - 7.33 (m, 2 H), 7.19 - 7.22 (m, 1 H), 6.91 (s, 1 H), 5.45 (s, 1 H), 4.83 (dd, 1 H, J = 7.6, 3.9 Hz), 3.87 (d, 2 H, J = 6.0 Hz), 3.44 - 3.56 (m, 2 H), 2.99 - 3.02 (m, 2 H), 2.48 - 2.52 (m, 2 H), 2.43 (s, 1 H), 2.06 - 2.21 (m, 4 H), 1.91 - 1.94 (m, 2 H), 1.79 - 1.81 (m, 2H), 1.635 (s, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 525.3 (M+ + H).

[0125] According to the above-described synthesis process of compound 1028, the compounds of Table 32 were synthesized using 2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 31.

Table 31. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
1029*	(R)-piperidin-3-ol	89
1030	(R)-piperidin-2-carboxamide hydrochloride	60
1115*	piperidin-4-ol	16

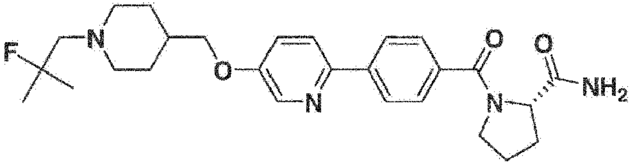
Compound No.	Reactant	Yield (%)

Table 32. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1029*	(R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-2-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.49 (t, 1 H, J = 7.4 Hz), 7.37 - 7.41 (m, 2 H), 7.22 - 7.29 (m, 2 H),7.19 (dd, 1 H, J = 8.7, 2.7 Hz), 3.90 - 3.93 (m, 1 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.37 - 3.61 (m, 3 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 3 H, J = 10.9 Hz), 1.91 - 2.05 (m, 2 H), 1.79 - 1.86 (m, 4 H), 1.60 - 1.69 (m, 2 H), 1.42 - 1.49 (m, 2H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 512.3 (M+ + H).
1030	(R)-1-(2'-cyano-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.65 (t, 1 H, J = 5.7 Hz), 7.38 (t, 2 H, J = 5.7 Hz), 7.30 (d, 2 H, J = 10.4 Hz), 7.20 (dd, 1 H, J = 8.7, 2.5 Hz), 6.30 (s, 1 H), 5.65 (s, 1 H), 5.45 (s, 1 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.59 - 3.63 (m, 1 H), 3.21 - 3.24 (m, 1H), 2.99 - 3.02 (m, 2 H), 2.43 - 2.48 (m, 2 H), 2.18 (t, 2 H, J = 11.0 Hz), 1.56 - 1.81 (m, 8 H), 1.42 - 1.48 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 539.3 (M+ + H).
1115*	3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(4-hydroxypiperidin-1-carbonyl)biphenyl-2-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1 H, J = 7.4 Hz), 7.34 - 7.38 (m, 2 H), 7.22 - 7.25 (m, 2 H), 7.17 (dd, 1 H, J = 8.8, 2.8 Hz), 4.20 (m, 1 H), 3.99 (s, 1 H), 3.83 (d, 2 H, J = 5.6 Hz), 3.59 (m, 1 H), 3.20 - 3.46 (s, 2 H), 2.96 - 2.99 (m, 2 H), 2.40 - 2.45 (m, 2 H), 2.12 - 2.18 (m, 2 H), 1.98 - 2.02 (m, 2 H), 1.75 - 1.87 (m, 3 H), 1.59 - 1.68 (m, 1 H), 1.21 - 1.55 (m, 2 H), 1.42 - 1.45 (m, 2 H), 1.37 (s, 3 H), ; 1.32 (s, 3 H); MS (ESI) m/z 512.2 (M+ + H).

Example 56. Compound 691: (S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0126]



Step 1. t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate: t-Butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 2 of comparative compound 431; 2.0 g, 6.82 mmol) was dissolved in ACN 10 mL. 6-chloropyridine-3-ol (1.06 g, 8.18 mmol), Cs_2CO_3 (3.33 g, 10.23 mmol) was added thereto, and refluxed with heating for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid

residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (1.6 g, 72%).

Step 2. 2-chloro-5-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate (1.6 g, 4.90 mmol) was dissolved in CH_2Cl_2 8 mL. 4 M HCl 1.47 mL was added thereto, following with stirring at room temperature for 2 hours. The reaction mixture was filtered, washed with hexane, and evaporated under reduced pressure to yield the title compound as white solid (1.25 g, 97%).

Step 3. 1-(4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 2-chloro-5-(piperidin-4-ylmethoxy)pyridine hydrochloride (1.25 g, 4.75 mmol) was dissolved in EtOH 6 mL. 2,2-dimethyloxirane (3.42 g, 47.5 mmol), K_2CO_3 (1.31 g, 9.5 mmol) and water 3 mL were added thereto. With a microwave radiation, the mixture was stirred at 110 °C for 20 minutes. After the completion of the reaction, EtOH was evaporated from the reaction mixture under reduced pressure, and then a little of water was added to thereto. The resulting precipitate was filtered, and dried under reduced pressure to yield the title compound as white solid (980 g, 69%).

Step 4. 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine: 1-(4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (980 mg, 3.28 mmol) was dissolved in CH_2Cl_2 6 mL. And then, DAST (793 mg, 4.92 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure to yield the title compound as yellow solid (460 mg, 46%).

Step 5. methyl 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1 -(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (230 mg, 0.77 mmol), 4-(methoxycarbonyl)phenylboronic acid (165 mg, 0.92 mmol), Pd(dppf)Cl_2 (62 mg, 0.08 mmol), Na_2CO_3 (162 mg, 1.53 mmol) were dissolved in DME 6 mL and water 2 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CH_2Cl_2) to yield the title compound as yellow solid (220 mg, 71 %).

Step 6. 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid: methyl 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate (220 mg, 0.55 mmol) was dissolved in THF:MeOH:Water = 2/1/0.5 mL. LiOH·H_2O (46 mg, 1.10 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure to yield the title compound as yellow solid (210 mg, 98%).

Step 7. Compound 691: 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (40 mg, 0.10 mmol), (S)-pyrrolidine-2-carboxamide (24 mg, 0.20 mmol) and BOP (91 mg, 0.21 mmol) were dissolved in DMF 1 mL. After stirring for 10 minutes at room temperature,

TEA (31 mg, 0.31 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as yellow solid (19 mg, 38%).
1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 1 H, J = 2.9 Hz), 7.97 (d, 2 H, J = 8.2 Hz), 7.68 (d, 1 H, J = 8.7 Hz), 7.52 (d, 2 H, J = 8.2 Hz), 3.90 (d, 2 H, J = 6.0 Hz), 3.14 (m, 3 H), 3.02 (m, 5 H), 2.46 (m, 2 H), 2.04 (m, 2 H), 1.73 (m, 2 H), 1.46 (m, 2 H), 1.36 (m, 8 H); MS (ESI) m/z 469 (M + H).

[0127] According to the above-described synthesis process of compound 691, the compounds of Table 34 were synthesized using 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid and the reactant of Table 33.

Table 33. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
692*	(R)-pyrrolidine-2-ylmethanol	51
693*	(S)-piperidin-3-ol	42
763*	(R)-pyrrolidine-3-ol	40
764*	(S)-pyrrolidine-3-ol	42
765*	(S)-pyrrolidine-2-ylmethanol	32
766*	(R)-piperidin-3-ol hydrochloride	30
804	piperidin-4-carboxamide	66
821	(R)-piperidin-2-carboxamide	49

Table 34. (* marks comparative compound)

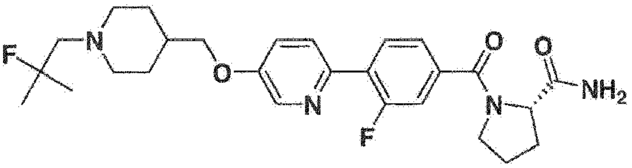
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
692*	(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2 H), 8.20 (d, 1 H, J = 8.0 Hz), 8.10 (d, 1 H, J = 10.8 Hz), 7.48 (t, 1 H, J = 7.4 Hz), 4.12 - 4.09 (m, 1 H), 3.96 (d, 2 H, J = 5.9 Hz), 3.58 - 3.54 (m, 1 H), 3.37 - 3.33 (m, 1 H), 3.25 - 3.20 (m, 1 H), 3.13 - 3.03 (m, 2 H), 2.56 - 2.45 (m, 2 H), 2.27 - 2.16 (m, 2 H), 2.05 - 1.81 (m, 6 H), 1.69 - 1.62 (m, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.37 - 1.28 (m, 2 H); MS (ESI) m/z 489 (M+ + H).
693*	(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1H, J = 2.7 Hz), 7.95 (d, 2 H, J = 8.4 Hz), 7.66 (d, 1 H, J = 8.7 Hz), 7.49 (d, 2 H, J = 8.3 Hz), 7.24 (m, 1 H), 3.88 (m, 4 H), 3.60 (m, 4 H), 3.01 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.09 (m, 2 H), 1.82 (m, 6 H), 1.44 (m, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 470 (M + H).
	(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
763*	yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.7 Hz), 7.97 - 7.94 (m, 2 H), 7.68 - 7.59 (m, 3 H), 7.28 - 7.25 (m, 1 H), 4.59 - 4.46 (m, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.85 - 3.81 (m, 2 H), 3.78 - 3.62 (m, 1 H), 3.56 - 3.46 (m, 1 H), 3.07 - 3.04 (m, 2 H), 2.53 - 2.48 (m, 2 H), 2.37 - 2.34 (m, 1 H), 2.26 - 2.20 (m, 2 H), 2.12 - 1.98 (m, 2 H), 1.84 - 1.82 (m, 3 H), 1.51 - 1.48 (m, 2 H), 1.42 (s, 3 H), 1.40 (s, 3 H); MS (ESI) m/z 456 (M+ + H).
764*	(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.7 Hz), 7.97 - 7.94 (m, 2 H), 7.68 - 7.59 (m, 3 H), 7.28 - 7.25 (m, 1 H), 4.59 - 4.46 (m, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.85 - 3.81 (m, 2 H), 3.78 - 3.62 (m, 1 H), 3.56 - 3.46 (m, 1 H), 3.07 - 3.04 (m, 2 H), 2.53 - 2.48 (m, 2 H), 2.37 - 2.34 (m, 1 H), 2.26 - 2.20 (m, 2 H), 2.12 - 1.98 (m, 2 H), 1.84 - 1.82 (m, 3 H), 1.51 - 1.48 (m, 2 H), 1.42 (s, 3 H), 1.40 (s, 3 H); MS (ESI) m/z 456 (M+ + H).
765*	(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 1 H, J = 2.9 Hz), 7.99 (d, 2 H, J = 8.2 Hz), 7.69 (d, 1 H, J = 8.7 Hz), 7.60 (d, 1 H, J = 8.2 Hz), 7.29 - 7.26 (m, 2 H), 4.95 - 4.93 (m, 1 H), 4.46 - 4.41 (m, 1 H), 3.90 (d, 2 H, J = 5.9 Hz), 3.85 - 3.74 (m, 2 H), 3.60 - 3.49 (m, 2 H), 3.03 (brs, 2 H), 2.51 - 2.46 (brs, 2 H), 2.27 - 2.18 (m, 2 H), 2.05 - 1.81 (m, 5 H), 1.78 - 1.63 (m, 2 H), 1.60 - 1.48 (m, 2 H), 1.42 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 470 (M+ + H).
766*	(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 2 H, J = 2.6 Hz), 7.97 (d, 2 H, J = 8.2 Hz), 7.68 (d, 1 H, J = 8.7 Hz), 7.51 (d, 2 H, J = 8.2 Hz), 7.28 - 7.25 (m, 1 H), 4.02 - 4.00 (m, 1 H), 3.91 (d, 2 H, J = 5.8 Hz), 3.80 - 3.46 (m, 3 H), 3.25 - 3.06 (m, 2 H), 2.67 - 2.49 (m, 2 H), 2.37 - 2.12 (m, 2 H), 2.05 - 1.94 (m, 2 H), 1.85 - 1.83 (m, 4 H), 1.71 - 1.66 (m, 3 H), 1.52 - 1.50 (m, 2 H), 1.43 (s, 3 H), 1.38 (s, 3 H); MS (ESI) m/z 471 (M+ + H).
804	1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.42 - 8.41 (m, 1 H), 8.00 (d, 2 H, J = 8.4 Hz), 7.71 (d, 1 H, J = 8.4 Hz), 7.51 (d, 2 H, J = 6.4 Hz), 7.29 - 7.28 (m, 1 H), 5.71 (d, 2 H, J = 30.8 Hz), 4.73 (brs, 1 H), 3.93 - 3.92 (m, 3 H), 3.05 - 3.02 (m, 4 H), 2.51-2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.4 Hz), 1.98 - 1.83 (m, 7 H), 1.58 - 1.22 (m, 8 H); MS (ESI) m/z 497 (M+ + H)
821	(R)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.38 (m, 1 H), 7.99 (d, 2 H, J = 8.0 Hz), 7.69 (d, 2 H, J = 8.7 Hz), 7.54 (d, 2 H, J = 7.6 Hz), 7.28 - 7.25 (m, 1 H), 6.52 (brs, 1 H), 5.53 (brs, 1 H), 5.29 (brs, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.78 (d, 1 H, J = 12.7 Hz), 3.12 - 3.10 (m, 1 H), 3.01 (d, 2 H, J = 11.2 Hz), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.34 (d, 1 H, J = 13.2 Hz), 2.19 (t, 2 H, J = 11.0

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	Hz), 2.05 - 1.43 (m, 8 H), 1.40 - 1.24 (m, 8 H); MS (ESI) m/z 497 (M+ + H).

Example 57. Compound 696: (S)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0128]



Step 1. methyl 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)pipendin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 5 of compound 691; 366 mg, 1.06 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (231 mg, 1.17 mmol), Pd(dppf)Cl_2 (87 mg, 0.11 mmol), Na_3CO_3 (225 mg, 2.12 mmol) were dissolved in DME 6 mL and water 2 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CH_2Cl_2) to yield the title compound as yellow solid (210 mg, 47%).

Step 2. 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid: Methyl 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate (220 mg, 0.53 mmol) was dissolved in THF/MeOH/H_2O = 2/1/0.5 mL. LiOH·H_2O (44 mg, 1.05 mmol) was added thereto, and refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using IN HCl. The resulting precipitate was filtered to yield the title compound as white solid (195 mg, 91%).

Step 3. Compound 696: 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (40 mg, 0.10 mmol), (R)-pyrrolidine-2-ylmethanol (23 mg, 0.20 mmol) and BOP (88 mg, 0.20 mmol) were dissolved in DMF 1 mL, following with stirring for 10 minutes at room temperature. TEA (30 mg, 0.30 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CF_2Cl_2) to yield the title compound as yellow solid (20 mg, 40%).
1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1 H, J = 2.8 Hz), 8.05 (t, 1 H, J = 7.9 Hz), 7.78 (d, 1 H, J = 8.8 Hz), 7.38 (m, 2 H), 7.27 (m, 2 H), 6.92 (s, 1 H), 5.51 (s, 1 H), 4.79 (m, 1 H), 3.91 (d, 2 H, J = 5.9

Hz), 3.55 (m, 2 H), 3.01 (m, 2 H), 2.46 (m, 3 H), 2.13 (m, 2 H), 2.06 (m, 2 H), 1.92 (m, 4 H), 1.35 (m, 5 H), 1.26 (s, 3 H); MS (ESI) m/z 501 (M + H).

[0129] According to the above-described synthesis process of compound 696, the compounds of Table 36 were synthesized using 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid and the reactant of Table 35.

Table 35. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
697*	(R)-pyrrolidine-2-ylmethanol	47
698*	(R)-piperidin-3-ol	39
699*	(S)-pyrrolidine-3-ol	17
813	piperidin-4-carboxamide hydrochloride	39
815*	(R)-pyrrolidine-3-ol	52

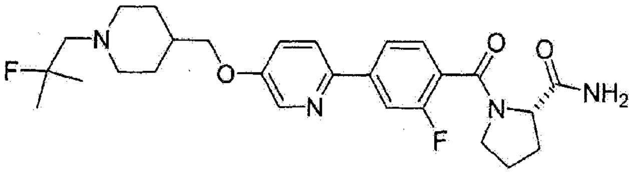
Table 36. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
697*	(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, 1 H, J = 2.9 Hz), 8.04 (t, 1 H, J = 7.9 Hz), 7.77 (d, 1 H, J = 8.4 Hz), 7.39 (d, 1 H, J = 8.0 Hz), 7.33 (d, 1 H, J = 11.4 Hz), 7.26 (m, 1 H), 4.73 (s, 1 H), 4.41 (m, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.76 (m, 2 H), 3.57 (m, 2 H), 3.01 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.19 (m, 3 H), 1.80 (m, 6 H), 1.47 (m, 5 H), 1.30 (s, 3 H); MS (ESI) m/z 488 (M + H).
698*	(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, 1 H, J = 2.8 Hz), 8.00 (t, 1 H, J = 7.9 Hz), 7.74 (m, 1 H), 7.25 (m, 3 H), 3.86 (m, 4 H), 3.33 (m, 3 H), 3.01 (m, 2 H), 2.50 (s, 3 H), 2.44 (s, 3 H), 2.20 (m, 2 H), 1.80 (m, 6 H), 1.66 (m, 2 H), 1.43 (m, 5 H), 1.31 (s, 3 H); MS (ESI) m/z 488 (M + H).
699*	(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.41 (m, 1 H), 8.01 (m, 1 H), 7.77 (d, 1 H, J = 8.6 Hz), 7.40 (m, 2 H), 7.25 (m, 1 H), 4.62 (m, 0.5 H), 4.50 (m, 0.5 H), 3.90 (m, 2 H), 3.79 (m, 2 H), 3.55 (m, 1 H), 2.90 (m, 2 H), 2.43 (m, 2 H), 2.01 (m, 2 H), 1.88 (m, 2 H), 1.59 (m, 4 H), 1.26 (m, 9 H); MS (ESI) m/z 474 (M + H).
813	1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.40 (m, 1 H), 8.00 (t, 1 H, J = 7.9 Hz), 7.75 (m, 1 H), 7.16 (m, 3 H), 5.63 (m, 2 H), 4.87 (s, 1 H), 3.89 (m, 3 H), 3.03 (m, 4 H), 2.42 (m, 3 H), 2.22 (m, 2 H), 1.51 (m, 7 H), 1.35 (m, 5 H), 1.25 (s, 3 H)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
815*	(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.40 (m, 1 H), 8.02 (t, 1 H, J = 2.8 Hz), 7.75 (m, 1 H), 7.31 (m, 2 H), 7.25 (m, 1 H), 4.76 (s, 1 H), 4.41 (m, 1 H), 3.89 (d, 2 H, J = 7.4 Hz), 3.75 (m, 2 H), 3.52 (m, 2 H), 3.00 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 1.92 (m, 2 H), 1.77 (m, 6 H), 1.45 (m, 5 H), 1.31 (m, 2 H)

Example 58. Compound 770: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0130]



<u>Step 1.</u> t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate: Piperidin-4-ylmethanol (33.0 g, 286.53 mmol) was dissolved in DCM (400 mL). TEA (47.9 mL, 343.84 mmol) was added thereto, $(Boc)_2O$ (68.79 g, 315.18 mmol) was added thereto, following with stirring at room temperature for 1 hour. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with DCM. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was recrystallized with HX : EA = (4: 1) to yield the title compound as yellow solid (59.0 g, 96%).

<u>Step 2.</u> t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate: t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (59.0 g, 274.05 mmol) was dissolved in DCM (400 mL). TEA (45.84 mL, 328.86 mmol) was added thereto. At 0 °C, MsCl (23.4 mL, 301.45 mmol) was added thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, reaction mixture was added with water, and extracted with DCM. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was recrystallized with HX : EA = (4 : 1) to yield the title compound as white solid (70.0 g, 87%).

<u>Step 3.</u> t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (3.00 g, 10.23 mmol) was dissolved in ACN (50 mL). CS_2CO_3 (4.99 g, 15.34 mmol) was added thereto. And then, 6-chloropyridine-3-ol (1.32 g, 10.23 mmol) was added thereto, following with stirring for 5 hours at the reflux temperature. After the completion of the reaction, the reaction mixture was added with water, and then extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2; hexane / EtOAc = 5/1) to yield the title compound as white solid (2.8

g, 83%).

Step 4. 2-chloro-5-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-carboxylate (2.80 g, 8.57 mmol) was dissolved in DCM (70 mL) was added thereto, following with stirring for 5 minutes. And then, 4 M HCl solution in 1,4-dioxane (42.84 mL, 171.35 mmol) was added dropwise slowly thereto, following with stirring for 1 hour at room temperature. After the completion of the reaction, the reaction mixture was filtered to yield the title compound as white solid (1.50 g, 77%).

Step 5. 1-(4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 2-chloro-5-(piperidin-4-ylmethoxy)pyridine hydrochloride (1.50 g, 5.70 mmol), 2,2-dimethyl oxirane (5.07 mL, 57.0 mmol) and K_2CO_3 (0.39 g, 2.85 mmol) were dissolved in EtOH (5 mL) / H_2O (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2; hexane / EtOAc = 4/1) to yield the title compound as white solid (1.3 g, 76%).

Step 6. 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine: 1-(4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (1.30 g, 4.35 mmol) was dissolved in CH_2Cl_2 (15 mL). At 0 °C, DAST (0.57 mL, 4.35 mmol) was added thereto little by little. The reaction mixture was stirred for 1 hour at room temperature. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2; hexane / EtOAc = 7/1) to yield the title compound as white solid (1.20 g, 92%).

Step 7. ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (0.60 g, 1.99 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.51 g, 2.39 mmol), Pd(dppf)Cl_2 (0.08 g, 0.10 mmol) and CS_2CO_3 (1.29 g, 3.98 mmol) were added to 1,4-dioxane (6 mL) / H_2O (2 mL). With a microwave radiation, the reaction was performed at 110 °C for 15 minutes. After the completion of the reaction, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2; hexane / EtOAc = 7/1) to yield the title compound as white solid (0.66 g, 76%).

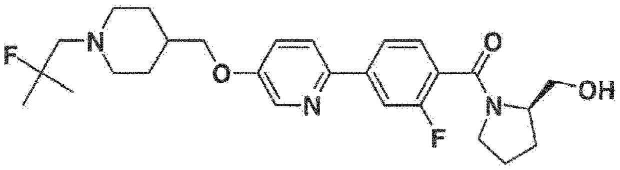
Step 8. 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid: Ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate (0.66 g, 0.35 mmol) was dissolved in THF (10 mL) / MeOH (10 mL) / H_2O (5 mL). LiOH-H_2O (0.32 g, 7.64 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified by the addition of IN HCl. The resulting precipitate was filtered to yield the title compound as white solid (0.60 g, 97%).

Step 9. Compound 770: 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (0.08 g, 0.19 mmol), L-prolinamide (0.03 g, 0.24 mmol), BOP (0.17 g, 0.39 mmol) and TEA (0.06 mL, 0.39 mmol) were dissolved in DMF (1 mL). At 60 °C, the reaction was performed for a day. After the completion of the reaction, the reaction mixture was added with a saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2; MC / MeOH = 10/1) to yield the title compound as yellow solid (0.03 g, 35%).

1H NMR (400 MHz, $CDCl_3$) δ 8.39 (m, 1 H), 7.78 - 7.75 (m, 2 H), 7.68 - 7.66 (m, 1 H), 7.50 (t, 1 H, J = 7.5 Hz), 7.29 - 7.26 (m, 1 H), 6.93 (brs, 1 H), 5.50 (brs, 1 H), 4.84 - 4.81 (m, 1 H), 3.90 (d, 2 H, J = 5.8 Hz), 3.55 - 3.40 (m, 2 H), 3.03 (brs, 2 H), 2.51 - 2.45 (m, 3 H), 2.21 - 2.19 (m, 2 H), 2.16 - 2.01 (m, 2 H), 1.93 - 1.90 (m, 1 H), 1.89 - 1.81 (m, 3 H), 1.57 - 1.48 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 501 (M+ + H).

Example 59. Comparative compound 694: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0131]



Step 1. ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 5 of compound 691; 230 mg, 0.77 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (195 mg, 0.92 mmol), $Pd(dppf)Cl_2$ (62 mg, 0.08 mmol) and Na_3CO_3 (162 mg, 1.35 mmol) were dissolved in DME 6 mL and water 2 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as yellow solid (210 mg, 68%).

Step 2. 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid: Ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate (210 mg, 0.49 mmol) was dissolved in $THF/MeOH/H_2O$ = 2/1/0.5 mL. $LiOH{\cdot}H_2O$ (41 mg, 0.97 mmol) was added thereto, and refluxed with heating and stirring for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure to yield the title compound as yellow solid (195 mg, 99%).

Step 3. Comparative compound 694: 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (40 mg, 0.10 mmol), (R)-pyrrolidine-2-ylmethanol (20 mg, 0.20 mmol), and BOP (88 mg, 0.20 mmol) were dissolved in DMF 1 mL. After stirring for 10 minutes at room temperature, TEA (30 mg, 0.30 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as yellow solid (22 mg, 45%).

1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.7 Hz), 7.75 (m, 2 H), 7.65 (m, 1 H), 7.49 (m, 1 H), 7.26 (m, 1 H), 4.78 (s, 1 H), 4.40 (m, 2 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.77 (m, 2 H), 3.43 (m, 2 H), 3.15 (m, 2 H), 3.00 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.19 (m, 2 H), 1.81 (m, 3 H), 1.68 (m, 1 H), 1.47 (m, 5 H), 1.34 (s, 3 H)

[0132] According to the above-described synthesis process of comparative compound 694, the compounds of Table 38 were synthesized using 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid and the reactant of Table 37.

Table 37. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
695*	(S)-pyrrolidine-3-ol	49
767*	(S)-piperidin-3-ol hydrochloride	42
768*	(R)-pyrrolidine-3-ol	41
769*	(S)-pyrrolidine-2-ylmethanol	38
771*	(R)-piperidin-3-ol hydrochloride	34
805	piperidin-4-carboxamide	72
822	(R)-piperidin-2-carboxamide	47
824	(S)-piperidin-2-carboxamide	61

Table 38. (* marks comparative compound)

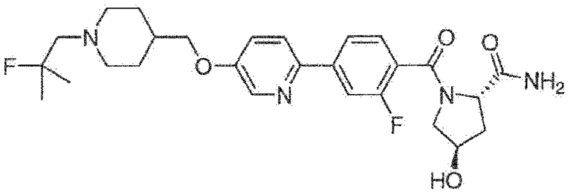
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
695*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 1 H), 7.72 (m, 2 H), 7.69 (m, 1 H), 7.48 (m, 1 H), 7.25 (m, 1 H), 4.57 (m, 0.5 H), 4.45 (m, 0.5 H), 3.89 (d, 2 H, J = 6.0 Hz), 3.73 (m, 3 H), 3.13 (m, 1 H), 3.02 (m, 2 H), 3.00 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.05 (m, 2 H), 1.99 (m, 2 H), 1.41 (m, 5 H), 1.35 (s, 3 H); MS (ESI) m/z 474 (M + H).
767*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 3.0 Hz), 7.76 - 7.71 (m, 2 H), 7.67 - 7.65 (m, 1 H), 7.48 - 7.44 (m, 1 H), 7.29 - 7.26 (m, 1 H), 4.12 - 3.90 (m, 3 H), 3.59 - 3.55 (m, 1 H), 3.49 - 3.46 (m, 1 H), 3.38 - 3.26 (m, 1 H), 3.25 - 3.02 (m, 1 H), 2.97 - 2.46 (m, 2 H), 2.21 - 2.28 (m, 2 H), 2.06 - 2.01 (m, 1 H), 1.98 - 1.91 (m, 1 H), 1.89 - 1.82 (m, 4 H), 1.68 - 1.62 (m, 4 H), 1.60 - 1.48 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 488(M+

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	+ H).
768*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.8 Hz), 7.76 - 7.72 (m, 2 H), 7.67 - 7.65 (m, 1 H), 7.54 - 7.49 (m, 1 H), 7.29 - 7.26 (m, 1 H), 4.62 - 4.49 (m, 1 H), 3.91 (d, 2 H, J = 5.8 Hz), 3.86 - 3.80 (m, 2 H), 3.79 - 3.61 (m, 2 H), 3.04 (brs, 2 H), 2.52 - 2.48 (m, 2 H), 2.29 - 2.18 (m, 2 H), 2.17 - 2.01 (m, 2 H), 1.99 - 1.83 (m, 4 H), 1.67 - 1.53 (m, 2 H), 1.43 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 474 (M+ + H).
769*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.9 Hz), 7.77 - 7.73 (m, 2 H), 7.67 (d, 1 H, J = 8.7 Hz), 7.52 - 7.48 (m, 1 H), 7.28 - 7.26 (m, 1 H), 4.77 - 4.74 (m, 1 H), 4.41 - 4.39 (m, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.83 - 3.77 (m, 2 H), 3.46 - 3.43 (m, 2 H), 3.02 (brs, 2 H), 2.51 - 2.45 (m, 2 H), 2.24 - 2.17 (m, 3 H), 1.91 - 1.87 (m, 1 H), 1.86 - 1.81 (m, 4 H), 1.79 - 1.71 (m, 1 H), 1.70 - 1.66 (m, 1 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 488 (M+ + H).
771*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 3.0 Hz), 7.76 - 7.71 (m, 2 H), 7.67 - 7.65 (m, 1 H), 7.48 - 7.44 (m, 1 H), 7.29 - 7.26 (m, 1 H), 4.12 - 3.90 (m, 3 H), 3.59 - 3.55 (m, 1 H), 3.49 - 3.46 (m, 1 H), 3.38 - 3.26 (m, 1 H), 3.25 - 3.02 (m, 1 H), 2.97 - 2.46 (m, 2 H), 2.21 - 2.28 (m, 2 H), 2.06 - 2.01 (m, 1 H), 1.98 - 1.91 (m, 1 H), 1.89 - 1.82 (m, 4 H), 1.68 - 1.62 (m, 4 H), 1.60 - 1.48 (m, 2 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 488 (M+ + H).
805	1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-y l)benzoyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.41 - 8.40 (m, 1 H), 7.78 - 7.68 (m, 3 H), 7.47 (t, 1 H, J = 7.2 Hz), 7.31 - 7.29 (m, 1 H), 5.75 (d, 2 H, J = 21.6 Hz), 4.77 (d, 2 H, J = 13.2 Hz), 3.93 (d, 2 H, J = 6.0 Hz), 3.73 (d, 1 H, J = 14.0 Hz), 3.13 - 2.93 (m, 4 H), 2.52 - 2.46 (m, 3 H), 2.22 (t, 2 H, J = 11.6 Hz), 2.05 - 1.78 (m, 7 H), 1.59 - 0.90 (m, 8 H); MS (ESI) m/z 515 (M+ + H)
822	(R)-1-(2-fluoro-4-(5-((l-(2-fluoro-2-methylpropyl)pipendm-4-yl)methoxy)pyridine-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.38 (m, 1 H), 7.79 - 7.75 (m, 2 H), 7.68 (d, 1 H, J = 8.8 Hz), 7.50 (t, 1 H, J = 7.7 Hz), 7.29 - 7.26 (m, 2 H), 6.33 (brs, 1 H), 5.58 (brs, 1 H), 5.47 (brs, 1 H), 3.90 (d, 2 H, J = 6.0 Hz), 3.59 (d, 1 H, J = 14.4 Hz), 3.29 - 3.16 (m, 1 H), 3.01 (d, 2 H, J = 11.4 Hz), 2.48 - 2.43 (m, 3 H), 2.18 (t, 2 H, J = 12.0 Hz), 1.85 - 1.60 (m, 8 H), 1.49 - 1.24 (m, 8 H); MS (ESI) m/z 515 (M+ + H).
	(S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)piperidin-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
824	1H NMR (400 MHz, $CDCl_3$) δ 8.39 - 8.35 (m, 1 H), 7.78 - 7.69 (m, 3 H), 7.60 (t, 1 H, J = 12.0 Hz), 7.36 - 7.25 (m, 1 H), 6.34 (brs, 1 H), 5.75 (brs, 1 H), 5.44 (brs, 1 H), 3.89 (d, 2 H, J = 4.0 Hz), 3.58 (d, 1 H, J = 12.8 Hz), 3.23 - 3.20 (m, 1 H), 3.00 (d, 2 H, J = 11.2 Hz), 2.48 - 2.37 (m, 3 H), 2.17 (t, 2 H, J = 11.0 Hz), 1.86 - 1.62 (m, 8 H), 1.59 - 1.29 (m, 8 H); MS (ESI) m/z 515 (M++ H)

Example 60. Compound 1067: (2S,4R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxamide

[0133]



Step 1. (2S,4R)-methyl 1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylate: 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (the product of synthesis step 2 of comparative compound 694; 200 mg, 0.49 mmol), (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (135 mg, 0.74 mmol), EDC (190 mg, 0.99 mmol), HOBt (134 mg, 0.99 mmol) and DIPEA (0.18 mL, 0.99 mmol) were dissolved in DMF (10 mL) at room temperature. The solution was stirred at 80 °C for 14 hours. The reaction mixture was added with water (20 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as red solid (230 mg, 88%).

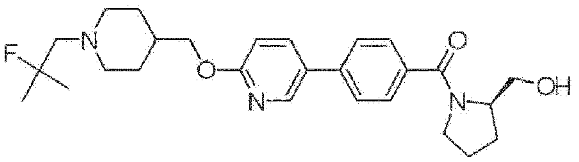
Step 2. (2S,4R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylic acid: (2S,4R)-methyl 1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylate(230 mg, 0.43 mmol) and $LiOH \cdot H_2O$ (36 mg, 0.86 mmol) were dissolved in THF (20 mL) / H_2O (5 mL) at room temperature. The solution was stirred at 60 °C for 14 hours. The reaction mixture was concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 3. Compound 1067: (2S,4R)-1-(2-fluoro-4-(5-((l-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylic acid (290 mg, 0.56 mmol), ammonium chloride (45 mg, 0.84 mmol), EDC (161 mg, 0.84 mmol), HOBt (114 mg, 0.84 mmol) and DIPEA (0.20 mL, 1.12 mmol) were dissolved in DMF (10 mL) at room temperature. The solution was stirred at 80 °C for 16 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as yellow solid (10 mg, 3%).

1H NMR (400 MHz, $CDCl_3$ + MeOD) δ 8.33 (m, 1 H), 7.72 - 7.64 (m, 3 H), 7.54 (m, 1 H), 7.26 (m, 1 H), 7.01 (br, 1 H), 5.99 (br, 1 H), 4.84 (m, 1 H), 4.42 (m, 1 H), 3.89 (m, 2 H), 3.68 (m, 1 H), 3.38 (m, 1 H), 2.99 (m, 2 H), 2.51 - 2.01 (m, 7 H), 1.80 (m, 2 H), 1.63 - 1.25 (m, 9 H); MS (ESI) m/z 517 (M+ + H).

Example 61.Synthesis of comparative compound 652: (R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0134]



Step 1. 5-bromo-2-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 596; 710 mg, 1.91 mmol) was dissolved in CH_2Cl_2 5 mL. 4 M HCl 526 µL was added thereto. And then, the reaction mixture was stirred for 1 hour at room temperature. The obtained reaction mixture was filtered to yield the title compound as white solid (580 mg, 98%).

Step 2. 1-(4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 5-bromo-2-(piperidin-4-ylmethoxy)pyridine hydrochloride (500 mg, 1.63 mmol) and K_2CO_3 (450 mg, 3.25 mmol) were suspended in EtOH 2 mL. Water 2 mL was added thereto, and the mixture was suspended with a little heating. 2,2-dimethyl oxirane (1.17 g, 16.25 mmol) was added thereto. With a microwave radiation, the reaction was performed at 110 °C for 20 minutes. The reaction mixture was added with water, and the resulting precipitate was filtered to yield the title compound as white solid (490 mg, 88%).

Step 3. 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine: 1-(4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (490 mg, 1.43 mmol) was dissolved in CH_2Cl_2 4 mL. Deoxo-Fluor (347 mg, 1.57 mmol) was added thereto. After stirring for 3 hours at room temperature, A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as yellow liquid (470 mg, 95%).

Step 4. methyl 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (270 mg, 0.78 mmol) and 4-(methoxycarbonyl)phenylboronic acid (169 mg, 0.94 mmol) were dissolved in dioxane 2 mL. Water 0.5 mL was added thereto. Pd(dbpf)Cl_2 (26 mg, 0.04 mmol) and CS_2CO_3 (510 mg, 1.56 mmol) were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was filtered through Celite. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) to yield the title compound as white solid (210 mg, 67%).

\Step 5. 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: methyl 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (210 mg, 0.52 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 0.5 mL were poured therein. LiOH (44 mg, 1.05 mmol) was added thereto, and refluxed with heating and stirring for a day. After acidification with 1 N HCl, the resulting precipitate was filtered to yield the title compound as white solid (110 mg, 54%).

Step 6. Comparative compound 652: 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (35 mg, 0.09 mmol), (R)-pyrrolidine-2-ylmethanol (14 mg, 0.14 mmol) and PyBOP (71 mg, 0.14 mmol) were dissolved in DMF 1 mL. DIPEA (23 mg, 0.18 mmol) was added thereto. The reaction was performed at room temperature for 10 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) to yield the title compound as white solid (23 mg, 54%).
1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1 H, J = 2.0 Hz), 7.78 (dd, 1 H, J = 8.6, 2.3 Hz), 7.56 (m, 4 H), 6.80 (d, 1 H, J = 8.6 Hz), 4.94 (s, 1 H), 4.41 (m, 2 H), 4.17 (d, 2 H, J = 6.1 Hz), 3.74 (m, 2 H), 3.55 (m, 2 H), 2.97 (d, 2 H, J = 11.2 Hz), 2.46 (s, 1 H), 2.40 (s, 1 H), 2.15 (m, 3 H), 1.76 (m, 5 H), 1.40 (m, 5 H), 1.23 (s, 3 H); MS (ESI) m/z 470 (M+ + H).

[0135] According to the above-described synthesis process of comparative compound 652, the compounds of Table 40 were synthesized using 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 39.

Table 39. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
653	L-prolinamide	57
654*	(S)-3-hydroxypiperidine	35
1076	(R)-piperidin-2-carboxamide hydrochloride	54
1077*	(R)-pyrrolidine-3-ol	65
1078*	(S)-pyrrolidine-3-ol	61
1079	(S)-piperidin-2-carboxamide hydrochloride	33

Table 40. (* marks comparative compound)

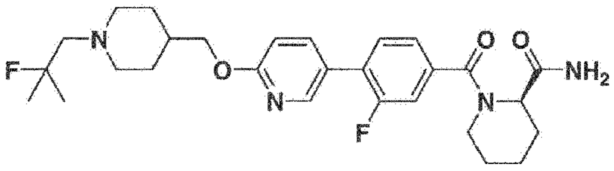
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
653	1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, 1 H, J = 2.1 Hz), 7.81 (dd, 1 H, J = 8.6, 2.4 Hz), 7.60 (m, 4 H), 6.99 (s, 1 H), 6.83 (d, 1 H, J = 8.6 Hz), 5.46 (s, 1 H), 4.83 (m, 1 H), 4.19 (d, 2 H, J = 6.2 Hz), 3.60 (m, 2 H), 3.02 (m, 2 H), 2.48 (m, 3 H), 2.17 (m, 2 H), 2.09 (m, 2 H), 1.86 (m, 4 H), 1.41 (m, 5 H), 1.35 (s, 3 H); MS (ESI) m/z 483 (M+ + H).
654*	(S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.3 Hz), 7.79 (dd, 1 H, J = 8.6, 2.6 Hz), 7.53 (m, 4 H), 6.82 (d, 1 H, J = 8.6 Hz), 4.19 (d, 2 H, J = 8.6 Hz), 4.19 (d, 2 H, J = 6.2 Hz), 3.99 (m, 2 H), 3.76 (m, 1 H), 3.37 (m, 2 H), 3.02 (m, 2 H), 2.51 (s, 2 H), 2.46 (s, 1 H), 1.98 (m, 5 H), 1.66 (m, 2 H), 1.45 (m, 5 H), 1.35 (s, 3 H); MS (ESI) m/z 470 (M+ + H).
1076	(R)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.81 - 7.78 (m, 1 H), 7.59 - 7.52 (m, 4 H), 6.83 (d, 1 H, J = 8.4 Hz), 6.46 (brs, 1 H), 5.39 (brs, 1 H), 5.28 (brs, 1 H), 4.19 (d, 2 H, J = 6.0 Hz), 3.79 (brs, 1 H), 3.12 (t, 1 H, J = 12.4 Hz), 2.98 (d, 2 H, J = 12.6 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.34 (d, 1 H, J = 13.6 Hz), 2.16 (t, 2 H, J = 10.8 Hz), 1.86 - 1.78 (m, 5 H), 1.67 - 1.55 (m, 4 H), 1.48 - 1.42 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 497 (M+ + H).
1077*	(R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.81 - 7.78 (m, 1 H), 7.64 - 7.61 (m, 2 H), 7.59 - 7.54 (m, 2 H), 6.82 (d, 1 H, J = 8.4 Hz), 4.62 (brs, 0.5 H), 4.49 (brs, 0.5 H), 4.19 (d, 2 H, J = 6.4 Hz), 3.86 - 3.76 (m, 2 H), 3.70 - 3.65 (m, 1 H), 3.60 - 3.48 (m, 1 H), 2.98 (d, 2 H, J = 11.6 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.19 - 2.13 (m, 2 H), 2.04 - 2.00 (m, 2 H), 1.81 - 1.78 (m, 4 H), 1.45 - 1.42 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 456 (M+ + H).
1078*	(S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.81 - 7.78 (m, 1 H), 7.64 - 7.61 (m, 2 H), 7.59 - 7.54 (m, 2 H), 6.82 (d, 1 H, J = 8.4 Hz), 4.62 (brs, 0.5 H), 4.49 (brs, 0.5 H), 4.19 (d, 2 H, J = 6.4 Hz), 3.86 - 3.76 (m, 2 H), 3.70 - 3.65 (m, 1 H), 3.60 - 3.48 (m, 1 H), 2.98 (d, 2 H, J = 11.6 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.19 - 2.13 (m, 2 H), 2.04 - 2.00 (m, 2 H), 1.81 - 1.78 (m, 4 H), 1.45 - 1.42 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 456 (M+ + H).
1079	(S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.81 - 7.78 (m, 1 H), 7.59 - 7.52 (m, 4 H), 6.83 (d, 1 H, J = 8.4 Hz), 6.46 (brs, 1 H), 5.39 (brs, 1 H), 5.28 (brs, 1 H), 4.19 (d, 2 H, J = 6.0 Hz), 3.79 (brs, 1 H), 3.12 (t, 1 H, J = 12.4 Hz), 2.98 (d, 2 H, J = 12.6 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.34 (d, 1 H, J = 13.6 Hz), 2.16 (t, 2 H, J = 10.8 Hz), 1.86 - 1.78 (m, 5 H), 1.67 - 1.55 (m, 4

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	H), 1.48 - 1.42 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 497 (M+ + H).

Example 62. Compound 862: (R)-1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide

[0136]



Step 1. methyl 3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 4 of comparative compound 784; 0.5 g, 1.45 mmol) was dissolved in 1,4-dioxane 12 mL and H_2O 3 mL. 2-Fluoro-4-(methoxycarbonyl)phenylboronic acid (0.29 g, 1.45 mmol), Pd(dbpf)Cl_2 (0.05 g, 0.07 mmol) and CS_2CO_3 (0.94 g, 2.90 mmol) were added thereto. With a microwave radiation, the mixture was heated at 120 °C for 45 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added and the resulting precipitate was filtered to yield the title compound as light-yellow solid (0.48 g, 79%).

Step 2. 3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (0.47 g, 1.12 mmol) was dissolved in THF 3 mL, H_2O 1 mL and MeOH 1 mL. $LiOH \cdot H_2O$ (0.24 g, 5.62 mmol) was added thereto, following with increasing the temperature slowly and stirring at 50 °C for a day. After the completion of the reaction, the solvent was distilled under reduced pressure. Excess amount of water was added thereto, and the resulting precipitate was filtered to yield the title compound as white solid (0.45 g, 99%).

Step 3. Compound 862: 3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (0.05 g, 0.12 mmol) and (R)-piperidin-2-carboxamide (0.032 g, 0.25 mmol) were dissolved in DMF 2 mL. DIPEA (0.10 mL, 0.62 mmol), EDCI (0.05 g, 0.25 mmol) and HOBt (0.03 g, 0.25 mmol) were added thereto slowly, following with stirring at 60 °C for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered, and dissolved in CH_2Cl_2 again. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (0.016 g, 25%).

1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 - 7.77 (m, 1 H), 7.49 - 7.45 (m, 1 H), 7.32 - 7.27 (m, 2 H), 6.84 (d, 1 H, J = 8.6 Hz), 6.40 (brs, 1 H), 5.26 (brs, 1 H), 4.20 (d, 2 H, J = 6.4 Hz), 3.78 (d, 1 H, J = 12.8 Hz), 3.19 - 3.17 (m, 1 H), 2.99 (d, 2 H, J = 9.6 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.34 (d, 1 H, J = 13.2 Hz), 2.17 (t, 2 H, J = 11.2 Hz), 2.05 - 1.54 (m, 8 H), 1.48 - 1.24 (m, 8 H)

[0137] According to the above-described synthesis process of compound 862, the compounds of Table 42 were synthesized using 3-fluoro-4-(6-((l-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 41.

Table 41.

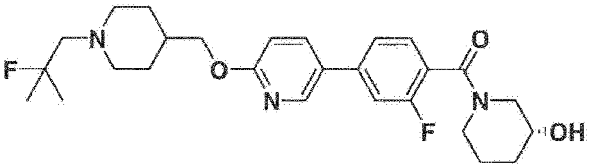
Compound No.	Reactant	Yield (%)
863	(S)-piperidin-2-carboxamide	53
864	piperidin-4-carboxamide	37

Table 42.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
863	(S)-1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.32 (brs, 1 H), 7.83 - 7.76 (m, 1 H), 7.52 - 7.43 (m, 1 H), 7.28 - 7.27 (m, 1 H), 6.83 - 6.81 (m, 2 H), 6.48 (brs, 1 H), 6.78 (brs, 1 H), 5.32 (brs, 1 H), 4.19 (d, 2 H, J = 6.0 Hz), 2.98 (d, 2 H, J = 11.4 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.37 - 2.26 (m, 1 H), 2.17 (t, 2 H, J = 11.0 Hz), 1.80 - 1.78 (m, 8 H), 1.45 - 1.25 (m, 8 H)
864	1-(3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.77 (d, 1 H, J = 7.2 Hz), 7.44 (t, 1 H, J = 7.8 Hz), 7.27 - 7.20 (m, 2 H), 6.82 (d, 1 H, J = 8.8 Hz), 5.74 (d, 2 H, J = 22.4 Hz), 4.63 (brs, 1 H), 4.18 (d, 2 H, J = 6.0 Hz), 3.87 (brs, 1 H), 3.17 - 2.96 (m, 4 H), 2.47 - 2.41 (m, 3 H), 2.17 (t, 2 H, J = 11.0 Hz), 2.02 - 1.77 (m, 7 H), 1.47 - 1.25 (m, 8 H)

Example 63. Comparative compound 784: (R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

[0138]



Step 1. t-butyl 4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-carboxylate: t-Butyl 4-(hydroxymethyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 431; 7.0 g, 32.51 mmol) was dissolved in DMF. 2,5-bromopyridine (8.47 g, 35.77 mmol) and NaH

(1.23 g, 48.77 mmol) were added thereto slowly, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g ISCO silica gel cartridge, 0 - 20 % EtOAc/hexane) to yield the title compound as white solid (11.8 g, 98%).

Step 2. 5-bromo-2-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-carboxylate (22.0 g, 59.26 mmol) was dissolved in 1,4-dioxane 300 mL. 4 M HCl in 1,4-dioxane (74.0 mL, 296.28 mmol) was added thereto. After the solvent was distilled out completely, the residue was washed with ether to yield the title compound as white solid (17.0 g, 93%).

Step 3. 1-(4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 5-bromo-2-(piperidin-4-ylmethoxy)pyridine hydrochloride (4.5 g, 14.63 mmol) was dissolved in EtOH 50 mL and H_2O 50 mL. 1,2-epoxy-2-methylpropane (10.55 g, 146.29 mmol) and K_2CO_3 (10.11 g, 73.15 mmol) were added slowly thereto. The mixture was stirred in a microwave at 110 °C for 20 minutes. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure, following with washing with H_2O three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (5.00 g, 99%).

Step 4. 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine: 1-(4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (10.20 g, 29.71 mmol) was dissolved in CH_2Cl_2 200 mL. DAST (4.32 mL, 32.69 mmol) was added dropwise slowly thereto at 0 °C, following with stirring at 0 °C for 2 hours. After the completion of the reaction, the reaction mixture was washed with a saturated $NaHCO_3$ aqueous solution several times. The CH_2CL_2 layer was distilled under reduced pressure. The concentrate was purified by column chromatography (4 g ISCO silica gel cartridge, 0 - 10 % EtOAc/hexane) to yield the title compound as white solid (5.80 g, 57%).

Step 5. ethyl 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (0.5 g, 1.45 mmol) was dissolved in 1,4-dioxane 12 mL and H_2O 3 mL. 4-(Ethoxycarbonyl)-3-fluorophenylboronic acid (0.31 g, 1.45 mmol), $Pd(dbpf)Cl_2$ (0.05 g, 0.07 mmol) and CS_2CO_3 (0.94 g, 2.90 mmol) were added thereto. The mixture was stirred in a microwave at 110 °C for 45 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. MeOH was added thereto. The resulting precipitate was filtered to yield the title compound as transparent oil (0.17 g, 27%).

Step 6. 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Ethyl 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (0.17 g, 0.39 mmol) was dissolved in THF (3 mL) / H_2O (1 mL) / MeOH 1 mL). LiOR·H_2O (0.08 g, 1.97

mmol) was added thereto, following with increasing the temperature slowly, and then refluxing with stirring at 80 °C for 30 minutes. After the completion of the reaction, the solvent was distilled under reduced pressure. Excess amount of water was added thereto, and the resulting precipitate was filtered to yield the title compound as yellow solid (0.12 g, 76%).

Step 7. Comparative compound 784: 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (0.04 g, 0.10 mmol) and (R)-piperidin-3-ol(0.02 g, 0.19 mmol) were dissolved in DMF 2 mL. DIPEA (0.06 g, 0.47 mmol), EDCI (0.04 g, 0.19 mmol) and HOBt (0.03 g, 0.19 mmol) were added thereto slowly, following with stirring at 60 °C for 3 hours. After the completion of the reaction, excess amount of water was added to the reaction mixture. The resulting precipitate was filtered, and dissolved in CH_2Cl_2 again. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 0 - 20 % MeOH/CH_2Cl_2) to yield the title compound as brown solid (0.02 g, 47%).
1H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.78 (d, 1 H, J = 2.0 Hz), 7.49 - 7.24 (m, 4 H), 6.83 (d, 1 H, J = 8.6 Hz), 4.20 (d, 2 H, J = 6.0 Hz), 4.10 - 3.11 (m, 5 H), 3.01 (brs, 2 H), 2.49 - 2.44 (m, 2 H), 2.18 - 1.61 (m, 9 H), 1.41 - 1.26 (m, 8 H); MS (ESI) m/z 488 (M+ + H).

[0139] According to the above-described synthesis process of comparative compound 784, the compounds of Table 44 were synthesized using 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 43.

Table 43. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
785*	(R)-pyrrolidine-3-ol	40
786*	(S)-pyrrolidine-3-ol	13
787*	(S)-pyrrolidine-2-ylmethanol	29
854	(R)-piperidin-2-carboxamide	49
855	(S)-piperidin-2-carboxamide	44
856	piperidin-4-carboxamide	27
657*	(R)-pyrrolidine-2-ylmethanol	58
658*	L-prolinamide	48
659*	(S)-3-hydroxypiperidine hydrochloride	60

Table 44. (* marks comparative compound)

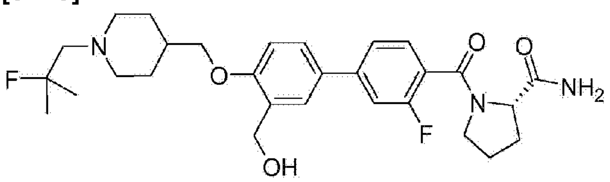
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
785*	(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.34 (t, 1 H, J = 2.6 Hz), 7.76 - 7.73 (m, 1 H), 7.50 - 7.45 (m, 1 H), 7.35 - 7.21 (m, 2 H), 6.81 (d, 1 H, J = 8.6 Hz), 4.57 (brs, 0.5 H), 4.45 (brs, 0.5 H), 4.18 (d, 2 H, J = 6.0 Hz), 3.82 - 3.32 (m, 5 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.19 - 1.97 (m, 4 H), 1.80 - 1.77 (m, 3 H), 1.48 - 1.25 (m, 8 H); MS (ESI) m/z 474 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
786*	(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 7.77 (d, 1 H, J = 8.6 Hz), 7.53 - 7.48 (m, 1 H), 7.37 - 7.25 (m, 1 H), 7.23 - 7.14 (m, 1 H), 6.83 (d, 1 H, J = 8.4 Hz), 4.62 (brs, 0.5 H), 4.49 (brs, 0.5 H), 4.20 (d, 2 H, J = 6.1 Hz), 3.85 - 3.57 (m, 4 H), 3.48 - 3.34 (m, 1 H), 3.04 (d, 2 H, J = 9.2 Hz), 2.52 (s, 1 H), 2.47 (s, 1 H), 2.35 - 1.80 (m, 7 H), 1.50 - 1.18 (m, 6 H); MS (ESI) m/z 474 (M+ + H).
787*	(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 7.76 (dt, 1 H, J = , 2.1 Hz), 7.49 (t, 1 H, J = 6.8 Hz), 7.36 (d, 1 H, J = 4.4 Hz), 7.26 (d, 1 H, J = 12.0 Hz), 6.82 (dd, 1 H, J = 8.8, 1.2 Hz), 4.39 - 4.37 (m, 1 H), 4.19 - 4.17 (m, 2 H), 3.82 - 3.73 (m, 2 H), 3.45 (t, 2 H, J = 6.4 Hz), 2.98 (d, 2 H, J = 10.8 Hz), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.22 - 2.13 (m, 3 H), 1.91 - 1.67 (m, 6 H), 1.48 - 1.33 (m, 8 H); MS (ESI) m/z 488 (M+ + H).
854	(R)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropy1)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 - 8.36 (m, 1 H), 7.79 - 7.76 (m, 1 H), 7.51 (t, 1 H, J = 7.6 Hz), 7.43 - 7.39 (m, 1 H), 6.84 (d, 1 H, J = 8.8 Hz), 6.31 (brs, 1 H), 5.65 (brs, 1 H), 5.44 (brs, 1 H), 4.20 (d, 2 H, J = 6.1 Hz), 3.60 (d, 1 H, J = 12.8 Hz), 3.23 - 3.2 1 (m, 1 H), 2.99 (d, 2 H, J = 11.2 Hz), 2.47 - 2.42 (m, 3 H), 2.17 (t, 2 H, J = 11.2 Hz), 1.80 - 1.63 (m, 8 H), 1.48 - 1.25 (m, 8 H); MS (ESI) m/z 515 (M+ + H).
855	(S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 - 8.36 (m, 1 H), 7.78 - 7.75 (m, 1 H), 7.51 (t, 1 H, J = 7.4 Hz), 7.41 - 7.39 (m, 1 H), 7.28 - 7.25 (m, 1 H), 6.83 (d, 1 H, J = 8.0 Hz), 6.33 (brs, 1 H), 5.74 (brs, 1 H), 5.48 (brs, 1 H), 4.19 (d, 2 H, J = 7.6 Hz), 3.60 (d, 1 H, J = 12.8 Hz), 3.32 - 3.21 (m, 1 H), 2.99 (d, 2 H, J = 11.2 Hz), 2.47 - 2.41 (m, 3 H), 2.17 (t, 2 H, J = 11.2 Hz), 1.80 - 1.62 (m, 8 H), 1.48 - 1.25 (m, 6 H); MS (ESI) m/z 515 (M+ + H).
856	1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1 H, J = 4.0 Hz), 7.77 (dd, 1 H, J = 8.5, 2.4 Hz), 7.45 (t, 1 H, J = 7.4 Hz), 7.37 - 7.23 (m, 2 H), 6.83 (d, 1 H, J = 8.4 Hz), 5.61 (d, 2 H, J = 12.8 Hz), 4.74 (d, 1 H, J = 13.2 Hz), 4.19 (d, 2 H, J = 6.2 Hz), 3.72 (d, 1 H, J = 13.9 Hz), 3.13 - 2.92 (m, 4 H), 2.48 - 2.42 (m, 3 H), 2.18 (t, 2 H, J = 11.2 Hz), 2.04 - 1.78 (m, 7 H), 1.48 - 0.88 (m, 8 H); MS (ESI) m/z 515 (M+ + H).
	(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
657*	1H NMR (400 MHz, CDCl$_3$) δ 8.35 (d, 1 H, J = 2.4 Hz), 7.76 (dd, 1 H, J = 7.4, 1.3 Hz), 7.50 (t, 1H, J = 7.5 Hz), 7.36 (dd, 1 H, J = 8.0, 1.5 Hz), 7.26 (dd, 1 H, J = 11.1, 1.6 Hz), 6.82 (d, 1 H, J = 8.6 Hz), 4.38 (m, 1 H), 4.18 (d, 2 H, J = 6.1 Hz), 3.76 (m, 2 H), 3.45 (m, 2 H), 2.97 (m, 2 H), 2.46 (s, 1 H), 2.41 (s, 1 H), 2.13 (m, 3 H), 1.87 (m, 1 H), 1.79 (m, 5 H), 1.44 (m, 5 H), 1.41 (s, 3 H); MS (ESI) m/z 488 (M + H).
658*	(S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 8.36 (d, 1 H, J = 2.4 Hz), 7.77 (dd, 1 H, J = 8.6, 1.3 Hz), 7.50 (t, 1H, J = 7.5 Hz), 7.38 (dd, 1 H, J = 7.9, 1.5 Hz), 7.28 (dd, 1 H, J = 10.8, 1.4 Hz), 6.92 (s, 1 H), 6.83 (d, 1 H, J = 8.6 Hz), 5.62 (s, 1 H), 4.80 (m, 1 H), 4.19 (d, 2 H, J = 6.2 Hz), 3.54 (m, 1 H), 3.43 (s, 1 H), 2.99 (m, 2 H), 2.45 (m, 2 H), 2.09 (m, 4 H), 1.93 (m, 1 H), 1.84 (m, 4 H), 1.46 (m, 5 H), 1.39 (s, 3 H); MS (ESI) m/z 501 (M + H).
659*	(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 8.33 (t, 1 H, J = 2.7 Hz), 7.74 (m, 1 H), 7.43 (t, 1H, J = 7.4 Hz), 7.32 (m, 1 H), 7.21 (m, 1 H), 6.80 (d, 1 H, J = 8.6 Hz), 4.17 (d, 2 H, J = 6.2 Hz), 3.62 (m, 1 H), 3.37 (m, 2 H), 3.13 (m, 2 H), 2.98 (m, 2 H), 2.78 (s, 1 H), 2.45 (s, 1 H), 2.40 (s, 1 H), 2.15 (t, 2 H, J = 11.1 Hz), 1.86 (m, 2 H), 1.76 (m, 4 H), 1.58 (m, 1 H), 1.40 (m, 5 H), 1.32 (s, 3 H); MS (ESI) m/z 488 (M + H).

Example 64. Comparative Compound 946 : (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0140]



Step 1. t-butyl 4-((4-bromo-2-formylphenoxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 2 of comparative compound 431; 1.00 g, 3.41 mmol) was dissolved in DMF (80 mL). K_2CO_3 (1.67 g, 5.11 mmol) was added thereto, and stirred for 5 minutes. 5-bromo-2-hydroxybenzaldehyde (685 mg, 3.41 mmol)was added thereto, following with stirring at 80 °C for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (840 mg, 61%).

Step 2. 5-bromo-2-(piperidin-4-ylmethoxy)benzaldehyde hydrochloride: t-butyl 4-((4-bromo-2-formylphenoxy)methyl)piperidin-1-carboxylate (840 mg, 2.11 mmol) was dissolved in CH_2Cl_2 (20 mL). 4 M HCl in 1,4-dioxane (1.06 mL, 4.22 mmol) was added thereto, following with stirring for 1 hour. The resulting precipitate was filtered to yield the title compound as white solid (500 mg, 70%).

Step 3. 5-bromo-2-((1-2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzaldehyde: 5-bromo-2-(piperidin-4-ylmethoxy)benzaldehyde hydrochloride(500 mg, 1.68 mmol) was dissolved in EtOH (5 mL) and H_2O (5 mL). 2,2-Dimethyloxirane (1.49 mL, 16.77 mmol) and K_2CO_3 (116 mg, 0.84 mmol) were added thereto slowly. With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material, which is the title compound as white solid (620 mg, 99%), was used without further purification.

Step 4. 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzaldehyde: 5-bromo-2-((1-2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)benzaldehyde (620 mg, 1.67 mmol) was dissolved in CH_2Cl_2 (10 mL). At 0 °C, DAST (221 μL, 1.67 mmol) was added slowly thereto. After stirring for 1 hour at room temperature, The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 40 % ~ 60 %) to yield the title compound as white solid (310 mg, 49%).

Step 5. (5-bromo-2-((l-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)methanol: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzaldehyde (310 mg, 0.83 mmol) was dissolved in THF (10 mL). At room temperature, $NaBH_4$ (95 mg, 2.50 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 50 %) to yield the title compound as white solid (200 mg, 64%).

Step 6. ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenyl-4-carboxylate: (5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)methanol (200 mg, 0.534 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (125 mg, 0.59 mmol), $Pd(dppf)Cl_2$ (44 mg, 0.05 mmol) and Cs_2CO_3 (348 mg, 1.07 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 40 % ~ 60 %) to yield the title compound as white solid (146 mg, 59%).

Step 7. 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenyl-4-carboxylic acid: Ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3' -(hydroxymethyl)biphenyl-4-carboxylate (146 mg, 0.32 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (66 mg, 1.58 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered to yield the title compound as white solid (120 mg, 87%).

Step 8. Comparative Compound 946: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), (S)-pyrrolidine-2-carboxamide (16 mg, 0.14 mmol), EDC (27 mg, 0.14 mmol), HOBt (19 mg, 0.14 mmol) and DIPEA (25 µL, 0.14 mmol) were dissolved in CH_2Cl_2 (1 mL), following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (21 mg, 42%).
1H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.55 (m, 1 H), 7.49 - 7.41 (m, 3 H), 7.33 - 7.27 (m, 1 H), 6.96 - 6.94 (m, 1 H), 5.50 (brs, 1 H), 5.31 - 4.81 (m, 3 H), 3.93 (d, 2 H, J = 5.4 Hz), 3.57 - 3.40 (m, 2 H), 3.03 (brs, 1 H), 2.51 - 2.43 (m, 3 H), 2.23 - 2.21 (m, 2 H), 2.16 - 2.03 (m, 3 H), 1.94 - 1.80 (m, 4 H), 1.69 (brs, 2 H), 1.43 (s, 3 H), 1.38 (s, 3 H), 1.32 - 1.28 (m, 2 H); MS (ESI) m/z 530 (M+ + H).

[0141] According to the above-described synthesis process of comparative compound 946, the compounds of Table 46 were synthesized using 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenyl-4-carboxylic acid and the reactant of Table 45.

Table 45. (* marks comparative compound)

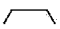
Compound No.	Reactant	Yield (%)
947*	(S)-pyrrolidine-3-ol	78

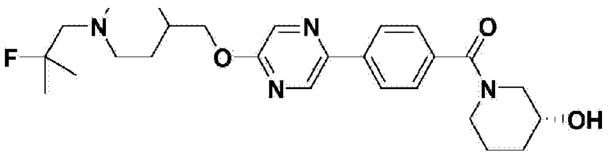
Table 46. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
947*	(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5'-(hydroxymethyl)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1 H), 7.54 - 7.44 (m, 2 H), 7.38 (d, 1 H, J = 8.0 Hz), 7.30 - 7.26 (m, 1 H), 6.93 (d, 1 H, J = 8.6 Hz), 4.77 (d, 2 H, J = 6.0 Hz), 4.61 (brs, 0.5 H), 4.48 (brs, 0.5 H), 3.93 (d, 2 H, J = 5.4 Hz), 3.85 - 3.78 (m, 2 H), 3.73 - 3.57 (m, 2 H), 3.46 (brs, 0.5 Hz), 3.33 (brs, 0.5 H), 3.08 (brs, 2 H), 2.50 (brs, 2 H), 2.18 - 2.00 (m, 4 H), 1.99 - 1.81 (m, 4 H), 1.45 (s, 3 H), 1.40 (s, 3 H), 1.29 - 1.23 (m, 2 H); MS (ESI) m/z 503 (M+ + H).

Example 65. Comparative compound 948: (R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

[0142]





Step 1. methyl 4-(5 -((1 -(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: To 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-iodopyrazine (the product of synthesis step 4 of comparative compound 944; 0.35 g, 0.89 mmol), 4-(methoxycarbonyl) phenylboronic acid (0.19 g, 1.06 mmol), Pd(dbpf)Cl_2 (0.03 g, 0.04 mmol) and Cs_2CO_3 (0.58 g, 1.78 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.21 g, 59%).

Step 2. 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid: Methyl 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (0.21 g, 0.52 mmol) and $LiOH \cdot H_2O$ (0.11 g, 2.62 mmol) were dissolved in THF (2 mL) / H_2O /MeOH (3 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.16 g, 78%).

Step 3. Comparative compound 948: 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (0.04 g, 0.10 mmol), EDCI (0.04 g, 0.20 mmol), HOBt (0.02 g, 0.20 mmol) and DIPEA (0.09 mL, 0.51 mmol) were dissolved in DMF (2 ml). At room temperature, (R)-piperidin-3-ol (0.02 g, 0.20 mmol) was added thereto, following with stirring at 60 °C for 12 hours. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as yellow solid (0.02 g, 49%).

1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 8.26 (s, 1 H), 7.93 (d, 2 H, J = 8.4 Hz), 7.51 (d, 2 H, J = 8.0 Hz), 4.20 (d, 2 H, J = 6.1 Hz), 3.98 - 3.25 (m, 5 H), 2.97 (d, 2 H, J = 11.2 Hz), 2.45 (s, 1 H), 2.39 (s, 1 H), 2.18 - 1.67 (m, 9 H), 1.44 - 1.32 (m, 8 H); MS (ESI) m/z 471 (M+ + H). According to the above-described synthesis process of comparative compound 948, the compounds of Table 48 were synthesized using 4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 47.

Table 47. (* marks comparative compound)

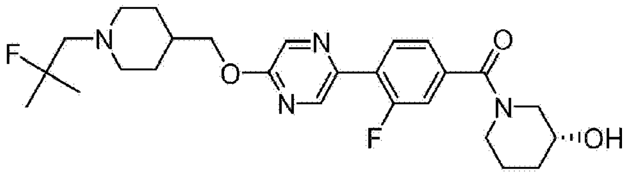
Compound No.	Reactant	Yield (%)
949*	(S)-pyrrolidine-3-ol	45
950*	(S)-pyrrolidine-2-carboxamide	40
951*	(S)-piperidin-3-ol	52
1080*	(R)-piperidin-2-carboxamide hydrochloride	62
1081*	(S)-piperidin-2-carboxamide hydrochloride	70

Table 48. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
949*	(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1 H), 8.26 (s, 1 H), 7.94 - 7.92 (m, 2 H), 7.64 - 7.59 (m, 2 H), 4.53 (d, 1 H, J = 52.8 Hz), 4.20 (d, 2 H, J = 6.0 Hz), 3.82 - 3.43 (m, 5 H), 2.97 (d, 2 H, J = 11.2 Hz), 2.45 (s, 1 H), 2.39 (s, 1 H), 2.15 (t, 2 H, J = 11.6 Hz), 2.10 - 1.53 (m, 5 H), 1.44 - 1.23 (m, 8 H); MS (ESI) m/z 457 (M+ + H).
950*	(S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 8.50 (s, 1 H), 8.27 (s, 1 H), 7.96 (d, 2 H, J = 8.2 Hz), 7.62 (d, 2 H, J = 8.4 Hz), 6.96 (brs, 1 H), 5.47 (brs, 1 H), 4.81 - 4.80 (m, 1 H), 4.20 (d, 2 H, J = 3.2 Hz), 3.61 - 3.53 (m, 2 H), 2.97 (d, 2 H, J = 11.6 Hz), 2.45 - 2.39 (m, 3 H), 2.17 - 1.66 (m, 6 H), 1.44 - 1.32 (m, 8 H); MS (ESI) m/z 484 (M+ + H).
951*	(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 8.48 (s, 1 H), 8.26 (s, 1 H), 7.93 (d, 2 H, J = 8.0 Hz), 7.51 (d, 2 H, J = 8.0 Hz), 4.20 (d, 2 H, J = 6.0 Hz), 3.98 - 3.22 (m, 5 H), 2.97 (d, 2 H, J = 11.6 Hz), 2.45 (s, 1H), 2.39 (s, 1 H), 2.17 (t, 2 H, J = 6.0 Hz), 1.78 - 1.67 (m, 7 H), 1.44 - 1.32 (m, 8 H); MS (ESI) m/z 471 (M+ + H).
1080*	(R)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 8.51 (s, 1 H), 8.28 (s, 1 H), 7.89 - 8.00 (m, 2 H), 7.51 - 7.56 (m, 2 H), 6.49 (s, 1 H), 5.56 (s, 1 H), 5.27 - 5.29 (m, 1 H), 4.21 (d, 2 H, J = 6.2 Hz), 3.74 - 3.77 (m, 1H), 3.08 - 3.14 (m, 1 H), 2.97 - 2.99 (m, 2 H), 2.41 - 2.46 (m, 2 H), 2.31 - 2.34 (m, 1 H), 2.13 - 2.19 (m, 2 H), 1.59 - 1.83 (m, 5 H), 1.53 - 1.56 (m, 3 H), 1.42 - 1.48 (m, 2 H), 1.38 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 498.3 (M+ + H).
1081*	(S)-1-(4-(5-((1-(2- fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, CDCl$_3$) δ 8.51 (s, 1 H), 8.28 (s, 1 H), 7.89 - 8.01 (m, 2 H), 7.54 - 7.56 (m, 2 H), 6.48 (s, 1 H), 5.50 (s, 1 H), 5.27 - 5.28 (m, 1 H), 4.21 (d, 2 H, J = 6.2 Hz), 3.74 - 3.78 (m, 1 H), 3.07 - 3.14 (m, 1 H), 2.97 - 2.99 (m, 2 H), 2.41 - 2.46 (m, 2 H), 2.31 - 2.35 (m, 1 H), 2.13 - 2.18 (m, 2 H), 1.76 - 1.87 (m, 5 H), 1.53 - 1.69 (m, 3 H), 1.43 - 1.48 (m, 2 H), 1.38 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 498.3 (M+ + H).

Example 66. Comparative compound 982: (R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

[0143]



Step 1. methyl 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: To 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-iodopyrazine (the product of synthesis step 4 of comparative compound 944; 0.50 g, 1.27 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (0.29 g, 1.39 mmol), Pd(dppf)Cl_2 (0.05 g, 0.06 mmol) and Cs_2CO_3 (0.82 g, 2.54 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc.. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.24 g, 45%).

Step 2. 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid: Methyl 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (0.24 g, 0.57 mmol) and $LiOH \cdot H_2O$ (0.12 g, 2.86 mmol) were dissolved in THF / MeOH (16 mL) / H_2O (4 mL) at room temperature. The solution was stirred at the same temperature for 2 hours, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.20 g, 86%).

Step 3. Comparative compound 982: 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) pyrazine-2-yl)benzoic acid (0.04 g, 0.09 mmol), (R)-piperidin-3-ol (0.01 g, 0.11 mmol), HOBt (0.02 g, 0.19 mmol), EDC (0.03 g, 0.19 mmol) and DIPEA (0.03 mL, 0.19 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.02 g, 41%).
1H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1 H), 8.32 (s, 1 H), 8.00 (t, 1 H, J = 7.8 Hz), 7.26 - 7.32 (m, 2 H), 4.23 (d, 2 H, J = 6.2 Hz), 3.27 - 3.95 (m, 5 H), 2.98 - 3.01 (m, 2 H), 2.42 - 2.48 (m, 2 H), 2.14-2.22 (m, 3 H), 1.77 - 2.05 (m, 4 H), 1.43 - 1.67 (m, 5 H), 1.40 (s, 3 H), 1.34 (s, 3 H); MS (ESI) m/z 489.2 (M+ + H).

[0144] According to the above-described synthesis process of comparative compound 982, the compounds of Table 50 were synthesized using 3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 49.
Table 49. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
983*	(S)-piperidin-3-ol hydrochloride	37
984*	(S)-pyrrolidine-3-ol	47
985*	(R)-pyrrolidine-2-ylmethanol	35
1072*	(S)-pyrrolidine-2-carboxamide	57
1073*	(R)-piperidin-2-carboxamide hydrochloride	27

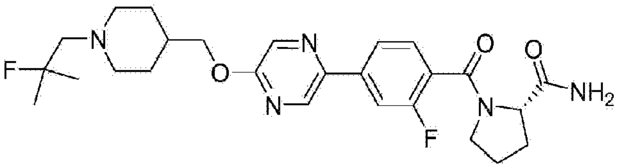
Table 50. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
983*	(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 8.33 (s, 1 H), 8.01 (t, 1 H, J = 7.8 Hz), 7.22 - 7.34 (m, 2 H), 4.24 (d, 2 H, J = 6.3 Hz), 3.35 - 3.96 (m, 5 H), 2.97 - 3.01 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.15 - 2.20 (m, 2 H), 1.68 - 2.05 (m, 6 H), 1.49 - 1.56 (m, 2 H), 1.43 - 1.47 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 489.2 (M+ + H).
984*	(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1 H), 8.33 (s, 1 H), 8.03 (t, 1 H, J = 7.7 Hz), 7.36 - 7.53 (m, 2 H), 4.51 - 4.63 (m, 1 H), 4.24 (d, 2 H, J = 6.2 Hz), 3.75 - 3.87 (m, 2 H), 3.46 - 3.71 (m, 2 H), 2.99 - 3.01 (m, 2 H), 2.43 - 2.55 (m, 2 H), 1.93 - 2.21 (m, 4 H), 1.60 - 1.82 (m, 4 H), 1.44 - 1.47 (m, 2 H), 1.41 (s, 3 H), 1.36 (s, 3 H); MS (ESI) m/z 475.2 (M+ + H).
985*	(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1 H), 8.33 (s, 1 H), 8.04 (t, 1 H, J = 7.9 Hz), 7.42 (d, 1 H, J = 8.1 Hz), 7.36 (d, 1 H, J = 11.4 Hz), 5.31 (s, 1 H), 4.40 - 4.45 (m, 1 H), 4.24 (d, 2 H, J = 6.3 Hz), 3.74 - 3.85 (m, 2 H), 3.49 - 3.60 (m, 2 H), 2.98 - 3.01 (m, 2 H), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.14 - 2.23 (m, 3 H), 1.64 - 1.93 (m, 6 H), 1.43 - 1.50 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 489.2 (M+ + H).
1072*	(S)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1 H), 8.30 (s, 1 H), 8.02 (t, 1 H, J = 7.8 Hz), 7.34 - 7.43 (m, 2 H), 6.87 (s, 1 H), 5.51 (s, 1 H), 4.77 (dd, 1 H, J = 7.4, 5.0 Hz), 4.21 (d, 2 H, J = 6.4 Hz), 3.51-3.64 (m, 2 H), 2.97 - 3.00 (m, 2 H), 2.41 - 2.47 (m, 2 H), 2.02 - 2.19 (m, 5 H), 1.75 - 1.90 (m, 4 H), 1.42 - 1.48 (m, 2 H), 1.37 (s, 3 H), 1.32 (s, 3 H); MS (ESI) m/z 502.2 (M+ + H).
1073*	(R)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1 H), 8.30 (s, 1 H), 8.03 (t, 1 H, J = 8.0 Hz), 7.26 - 7.33 (m, 2 H), 6.36 (s, 1 H), 5.41 (s, 1 H), 5.24 - 5.28 (m, 1 H),4.21 (d, 2 H, J = 6.0 Hz), 3.71 - 3.74 (m, 1 H), 3.09 -

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	3.16 (m, 1 H), 2.99 - 3.01 (m, 2 H), 2.43 - 2.48 (m, 2 H), 2.29 - 2.32 (m, 1 H), 2.14 - 2.20 (m, 2 H), 1.43 - 1.83 (m, 10 H), 1.38 (s, 3 H), 1.33 (s, 3 H); MS (ESI) m/z 516.2 (M+ + H).

Example 67. Comparative Compound 944 : (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0145]



Step 1. t-butyl 4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 431; 2.70 g, 12.54 mmol), 2-bromo-5-iodopyrazine (3.57 g, 12.54 mmol) and NaH (0.36 g, 15.05 mmol) were dissolved in 70 °C for THF (30 mL), following with stirring at the same temperature for 6 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (4.04 g, 76%).

Step 2. 2-iodo-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride: t-butyl 4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-carboxylate (4.00 g, 9.54 mmol) was dissolved in CH_2Cl_2 (30 mL). At room temperature, 4 M HCl solution in 1,4-dioxane (11.92 mL, 47.70 mmol) was added thereto, following with stirring at the same temperature for 2 hours. The reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (3.20 g, 94%).

Step 3. 1-(4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: To 2-iodo-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (1.20 g, 3.37 mmol), 2,2-dimethyl oxirane (3.00 mL, 33.74 mmol) and K_2CO_3 (2.33 g, 16.87 mmol), EtOH (8 mL) / H_2O (2 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (1.30 g, 98%).

Step 4. 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-iodopyrazine: 1-(4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (1.30 g, 3.32 mmol) and DAST (0.53 mL, 3.98 mmol) were dissolved in CH_2Cl_2 (20 mL) at 0 °C, following with stirring at room temperature for 2 hours. The reaction mixture was added with water, and extracted with EtOAc.

The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (0.81 g, 62%).

Step 5. ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: To 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-iodopyrazine (250 mg, 0.64 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (162 mg, 0.76 mmol), Pd(dppf)Cl_2 (26 mg, 0.03 mmol) and Cs_2CO_3 (414 mg, 1.27 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 0 % ~ 15 %) to yield the title compound as white solid (162 mg, 58%).

Step 6. 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid: Ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (158 mg, 0.36 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). At room temperature, $LiOH{\cdot}H_2O$ (77 mg, 1.82 mmol) was added thereto, following with stirring for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (120 mg, 81%).

Step 7. Comparative Compound 944: 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (30 mg, 0.07 mmol), EDC (28 mg, 0.15 mmol) and HOBt (20 mg, 0.15 mmol) was added thereto, DIPEA (26 μL, 0.15 mmol) were dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (17 mg, 0.15 mmol) was added thereto, following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (20 mg, 53%).
1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 8.29 (s, 1 H), 7.78 - 7.51 (m, 2 H), 7.53 (t, 1 H, J = 7.5 Hz), 6.91 (s, 1 H), 5.54 (s, 1 H), 4.84 - 4.81 (m, 1 H), 4.33 (d, 2 H, J = 5.6 Hz), 3.85 - 3.81 (m, 2 H), 3.56 - 3.38 (m, 2 H), 3.26 - 3.21 (m, 2 H), 2.92 - 2.85 (m, 2 H), 2.51 - 2.46 (m, 1 H), 2.27 - 2.26 (m, 2 H), 2.18 - 2.06 (m, 6 H), 1.66 (s, 3 H), 1.60 (s, 3 H); MS (ESI) m/z 502 (M+ + H).

[0146] According to the above-described synthesis process of comparative compound 944, the compounds of Table 52 were synthesized using 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 51.

Table 51. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
945*	(R)-piperidin-3-ol hydrochloride	49

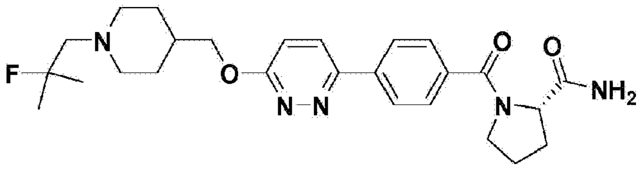
Compound No.	Reactant	Yield (%)
986*	(S)-piperidin-2-ol hydrochloride	54
987*	(S)-pyrrolidine-3-ol	53
988*	(R)-pyrrolidine-2-ylmethanol	54

Table 52. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
945*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 8.28 (s, 1 H), 7.75 - 7.69 (m, 2 H), 7.49 (t, 1 H, J = 7.2 Hz), 4.24 (d, 2 H, J = 6.2 Hz), 4.11 - 4.08 (m, 1 H), 3.94 (brs, 1 H), 3.58 - 3.55 (m, 1 H), 3.46 - 3.19 (m, 1 H), 3.14 - 2.96 (m, 2 H), 2.64 - 2.50 (m, 2 H), 2.18 (brs, 2 H), 2.01 - 1.81 (m, 6 H), 1.72 - 1.50 (m, 5 H), 1.43 (s, 3 H), 1.38 (s, 3 H); MS (ESI) m/z 489 (M+ + H).
986*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 8.29 (s, 1 H), 7.70 - 7.76 (m, 2 H), 7.48 - 7.53 (m, 1 H), 4.23 (d, 2 H, J = 6.2 Hz), 3.74 - 4.12 (m, 2 H), 3.25 - 3.58 (m, 3 H), 3.10 - 3.15 (m, 2 H), 2.98 - 3.01 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.18 (t, 2 H, J = 10.9 Hz), 1.62 - 2.03 (m, 6 H), 1.43 - 1.56 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 489.2 (M+ + H).
987*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanol
	1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 8.29 (s, 1 H), 7.70 - 7.76 (m, 2 H), 7.52 - 7.57 (m, 1 H), 4.51 - 4.63 (m, 1 H), 4.23 (d, 2 H, J = 6.2 Hz), 3.42 - 3.86 (m, 3 H), 3.33 - 3.36 (m, 1 H), 2.98 - 3.01 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.11 - 2.20 (m, 3 H), 2.01 - 2.07 (m, 3 H), 1.78 - 1.85 (m, 2 H), 1.43 - 1.63 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 475.2 (M+ + H).
988*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 8.28 (s, 1 H), 7.71 - 7.74 (m, 2 H), 7.53 (t, 1 H, J = 7.5 Hz), 4.39 - 4.41 (m, 1 H), 4.22 (d, 2 H, J = 6.2 Hz), 3.75 - 3.85 (m, 2 H), 3.43 - 3.46 (m, 2 H), 3.00 - 2.98 (m, 2 H), 2.48 (s, 1 H), 2.43 (s, 1 H), 2.14 - 2.24 (m, 3 H), 1.67 - 1.92 (m, 7 H), 1.40 (s, 3 H), 1.34 (s, 3 H), 1.21 - 1.31 (m, 2 H); MS (ESI) m/z 489.2 (M+ + H).

Example 68. Comparative Compound 989: (S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0147]



Step 1. t-butyl 4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 431; 3.00 g, 13.94 mmol) and NaH (0.50 g, 20.90 mmol) were dissolved in DMF (100 mL). At 0 °C, 3,6-dichloropyridazine (2.49 g, 16.72 mmol) was added thereto, following with stirring at room temperature for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 0 % to 50 %), and concentrated to yield the title compound as white solid (2.60 g, 56%).

Step 2. 3-chloro-6-(piperidin-4-ylmethoxy)pyridazine hydrochloride: t-butyl 4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-carboxylate (2.60 g, 7.93 mmol) and 4.0 M solution in 1,4-dioxane (9.91 mL, 39.66 mmol) were dissolved in MeOH (30 mL) at room temperature. The solution was stirred at the same temperature for 3 hours, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (1.80 g, 85%).

Step 3. 1-(4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: To 3-chloro-6-(piperidin-4-ylmethoxy)pyridazine hydrochloride (0.60 g, 2.27 mmol), 2,2-dimethyloxirane (1.64 g, 22.71 mmol) and K_2CO_3 (0.63 g, 4.54 mmol), EtOH (4 mL) / H_2O (4 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature, following with concentrating under reduced pressure. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.44 g, 64%).

Step 4. 3-chloro-6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine: 1-(4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (0.55 g, 1.84 mmol) was dissolved in CH_2Cl_2 (8 mL). At 0 °C, DAST (0.26 mL, 2.02 mmol) was added thereto, following with stirring at room temperature for 5 hours. The reaction mixture was added with water, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.40 g, 72%, yellow oil).

Step 5. methyl 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate: To 3-chloro-6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine (0.20 g, 0.66 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.13 g, 0.73 mmol), Pd(dppf)Cl_2 (0.05 g, 0.07 mmol) and Na_2CO_3 (0.14 g, 1.33 mmol), DME (12 mL) / water (3 mL) was added. With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.17 g, 63%).

Step 6. 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid: Methyl 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate (0.17 g, 0.42 mmol) and $LiOH \cdot H_2O$ (0.04 g, 0.85 mmol) were added in THF/MeOH (6/3 mL) / water (2 mL). The mixture was refluxed with heating for 8 hours, and then cooled to room temperature, following with concentrating under reduced pressure. The concentrate was added with water (2 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as yellow solid (0.12 g, 73%).

Step 7. Comparative Compound 989: 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid (0.03 g, 0.08 mmol), EDC (0.03 g, 0.16 mmol), HOBt (0.02 g, 0.16 mmol) and DIPEA (0.04 mL, 0.23 mmol) were dissolved in DMF (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.01 g, 0.12 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 5 %), and concentrated to yield the title compound as colorless oil (2 mg, 5%).
1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 2 H, J = 8.3 Hz), 7.82 (d, 1 H, J = 9.2 Hz), 7.67 (d, 2 H, J = 8.3 Hz), 7.09 (d, 2 H, J = 8.3 Hz), 6.97 (s, 1 H), 5.52 (s, 1 H), 4.82 (m, 1 H), 4.48 (d, 2 H, J = 6.3 Hz), 3.60 (m, 3 H), 3.07 (m, 1 H), 2.44 (m, 4 H), 1.62 (m, 4 H), 1.45 (m, 9 H).

[0148] According to the above-described synthesis process of comparative compound 989, the compounds of Table 54 were synthesized using 4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid and the reactant of Table 53.

Table 53. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
990*	(R)-piperidin-3-ol	54

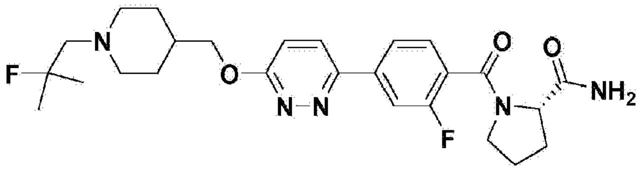
Table 54. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
990*	(R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, 2 H, J = 8.2 Hz), 7.80 (d, 1 H, J = 9.2 Hz), 7.55 (d, 2 H, J = 8.2 Hz), 7.06 (d, 1 H, J = 9.2 Hz), 4.44 (d, 2 H, J = 6.5 Hz), 4.08 - 3.09 (m, 5 H), 2.98 (m, 2 H), 2.47 - 2.41 (m, 2 H), 2.14 (m, 2 H), 1.87 (m, 7 H), 1.42 (m, 9 H).

Example 69. Comparative Compound 991: (S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-

methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0149]



__Step 1.__ ethyl 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate: 3-chloro-6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine (the product of synthesis step 4 of comparative compound 989; 0.20 g, 0.66 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.16 g, 0.73 mmol), Pd(dppf)Cl_2 (0.05 g, 0.06 mmol) and Na_2CO_3 (0.14 g, 1.33 mmol) were dissolved in DME (12 mL) / water (3 mL) at 120 °C, following with stirring at the same temperature for 20 minutes. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.17 g, 59%).

__Step 2.__ 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid: Ethyl 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate (0.17 g, 0.39 mmol) and $LiOH{\cdot}H_2O$ (0.03 g, 0.78 mmol) were added to THF/MeOH (6/3 mL) / water (2 mL). The mixture was refluxed with heating for 8 hours, and then cooled to room temperature, following with concentrating under reduced pressure. The concentrate was added with water (2 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as yellow solid (0.13 g, 81%).

__Step 3.__ Comparative Compound 991: 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid (0.03 g, 0.07 mmol), EDC (0.03 g, 0.15 mmol), HOBt (0.02 g, 0.15 mmol) and DIPEA (0.03 g, 0.22 mmol) were dissolved in DMF (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.01 g, 0.11 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 5 %), and concentrated to yield the title compound as colorless oil (2 mg, 5 %).

[0150] According to the above-described synthesis process of comparative compound 991, the compounds of Table 56 were synthesized using 2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid and the reactant of Table 55.

Table 55. (* marks comparative compound)

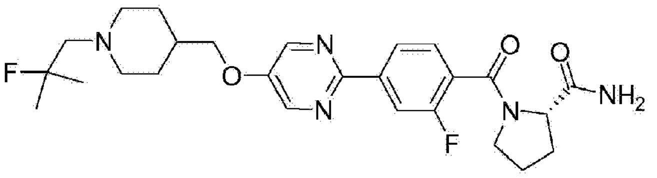
Compound No.	Reactant	Yield (%)
992*	(S)-piperidin-3-ol	57

Table 56. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
992*	(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.78 (m, 3 H), 7.51 (t, 1 H, J = 7.3 Hz), 7.07 (d, 1 H, J = 9.2 Hz), 4.44 (d, 2 H, J = 6.5 Hz), 4.08 - 3.62 (m, 2 H), 3.58 - 3.02 (m, 3 H), 2.99 (m, 2 H), 2.47 - 2.42 (m, 2 H), 2.14 (m, 2 H), 2.02 - 1.60 (m, 10 H), 1.41 (m, 9 H)

Example 70. Compound 1032 : (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0151]



Step 1. t-butyl 4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((methylsulfonyloxy)methyl)piperidin-1-carboxylate (the product of synthesis step 2 of comparative compound 431; 2.00 g, 6.82 mmol) was dissolved in DMF (80 mL). K_2CO_3 (3.33 g, 10.23 mmol) was added thereto, and stirred for 5 minutes. 2-chloropyrimidin-5-ol (890 mg, 6.82 mmol) was added thereto, following with stirring at 80 °C for 5 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (2.10 g, 94%).

Step 2. 2-chloro-5-(piperidin-4-ylmethoxy)pyrimidine hydrochloride: t-butyl 4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-carboxylate (2.10 g, 6.41 mmol) was dissolved in CH_2Cl_2 (50 mL). 4 M HCl in 1,4-dioxane (32.03 mL, 128.12 mmol) was added thereto, following with stirring for 1 hour. The resulting precipitate was filtered to yield the title compound as white solid (1.50 g, 88%).

Step 3. 1-(4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol: 2-chloro-5-(piperidin-4-ylmethoxy)pyrimidine hydrochloride (1.50 g, 5.68 mmol), 2,2-dimethyloxirane (5.06 mL, 56.79 mmol) and K_2CO_3 (392 mg, 2.84 mmol) were dissolved in EtOH (5 mL) and H_2O (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material, which is the title compound as white solid (1.70 g, 99%), was used without further purification.

Step 4. 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidine: 1-(4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol (1.70 g, 5.67 mmol) was dissolved in CH_2Cl_2 (15 mL). At 0 °C, DAST (749 μL, 5.67 mmol) was added slowly thereto. After stirring for 1 hour at room temperature, The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained material, which is the title compound as white solid (1.20 g, 70%), was used without further purification.

Step 5. ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoate: 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidine (600 mg, 1.99 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (421 mg, 1.99 mmol), $Pd(dppf)Cl_2$ (81 mg, 0.10 mmol) and Cs_2CO_3 (1.30 g, 3.98 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (480 mg, 55%).

Step 6. 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoic acid: Ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoate (480 mg, 1.11 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (232 mg, 5.54 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. The reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered to yield the title compound as white solid (360 mg, 80%).

Step 7. Compound 1032: 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoic acid (40 mg, 0.10 mmol), (S)-pyrrolidine-2-carboxamide (23 mg, 0.20 mmol), EDC (38 mg, 0.20 mmol) and HOBt (27 mg, 0.20 mmol) was added thereto., DIPEA (35 μL, 0.20 mmol) was dissolved in CH_2Cl_2 (1 mL), following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (21 mg, 42%).
1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2 H), 8.23 (d, 1 H, J = 6.6 Hz), 8.16 (d, 1 H, J = 10.2 Hz), 7.51 (t, 1 H, J = 7.4 Hz), 6.94 (brs, 1 H), 5.56 (brs, 1 H), 4.84 - 4.81 (m, 1 H), 3.96 (d, 2 H, J = 5.9 Hz), 3.55 - 3.49 (m, 1 H), 3.43 - 3.37 (m, 1 H), 3.03 (brs, 2 H), 2.51 - 2.45 (m, 2 H), 2.19 (brs, 2 H), 2.16 - 2.01 (m, 3 H), 1.96 - 1.81 (m, 4 H), 1.70 - 1.36 (m, 8 H); MS (ESI) m/z 502 (M+ + H).

[0152] According to the above-described synthesis process of compound 1032, the compounds of

Table 58 were synthesized using 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoic acid and the reactant of Table 57.

Table 57. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
1033*	(R)-piperidin-3-ol hydrochloride	37
1034*	(S)-piperidin-3-ol hydrochloride	39
1035*	(R)-pyrrolidine-3-ol	36
1037	(R)-piperidin-2-carboxamide hydrochloride	28

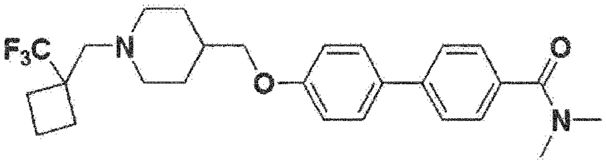
Table 58. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1033*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2 H), 8.20 (d, 1 H, J = 8.0 Hz), 8.10 (d, 1 H, J = 10.8 Hz), 7.48 (t, 1 H, J = 7.4 Hz), 4.12 - 4.09 (m, 1 H), 3.96 (d, 2 H, J = 5.9 Hz), 3.58 - 3.54 (m, 1 H), 3.37 - 3.33 (m, 1 H), 3.25 - 3.20 (m, 1 H), 3.13 - 3.03 (m, 2 H), 2.56 - 2.45 (m, 2 H), 2.27 - 2.16 (m, 2 H), 2.05 - 1.81 (m, 6 H), 1.69 - 1.62 (m, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.37 - 1.28 (m, 2 H); MS (ESI) m/z 489 (M+ + H).
1034*	(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2 H), 8.20 (d, 1 H, J = 8.0 Hz), 8.10 (d, 1 H, J = 10.8 Hz), 7.48 (t, 1 H, J = 7.4 Hz), 4.12 - 4.09 (m, 1 H), 3.96 (d, 2 H, J = 5.9 Hz), 3.58 - 3.54 (m, 1 H), 3.37 - 3.33 (m, 1 H), 3.25 - 3.20 (m, 1 H), 3.13 - 3.03 (m, 2 H), 2.56 - 2.45 (m, 2 H), 2.27 - 2.16 (m, 2 H), 2.05 - 1.81 (m, 6 H), 1.69 - 1.62 (m, 3 H), 1.47 (s, 3 H), 1.42 (s, 3 H), 1.37 - 1.28 (m, 2 H); MS (ESI) m/z 489 (M+ + H).
1035*	(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 2 H), 8.21 - 8.18 (m, 1 H), 8.13 - 8.08 (m, 1 H), 7.55 - 7.49 (m, 1 H), 4.61 (brs, 0.5 H), 4.48 (brs, 0.5 H), 3.96 (d, 2 H, J = 5.8 Hz), 3.85 - 3.71 (m, 2 H), 3.65 - 3.55 (m, 1 H), 3.46 - 3.42 (m, 0.5 H), 3.34 - 3.31 (m, 0.5 H), 3.04 (brs, 2 H), 2.49 (brs, 2 H), 2.20 - 2.00 (m, 6 H), 1.99 - 1.85 (m, 3 H), 1.42 (s, 3 H), 1.37 (s, 3 H); MS (ESI) m/z 475 (M+ + H).
1037	(R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.52 - 8.42 (m, 2 H), 8.25 (d, 1 H, J = 8.0 Hz), 8.13 (d, 1 H, J = 11.1 Hz), 7.52 (t, 1 H, J = 7.5 Hz), 6.32 (brs, 1 H), 5.65 (brs, 1 H), 5.46 (brs, 1 H), 3.96 (d, 2 H, J = 6.0 Hz), 3.58 (d, 1 H, J = 13.0 Hz), 3.22 - 3.21 (m, 1 H), 3.01 - 2.96 (m, 2 H), 2.49 - 2.44 (m, 3 H), 2.19 - 2.17 (m, 2 H), 1.83 - 1.74 (m, 5 H), 1.63 - 1.60 (m, 3 H), 1.46 (brs, 2 H), 1.41 (s, 3 H), 1.35 (s, 3 H); MS (ESI) m/z 516 (M+ + H).

Example 71. Comparative compound 631: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclobutyl)

methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

[0153]



Step 1. t-butyl 4-((4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((4-bromophenoxy)methyl)piperidin-1-carboxylate (the product of synthesis step 3 of comparative compound 431; 3.45 g, 9.32 mmol) and 4-hydroxyphenylboronic acid(1.41 g, 10.25 mmol) were dissolved in dioxane 12 mL. Water 3 mL was added thereto. Pd(dbpf)Cl_2 (607 mg, 0.93 mmol) and Cs_2CO_3 (6.07 g, 18.64 mmol) were added thereto, and refluxed with heating for a day. The reaction mixture was filtered through Celite, and the obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution and water, dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/CH_2Cl_2), and then recrystallized with CH_2Cl_2 and hexane to yield the title compound as white solid (2.50 g, 70%).

Step 2. 4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride: t-butyl 4-((4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate (2.50 g, 6.51 mmol) was dissolved in CH_2Cl_2 6 mL. 4 M HCl 1.79 mL was added thereto, following with stirring for 1 hour at room temperature. The obtained reaction mixture was filtered to yield the title compound as white solid (2.00 g, 96%).

Step 3. 4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate: 4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride (1.50 g, 4.69 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (946 mg, 5.63 mmol) and PyBOP (3.66 g, 7.04 mmol) were dissolved in DMF 4 mL. DIPEA (3.63 g, 28.14 mmol) was added thereto. At 50 °C, the reaction was performed for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/CH_2Cl_2) to yield the title compound as yellow solid (1.16 g, 42%).

Step 4. 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol: 4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate (1.16 g, 2.67 mmol) was dissolved in dry THF 15 mL, and then cooled with ice bath. LAH (1 M in THF, 8.03 mL, 8.03 mmol) was added dropwise slowly thereto, following with increasing the temperature to 50 °C and stirring for a day. Water was poured into the reaction mixture. The formed solid was removed by filtration, and the filtrate was extracted with EtOAc three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/Hexane) to yield the title compound as white solid (640 mg, 57%).

Step 5. 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate: 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol (640 mg, 1.53 mmol) was dissolved in CH_2Cl_2 6 mL. At 0 °C, pyridine (181 mg, 2.29 mmol) and trifluoromethanesulfonic anhydride (560 mg, 1.98 mmol) were added thereto, The reaction was performed at room temperature for 3 hours. The reaction mixture was added with water, and extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/Hexane) to yield the title compound as white solid (590 mg, 70%).

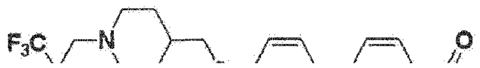
Step 6. methyl 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate (200 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol) and dppp (9 mg, 0.02) were dissolved in DMSO 3 mL. MeOH 3 mL was added thereto, following with sufficient CO gas flowing. Lastly, TEA (184 mg, 1.81 mmol) was added thereto, following with stirring at 120 °C for 4 hours. The reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with EtOAc. The obtained organic layer was concentrated under reduced pressure, and purified by silica gel column chromatography ($EtOAc/CH_2Cl_2$) to yield the title compound as pink solid (105 mg, 62%).

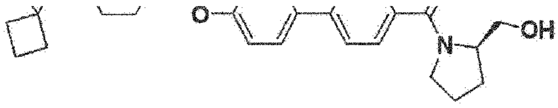
Step 7. 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (105 mg, 0.23 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 0.5 mL were poured therein. LiOH (19 mg, 0.46 mmol) was added thereto, and refluxed with heating and stirring for 5 hours. After acidification with 1 N HCl, the resulting precipitate was filtered to yield the title compound as white solid (98 mg, 96%).

Step 8. Comparative compound 631: 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)-piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), dimethylamine hydrochloride (11 mg, 0.13 mmol) and PyBOP (52 mg, 0.10 mmol) were dissolved in DMF 0.5 mL. DIPEA (43 mg, 0.34 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$) to yield the title compound as white solid (16 mg, 50%).
1H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 6 H), 6.98 (d, 2 H, J = 6.8 Hz), 3.85 (d, 2 H, J = 6.0 Hz), 3.14 (s, 3 H), 3.05 (s, 3 H), 2.85 (m, 2 H), 2.53 (s, 2 H), 2.19 (m, 4 H), 2.01 (m, 3 H), 1.96 (m, 1 H), 1.83 (m, 3 H), 1.46 (m, 2 H); MS (ESI) m/z 475 (M+ + H).

Example 72. Comparative compound 633: (R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

[0154]





[0155] 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (30 mg, 0.07 mmol), (R)-prolinol (14 mg, 0.13 mmol) and PyBOP (52 mg, 0.10 mmol) were dissolved in DMF 0.5 mL following with stirring for 10 minutes at room temperature. DIPEA (43 mg, 0.34 mmol) was added thereto, following with stirring at room temperature for 8 hours. Water was poured into the reaction mixture. The formed solid was filtered, and dried to yield the title compound as white solid (17 mg, 47%).
1H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 6 H), 6.99 (d, 2 H, J = 8.7 Hz), 5.01 (d, 1 H, J = 8.7 Hz), 4.46 (m, 1 H), 3.77 (m, 4 H), 3.53 (m, 2 H), 2.90 (m, 2 H), 2.54 (s, 2 H), 2.22 (m, 5 H), 2.11 (m, 3 H), 1.92 (m, 6 H), 1.64 (m, 2 H), 1.48 (m, 2 H); MS (ESI) m/z 531 (M+ + H).

[0156] According to the above-described synthesis process of comparative compound 631 (Step 8), the compounds of Table 60 were synthesized using 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 59.

Table 59. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
632*	(S)-3-pyrrolidinol	46
634*	3-hydroxypiperidine	45
635	L-prolinamide	43
636*	2-aminoethanol	57
637*	2-(methylamino)ethanol	58
794*	(R)-piperidin-3-ol hydrochloride	40
795*	(S)-piperidin-3-ol	40
796*	(R)-pyrrolidine-3-ol	44
797*	(S)-pyrrolidine-2-ylmethanol	43
798	piperidin-4-carboxamide	50

Table 60. (* marks comparative compound)

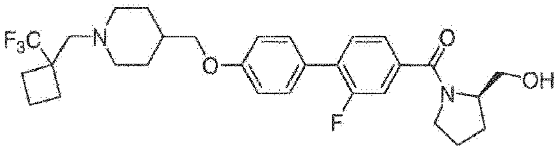
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
632*	(S)-(3-hydroxypyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 6 H), 6.97 (d, 2 H, J = 8.8 Hz), 4.59 (m, 1 H), 3.79 (m, 4 H), 3.63 (m, 1 H), 3.55 (m, 1 H), 3.14 (m, 1 H), 2.90 (m, 2 H), 2.68 (s, 1 H), 2.54 (s, 2 H), 2.23 (m, 4 H), 2.04 (m, 4 H), 1.87 (m, 4 H), 1.31 (m, 2 H); MS (ESI) m/z 517 (M+ + H).
	(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
634*	yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 6 H), 6.98 (d, 2 H, J = 6.9 Hz), 3.85 (m, 5 H), 3.46 (m, 3 H), 2.89 (m, 2 H), 2.54 (s, 2 H), 2.22 (m, 4 H), 1.96 (m, 10 H), 1.46 (m, 3 H); MS (ESI) m/z 531 (M+ + H).
635	(S)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 5 H), 6.98 (d, 2 H, J = 8.7 Hz), 5.64 (s, 1 H), 4.82 (m, 1 H), 3.85 (d, 2 H, J = 8.7 Hz), 2.89 (m, 2 H), 2.49 (s, 2 H), 2.43 (m, 1 H), 2.15 (m, 4 H), 2.11 (m, 5 H), 1.93 (m, 4 H), 1.41 (m, 2 H); MS (ESI) m/z 544 (M+ + H).
636*	N-(2-hydroxyethyl)-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 2 H, J = 8.4 Hz), 7.62 (d, 2 H, J = 8.4 Hz), 7.55 (d, 2 H, J = 8.8 Hz), 6.98 (d, 2 H, J = 8.7 Hz), 6.67 (t, 1 H, J = 5.3 Hz), 3.86 (m, 4 H), 3.66 (m, 2 H), 2.90 (m, 2 H), 2.73 (s, 1 H), 2.66 (s, 2 H), 2.24 (m, 4 H), 2.06 (m, 3 H), 1.88 (m, 4 H), 1.45 (m, 2 H); MS (ESI) m/z 491 (M+ + H).
637*	N-(2-hydroxyethyl)-N-methyl-4' -((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 6 H), 6.98 (d, 2 H, J = 8.7 Hz), 3.57 (m, 7 H), 3.12 (s, 3 H), 2.90 (m, 2 H), 2.54 (s, 4 H), 2.19 (m, 4 H), 2.04 (m, 3 H), 1.93 (m, 1 H), 1.83 (m, 3 H), 1.40 (m, 2 H); MS (ESI) m/z 505 (M+ + H).
794*	(R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 6 H), 6.98 (d, 2 H, J = 8.7 Hz), 3.85 (m, 4 H), 3.45 (m, 3 H), 2.90 (m, 2 H), 2.54 (m, 2 H), 2.21 (m, 4 H), 1.96 (m, 11 H), 1.46 (m, 3 H); MS (ESI) m/z 531 (M+ + H).
795*	(S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.1 Hz), 7.52 (d, 2 H, J = 8.6 Hz), 7.47 (d, 2 H, J = 8.0 Hz), 6.98 (d, 2 H, J = 8.6 Hz), 3.86 (m, 4 H), 3.44 (m, 3 H), 2.90 (m, 2 H), 2.55 (s, 2 H), 2.23 (m, 4 H), 1.98 (m, 11 H), 1.44 (m, 3 H); MS (ESI) m/z 531 (M+ + H).
796*	(R)-(3-hydroxypyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	MS (ESI) m/z 517 (M+ + H).
797*	(S)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 6 H), 6.97 (d, 2 H, J = 8.6 Hz), 4.57 (s, 0.5 H), 4.44 (s, 0.5 H), 3.79 (m, 4 H), 3.63 (m, 1 H), 3.54 (m, 1 H), 2.83 (m, 3 H), 2.54 (s, 2 H), 2.23 (m, 4 H), 1.92 (m, 10 H), 1.80 (m, 2 H); MS

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(ESI) m/z 531 (M+ + H).
798	1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.2 Hz), 7.52 (d, 2 H, J = 8.7 Hz), 7.44 (d, 2 H, J = 8.1 Hz), 6.97 (d, 2 H, J = 8.7 Hz), 5.70 (m, 2 H), 4.69 (s, 1 H), 3.90 (m, 3 H), 2.71 (m, 4 H), 2.55 (s, 2 H), 2.42 (m, 1 H), 2.23 (m, 4 H), 1.96 (m, 11 H), 1.46 (m, 2 H); MS (ESI) m/z 558 (M+ + H).

Example 73. Comparative compound 917: (R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0157]



Step 1. methyl 2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (the product of synthesis step 2 of comparative compound 842; 0.78 g, 1.92 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (0.45 g, 2.30 mmol), $Pd(dppf)Cl_2$ (0.07 g, 0.09 mmol) and Cs_2CO_3 (1.25 g, 3.84 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 100 %), and concentrated to yield the title compound as white solid (0.54 g, 59%).

Step 2. 2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylic acid: Methyl 2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.54 g, 1.13 mmol) and $LiOH{\cdot}H_2O$ (0.23 g, 5.68 mmol) were dissolved in THF / MeOH (16 mL) / H_2O (4mL) at room temperature. The solution was stirred at the same temperature for 1 hour. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.50 g, 94%).

Step 3. Compound 917: 2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.07 g, 0.15 mmol), (R)-pyrrolidine-2-ylmethanol (0.01 g, 0.18 mmol), HOBt (0.04 g, 0.30 mmol), EDC (0.05 g, 0.30 mmol) and DIPEA (0.05 mL, 0.30 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc.

The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, dichloromethane / methanol = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.05 g, 69%).

1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.51 (m, 3 H), 7.31 - 7.37 (m, 2 H), 6.99 (d, 2 H, J = 8.6 Hz), 4.75 (s, 1 H), 4.40 - 4.45 (m, 1 H), 3.74 - 3.87 (m, 4 H), 3.51 - 3.65 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 5 H), 1.87 - 2.11 (m, 6 H), 1.72 - 183 (m, 4 H), 1.43 - 1.49 (m, 2 H); MS (ESI) m/z 549.2 (M+ + H).

[0158] According to the above-described synthesis process of comparative compound 917, the compounds of Table 62 were synthesized using 2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 61.

Table 61. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
918	L-prolinamide	58
919*	(R)-piperidin-3-ol hydrochloride	67
920*	(S)-piperidin-3-ol hydrochloride	76
921*	(S)-pyrrolidine-3-ol	54

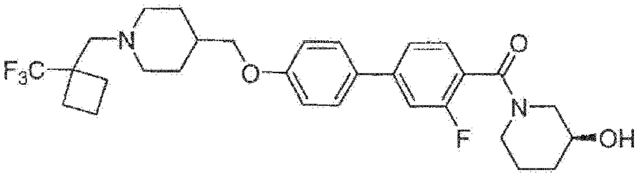
Table 62. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
918	(S)-1-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.51 (m, 3 H), 7.33 - 7.39 (m, 2 H), 6.98 - 7.00 (m, 2 H), 6.92 (s, 1 H), 5.48 (s, 1 H), 4.81 (dd, 1 H, J = 7.4, 5.2 Hz), 3.86 (d, 2 H, J = 6.0 Hz), 3.56 - 3.69 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.46 - 2.52 (m, 1 H), 2.20 - 2.28 (m, 4 H), 1.91 - 2.16 (m, 5 H), 1.80 - 1.90 (m, 5 H), 1.40 - 1.49 (m, 2 H); MS (ESI) m/z 562.3 (M+ + H).
919*	(R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.50 (m, 3 H), 7.22 - 7.27 (m, 2 H), 6.97 - 7.01 (m, 2 H), 3.85 - 3.95 (m, 3 H), 3.37 - 3.62 (m, 3 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 4 H), 2.00 - 2.11 (m, 2 H), 1.90 - 1.99 (m, 4 H), 1.80 - 1.89 (m, 3 H), 1.57 - 1.78 (m, 4 H), 1.39 - 1.50 (m, 2 H); MS (ESI) m/z 549.3 (M+ + H).
920*	(S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.50 (m, 3 H), 7.22 - 7.27 (m, 2 H), 6.97 - 7.00 (m, 2 H), 3.79 - 3.95 (m, 3 H), 3.34 - 3.67 (m, 3 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 4 H), 2.00 - 2.15 (m, 2 H), 1.82 - 1.99 (m, 4 H), 1.77 - 1.81 (m, 4 H), 1.50 - 1.64 (m, 3 H), 1.40 - 1.49 (m, 2 H); MS (ESI) m/z 549.3 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
921*	(S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.53 (m, 3 H), 7.31 - 7.41 (m, 2 H), 6.97 - 17.01 (m, 2 H), 4.51 - 4.63 (m, 1 H), 3.77 - 3.87 (m, 4 H), 3.50 - 3.71 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.22 - 2.28 (m, 4 H), 2.11 - 2.21 (m, 6 H), 1.66 - 1.89 (m, 4 H), 1.40 - 1.49 (m, 2 H); MS (ESI) m/z 535.2 (M+ + H).

Example 74. Comparative compound 842: (S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0159]



Step 1. (4-((4-bromophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl)methanone: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 1 of comparative compound 498; 2.00 g, 6.52 mmol) was dissolved in CH_2Cl_2 (40 mL). EDC (2.50 g, 13.05 mmol), HOBt (1.76 g, 13.05 mmol), DIPEA (2.31 mL, 13.05 mmol), 1-(trifluoromethyl) cyclobutanecarboxylic acid (1.09 g, 6.52 mmol) was added thereto, following with stirring at room temperature for 12 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1 / 4) to yield the title compound as white solid (2.10 g, 76%).

Step 2. 4-((4-bromophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine: (4-((4-bromophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl)methanone (812 mg, 1.93 mmol) was dissolved in THF (10 mL). 2.0 M Borane dimethyl sulfide complex solution in THF (4.83 mL, 9.66 mmol) was added thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1 / 8) to yield the title compound as yellow solid (480 mg, 61%).

Step 3. methyl 3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromophenoxy)methyl)-1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidine (480 mg, 1.18 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (300 mg, 1.42 mmol), $Pd(dppf)Cl_2$ (97 mg, 1.42 mmol) and Cs_2CO_3 (770 mg, 2.36 mmol), DME (6 mL)/ H_2O (2 mL) was added, and refluxed with heating for a day. After the completion of the reaction, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (EtOAc/hexane = 1 / 7) to yield the title compound as white solid (250 mg, 42%).

Step 4. 3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (250 mg, 0.51 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). At room temperature, $LiOH{\cdot}H_2O$ (106 mg, 2.53 mmol) was added thereto, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was acidified with 1 N HCl. The resulting precipitate was filtered, and dried to yield the title compound as white solid (201 mg, 85%).

Step 5. Comparative compound 842: 3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (40 mg, 0.09 mmol), EDC (33 mg, 0.17 mmol) and HOBt (23 mg, 0.17 mmol) was added thereto, DIPEA (30 μL, 0.17 mmol) were dissolved in (S)-piperidin-3-ol hydrochloride (24 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (1 mL), following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5%) to yield the title compound as yellow solid (24 mg, 50%).
1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2 H, J = 8.6 Hz), 7.45 - 7.38 (m, 2 H), 7.27 - 7.26 (m, 1 H), 6.98 (d, 2 H, J = 8.6 Hz), 4.11 - 3.94 (m, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.62 - 3.50 (m, 1 H), 3.40 - 3.27 (m, 1 H), 2.90 (d, 2 H, J = 10.9 Hz), 2.54 (s, 2 H), 2.28 - 2.20 (m, 4 H), 2.11 - 2.01 (m, 10 H), 1.99 - 1.63 (m, 3 H), 1.49 - 1.34 (m, 3 H); MS (ESI) m/z 549 (M+ + H).

[0160] According to the above-described synthesis process of comparative compound 842, the compounds of Table 64 were synthesized using 3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 63.

Table 63. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
843	(S)-pyrrolidine-3-carboxamide	41
844*	(R)-pyrrolidine-2-ylmethanol	42
845*	(S)-pyrrolidine-3-ol	32
846*	(R)-piperidin-3-ol hydrochloride	50

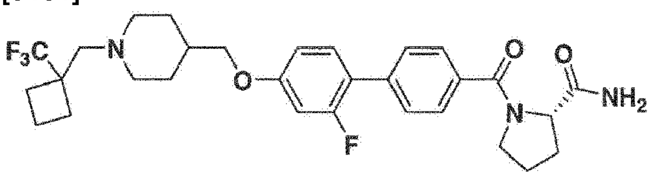
Table 64. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(S)-1-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
843	1H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.45 (m, 2 H), 7.43 - 7.40 (m, 2 H), 7.32 - 7.29 (m, 1 H), 7.00 - 6.95 (m, 2 H), 5.52 (brs, 1 H), 4.84 - 4.81 (m, 1 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.56 - 3.53 (m, 1 H), 3.47 - 3.42 (m, 1 H), 2.90 (d, 2 H, J = 11.2 Hz), 2.54 (s, 2 H), 2.50 - 2.46 (m, 1 H), 2.28 - 2.19 (m, 4 H), 2.14 - 2.11 (m, 4 H), 2.09 - 2.01 (m, 1 H), 1.99 - 1.91 (m, 2 H), 1.89 - 1.81 (m, 3 H), 1.68 (brs, 1 H), 1.46 - 1.43 (m, 2 H); MS (ESI) m/z 562 (M+ + H).
844*	(R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.53 - 7.46 (m, 3 H), 7.42 - 7.39 (m, 1 H), 7.31 - 7.27 (m, 1 H), 6.98 (d, 2 H, J = 8.7 Hz), 4.79 (d, 1 H, J = 6.1 Hz), 4.42 - 4.40 (m, 1 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.84 - 3.81 (m, 1 H), 3.49 - 3.46 (m, 2 H), 2.90 (d, 2 H, J = 11.2 Hz), 2.54 (s, 2 H), 2.28 - 2.20 (m, 5 H), 2.18 - 1.99 (m, 3 H), 1.96 - 1.86 (m, 2 H), 1.83 - 1.80 (m, 4 H), 1.77 - 1.66 (m, 2 H), 1.50 - 1.43 (m, 2 H); MS (ESI) m/z 549 (M+ + H).
845*	(S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.45 (m, 3 H), 7.40 - 7.37 (m, 1 H), 7.30 - 7.25 (m, 1 H), 6.98 (d, 2 H, J = 8.1 Hz), 4.62 - 4.49 (m, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.79 - 3.61 (m, 1 H), 3.59 - 3.35 (m, 1 H), 2.91 (d, 2 H, J = 11.2 Hz), 2.55 (s, 2 H), 2.28 - 2.22 (m, 4 H), 2.19 - 2.01 (m, 5 H), 1.99 - 1.90 (m, 2 H), 1.89 - 1.81 (m, 4 H), 1.49 - 1.43 (m, 2 H); MS (ESI) m/z 535 (M+ + H).
846*	(R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, 2 H, J = 8.6 Hz), 7.45 - 7.38 (m, 2 H), 7.27 - 7.26 (m, 1 H), 6.98 (d, 2 H, J = 8.6 Hz), 4.11 - 3.94 (m, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.62 - 3.50 (m, 1 H), 3.40 - 3.27 (m, 1 H), 2.90 (d, 2 H, J = 10.9 Hz), 2.54 (s, 2 H), 2.28 - 2.20 (m, 4 H), 2.11 - 2.01 (m, 10 H), 1.99 - 1.63 (m, 3 H), 1.49 - 1.34 (m, 3 H); MS (ESI) m/z 549 (M+ + H).

Example 75. Compound 833: (S)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0161]



Step 1. t-butyl 4-((2-fluoro-4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 704; 3.7 g, 9.53 mmol), 4-hydroxyphenylboronic acid (1.31 g, 9.53 mmol),

$Pd(dppf)Cl_2$ (778 mg, 0.95 mmol), Na_2CO_3 (2.02 g, 19.06 mmol) were dissolved in DME 15 mL and water 5 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (2.8 g, 73%).

Step 2. 2'-fluoro-4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride: t-butyl 4-((2-fluoro-4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate (2.8 g, 6.97 mmol) was dissolved in CH_2Cl_2 15 mL. 4 M HCl 2.09 mL was added thereto, following with stirring at room temperature for 2 hours. The reaction mixture was filtered, washed with EtOAc, and evaporated under reduced pressure to yield the title compound as white solid (2.3 g, 97%).

Step 3. 2'-fluoro-4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate: 2'-fluoro-4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride (1.5 g, 4.44 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (1.12 g, 6.66 mmol) and BOP (3.93 g, 8.88 mmol) were dissolved in DMF 6 mL. After stirring for 10 minutes at room temperature, TEA (1.35 g, 13.32 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, EtOAc/hexane) to yield the title compound as white solid (580 mg, 29%).

Step 4. 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol: 2'-fluoro-4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl) piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate (1.38 g, 2.23 mmol) was dissolved in dry THF 20 mL. At 0 °C, LAH (6.88 mmol) was added thereto, following with stirring at 60 °C for a day. After the completion of the reaction, the reaction mixture was added with a little of water, and then extracted with excess amount of EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 15 - 20 % EtOAc/hexane) to yield the title compound as white solid (980 mg, 97%).

Step 5. 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate: 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol (980 mg, 2.24 mmol) was dissolved in dry CH_2Cl_2 6 mL. Pyridine (266 mg, 3.36 mmol) was added thereto. And then, trifluoromethanesulfonic anhydride (266 mg, 3.36 mmol) was added thereto at 0 °C, following with stirring at room temperature for 3 hours. The reaction mixture was added with water, and extracted with CH_2Cl_2 twice. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (880 mg, 69%).

Step 6. methyl 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-

4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate (880 mg, 1.55 mmol), $Pd(OAc)_2$ (17 mg, 0.08 mmol) and dppp (40 mg, 0.09 mmol) were dissolved in DMSO 6 mL. MeOH 6 mL was added thereto, following with sufficient infusion of carbon monoxide (CO). And then, TEA (782 mg, 7.73 mmol) was added thereto, following with stirring at 120 °C for 6 hours. After filtering through Celite, the reaction mixture was diluted with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (470 mg, 63%).

Step 7. 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (470 mg, 0.98 mmol) was dissolved in $THF/MeOH/H_2O$ = 6/3/2 mL. $LiOH \cdot H_2O$ (82 mg, 1.96 mmol) was added thereto, and refluxed with heating for 3 hours. After the completion of the reaction, the solvent was evaporated under reduced pressure, following with adjusting pH to below 6 using 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (410 mg, 89%).

Step 8. Compound 833: 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (40 mg, 0.09 mmol), (S)-pyrrolidine-2-carboxamide (15 mg, 0.13 mmol) and BOP (76 mg, 0.17 mmol) were dissolved in DMF 1 mL. After stirring for 10 minutes at room temperature, TEA (26 mg, 0.26 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as white solid (22 mg, 45%).
1H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 4 H), 7.35 (t, 1 H, J = 4.8 Hz), 6.99 (s, 1 H), 6.73 (m, 2 H), 5.50 (s, 1 H), 4.82 (t, 2 H, J = 2.1 Hz), 3.83 (d, 2 H, J = 5.9 Hz), 3.58 (m, 2 H), 2.90 (m, 2 H), 2.49 (m, 3 H), 2.30 (m, 4 H), 2.09 (m, 5 H), 1.89 (m, 5 H), 0.98 (m, 2 H)

[0162] According to the above-described synthesis process of compound 833, the compounds of Table 66 were synthesized using 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 65.

Table 65. (* marks comparative compound)

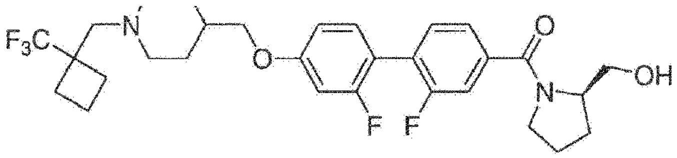
Compound No.	Reactant	Yield (%)
834*	(R)-piperidin-3-ol	50
835*	(S)-pyrrolidine-3-ol	41
836*	(S)-piperidin-3-ol	46
877	(R)-piperidin-2-carboxamide hydrochloride	61
878	(S)-piperidin-2-carboxamide hydrochloride	55
882	(R)-piperidin-3-carboxamide hydrochloride	69

Table 66. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
834*	(R)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 2 H), 7.49 (m, 2 H), 7.34 (t, 1 H, J = 8.8 Hz), 6.73 (m, 2 H), 3.86 (m, 4 H), 3.46 (m, 3 H), 2.90 (m, 2 H), 2.55 (m, 2 H), 2.24 (m, 4 H), 1.96 (m, 12 H), 1.26 (m, 2 H).
835*	(S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 4 H), 7.34 (t, 1 H, J = 8.8 Hz), 6.73 (m, 2 H), 4.58 (s, 0.5 H), 4.44 (s, 0.5 H), 3.83 (m, 4 H), 3.54 (m, 2 H), 2.91 (m, 2 H), 2.72 (m, 1 H), 2.55 (s, 2 H), 2.23 (m, 4 H), 2.07 (m, 9 H), 1.42 (m, 2 H).
836*	(S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 4 H), 7.35 (t, 1 H, J = 8.9 Hz), 6.76 (m, 2 H), 3.84 (m, 4 H), 3.65 (m, 3 H), 3.05 (m, 2 H), 2.55 (m, 2 H), 2.35 (m, 4 H), 1.94 (m, 10 H), 1.26 (m, 4 H).
877	(R)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.44 (m, 4 H), 7.35 (t, 1 H, J = 8.7 Hz), 6.81 - 6.68 (m, 2 H), 3.84 (d, 3 H, J = 5.8 Hz), 3.12 (t, 1 H, J = 13.1 Hz), 2.91 (d, 2 H, J = 10.0 Hz), 2.55 (s, 2 H), 2.35 (d, 1 H, J = 12.8 Hz), 2.30 - 1.35 (m, 19 H); MS (ESI) m/z 576 (M+ + H).
878	(S)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.64 - 7.43 (m, 4 H), 7.35 (t, 1 H, J = 8.9 Hz), 6.83 - 6.67 (m, 2 H), 3.84 (d, 3 H, J = 6.0 Hz), 3.13 (t, 1 H, J = 12.7 Hz), 2.91 (d, 2 H, J = 9.5 Hz), 2.55 (s, 2 H), 2.35 (d, 1 H, J = 12.8 Hz), 2.30 - 1.37 (m, 19 H); MS (ESI) m/z 576 (M+ + H).
882	(R)-1-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2 H, J = 6.8 Hz), 7.46 (d, 2 H, J = 8.3 Hz), 7.35 (t, 1 H, J = 8.8 Hz), 6.81 - 6.68 (m, 2 H), 3.84 (d, 3 H, J = 5.5 Hz), 3.62 - 3.52 (m, 1 H), 3.51 - 3.40 (m, 1 H), 2.89 (s, 2 H), 2.54 (s, 3 H), 2.32 - 1.36 (m, 20 H); MS (ESI) m/z 576 (M+ + H).

Example 76. Comparative compound 908: (2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0163]



Step 1. (4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl) methanone: 4-((4-bromo-3-fluorophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 2 of comparative compound 704; 2.60 g, 8.00 mmol), DIPEA (2.77 mL, 16.01 mmol), HOBt (2.16 g, 16.01 mmol), EDC (3.07 g, 16.01 mmol) and 1-(trifluoromethyl)cyclobutanecarboxylic acid (1.61 g, 9.61 mmol) were dissolved in DMF (30 mL) at 60 °C, following with stirring at the same temperature for 18 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as yellow oil (2.83 g, 80%).

Step 2. 4-((4-bromo-3-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidine: (4-((4-bromo-3-fluorophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl)methanone (1.40 g, 3.33 mmol) was dissolved in THF (30 mL). At 0 °C, 2.0 M $BH_3 \cdot SMe_2$ in THF (8.3 mL, 16.66 mmol) was added thereto, following with stirring at 60 °C for 2 hours The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 5 % to 20 %), and concentrated to yield the title compound as white solid (1.84 g, 67%).

Step 3. methyl 2,2'-difluoro-4'-((4-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromo-3-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (0.80 g, 1.89 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (0.44 g, 2.26 mmol), $Pd(dppf)Cl_2$ (0.07 g, 0.09 mmol) and Cs_2CO_3 (1.23 g, 3.78 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.39 g, 42%).

Step 4. 2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 2,2'-difluoro-4'-((4-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.39 g, 0.78 mmol) and $LiOH \cdot H_2O$ (0.16 g, 3.92 mmol) were dissolved in THF/ MeOH (20 mL) / H_2O (5 mL) at room temperature. The solution was stirred at the same temperature for 1 hour. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.21 g, 55%).

Step 5. Comparative compound 908: 2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.08

mmol), (R)-pyrrolidine-2-ylmethanol (0.01 g, 0.09 mmol), HOBt (0.02 g, 0.16 mmol), EDC (0.03 g, 0.16 mmol) and DIPEA (0.02 mL, 0.16 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g, methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.02 g, 57%).

1H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, 1 H, J = 7.3 Hz), 7.27 - 7.37 (m, 3 H), 6.78 (dd, 1 H, J = 8.5, 2.5 Hz), 6.73 (dd, 1 H, J = 11.9, 2.4 Hz), 4.40 - 4.44 (m, 1 H), 3.74 - 3.84 (m, 4 H), 3.53 - 3.64 (m, 2 H), 2.89 -2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 4 H), 1.65 - 2.11 (m, 10 H), 1.40 - 1.48 (m, 2 H), 1.25 - 1.26 (m, 2 H); MS (ESI) m/z 567.2 (M+ + H).

[0164] According to the above-described synthesis process of comparative compound 908, the compounds of Table 68 were synthesized using 2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 67.

Table 67. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
909	L-prolinamide	52
910*	(R)-piperidin-3-ol hydrochloride	74
911*	(S)-piperidin-3-ol hydrochloride	76

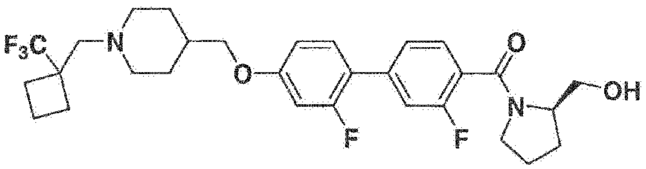
Table 68. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
909	(2S)-1-(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.45 (m, 4 H), 6.92 (s, 1 H), 6.79 (dd, 1 H, J = 8.5, 2.4 Hz), 6.73 (dd, 1 H, J = 11.9, 2.4 Hz), 5.55 (s, 1 H), 4.80 (dd, 1 H, J = 7.6, 5.0 Hz), 3.84 (d, 2 H, J = 6.0 Hz), 3.58 - 3.67 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.44 - 2.47 (m, 1 H), 2.19 - 2.28 (m, 4 H), 1.71 - 2.14 (m, 10 H), 1.39 - 1.48 (m, 2 H); MS (ESI) m/z 580.3 (M+ + H).
910*	(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, 1 H, J = 7.5 Hz), 7.23 - 7.30 (m, 3 H), 6.78 (dd, 1 H, J = 8.5, 2.4 Hz), 6.73 (dd, 1 H, J = 11.9, 2.4 Hz), 3.83 - 3.97 (m, 4 H), 3.36 - 3.59 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 4 H), 1.80 - 2.11 (m, 10 H), 1.35 - 1.46 (m, 2 H), 1.26 - 1.34 (m, 2 H); MS (ESI) m/z 567.3 (M+ + H).
911*	(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone
	1 H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, 1 H, J = 7.4 Hz), 7.23 - 7.30 (m, 3 H), 6.78 (dd, 1 H, J = 8.5, 2.5 Hz), 6.73 (dd, 1 H, J = 11.9, 2.4 Hz), 3.78 -

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	3.96 (m, 3 H), 3.32 - 3.62 (m, 3 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.20 - 2.28 (m, 4 H), 1.68 - 2.11 (m, 10 H), 1.58 - 1.60 (m, 2 H), 1.40 - 1.48 (m, 2 H); MS (ESI) m/z 567.3 (M+ + H).

Example 77. Comparative compound 912: (R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0165]



Step 1. ethyl 2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromo-3-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (the product of synthesis step 2 of comparative compound 908; 0.80 g, 1.89 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.48 g, 2.26 mmol), Pd(dppf)Cl_2 (0.07 g, 0.09 mmol) and Cs_2CO_3 (1.23 g, 3.78 mmol), DME (9 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.70 g, 75%).

Step 2. 2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Ethyl 2',3-difluoro-4'-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.70 g, 1.36 mmol) and LiOH·H_2O (0.28 g, 6.84 mmol) were dissolved in THF/ MeOH (20 mL) / H_2O (5 mL) at room temperature. The solution was stirred at the same temperature for 1 hour. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.66 g, 99%).

Step 3. Comparative compound 912: 2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.07 g, 0.14 mmol), (R)-pyrrolidine-2-ylmethanol (0.01 g, 0.17 mmol), HOBt (0.03 g, 0.29 mmol), EDC (0.05 g, 0.29 mmol) and DIPEA (0.05 mL, 0.29 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.07 g, 90%).

1H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, J = 7.5 Hz), 7.27 - 7.38 (m, 2 H), 6.78 (dd, 1 H, J = 8.6, 2.4 Hz), 6.72 (dd, 1 H, J = 12.7, 2.3 Hz), 4.78 - 4.79 (s, 1 H), 4.40 - 4.44 (m, 1 H), 3.75 - 3.84 (m, 4 H), 3.46 - 3.50 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.19 - 2.28 (m, 5 H), 2.01 - 2.11 (m, 3 H), 1.90 - 1.99 (m, 2 H), 1.82 - 1.89 (m, 4 H), 1.64 - 1.79 (m, 2 H), 1.42 - 1.48 (m, 2 H); MS (ESI) m/z 567.3 (M+ + H).

[0166] According to the above-described synthesis process of comparative compound 912, the compounds of Table 70 were synthesized using 2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 69.

Table 69. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
913	L-prolinamide	81
914*	(R)-piperidin-3-ol hydrochloride	97
915*	(S)-piperidin-3-ol hydrochloride	14
916*	(S)-pyrrolidine-3-ol	98

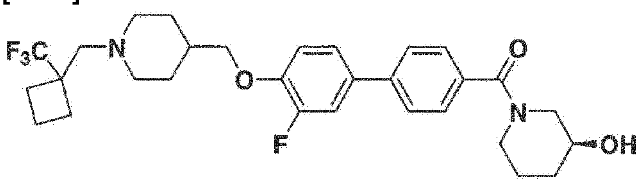
Table 70. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
913	(S)-1-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.50 (m, 1 H), 7.28 - 7.37 (m, 2 H), 6.96 (s, 1 H), 6.77 (dd, 1 H, J = 8.6, 2.3 Hz), 6.71 (dd, 1 H, J = 12.7, 2.3 Hz), 5.86 (s, 1 H), 4.80 (dd, 1 H, J = 8.0, 4.1 Hz), 3.95 - 4.12 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.41 - 3.58 (m, 1 H), 2.88 - 2.91 (m, 2 H), 2.54 (s, 2 H), 2.38 - 2.41 (m, 1 H), 2.21 - 2.27 (m, 5 H), 2.19 - 2.18 (m, 5 H), 1.78 - 1.93 (m, 3 H), 1.41 - 1.48 (m, 2 H), 1.24 - 1.26 (m, 2 H); MS (ESI) m/z 580.3 (M+ + H).
914*	(R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.4 Hz), 7.26 - 7.37 (m, 3 H), 6.78 (dd, 1 H, J = 8.6, 2.4 Hz), 6.72 (dd, 1 H, J = 12.7, 2.4 Hz), 3.95 - 4.12 (m, 1 H), 3.84 (d, 2 H, J = 6.0 Hz), 3.52 - 3.61 (m, 1 H), 3.11 - 3.37 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.19 - 2.28 (m, 4 H), 1.79 - 2.11 (m, 9 H), 1.42 - 1.48 (m, 2 H), 1.32 - 1.30 (m, 4 H); MS (ESI) m/z 567.3 (M+ + H).
915*	(S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.4 Hz), 7.26 - 7.37 (m, 3 H), 6.78 (dd, 1 H, J = 8.6, 2.4 Hz), 6.72 (dd, 1 H, J = 12.6, 2.3 Hz), 3.94 - 4.14 (m, 1 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.37 - 3.62 (m, 1 H), 3.14 - 3.29 (m, 2 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.19 - 2.28 (m, 4 H), 1.79 - 2.11 (m, 10 H), 1.40 - 1.48 (m, 3 H), 1.26 - 1.28 (m, 2 H); MS (ESI) m/z 567.2 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
916*	(S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.50 (m, 1 H), 7.25 - 7.36 (m, 3 H), 6.70-6.79 (m, 2 H), 4.48 - 4.61 (m, 1 H), 3.78 - 3.84 (m, 3 H), 3.66 - 3.74 (m, 1 H), 3.57 - 3.61 (m, 1 H), 3.35 - 3.48 (m, 1 H), 2.89 - 2.92 (m, 2 H), 2.54 (s, 2 H), 2.22 - 2.30 (m, 5 H), 2.01 - 2.19 (m, 5 H), 1.86 - 1.99 (m, 1 H), 1.79 - 1.82 (m, 3 H), 1.39 - 1.48 (m, 2 H); MS (ESI) m/z 553.3 (M+ + H).

Example 78. Comparative compound 883: (S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0167]



Step 1. t-butyl 4-((3-fluoro-4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 725; 3.75 g, 9.67 mmol), 4-hydroxyphenylboronic acid (1.33 g, 9.67 mmol), $Pd(dppf)Cl_2$ (789 mg, 0.97 mmol) and Na_2CO_3 (2.04 g, 19.32 mmol) were dissolved in DME 15 mL and water 5 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (2.90 g, 75%).

Step 2. 3'-fluoro-4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride: t-butyl 4-((3-fluoro-4'-hydroxybiphenyl-4-yloxy)methyl)piperidin-1-carboxylate (2.90 g, 7.22 mmol) was dissolved in CH_2Cl_2 15 mL. 4 M HCl 2.17 mL was added thereto, following with stirring at room temperature for 2 hours. The reaction mixture was filtered, washed with EtOAc, and evaporated under reduced pressure to yield the title compound as white solid (2.40 g, 98%).

Step 3. 3-fluoro-4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate: 3'-fluoro-4'-(piperidin-4-ylmethoxy)biphenyl-4-ol hydrochloride (0.83 g, 2.46 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (0.62 g, 3.69 mmol) and BOP (2.17 g, 4.93 mmol) were dissolved in DMF 6 mL. After stirring for 10 minutes at room temperature, TEA (0.75 g, 7.39 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, EtOAc/hexane) to yield the title compound as white solid (500 mg, 45%).

Step 4. 3 '-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol: 3-fluoro-4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl) piperidin-4-yl)methoxy)biphenyl-4-yl 1-(trifluoromethyl)cyclobutanecarboxylate (672 mg, 1.12 mmol) was dissolved in dry THF 15 mL. At 0 °C, LAH (3.35 mmol) was added thereto, following with stirring at 60 °C for a day. After the completion of the reaction, the reaction mixture was added with a little of water, and then extracted with excess amount of EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g ISCO silica gel cartridge, 15 - 20 % EtOAc/hexane) to yield the title compound as white solid (485 mg, 99%).

Step 5. 3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate: 3 '-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-ol (485 mg, 1.11 mmol) was dissolved in dry CH_2Cl_2 6 mL. Pyridine (132 mg, 1.66 mmol) was added thereto. And then, trifluoromethanesulfonic anhydride (401 mg, 1.44 mmol) was added thereto at 0 °C, following with stirring at room temperature for 3 hours. The reaction mixture was added with water, and extracted with CH_2Cl_2 twice. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (395 mg, 62%).

Step 6. methyl 3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylate: 3' -fluoro-4' -((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate (785 mg, 1.38 mmol), $Pd(OAc)_2$ (16 mg, 0.07 mmol) and dppp (35 mg, 0.08 mmol) were dissolved in DMSO 3 mL. MeOH 2 mL was added thereto, following with sufficient infusion of carbon monoxide (CO). TEA (697 mg, 6.89 mmol) was added thereto, following with stirring at 120 °C for 4 hours. The reaction mixture was diluted with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/CH_2Cl_2) to yield the title compound as white solid (380 mg, 57%).

Step 7. 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylic acid: Methyl 3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylate (420 mg, 0.88 mmol) was dissolved in THF/ MeOH/H_2O = 6/3/2 mL. $LiOH{\cdot}H_2O$ (73 mg, 1.75 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using IN HCl. The resulting precipitate was filtered to yield the title compound as white solid (380 mg, 93%).

Step 8. Comparative compound 883: 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (50 mg, 0.11 mmol), EDC (33 mg, 0.22 mmol), HOBt (29 mg, 0.22 mmol) and DIPEA (42 mg, 32 mmol) were dissolved in DMF 1 mL. After stirring for 10 minutes at room temperature, (S)-piperidin-3-ol (16 mg, 0.16 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with

EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as white solid (35 mg, 59%).
1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 4 H), 7.29 (m, 2 H), 7.00 (t, 1 H, J = 8.5 Hz), 3.90 (m, 4 H), 3.59 (m, 3 H), 2.88 (m, 2 H), 2.53 (s, 2 H), 2.21 (m, 4 H), 1.98 (m, 10 H), 1.24 (m, 3 H); MS (ESI) m/z 549 (M + H).

[0168] According to the above-described synthesis process of comparative compound 883, the compounds of Table 72 were synthesized using 2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 71

Table 71. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
837	(S)-pyrrolidine-2-carboxamide	47
838*	(R)-pyrrolidine-2-ylmethanol	44
839*	(S)-pyrrolidine-3-ol	52
840*	(R)-piperidin-3-ol	42
884	(S)-piperidin-3-carboxamide hydrochloride	48
885	(R)-piperidin-3-carboxamide hydrochloride	50
886	(R)-piperidin-2-carboxamide hydrochloride	61
887	(S)-piperidin-2-carboxamide hydrochloride	56

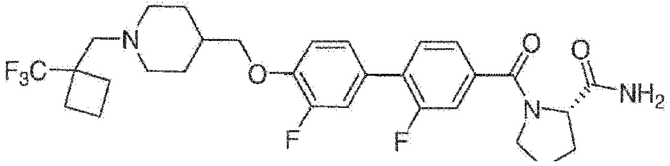
Table 72. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
837	(S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 (m, 4 H), 7.33 (m, 2 H), 7.02 (m, 2 H), 5.57 (s, 1 H), 4.82 (t, 1 H, J = 6.2 Hz), 3.92 (d, 2 H, J = 6.2 Hz), 3.58 (m, 2 H), 2.91 (m, 2 H), 2.45 (m, 3 H), 2.25 (m, 4 H), 2.13 (m, 6 H), 1.98 (m, 4 H), 1.26 (m, 2 H).
838*	(R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 4 H), 7.31 (m, 2 H), 7.03 (t, 1 H, J = 8.5 Hz), 4.94 (m, 1 H), 4.43 (m, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.78 (m, 2 H), 3.55 (m, 2 H), 3.13 (s, 1 H), 3.04 (s, 1 H), 2.89 (m, 2 H), 2.25 (s, 2 H), 2.23 (m, 5 H), 1.98 (m, 8 H), 1.42 (m, 2 H).
839*	(S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (m, 4 H), 7.30 (m, 2 H), 7.01 (t, 1 H, J = 8.5 Hz), 4.58 (s, 0.5 H), 4.45 (s, 0.5 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.91 (d, 2

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	H, J = 6.2 Hz), 3.64 (m, 2 H), 3.54 (m, 1 H), 3.52 (m, 1 H), 2.91 (d, 2 H, J = 11.0 Hz), 2.81 (s, 0.5 H), 2.72 (s, 0.5 H), 2.55 (s, 2 H), 2.23 (m, 4 H), 2.04 (m, 10 H), 1.46 (m, 2 H).
840*	(R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 4 H), 7.33 (m, 2 H), 7.02 (t, 1 H, J = 8.5 Hz), 3.92 (m, 4 H), 3.57 (m, 3 H), 3.16 (m, 2 H), 2.68 (m, 2 H), 2.24 (m, 4 H), 2.04 (m, 10 H), 1.85 (m, 2 H), 1.26 (m, 2 H).
884	(S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2 H, J = 8.1 Hz), 7.44 (d, 2 H, J = 8.3 Hz), 7.30 (m, 2 H), 7.01 (t, 1 H, J = 8.5 Hz), 6.75 (s, 1 H), 5.44 (s, 1 H), 4.12 (m, 1 H), 3.90 (d, 2 H, J = 6.2 Hz), 3.77 (m, 1 H), 3.55 (m, 1 H), 3.26 (m, 1 H), 2.90 (m, 2 H), 2.54 (m, 2 H), 2.54 - 1.46 (m, 16 H), 1.12 (m, 2 H).
885	(R)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2 H, J = 8.0 Hz), 7.45 (d, 2 H, J = 8.1 Hz), 7.30 (m, 2 H), 7.02 (t, 1 H, J = 8.5 Hz), 6.80 (s, 1 H), 5.70 (s, 1 H), 4.16 (s, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.63 (m, 1 H), 3.37 (m, 1 H), 2.90 (m, 2 H), 2.55 (s, 2 H), 2.22 - 1.62 (m, 16 H), 1.43 (m, 3 H).
886	(R)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, 2 H, J = 8.1 Hz), 7.44 (d, 2 H, J = 8.3 Hz), 7.31 (m, 2 H), 7.01 (t, 1 H, J = 8.5 Hz), 6.75 (s, 1 H), 5.54 (s, 1 H), 4.12 (m, 1 H), 3.90 (d, 2 H, J = 6.2 Hz), 3.77 (m, 1 H), 3.55 (m, 1 H), 3.26 (m, 1 H), 2.90 (m, 2 H), 2.54 - 1.61 (m, 15 H), 1.20 (m, 3 H); MS (ESI) m/z 576 (M + H).
887	(S)-1-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 4 H), 7.31 (m, 2 H), 7.02 (t, 1 H, J = 8.5 Hz), 6.49 (s, 1 H), 5.51 (s, 1 H), 5.27 (s, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.78 (m, 2 H), 3.11 (m, 1 H), 2.89 (m, 2 H), 2.54 (s, 2 H), 1.97 - 1.24 (m, 14 H); MS (ESI) m/z 576 (M + H).

Example 79. Compound 847: (S)-1-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0169]



Step 1. (4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl) methanone: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 2 of comparative compound 725; 3.90 g, 12.01 mmol) was dissolved in CH_2Cl_2 (50 mL). EDC (4.61 g, 24.03 mmol), HOBt (3.25 g, 24.03 mmol), DIPEA (4.25 mL, 24.03 mmol), 1-(trifluoromethyl)cyclobutanecarboxylic acid (2.02 g, 12.01 mmol) was added thereto, following with stirring at room temperature for a day. After the completion of the reaction, the reaction mixture was added with water, and extracted with CH_2Cl_2. The obtained organic layer was extracted with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (3.10 g, 58%).

Step 2. 4-((4-bromo-2-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidine: (4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclobutyl)methanone (2.28 g, 5.20 mmol) was dissolved in THF (50 mL). At 0 °C, 2.0 M Borane dimethyl sulfide complex solution in THF (13.01 mL, 26.01 mmol) was added thereto, following with stirring at 50 °C for 5 hours. After the completion of the reaction, the reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 20 % ~ 80 %) to yield the title compound as white solid (1.50 g, 68%).

Step 3. methyl 2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromo-2-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (800 mg, 1.89 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (448 mg, 2.26 mmol), Pd(dppf)Cl_2 (154 mg, 0.19 mmol) and CS_2CO_3 (1.23 g, 3.77 mmol), DME (6 mL) / H_2O (2 mL) was added, With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (535 mg, 57%).

Step 4. 2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 2,3'-difluoro-4'-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (535 mg, 1.08 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). At room temperature, $LiOH\cdot H_2O$ (226 mg, 5.38 mmol) was added thereto, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (400 mg, 76%).

Step 5. Compound 847: 2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (50 mg, 0.10 mmol), EDC (40 mg, 0.21 mmol), HOBt (28 mg, 0.21 mmol) and DIPEA (37 µL, 0.21 mmol) were dissolved in CH_2Cl_2 (1 mL). (S)-pyrrolidine-2-carboxamide (24 mg, 0.21 mmol) was added thereto, following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (43 mg, 71%).

1H NMR (400 MHz, $CDCl_3$) δ 7.48 - 7.45 (m, 1 H), 7.40 - 7.27 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 6.91 (brs, 1 H), 5.60 (brs, 1 H), 4.81 - 4.78 (m, 1 H), 3.92 (d, 2 H, J = 6.2 Hz), 3.68 - 3.54 (m, 2 H), 2.90 (d, 2 H, J = 11.3 Hz), 2.54 (s, 2 H), 2.49 - 2.42 (m, 1 H), 2.27 - 2.20 (m, 4 H), 2.16 - 1.98 (m, 5 H), 1.96 - 1.91 (m, 4 H), 1.90 - 1.73 (brs, 1 H), 1.48 - 1.42 (m, 2 H); MS (ESI) m/z 580(M+ + H).

[0170] According to the above-described synthesis process of compound 847, the compounds of Table 74 were synthesized using 2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 73.

Table 73. (* marks comparative compound)

Compound No	Reactant	Yield (%)
848*	(R)-piperidin-3-ol hydrochloride	66
849*	(R)-pyrrolidine 2-ylmethanol	68
850*	(S)-piperidin-3-ol hydrochloride	64
851*	(S)-pyrrolidine-3-ol	61

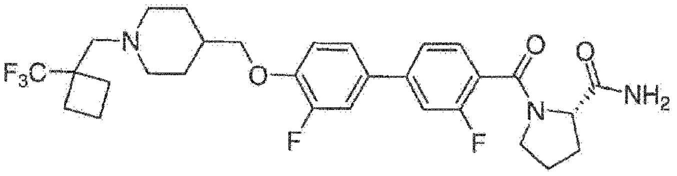
Table 74. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
848*	(R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.8 Hz), 7.33 - 7.22 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 3.93 - 3.79 (m, 3 H), 3.74 (brs, 1 H), 3.59 - 3.39 (m, 3 H), 2.90 (d, 2 H, J = 11.2 Hz), 2.48 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.19 - 2.04 (m, 2 H), 2.03 - 1.91 (m, 8 H), 1.90 - 1.61 (brs, 2 H), 1.48 - 1.40 (m, 2 H); MS (ESI) m/z 567 (M+ + H).
849*	(R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1 H, J = 7.8 Hz), 7.38 - 7.26 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.71 (brs, 1 H), 4.44 - 4.42 (m, 1 H), 3.92 (d, 2 H, J = 6.3 Hz), 3.83 - 3.77 (m, 2 H), 3.61 - 3.54 (m, 2 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 5 H), 2.11 - 1.83 (m, 8 H), 1.70 - 1.65 (m, 2 H), 1.46 - 1.42 (m, 2 H); MS (ESI) m/z 567 (M+ + H).
850*	(S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.8 Hz), 7.33 - 7.22 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 3.93 - 3.79 (m, 3 H), 3.74 (brs, 1 H), 3.59 - 3.39 (m, 3 H), 2.90 (d, 2 H, J = 11.2 Hz), 2.48 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.19 - 2.04 (m, 2 H), 2.03 - 1.91 (m, 8 H), 1.90 - 1.61 (brs, 2 H), 1.48 - 1.40 (m, 2 H); MS (ESI) m/z 567 (M+ + H).
	(S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
851*	yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 - 7.26 (m, 5 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.62 - 4.51 (m, 1 H), 3.92 (d, 2 H, J = 6.3 Hz), 3.87 - 3.81 (m, 2 H), 3.79 - 3.77 (m, 1 H), 3.71 - 3.49 (m, 1 H), 2.90 (d, 2 H, J = 11.3 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.18 - 1.92 (m, 5 H), 1.91 - 1.83 (m, 4 H), 1.66 (s, 1 H), 1.48 - 1.42 (m, 2 H); MS (ESI) m/z 553 (M+ + H).

Example 80. Compound 901: (S)-1-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0171]



Step 1. ethyl 3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: To 4-((4-bromo-2-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (the product of synthesis step 2 of compound 847; 627 mg, 1.48 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (345 mg, 1.63 mmol), Pd(dppf)Cl_2 (121 mg, 0.15 mmol) and Cs_2CO_3 (963 mg, 2.96 mmol), DME (6 mL) / H_2O (2 mL) was added, With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (580 mg, 76%).

Step 2. 3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Ethyl 3,3'-difluoro-4'-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (580 mg, 1.13 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). At room temperature, LiOH·H_2O (238 mg, 5.67 mmol) was added thereto, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (500 mg, 91%).

Step 3. Compound 901: 3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (60 mg, 0.12 mmol), EDC (48 mg, 0.25 mmol), HOBt (34 mg, 0.25 mmol) and DIPEA (44 μL, 0.25 mmol) were dissolved in CH_2Cl_2 (1 mL). (S)-pyrrolidine-2-carboxamide(28 mg, 0.25 mmol) was added thereto, following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced

pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (46 mg, 64%).
1H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, J = 7.5 Hz), 7.41 - 7.27 (m, 4 H), 7.03 (t, 1 H, J = 8.5 Hz), 6.93 (brs, 1 H), 5.65 (brs, 1 H), 4.83 - 4.80 (m, 1 H), 3.91 (d, 2 H, J = 6.3 Hz), 3.55 - 3.53 (m, 1 H), 3.44 - 3.41 (m, 1 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.47 - 2.44 (m, 1 H), 2.27 - 2.19 (m, 4 H), 2.15 - 1.82 (m, 10 H), 1.46 - 1.42 (m, 2 H); MS (ESI) m/z 580 (M+ + H).

[0172] According to the above-described synthesis process of compound 901, the compounds of Table 76 were synthesized using 3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 75.

Table 75. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
902*	(R)-piperidin-3-ol hydrochloride	66
903*	(R)-pyrrolidine-2-ylmethanol	62
904*	(S)-piperidin-3-ol hydrochloride	55
905*	(S)-pyrrolidine-3-ol	61
936*	1-(piperazin-1-yl)ethanone	79

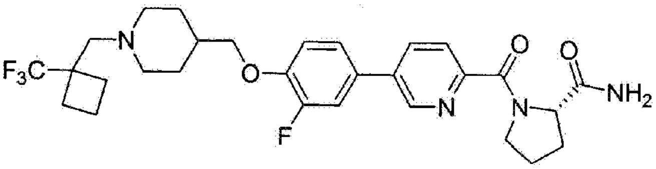
Table 76. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
902*	(R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.4 Hz), 7.38 - 7.23 (m, 4 H), 7.02 (t, 1 H, J = 8.5 Hz), 4.07 (brs, 1 H), 3.91 (d, 2 H, J = 6.3 Hz), 3.60 - 3.56 (m, 1 H), 3.37 - 3.26 (m, 1 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.10 - 1.83 (m, 10 H), 1.70 - 1.62 (m, 2 H), 1.48 - 1.40 (m, 3 H); MS (ESI) m/z 567 (M+ + H).
903*	(R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.48 (t, 1 H, J = 7.5 Hz), 7.39 - 7.29 (m, 1 H), 7.29 - 7.26 (m, 3 H), 7.03 (t, 1 H, J = 8.4 Hz), 4.77 (brs, 1 H), 4.41 - 4.39 (m, 1 H), 3.91 (d, 2 H, J = 6.3 Hz), 3.82 - 3.75 (m, 2 H), 3.48 - 3.44 (m, 2 H), 2.90 (d, 2 H, J = 11.1 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 5 H), 2.19 - 1.69 (m, 10 H), 1.46 - 1.43 (m, 2 H); MS (ESI) m/z 567 (M+ + H).
904*	(S)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 (t, 1 H, J = 7.4 Hz), 7.38 - 7.23 (m, 4 H), 7.02 (t, 1 H, J = 8.5 Hz), 4.07 (brs, 1 H), 3.91 (d, 2 H, J = 6.3 Hz), 3.60 - 3.56 (m, 1 H), 3.37 - 3.26 (m, 1 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.10 - 1.83 (m, 10 H), 1.70 - 1.62 (m, 2 H), 1.48 - 1.40 (m, 3 H); MS (ESI) m/z 567 (M+ + H).
	(S)-(3,3'-difluoro-4'-((1-((1-(triflllloromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
905*	1H NMR (400 MHz, $CDCl_3$) δ 7.51 - 7.46 (m, 1 H), 7.37 - 7.23 (m, 4 H), 7.02 (t, 1 H, J = 8.5 Hz), 4.62 - 4.51 (m, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.83 - 3.78 (m, 1 H), 3.73 - 3.58 (m, 1 H), 3.48 - 3.36 (m, 1 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.27 - 2.20 (m, 4 H), 2.19 - 1.83 (m, 9 H), 1.71 (brs, 1 H), 1.46 - 1.42 (m, 2 H); MS (ESI) m/z 553 (M+ + H).
936*	1-(4-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.46 (m, 1 H), 7.44 - 7.41 (m, 1 H), 7.39 - 1H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.46 (m, 1 H), 7.44 - 7.41 (m, 1 H), 7.39 - 7.26 (m, 3 H), 7.03 (t, 1 H, J = 8.5 Hz), 3.92 (d, 2 H, J = 6.3 Hz), 3.85 - 3.75 (m, 3 H), 3.71 - 3.60 (m, 2 H), 3.59 - 3.39 (m, 2 H), 2.90 (d, 2 H, J = 11.5 Hz), 2.54 (s, 2 H), 2.28 - 1.83 (m, 13 H), 1.67 (brs, 1 H), 1.48 - 1.42 (m, 2 H), 1.39 - 1.38 (m, 1 H); MS (ESI) m/z 594 (M+ + H).

Example 81. Compound 906: (S)-1-(5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piper,idin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide

[0173]



__Step 1.__ methyl 5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)picolinate: To 4-((4-bromo-2-fluorophenoxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine (the product of synthesis step 2 of compound 847; 856 mg, 2.02 mmol), 6-methoxycarbonyl)pyridine-3-yl boronic acid (402 mg, 2.22 mmol), $Pd(dppf)Cl_2$ (165 mg, 0.20 mmol) and Cs_2CO_3 (1.31 g, 4.04 mmol), DME (6 mL) / H_2O (2 mL) was added, With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (80 mg, 8%).

__Step 2.__ 5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)metoxy)phenyl)picolinic acid: Methyl 5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)picolinate (80 mg, 0.17 mmol) was dissolved in THF (10 mL) and H_2O (5 mL). At room temperature, $LiOH \cdot H_2O$ (35 mg, 0.83 mmol) was added thereto, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (60 mg, 77%).

<u>**Step 3.**</u> Compound 906: 5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)metoxy)phenyl)picolinic acid (60 mg, 0.12 mmol), EDC (48 mg, 0.25 mmol), HOBt (34 mg, 0.25 mmol) and DIPEA (44 µL, 0.25 mmol) were dissolved in CH_2Cl_2 (1 mL). (S)-pyrrolidine-2-carboxamide (28 mg, 0.25 mmol) was added thereto, following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (46 mg, 64%).

1H NMR (400 MHz, $CDCl_3$) δ 8.77 - 8.72 (m, 1 H), 8.09 - 7.91 (m, 2 H), 7.37 - 7.27 (m, 2 H), 7.07 (t, 1 H, J = 8.7 Hz), 6.94 (brs, 0.5 H), 6.53 (brs, 0.5 H), 5.53 (brs, 1 H), 5.06 - 5.05 (m, 0.5 H), 4.86 - 4.83 (m, 0.5 H), 4.07 - 3.82 (m, 3 H), 2.90 (d, 2 H, J = 11.4 Hz), 2.54 (s, 2 H), 2.41 - 2.37 (m, 1 H), 2.36 - 1.78 (m, 15 H), 1.48 - 1.40 (m, 2 H); MS (ESI) m/z 563 (M+ + H).

[0174] According to the above-described synthesis process of compound 906, the compounds of Table 78 were synthesized using 5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)metoxy)phenyl)picolinic acid and the reactant of Table 77.

Table 77. (* marks comparative compound)

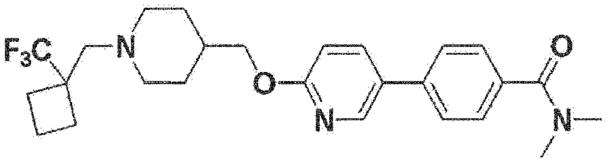
Compound No.	Reactant	Yield (%)
907*	(R)-piperidin-3-ol hydrochloride	48

Table 78. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
907*	(R)-(5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)pyridine-2-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.71 - 8.70 (m, 1 H), 7.98 (d, 1 H, J = 8.1 Hz), 7.85 (d, 1 H, J = 8.2 Hz), 7.36 - 7.27 (m, 2 H), 7.07 (t, 1 H, J = 8.4 Hz), 5.72 (s, 1 H), 4.61 (d, 1 H, J = 12.6 Hz), 4.09 - 4.04 (m, 2 H), 3.93 (d, 2 H, J = 6.3 Hz), 3.28 (d, 1 H, J = 13.0 Hz), 2.99 - 2.89 (m, 3 H), 2.54 (s, 2 H), 2.28 - 1.83 (m, 12 H), 1.70 - 1.60 (m, 3 H), 1.48 - 1.40 (m, 2 H); MS (ESI) m/z 550 (M+ + H).

Example 82. Comparative compound 576: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzamide

[0175]

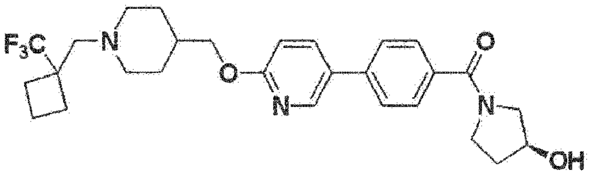


[0176] 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of comparative compound 574; 20 mg, 0.05 mmol), dimethylamine (4 mg, 0.09 mmol), EDC (17 mg, 0.09 mmol) and HOBt (12 mg, 0.09 mmol) were dissolved in DMF 1 mL. DIPEA (11 mg, 0.09 mmol) was added thereto. The reaction was performed at room temperature for 16 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (9 mg, 42%).

1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.5 Hz), 7.80 (dd, 1 H, J = 8.6, 2.6 Hz), 7.52 (m, 4 H), 6.83 (d, 1 H, J = 8.5 Hz), 4.20 (d, 2 H, J = 6.2 Hz), 3.14 (s, 3 H), 3.05 (s, 3 H), 2.88 (m, 2 H), 2.26 (s, 2 H), 2.06 (m, 4 H), 1.90 (m, 7 H), 1.43 (m, 2 H); MS (ESI) m/z 476 (M+ + H).

Example 83. Comparative compound 578:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone

[0177]

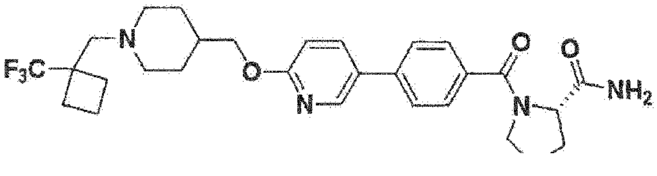


[0178] 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of comparative compound 574; 30 mg, 0.07 mmol), (S)-pyrrolidine-3-ol (11 mg, 0.13 mmol) and BOP (59 mg, 0.13 mmol) were dissolved in DMF 1 mL. TEA (13 mg, 0.13 mmol) was added thereto. At 50 °C, the reaction was performed for 16 hours. The reaction mixture was added with water, and extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (5-10 % MeOH/CH_2Cl_2) to yield the title compound as white solid (13 mg, 38%).

1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.79 (m, 1 H), 7.62 (m, 2 H), 7.54 (m, 2 H), 6.82 (d, 1 H, J = 8.5 Hz), 4.58 (m, 1 H), 4.19 (d, 2 H, J = 6.2 Hz), 3.81 (m, 2 H), 3.63 (m, 1 H), 3.57 (m, 1 H), 2.99 (m, 2 H), 2.66 (s, 3 H), 2.63 (s, 3 H), 2.26 (s, 2 H), 2.20 (m, 2 H), 2.04 (m, 3 H), 1.79 (m, 2 H), 1.43 (m, 2 H); MS (ESI) m/z 518 (M+ + H).

Example 84. Compound 581: (S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0179]



[0180] 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of comparative compound 574; 50 mg, 0.11 mmol), L-prolinamide (26 mg, 0.22 mmol), EDC (43 mg, 0.22 mmol) and HOBt (30 mg, 0.22 mmol) were dissolved in DMF 1 mL. DIPEA (29 mg, 0.22 mmol) was added thereto. At 60 °C, the reaction was performed for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water, and dried to yield the title compound as white solid (40 mg, 66%).
1H NMR (400 MHz, CDCl$_3$) δ 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.60 (dd, 4 H, J = 19.3, 8.3 Hz), 7.00 (m, 1 H), 6.83 (d, 1 H, J = 8.7 Hz), 5.54 (m, 1 H), 4.84 (m, 1 H), 4.21 (m, 2 H), 3.65 - 3.54 (m, 2 H), 2.88 - 2.65 (m, 2 H), 2.52 - 2.47 (m, 2 H), 2.22 - 1.79 (m, 15 H), 1.46 (m, 2 H); MS (ESI) m/z 545 (M+ + H).

[0181] According to the above-described synthesis process of compound 581, the compounds of Table 80 were synthesized using 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 79.

Table 79. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
579*	(R)-prolinol	30
588*	piperidin-4-yl methanol	71
595*	3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine	45
671*	D-prolinamide	41
672*	(S)-3-hydroxypiperidine hydrochloride	48
673*	(R)-3-hydroxypiperidine hydrochloride	44

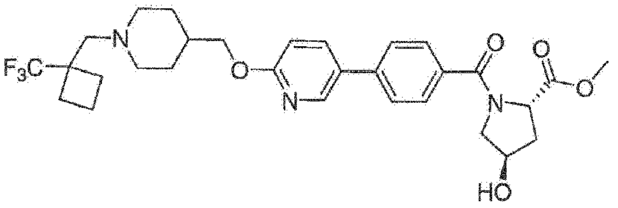
Table 80. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
579*	(R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, CDCl$_3$) δ 8.39 (d, 1 H, J = 2.4 Hz), 7.81 (dd, 1 H, J = 8.6, 2.5 Hz), 7.56 (m, 4 H), 6.83 (d, 1 H, J = 8.6 Hz), 4.94 (m, 1 H), 4.45 (m, 1 H), 4.20 (d, 2 H, J = 6.2 Hz), 3.79 (m, 2 H), 3.59 (m, 2 H), 2.88 (m, 2 H), 2.52 (s, 2 H), 2.11 (m, 5 H), 2.04 (m, 3 H), 1.89 (m, 2 H), 1.85 (m, 4 H), 1.68 (m, 1 H), 1.46 (m, 2 H); MS (ESI) m/z 532 (M+ + H).
588*	(4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, CDC13) δ 8.37 (d, 1 H, J = 2.2 Hz), 7.79 (dd, 1 H, J = 8.4, 2.3 Hz), 7.51 (dd, 4 H, J = 19.3, 8.3 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 4.78 (m, 1 H), 4.20 (m, 2 H), 3.87 (m, 1 H), 3.55 (m, 2 H), 3.20 - 2.70 (m, 4 H), 2.54 (m, 2 H), 2.22 (m, 4 H), 2.15 - 1.65 (m, 11 H), 1.49 - 1.20 (m, 4 H); MS (ESI) m/z 546 (M+ +H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
595*	(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazine-7(8H)-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, 1 H, J = 2.3 Hz), 7.81 (dd, 1 H, J = 8.6, 2.6 Hz), 7.60 (m, 4 H), 6.86 (d, 1 H, J = 8.6 Hz), 5.10 (s, 2 H), 4.28 (m, 2 H), 4.21 (m, 4 H), 2.90 (d, 2 H, J = 11.2 Hz), 2.53 (s, 2 H), 2.18 (m, 4 H), 2.02 (m, 2 H), 1.98 (m, 1 H), 1.92 (m, 1 H), 1.82 (m, 3 H), 1.47 (m, 2 H); MS (ESI) m/z 623 (M+ + H).
671*	(R)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.60 (dd, 4 H, J = 19.3, 8.3 Hz), 6.99 (m, 1 H), 6.83 (d, 1 H, J = 8.7 Hz), 5.44 (m, 1 H), 4.84 (m, 1 H), 4.21 (m, 2 H), 3.64 - 3.57 (m, 2 H), 2.90 (m, 2 H), 2.53 - 2.49 (m, 3 H), 2.24 - 2.18 (m, 4 H), 2.11 - 2.00 (m, 5 H), 2.00 - 1.80 (m, 5 H), 1.46 (m, 2 H); MS (ESI) m/z 545 (M+ + H).
672*	(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.53 (dd, 4 H, J = 19.3, 8.3 Hz), 6.83 (d, 1 H, J = 8.7 Hz), 4.20 (m, 2 H), 4.05 - 3.20 (m, 15 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.24 - 2.19 (m, 4 H), 2.15 - 1.75 (m, 9 H), 1.75 - 1.60 (m, 2 H), 1.46 (m, 2 H); MS (ESI) m/z 532 (M+ + H).
673*	(S)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.53 (dd, 4 H, J = 19.3, 8.3 Hz), 6.83 (d, 1 H, J = 8.7 Hz), 4.20 (m, 2 H), 4.05 - 3.20 (m, 15 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.24 - 2.19 (m, 4 H), 2.15 - 1.75 (m, 9 H), 1.75 - 1.60 (m, 2 H), 1.46 (m, 2 H); MS (ESI) m/z 532 (M+ + H).

Example 85. Comparative compound 931: (2S,4R)-methyl 4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxylate

[0182]

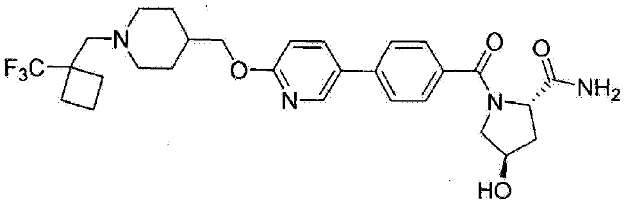


[0183] 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of comparative compound 574; 300 mg, 0.67 mmol), (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (182 mg, 1.00 mmol), EDC (257 mg, 1.34 mmol), HOBt (181 mg, 1.34 mmol) and DIPEA (0.24 mL, 1.34 mmol) were dissolved in DMF (5 mL) at room temperature. The solution was stirred at 80 °C for 12 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 5 % to 80 %), and concentrated to yield the title compound as white solid (250 mg, 65%).

1H NMR (400 MHz, $CDCl_3$) δ 8.34 (m, 1 H), 7.78 (m, 1 H), 7.63 (m, 2 H), 7.52 (m, 2 H), 6.80 (m, 1 H), 4.86 (m, 1 H), 4.55 (m, 1 H), 4.18 (m, 2 H), 3.85 - 3.61 (m, 6 H), 3.02 (m, 2 H), 2.68 (m, 2 H), 2.40 - 2.11 (m, 8 H), 2.10 - 1.79 (m, 5 H), 1.57 (m, 2 H); MS (ESI) m/z 576 (M+ + H).

Example 86. Compound 933: (2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0184]



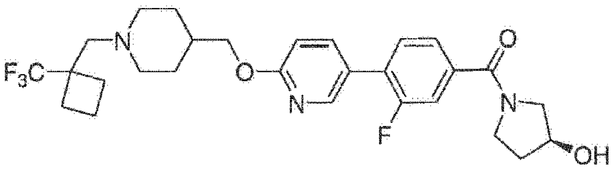
Step 1. (2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxylic acid: (2S,4R)-methyl 4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3 - yl)benzoyl)pyrrolidine-2-carboxylate(400 mg, 0.70 mmol) and $LiOH \cdot H_2O$ (58 mg, 1.39 mmol) were dissolved in THF (10 mL) / H_2O (5 mL) at room temperature. The solution was stirred at 60 °C for 10 hours. The reaction mixture was concentrated under reduced pressure to remove the solvent. The concentrate was added with 1 M-HCl aqueous solution, and concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 2. Compound 933: (2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxylic acid (400 mg, 0.71 mmol), ammonium chloride (57 mg, 1.07 mmol), EDC (205 mg, 1.07 mmol), HOBt (144 mg, 1.07 mmol) and DIPEA (18 mg, 1.43 mmol) were dissolved in DMF (10 mL) at room temperature. The solution was stirred at 60 °C for 10 hours. The reaction mixture was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as brown solid (110 mg, 28%).

1H NMR (400 MHz, $CDCl_3$ + MeOD) δ 8.33 (m, 1 H), 7.79 (m, 1 H), 7.62 (m, 2 H), 7.54 (m, 2 H), 7.22 (br, 1 H), 6.80 (m, 1 H), 5.97 (br, 1 H), 4.86 (m, 1 H), 4.41 (m, 1 H), 4.18 (m, 2 H), 3.78 (m, 1 H), 3.55 (m, 1 H), 2.78 (m, 2 H), 2.60 - 1.65 (m, 16 H), 1.42 (m, 2 H); MS (ESI) m/z 561 (M+ + H),

Example 87. Comparative compound 715:(S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone

[0185]



Step 1. ethyl 1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-carboxylate: 1-(trifluoromethyl)cyclobutanecarboxylic acid (500 mg, 2.97 mmol), ethyl piperidin-4-carboxylate (514 mg, 3.27 mmol), EDC (1.14 g, 5.94 mmol) and HOBt (803 mg, 5.95 mmol) were dissolved in CH_2Cl_2 10 mL. DIPEA (1.05 mL, 5.95 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The extracted organic layer was dried over $MgSO_4$, and then filtered. The filtrate was purified by silica gel column chromatography (10-30 % EtOAc/hexane) to yield the title compound as colorless oil (850 mg, 93%).

Step 2. (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol: Ethyl 1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-carboxylate(1.73 g, 5.63 mmol) was dissolved in dry THF 40 mL. At 0 °C, LAH (1 M in THF, 28.15 mL, 28.15 mmol) was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. The reaction was quenched by addition of MeOH slowly at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (1.4 g, 99%).

Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyridine: (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol(760 mg, 3.02 mmol) was dissolved in THF 10 mL. At 0 °C, NaH (109 mg, 4.54 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine(788 mg, 3.32 mmol) in THF was added slowly thereto. At 50 °C, the reaction was performed for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (1.10 g, 89%).

Step 4. methyl 3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine (550 mg, 1.35 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid(294 mg, 1.48 mmol), Pd(dbpf)Cl_2 (26 mg, 0.04 mmol), CS_2CO_3 (1.31 g, 4.05 mmol) were added into a microwave reactor, and then 1,4-dioxane 4 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed for 30 minutes at 110 °C. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and then extracted with EtOAc.

The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (300 mg, 46%).

Step 5. 3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (488 mg, 1.02 mmol) was dissolved in the mixed solvents of THF 10 mL / water 10 mL. $LiOH{\cdot}H_2O$ (85 mg, 2.03 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (410 mg, 86%).

Step 6. Comparative compound 715: 3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (14 mg, 0.16 mmol), EDC (41 mg, 0.21 mmol) and HOBt (29 mg, 0.21 mmol) were dissolved in DMF 2 mL. DIPEA (0.04 mL, 0.21 mmol) was added thereto, the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as white solid (25 mg, 43%).
1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 (d, 1 H, J = 8.8 Hz), 7.47 - 7.33 (m, 3 H), 6.83 (dd, 1 H, J = 10.2, 3.6 Hz), 4.62 - 6.51 (m, 1 H), 4.21 (d, 2 H, J = 5.5 Hz), 3.87 - 3.49 (m, 4 H), 2.90 (m, 2 H), 2.54 (s, 2 H), 2.22 - 1.80 (m, 15 H), 1.26 (m, 2 H); MS (ESI) m/z 536 (M+ + H).

[0186] According to the above-described synthesis process of comparative compound 715, the compounds of Table 82 were synthesized using 3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 81.

Table 81. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
716*	(R)-pyrrolidine-2-ylmethanol	42
717	L-prolinamide	37
718*	(R)-piperidin-3-ol hydrochloride	48
719*	(S)-piperidin-3-ol hydrochloride	37

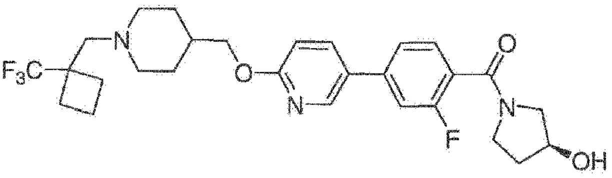
Table 82. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
716*	(R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1 H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 (dt, 1 H, J = 8.6, 2.1 Hz), 7.46 (m, 1 H), 7.38 (m, 2 H), 6.83 (dd, 1 H, J = 10.2, 3.6 Hz), 4.66 (dd, 1 H, J = 10.2, 3.6 Hz), 4.43 (m, 1 H), 4.21 (d, 2 H, J = 5.5 Hz), 3.84 - 3.76 (m, 2 H), 3.61 - 3.54 (m, 2 H), 2.89 (m, 2 H), 2.53 (s, 2 H), 2.22 (m, 4 H), 2.09 - 1.79 (m, 10 H), 1.43 (m, 2 H); MS (ESI) m/z 550 (M+ + H).

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
717	(S)-1 -(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 (dt, 1 H, J = 8.6, 2.1 Hz), 7.46 (m, 1 H), 7.38 (m, 2 H), 6.89 (br, 1 H), 6.83 (dd, 1 H, J = 10.2, 3.6 Hz), 5.55 (br, 1 H), 4.79 (m, 1 H), 4.21 (d, 2 H, J = 5.5 Hz), 3.60 (m, 2 H), 2.89 (m, 2 H), 2.54 - 2.45 (m, 3 H), 2.23 (m, 4 H), 2.14 - 1.79 (m, 10 H), 1.43 (m, 2 H); MS (ESI) m/z 563 (M+ + H).
718*	(R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 (dt, 1 H, J = 8.6, 2.1 Hz), 7.46 (m, 1 H), 7.29 (m, 2 H), 6.83 (dd, 1 H, J = 10.2, 3.6 Hz), 4.21 (m, 2 H), 4.00 - 3.22 (m, 6 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.23 (m, 4 H), 2.15 - 1.79 (m, 10 H), 1.62 (m, 2 H), 1.44 (m, 2 H); MS (ESI) m/z 550 (M+ + H).
719*	(S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1 H), 7.79 (dt, 1 H, J = 8.6, 2.1 Hz), 7.45 (t, 1 H, J = 7.8 Hz), 7.30 - 7.25 (m, 2 H), 6.83 (dd, 1 H, J = 10.2, 3.6 Hz), 4.21 (m, 2 H), 4.00 - 3.22 (m, 7 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.22 (m, 4 H), 2.15 - 1.62 (m, 10 H), 1.62 (m, 2 H); MS (ESI) m/z 550 (M+ + H).

Example 88. Comparative compound 720:(S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone

[0187]



Step 1. ethyl 2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine (the product of synthesis step 3 of comparative compound 715; 250 mg, 0.61 mmol), 3-fluoro-4-(ethoxycarbonyl)phenylboronic acid (143 mg, 0.68 mmol), $Pd(dbpf)Cl_2$ (12 mg, 0.02 mmol), CS_2CO_3 (596 mg, 1.84 mmol) were added into a microwave reactor, and then 1,4-dioxane 3 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and then extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (200 mg, 66%).

Step 2. 2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Ethyl 2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (533 mg, 1.08 mmol) was dissolved in the mixed solvents of THF 10 mL / water 10 mL. $LiOH \cdot H_2O$ (90 mg, 2.16 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (350 mg, 70%).

Step 3. Comparative compound 720: 2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (14 mg, 0.16 mmol), EDC (41 mg, 0.21 mmol) and HOBt (29 mg, 0.21 mmol) were dissolved in DMF 2 mL. DIPEA (0.04 mL, 0.21 mmol) was added thereto, and the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as white solid (21 mg, 37%).

^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (t, 1 H, *J* = 1.8 Hz), 7.78 (dt, 1 H, *J* = 8.6, 1.3 Hz), 7.51 (m, 1 H), 7.37 (dd, 1 H, *J* = 10.2, 3.6 Hz), 7.27 (m, 1 H), 6.83 (d, 1 H, *J* = 8.5 Hz), 4.60 (m, 1 H), 4.21 (d, 2 H, *J* = 5.8 Hz), 3.84 - 3.25 (m, 5 H), 2.88 (m, 2 H), 2.53 (m, 2 H), 2.21 - 1.79 (m, 14 H), 1.42 (m, 2 H); MS (ESI) m/z 536.1 (M^+ + H).

[0188] According to the above-described synthesis process of comparative compound 720, the compounds of Table 84 were synthesized using 2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 83.

Table 83. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
721*	(R)-pyrrolidine-2-ylmethanol	41
722	L-prolinamide	32
723*	(R)-piperidin-3-ol hydrochloride	36
724*	(S)-piperidin-3-ol hydrochloride	37

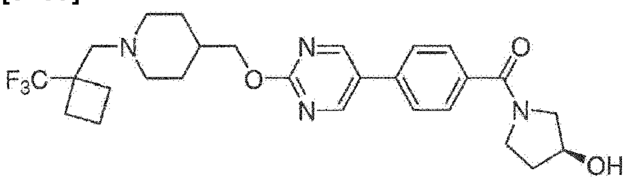
Table 84. (* marks comparative compound)

Compound No.	Compound Name, ^1H-NMR, MS (ESI)
721*	(R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (t, 1 H, J = 1.8 Hz), 7.78 (dt, 1 H, J = 8.6, 1.3 Hz), 7.51 (m, 1 H), 7.37 (dd, 1 H, J = 10.2, 3.6 Hz), 7.27 (m, 1 H), 6.83 (d, 1 H, J = 8.5 Hz), 4.70 (m, 1 H), 4.41 (m, 1 H), 4.21 (m, 2 H), 3.84 - 3.77 (m, 2 H), 3.46 (m, 2 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.24 - 1.78 (m, 16 H), 1.42 (m, 2 H); MS (ESI) m/z 550 (M+ + H).
	(S)-1-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
722	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (t, 1 H, J = 1.8 Hz), 7.78 (dt, 1 H, J = 8.6, 1.3 Hz), 7.50 (m, 1 H), 7.39 (dd, 1 H, J = 10.2, 3.6 Hz), 7.27 (m, 1 H), 6.90 (br, 1 H), 6.83 (d, 1 H, J = 8.5 Hz), 5.51 (br, 1 H), 4.83 (m, 1 H), 4.21 (m, 2 H), 3.52 - 3.44 (m, 2 H), 2.89 (m, 2 H), 2.49 (m, 3 H), 2.22 (m, 4 H), 2.21 - 1.61 (m, 12 H), 1.42 (m, 2 H); MS (ESI) m/z 563 (M+ + H).
723*	(R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (t, 1 H, J = 1.8 Hz), 7.78 (dt, 1 H, J = 8.6, 1.3 Hz), 7.47 (m, 1 H), 7.36 (dd, 1 H, J = 10.2, 3.6 Hz), 7.27 (m, 1 H), 6.83 (d, 1 H, J = 8.5 Hz), 4.22 (m, 2 H), 4.12 - 3.95 (m, 2 H), 3.80 - 3.16 (m, 5 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.41 - 1.71 (m, 16 H), 1.47 (m, 2 H); MS (ESI) m/z 550 (M+ + H).
724*	(S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 1 H), 7.78 (dt, 1 H, J = 8.6, 1.3 Hz), 7.47 (m, 1 H), 7.36 (dd, 1 H, J = 10.2, 3.6 Hz), 7.25 (m, 1 H), 6.83 (d, 1 H, J = 8.5 Hz), 4.22 - 3.61 (m, 4 H), 3.57 - 3.13 (m, 4 H), 2.89 - 2.70 (m, 2 H), 2.60 - 2.45 (m, 2 H), 2.24 - 1.63 (m, 14 H), 1.47 (m, 3 H); MS (ESI) m/z 550 (M+ + H).

Example 89. Comparative compound 970:(S)-(3-hydroxypyrrolidine-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone

[0189]



Step 1. 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidine: (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol (760 mg, 3.02 mmol) was dissolved in THF (40 mL). At 0 °C, NaH (143 mg, 5.97 mmol) was added thereto, and stirred for 30 minutes. 5-bromo-2-iodopyrimidine (1.25 g, 4.38 mmol) was added thereto, following with stirring at 55 °C for 10 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 2. methyl 4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidine (450 mg, 1.10 mmol), 4-(methoxycarbonyl)phenylboronic acid (218 mg, 1.21 mmol), $Pd(dbpf)Cl_2$ (22 mg, 0.03 mmol) and CS_2CO_3 (1.07 g, 3.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (300 mg, 59%).

Step 3. 4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid: Methyl 4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate (300 mg, 0.65 mmol) and $LiOH{\cdot}H_2O$ (27 mg, 0.65 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 6 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (290 mg, 99%).

Step 4. Comparative compound 970: 4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (15 mg, 0.17 mmol), EDC (32 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol) and DIPEA (0.04 mL, 0.22 mmol) were dissolved in DMF (4 mL) at room temperature. The solution was stirred at 60 °C for 16 hours , added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as white solid (20 mg, 35%).
1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 2 H), 7.69 - 7.55 (m, 4 H), 4.63 - 4.48 (m, 1 H), 4.28 (m, 2 H), 3.88 - 3.45 (m, 4 H), 2.90 (m, 2 H), 2.52 (s, 2 H), 2.22 - 1.83 (m, 14 H), 1.46 (m, 2 H); MS (ESI) m/z 519 (M+ + H).

[0190] According to the above-described synthesis process of comparative compound 970, the compounds of Table 86 were synthesized using 4-(2-((1-((1-(trifluoromethyl)cyclobutyl)-methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid and the reactant of Table 85.

Table 85. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
971*	(R)-pyrrolidine-2-ylmethanol	34
972*	(R)-piperidin-3-ol hydrochloride	34
973	L-prolinamide	33

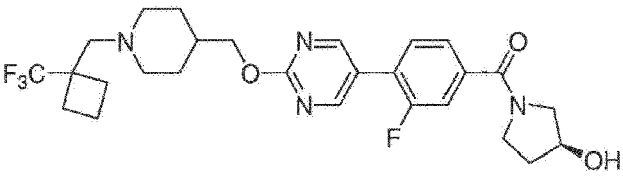
Table 86. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
971*	(R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(2-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 2 H), 7.66 - 7.57 (m, 4 H), 4.81 (m, 1 H), 4.45 (m, 1 H), 4.28 (m, 2 H), 3.85 - 3.77 (m, 2 H), 3.57 (m, 2 H), 2.89

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	(m, 2 H), 2.52 (s, 2 H), 2.21 (m, 4 H), 2.20 - 1.60 (m, 11 H), 1.48 (m, 2 H); MS (ESI) m/z 533 (M+ + H).
972*	(R)-(3-hydroxypiperidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 2 H), 7.56 - 7.53 (m, 4 H), 4.31 (m, 2 H), 3.97 - 3.38 (m, 3 H), 2.89 (m, 2 H), 2.52 (s, 2 H), 2.29 - 1.73 (m, 14 H), 1.64 (m, 2 H), 1.44 (m, 2 H), 1.29 (m, 2 H); MS (ESI) m/z 533 (M+ + H).
973	(S)-1-(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 2 H), 7.67 - 7.57 (m, 4 H), 6.94 (br, 1 H), 5.53 (br, 1 H), 4.82 (m, 1 H), 4.29 (m, 2 H), 3.65 - 3.51 (m, 2 H), 2.90 (m, 2 H), 2.50 (m, 3 H), 2.29 - 1.85 (m, 14 H), 1.48 (m, 2 H); MS (ESI) m/z 546 (M+ + H).

Example 90. Comparative compound 974:(S)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone

[0191]



Step 1. methyl 3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidine (the product of synthesis step 1 of comparative compound 970; 450 mg, 1.10 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (240 mg, 1.21 mmol), Pd(dbpf)Cl_2 (22 mg, 0.03 mmol) and CS_2CO_3 (1.07 mg, 3.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (300 mg, 57%).

Step 2. 3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid: Methyl 3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate (300 mg, 0.62 mmol) and LiOH·H_2O (52 mg, 1.25 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 6 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (250 mg, 86%).

Step 3. Comparative compound 974: 3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (14 mg, 0.16 mmol), EDC (31 mg, 0.16 mmol), HOBt (22 mg, 0.16 mmol) and DIPEA (0.04 mL, 0.21 mmol) were dissolved in DMF (4 mL) at room temperature. The solution was stirred at 60 °C for 16 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as white solid (20 mg, 35%).

1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2 H), 7.46 - 7.37 (m, 3 H), 4.63 - 4.52 (m, 1 H), 4.28 (m, 2 H), 3.88 - 3.47 (m, 4 H), 2.88 (m, 2 H), 2.52 (s, 2 H), 2.25 - 1.78 (m, 14 H), 1.47 (m, 2 H); MS (ESI) m/z 537 (M+ + H).

[0192] According to the above-described synthesis process of comparative compound 974, the compounds of Table 88 were synthesized using 3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid and the reactant of Table 87.

Table 87. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
975*	(R)-pyrrolidine-2-ylmethanol	34
976*	(R)-piperidin-3-ol hydrochloride	34
977	L-prolinamide	33

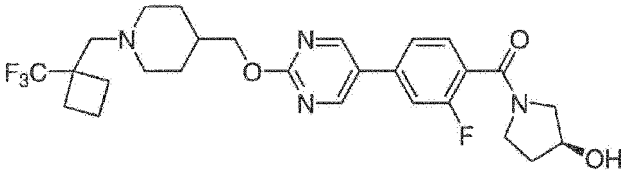
Table 88. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
975*	(R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyri¯olidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2 H), 7.50 - 7.37 (m, 3 H), 4.58 (m, 1 H), 4.41 (m, 1 H), 4.28 (m, 2 H), 3.87 - 3.74 (m, 2 H), 3.56 (m, 2 H), 2.90 (m, 2 H), 2.53 (s, 2 H), 2.31 - 1.65 (m, 15 H), 1.48 (m, 2 H); MS (ESI) m/z 551 (M+ + H).
976*	(R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.70 (s, 2 H), 7.45 (m, 1 H), 7.29 (m, 2 H), 4.30 (m, 2 H), 3.97 - 3.35 (m, 5 H), 2.90 (m, 2 H), 2.53 (m, 2 H), 2.37 - 1.58 (m, 16 H), 1.49 (m, 2 H); MS (ESI) m/z 551 (M+ + H).
	(S)-1-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
977	1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 2 H), 7.50 - 7.40 (m, 3 H), 6.83 (br, 1 H), 5.55 (br, 1 H), 4.78 (m, 1 H), 4.29 (m, 2 H), 3.66 - 3.54 (m, 2 H), 2.89 (m, 2 H), 2.53 - 2.43 (m, 3 H), 2.25 - 1.68 (m, 14 H), 1.49 (m, 2 H); MS (ESI) m/z 564 (M+ + H).

Example 91. Comparative compound 978:(S)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone

[0193]



Step 1. ethyl 2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidine (the product of synthesis step 1 of comparative compound 970; 450 mg, 1.10 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (257 mg, 1.21 mmol), $Pd(dbpf)Cl_2$ (22 mg, 0.03 mmol) and CS_2CO_3 (1.07 mg, 3.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (300 mg, 55%).

Step 2. 2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyrimidin-5-yl)benzoic acid: Ethyl 2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoate (300 mg, 0.61 mmol) and $LiOH \cdot H_2O$ (51 mg, 1.21 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 6 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (280 mg, 99%).

Step 3. Comparative compound 978: 2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (14 mg, 0.16 mmol), EDC (31 mg, 0.16 mmol), HOBt (22 mg, 0.16 mmol) and DIPEA (0.04 mL, 0.21 mmol) were dissolved in DMF (4 mL) at room temperature. After stirring at 60 °C for 16 hours, the reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under

reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as white solid (20 mg, 35%).
1H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2 H), 7.55 (m, 1 H), 7.37 (m, 1 H), 7.26 (m, 1 H), 4.62 - 4.51 (m, 1 H), 4.29 (m, 2 H), 3.84 - 3.32 (m, 4 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.35 - 1.62 (m, 14 H), 1.48 (m, 2 H); MS (ESI) m/z 537 (M+ + H).

[0194] According to the above-described synthesis process of comparative compound 978, the compounds of Table 90 were synthesized using 2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoic acid and the reactant of Table 89.

Table 89. (* marks comparative compound)

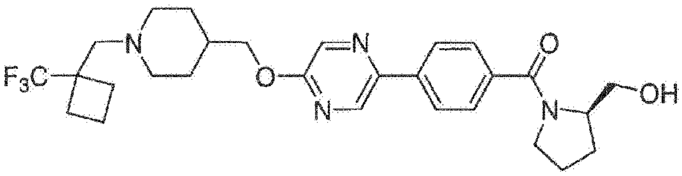
Compound No.	Reactant	Yield (%)
979*	(R)-pyrrolidine-2-ylmethanol	36
980*	(R)-piperidin-3-ol hydrochloride	34
981	L-prolinamide	33

Table 90. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
979*	(R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2 H), 7.56 (m, 1 H), 7.38 (m, 1 H), 7.28 (m, 1 H), 4.61 (m, 1 H), 4.39 (m, 1 H), 4.28 (m, 2 H), 3.84 - 3.78 (m, 2 H), 3.45 (m, 2 H), 2.89 (m, 2 H), 2.53 (s, 2 H), 2.22 (m, 4 H), 2.18 - 1.62 (m, 11 H), 1.48 (m, 2 H); MS (ESI) m/z 551 (M+ + H).
980*	(R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2 H), 7.52 (m, 1 H), 7.37 (m, 1 H), 7.25 (m, 1 H), 4.29 (m, 2 H), 4.10 - 3.08 (m, 7 H), 2.89 (m, 2 H), 2.53 (m, 2 H), 2.28 - 1.61 (m, 14 H), 1.48 (m, 2 H); MS (ESI) m/z 551 (M+ + H).
981	(S)-1-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.71 (m, 2 H), 7.56 (m, 1 H), 7.39 (m, 1 H), 7.28 (m, 1 H), 6.88 (br, 1 H), 5.55 (br, 1 H), 4.82 (m, 1 H), 4.29 (m, 2 H), 3.54 - 3.41 (m, 2 H), 2.89 (m, 2 H), 2.50 (m, 3 H), 2.38 - 1.81 (m, 14 H), 1.48 (m, 2 H); MS (ESI) m/z 564 (M+ + H).

Example 92. Comparative compound 1007: (R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)methanone

[0195]



Step 1. 2-iodo-5-((l-((l-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine: (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol(880 mg, 3.50 mmol) was dissolved in THF (30 mL). At 0 °C, NaH (126 mg, 5.25 mmol) was added thereto, and stirred for 30 minutes. 2-bromo-5-iodopyrazine (1.09 g, 3.85 mmol) was added thereto, following with stirring at 55 °C for 10 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process.

Step 2. methyl 4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyrazine-2-yl)benzoate: 2-iodo-5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine (350 mg, 0.77 mmol), 4-(methoxycarbonyl)phenylboronic acid (152 mg, 0.85 mmol), Pd(dbpf)Cl_2 (15 mg, 0.02 mmol) and CS_2CO_3 (747 mg, 2.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (210 mg, 59%).

Step 3. 4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid: Methyl 4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (210 mg, 0.45 mmol) and $LiOH \cdot H_2O$ (38 mg, 0.91 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 4 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (200 mg, 98%).

Step 4. Comparative compound 1007: 4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (50 mg, 0.11 mmol), (R)-pyrrolidine-2-ylmethanol (17 mg, 0.17 mmol), EDC (32 mg, 0.17 mmol), HOBt (23 mg, 0.17 mmol) and DIPEA (0.04 mL, 0.22 mmol) were dissolved in DMF (2 mL) at room temperature. The solution was stirred at 60 °C for 16 hours. The concentrate was added with water (4 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as beige solid (25 mg, 42%).
1H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1 H), 8.29 (s, 1 H), 7.98 (d, 2 H, J = 8.2 Hz), 7.63 (d, 2 H, J = 8.2 Hz), 4.91 (d, 1 H, J = 6.7 Hz), 4.44 (q, 1 H, J = 7.2 Hz), 4.24 (d, 2 H, J = 5.4 Hz), 3.81 (m, 2 H), 3.55 (m, 2 H), 2.89 (m, 2 H), 2.53 (s, 2 H), 2.25 - 1.62 (m, 15 H), 1.45 (m, 2 H); MS (ESI) m/z 533 (M+ + H).

[0196] According to the above-described synthesis process of comparative compound 1007, the compounds of Table 92 were synthesized using 4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 91.

Table 91. (* marks comparative compound)

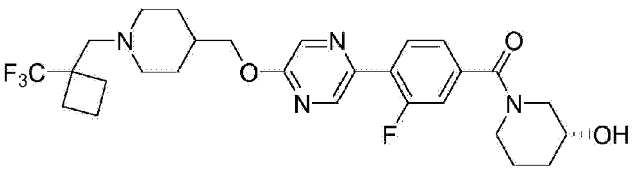
Compound No.	Reactant	Yield (%)
1008*	(R)-piperidin-3-ol hydrochloride	37
1009*	L-prolinamide	36

Table 92. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1008*	(R)-(3-hydroxypiperidin-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.51 (m, 1 H), 8.29 (m, 1 H), 7.96 (m, 2 H), 7.53 (m, 2 H), 4.23 (m, 2 H), 4.04 - 3.02 (m, 7 H), 2.90 (m, 2 H), 2.54 (s, 2 H), 2.38 - 1.44 (m, 16 H); MS (ESI) m/z 533 (M+ + H).
1009*	(S)-1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.52 (m, 1 H), 8.29 (m, 1 H), 7.98 (d, 2 H, J = 8.2 Hz), 7.65 (d, 2 H, J = 8.2 Hz), 6.99 (br, 1 H), 5.51 (br, 1 H), 4.83 (m, 1 H), 4.24 (m, 2 H), 3.62 (m, 2 H), 2.90 (m, 2 H), 2.54 - 2.45 (m, 3 H), 2.25 - 1.62 (m, 14 H), 1.45 (m, 2 H); MS (ESI) m/z 546 (M+ + H).

Example 93. Comparative compound 1010: (R)-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

[0197]



<u>Step 1.</u> methyl 3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: 2-iodo-5-((1-((1-(trifluoromethyl)cyclobutyl)-methyl)piperidin-4-yl)methoxy)pyrazine (the product of synthesis step 1 of comparative compound 1007; 350 mg, 0.77 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (167 mg, 0.85 mmol), $Pd(dbpf)Cl_2$ (15 mg, 0.02 mmol) and Cs_2CO_3 (747 mg, 2.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The

obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (210 mg, 57%).

Step 2. 3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyrazine-2-yl)benzoic acid: Methyl 3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (210 mg, 0.44 mmol) and $LiOH{\cdot}H_2O$ (37 mg, 0.87 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 4 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (200 mg, 98%).

Step 3. Comparative compound 1010: 3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (50 mg, 0.11 mmol), (R)-piperidin-3-ol hydrochloride (22 mg, 0.16 mmol), EDC (31 mg, 0.16 mmol), HOBt (22 mg, 0.16 mmol) and DIPEA (0.04 mL, 0.21 mmol) were dissolved in DMF (2 mL) at room temperature. The solution was stirred at 60 °C for 16 hours. The concentrate was added with water (4 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as beige solid (21 mg, 36%).
1H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1 H), 8.33 (m, 1 H), 8.02 (t, 1 H, J = 7.8 Hz), 7.32 (m, 2 H), 4.33 (m, 2 H), 4.04 - 3.21 (m, 7 H), 2.90 (m, 2 H), 2.54 (s, 2 H), 2.35 - 1.44 (m, 16 H); MS (ESI) m/z 551 (M+ + H).

[0198] According to the above-described synthesis process of comparative compound 1010, the compounds of Table 94 were synthesized using 3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 93.

Table 93.

Compound No.	Reactant	Yield (%)
1011*	L-prolinamide	40

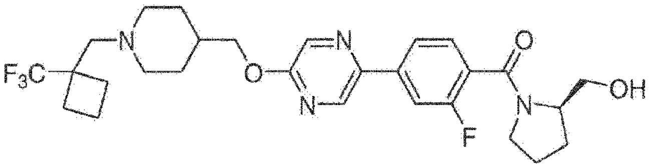
Table 94.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1011*	(S)-1-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1 H), 8.33 (s, 1 H), 8.05 (t, 1 H, J = 7.9 Hz), 7.43 (m, 2 H), 6.90 (s, 1 H), 5.53 (s, 1 H), 4.79 (dd, 1 H, J = 10.2, 3.6 Hz), 4.25 (d, 2 H, J = 6.0 Hz), 3.67 - 3.51 (m, 2 H), 2.90 (m, 2 H), 2.54 - 2.42 (m, 3 H), 2.16 - 1.66 (m, 14 H), 1.47 (m, 2 H); MS (ESI) m/z 564 (M+ + H).

Example 94. Comparative compound 1012: (R)-(2-fluoro-4-(5-((1-((1-

(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0199]



<u>Step 1.</u> ethyl 2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: 2-iodo-5-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrazine (the product of synthesis step 1 of comparative compound 1007; 350 mg, 0.77 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (179 mg, 0.85 mmol), Pd(dbpf)Cl_2 (15 mg, 0.02 mmol) and Cs_2CO_3 (747 mg, 2.31 mmol) were added to 1,4-dioxane (10 mL) / water (5 mL). With a microwave radiation, the mixture was heated at 110 °C for 45 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc/hexane = 5 % to 25 %), and concentrated to yield the title compound as white solid (300 mg, 79%).

<u>Step 2.</u> 2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyrazine-2-yl)benzoic acid: Ethyl 2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (300 mg, 0.61 mmol) and LiOH·H_2O (51 mg, 1.21 mmol) were dissolved in THF (10 mL) / water (5 mL) at room temperature. The solution was stirred at 60 °C for 4 hours. The reaction mixture was concentrated under reduced pressure. The concentrate was added with 1M HCl aqueous solution (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (280 mg, 99%).

<u>Step 3.</u> Comparative compound 1012: 2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (50 mg, 0.11 mmol), (R)-pyrrolidine-2-ylmethanol (16 mg, 0.16 mmol), EDC (31 mg, 0.16 mmol), HOBt (22 mg, 0.16 mmol) and DIPEA (0.04 mL, 0.21 mmol) were dissolved in DMF (2 mL) at room temperature. The solution was stirred at 60 °C for 16 hours. The concentrate was added with water (4 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as beige solid (24 mg, 41%).
1H NMR (400 MHz, $CDCl_3$) δ 8.52 (m, 1 H), 8.29 (m, 1 H), 7.75 (m, 2 H), 7.53 (m, 1 H), 4.72 (m, 1 H), 4.40 (m, 1 H), 4.23 (d, 2 H, J = 5.4 Hz), 3.84 - 3.78 (m, 2 H), 3.45 (m, 2 H), 2.89 (m, 2 H), 2.54 (s, 2 H), 2.24 - 1.64 (m, 15 H), 1.45 (m, 2 H); MS (ESI) m/z 551 (M+ + H).

[0200] According to the above-described synthesis process of comparative compound 1012, the compounds of Table 96 were synthesized using 2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid and the reactant of Table 95.

Table 95. (* marks comparative compound)

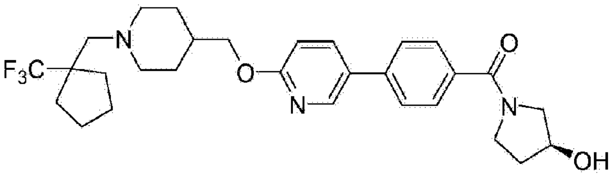
Compound No.	Reactant	Yield (%)
1013*	(R)-piperidin-3-ol hydrochloride	43
1014*	L-prolinamide	42

Table 96. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1013*	(R)-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1 H), 8.28 (s, 1 H), 7.73 (m, 2 H), 7.49 (m, 1 H), 4.28 (m, 2 H), 4.17 - 3.11 (m, 7 H), 2.89 (m, 2 H), 2.54 (s, 2 H), 2.35 - 1.44 (m, 16 H); MS (ESI) m/z 551 (M+ + H).
1014*	(S)-1-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.51 (m, 1 H), 8.29 (m, 1 H), 7.77 (m, 2 H), 7.52 (m, 1 H), 6.91 (s, 1 H), 5.50 (s, 1 H), 4.82 (m, 1 H), 4.25 (m, 2 H), 3.53 (m, 1 H), 3.42 (m, 1 H), 2.91 (m, 2 H), 2.54 - 2.46 (m, 3 H), 2.26 - 1.75 (m, 14 H), 1.46 (m, 2 H); MS (ESI) m/z 564 (M+ + H).

Example 95. Comparative compound 772:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone

[0201]



Step 1. ethyl 1-(1-(trifluoromethyl)cyclopentanecarbonyl)piperidin-4-carboxylate: 1-(trifluoromethyl)cyclopentanecarboxylic acid(500 mg, 2.74 mmol), ethyl piperidin-4-carboxylate(518 mg, 3.29 mmol), EDC (1.05 g, 5.49 mmol) and HOBt (742 mg, 5.49 mmol) were dissolved in DMF 5 mL. DIPEA (0.97 mL, 5.49 mmol) was added thereto, and the reaction was performed at 60°C for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The extracted organic layer was dried over $MgSO_4$, and then filtered. The filtrate was purified by silica gel column chromatography (10-30 % EtOAc/hexane) to yield the title compound as colorless oil (400 mg, 45%).

Step 2. (1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methanol: Ethyl 1-(1-(trifluoromethyl)cyclopentanecarbonyl)piperidin-4-carboxylate(1.06 g, 3.30 mmol) was dissolved in dry THF 20 mL. At 0°C, LAH (1 M in THF, 16.49 mL, 16.49 mmol) was added slowly thereto. The reaction was performed at 50 °C for 10 hours. The reaction was quenched by slow addition of MeOH at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (844 mg, 96%).

Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine: (1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methanol (844 mg, 3.18 mmol) was dissolved in THF 10 mL. At 0 °C, NaH (115 mg, 4.77 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine (829 mg, 3.50 mmol) in THF was added slowly thereto. The reaction was performed at 50 °C for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (900 mg, 67%).

Step 4. methyl 4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine (400 mg, 0.95 mmol), 4-(methoxycarbonyl)phenylboronic acid (188 mg, 1.04 mmol), $Pd(dbpf)Cl_2$ (19 mg, 0.03 mmol), Cs_2CO_3 (922 mg, 2.85 mmol) were added into a microwave reactor, and then 1,4-dioxane 4 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and then extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (330 mg, 73%).

Step 5. 4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (330 mg, 0.69 mmol) was dissolved in the mixed solvents of THF 4 mL / water 4 mL. $LiOH{\cdot}H_2O$ (58 mg, 1.38 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (300 mg, 94%).

Step 6. Comparative compound 772: 4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (50 mg, 0.11 mmol), (S)-pyrrolidine-3-ol (14 mg, 0.16 mmol), EDC (41 mg, 0.22 mmol) and HOBt (29 mg, 0.22 mmol) were dissolved in DMF 2 mL. DIPEA (0.04 mL, 0.22 mmol) was added thereto, and the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as white solid (21 mg, 37%).
1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.80 (dd, 1 H, J = 10.2, 3.6 Hz), 7.65 - 7.53 (m, 4 H), 6.83 (d, 1 H, J = 8.6 Hz), 4.62 - 4.50 (m, 1H), 4.29 - 4.18 (m, 2 H), 3.87 - 3.48 (m, 5 H), 2.89 (m, 2 H), 2.47 (s, 2 H), 2.30 (t, 2 H, J = 11.2 Hz), 2.20 - 1.96 (m, 3 H), 1.87 - 1.76 (m, 10 H), 1.45 (m, 2 H); MS (ESI) m/z 532 (M+ + H).

[0202] According to the above-described synthesis process of comparative compound 772, the compounds of Table 98 were synthesized using 4-(6-((1-((1-

(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 97.

Table 97. (* marks comparative compound)

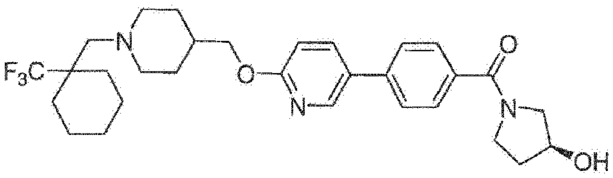
Compound No.	Reactant	Yield (%)
773*	(R)-pyrrolidine-2-ylmethanol	42
774	L-prolinamide	40
775*	(R)-piperidin-3-ol hydrochloride	37

Table 98. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
773*	(R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.3 Hz), 7.80 (dd, 1 H, J = 10.2, 3.6 Hz), 7.62 - 7.56 (m, 4 H), 6.83 (d, 1 H, J = 8.6 Hz), 4.91 (d, 1 H, J = 7.2 Hz), 4.47 - 4.42 (m, 1 H), 4.30 - 4.18 (m, 2 H), 3.86 - 3.51 (m, 4 H), 3.23 (m, 1 H), 2.90 - 2.81 (m, 2 H), 2.47 (s, 2 H), 2.32 - 2.19 (m, 3 H), 2.17 - 1.65 (m, 13 H), 1.42 (m, 2 H); MS (ESI) m/z 546 (M+ + H).
774	(S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1 H), 7.80 (dd, 1 H, J = 10.2, 3.6 Hz), 7.64 - 7.53 (m, 4 H), 6.98 (br, 1 H), 6.83 (d, 1 H, J = 8.6 Hz), 5.45 (br, 1 H), 4.84 (dd, 1 H, J = 10.2, 3.6 Hz), 4.31 - 4.19 (m, 2 H), 3.67 - 3.54 (m, 2 H), 3.23 (m, 1 H), 2.89 - 2.80 (m, 2 H), 2.52 - 2.47 (m, 3 H), 2.32 (m, 2 H), 2.16 (m, 4 H), 1.98 - 1.68 (m, 9 H), 1.42 (m, 2 H); MS (ESI) m/z 559 (M+ + H).
775*	(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.3 Hz), 7.80 (dd, 1 H, J = 10.2, 3.6 Hz), 7.56 (d, 1 H, J = 8.4 Hz), 7.51 (d, 1 H, J = 8.3 Hz), 6.82 (d, 1 H, J = 8.6 Hz), 4.25 - 3.20 (m, 9 H), 2.89 (m, 2 H), 2.47 (s, 2 H), 2.30 (t, 2 H, J = 11.0 Hz), 2.09 - 1.68 (m, 14 H), 1.42 (m, 2 H); MS (ESI) m/z 546 (M+ + H).

Example 96. Comparative compound 776:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone

[0203]



Step 1. ethyl 1-(1-(trifluoromethyl)cyclohexanecarbonyl)piperidin-4-carboxylate: 1-(trifluoromethyl)cyclohexanecarboxylic acid(500 mg, 2.55 mmol), ethyl piperidin-4-carboxylate (481

mg, 3.06 mmol), EDC (977 mg, 5.09 mmol) and HOBt (689 mg, 5.09 mmol) were dissolved in DMF 5 mL. DIPEA (0.90 mL, 5.09 mmol) was added thereto. The reaction was performed at 60 °C for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution and extracted with EtOAc. The extracted organic layer was dried over $MgSO_4$, and then filtered. The filtrate was purified by silica gel column chromatography (10-30 % EtOAc/hexane) to yield the title compound as colorless oil (250 mg, 29%).

Step 2. (1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methanol: Ethyl 1-(1-(trifluoromethyl)cyclohexanecarbonyl)piperidin-4-carboxylate (576 mg, 1.72 mmol) was dissolved in dry THF 10 mL. At 0 °C, LAH (1 M in THF, 8.59 mL, 8.59 mmol) was added slowly thereto. The reaction was performed at 50 °C for 10 hours. The reaction was quenched by slow addition of MeOH at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (430 mg, 90%).

Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine: (1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methanol(430 mg, 1.54 mmol) was dissolved in THF 10 mL. At 0 °C, NaH (55 mg, 2.31 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine(401 mg, 1.69 mmol) in THF was added slowly thereto. The reaction was performed at 50 °C for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (380 mg, 57%).

Step 4. methyl 4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy) pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine (380 mg, 0.87 mmol), 4-(methoxycarbonyl)phenylboronic acid(173 mg, 0.96 mmol), $Pd(dbpf)Cl_2$ (17 mg, 0.03 mmol), Cs_2CO_3 (848 mg, 2.62 mmol) were added into a microwave reactor, and then 1,4-dioxane 4 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (250 mg, 58%).

Step 5. 4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (250 mg, 0.51 mmol) was dissolved in the mixed solvents of THF 4 mL / water 4 mL. $LiOH{\cdot}H_2O$ (43 mg, 1.02 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (210 mg, 87%).

Step 6. Comparative compound 776: 4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (45 mg, 0.09 mmol), (S)-pyrrolidine-3-ol (12 mg, 0.14 mmol), EDC (36 mg, 0.19 mmol) and HOBt (26 mg, 0.19 mmol) were dissolved in DMF 2 mL. DIPEA (0.03 mL, 0.19 mmol) was added thereto, the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as white solid (24 mg, 47%). 1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.80 (m, 1 H), 7.67 - 7.54 (m, 4 H), 6.81 (m, 1 H), 4.61 - 4.45 (m, 1 H), 4.28 - 4.17 (m, 2 H), 3.84 - 3.48 (m, 4 H), 2.87 (m, 2 H), 2.48 (s, 2 H), 2.32 - 2.00 (m, 5 H), 1.88 - 1.35 (m, 15 H); MS (ESI) m/z 546 (M+ + H).

[0204] According to the above-described synthesis process of comparative compound 776, the compounds of Table 100 were synthesized using 4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 99.

Table 99. (* marks comparative compound)

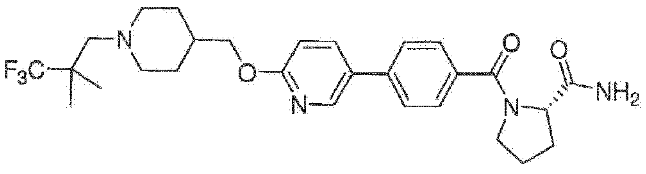
Compound No.	Reactant	Yield (%)
777*	(R)-pyrrolidine-2-ylmethanol	42
778	L-prolinamide	28
779*	(R)-piperidin-3-ol hydrochloride	38

Table 100. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
777*	(R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (m, 1 H), 7.80 (m, 1 H), 7.62 - 7.56 (m, 4 H), 6.83 (m, 1 H), 4.89 (m, 1 H), 4.54 (m, 1 H), 4.30 - 4.18 (m, 2 H), 3.84 - 3.48 (m, 4 H), 2.87 (m, 2 H), 2.48 (s, 2 H), 2.32 - 2.18 (m, 3 H), 1.90 - 1.35 (m, 18 H); MS (ESI) m/z 560 (M+ + H).
778	(S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (m, 1 H), 7.80 (m, 1 H), 7.64 - 7.56 (m, 4 H), 7.00 (s, 1 H), 6.83 (m, 1 H), 5.58 (s, 1 H), 4.82 (m, 1 H), 4.30 - 4.18 (m, 2 H), 3.66 - 3.56 (m, 2 H), 2.85 (m, 2 H), 2.48 (m, 3 H), 2.32 (m, 2 H), 2.10 (m, 2 H), 1.93 - 1.35 (m, 16 H); MS (ESI) m/z 573 (M+ + H).
779*	(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl) piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (m, 1 H), 7.78 (m, 1 H), 7.56 - 7.49 (m, 4 H), 6.83 (m, 1 H), 4.17 (m, 2 H), 4.04 - 3.18 (m, 6 H), 2.85 (m, 2 H), 2.48 (m, 2 H), 2.32 (m, 2 H), 2.03 - 1.35 (m, 19 H); MS (ESI) m/z 560 (M+ + H).

Example 97. Compound 828: (S)-1-(4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0205]



Step 1. ethyl 1-(3,3,3-trifluoro-2,2-dimethylpropanoyl)piperidin-4-carboxylate: 3,3,3-trifluoro-2,2-dimethylpropanoic acid (500 mg, 3.20 mmol), ethyl piperidin-4-carboxylate (604 mg, 3.84 mmol), EDC (1.23 g, 6.41 mmol) and HOBt (866 mg, 6.41 mmol) were dissolved in DMF 15 mL. DIPEA (1.13 mL, 6.41 mmol) was added thereto, and the reaction was performed at 60 °C for 8 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution and extracted with EtOAc. The extracted organic layer was dried over $MgSO_4$, and then filtered. The filtrate was purified by silica gel column chromatography (10-30 % EtOAc/hexane) to yield the title compound as colorless oil (300 mg, 36%).

Step 2. (1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methanol: Ethyl 1-(3,3,3-trifluoro-2,2-dimethylpropanoyl)piperidin-4-carboxylate (260 mg, 0.88 mmol) was dissolved in dry THF 20 mL. At 0 °C, LAH (1 M in THF, 4.40 mL, 4.40 mmol) was added slowly thereto and the reaction was performed at 50 °C for 10 hours. The reaction was quenched by slow addition of MeOH at 0 °C. The reaction mixture was added with water, and then extracted with EtOAc. The obtained extracted organic layer was dried over $MgSO_4$, and then filtered to yield the title compound as colorless oil (170 mg, 81%).

Step 3. 5-bromo-2-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine: (1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methanol(170 mg, 0.71 mmol) was dissolved in THF 10 mL. At 0°C, NaH (26 mg, 1.07 mmol) was added slowly thereto. The reaction was performed at room temperature for 20 minutes. At 0 °C, 2,5-dibromopyridine (185 mg, 0.78 mmol) in THF was added slowly thereto, and the reaction was performed at 50 °C for 10 hours. After the completion of the reaction, the reaction mixture was added with ice water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as colorless oil (260 mg, 93%).

Step 4. methyl 4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine (260 mg, 0.66 mmol), 4-(methoxycarbonyl)phenylboronic acid(130 mg, 0.72 mmol), Pd(dbpf)Cl_2 (13 mg, 0.02 mmol), Cs_2CO_3 (640 mg, 1.97 mmol) were added into a microwave reactor, and then 1,4-dioxane 6 mL and water 3 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and then extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (200 mg, 68%).

Step 5. 4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (200 mg, 0.44 mmol) was dissolved in the mixed solvents of THF 10 mL / water 10 mL. $LiOH{\cdot}H_2O$ (37 mg, 0.89 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (150 mg, 77%).

Step 6. Compound 828: 4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (40 mg, 0.09 mmol), L-prolinamide (16 mg, 0.14 mmol), EDC (35 mg, 0.18 mmol) and HOBt (25 mg, 0.18 mmol) were dissolved in DMF 2 mL. DIPEA (24 mg, 0.18 mmol) was added thereto, and the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as white solid (20 mg, 41%).
1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.1 Hz), 7.81 (dd, 1 H, J = 10.2, 3.6 Hz), 7.64 - 7.56 (m, 4 H), 6.99 (s, 1 H), 6.83 (d, 1 H, J = 8.6 Hz), 5.56 (s, 1 H), 4.82 (dd, 1 H, J = 10.2, 3.6 Hz), 4.19 (d, 2 H, J = 4.8 Hz), 3.66 - 3.56 (m, 2 H), 2.83 (d, 2 H, J = 9.0 Hz), 2.47 - 2.30 (m, 4 H), 2.10 (m, 2 H), 1.90 - 1.70 (m, 5 H), 1.42 (m, 2 H), 1.11 (m, 6 H); MS (ESI) m/z 423 (M+ + H).

[0206] According to the above-described synthesis process of compound 828, the compounds of Table 102 were synthesized using 4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 101.

Table 101. (* marks comparative compound)

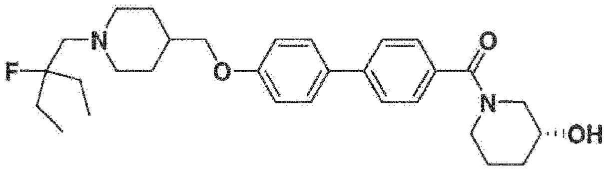
Compound No.	Reactant	Yield (%)
829*	(R)-piperidin-3-ol hydrochloride	41

Table 102. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
829*	(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.1 Hz), 7.80 (dd, 1 H, J = 10.2, 3.6 Hz), 7.56 - 7.49 (m, 4 H), 6.83 (d, 1 H, J = 8.6 Hz), 4.19 (d, 2 H, J = 4.8 Hz), 4.00 - 3.10 (m, 7 H), 2.83 (d, 2 H, J = 9.0 Hz), 2.40 - 2.30 (m, 4 H), 2.00 - 1.39 (m, 8 H), 1.11 (m, 6 H); MS (ESI) m/z 520 (M+ + H).

Example 98. Comparative compound 809: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0207]



Step 1. 2,2-diethyloxirane: 3-methylenepentane (2 g, 23.76 mmol) and m-CPBA (6.56 g, 38.02 mmol) were dissolved in CH_2Cl_2 30 mL. At 0 °C, the reaction was performed for a day. The reaction

mixture was added with saturated Na_2SO_3 aqueous solution, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure to yield the title compound as colorless oil (1.8 g, 75%).

Step 2. 3-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 4 of comparative compound 686; 500 mg, 1.85 mmol) was dissolved in EtOH 4 mL. 2,2-diethyloxirane (the product of synthesis step 1 of compound 809; 930 mg, 9.25 mmol), K_2CO_3 (512 mg, 3.70 mmol) and water 2 mL were added thereto, With a microwave radiation, the mixture was stirred at 110 °C for 20 minutes. After the completion of the reaction, EtOH was evaporated from the reaction mixture under reduced pressure, and then a little of water was added to thereto. The resulting precipitate was filtered, and dried under reduced pressure to yield the title compound as white solid (600 mg, 87%).

Step 3. 4-((4-bromophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine: 3-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (596 mg, 1.61 mmol) was dissolved in CH_2Cl_2 5 mL. DAST (285 mg, 1.77 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 15 - 20 % EtOAc/Hexane) to yield the title compound as white solid (520 mg, 87%).

Step 4. methyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine (130 mg, 0.35 mmol), 4-(methoxycarbonyl)phenylboronic acid (69 mg, 0.38 mmol), Pd(dbpf)Cl_2 (11 mg, 0.02 mmol) and Cs_2CO_3 (228 mg, 0.70 mmol) were dissolved in 1,4-dioxane 4 mL and water 1 mL. With a microwave radiation, the reaction was performed at 120 °C for 15 minutes. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (105 mg, 70%).

Step 5. 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (105 mg, 0.25 mmol) was dissolved in THF:MeOH:water = 3/1.5/1 mL. LiOH·H_2O (21 mg, 0.49 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (72 mg, 71 %).

Step 6. Comparative compound 809: 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (35 mg, 0.09 mmol), (R)-piperidin-3-ol (13 mg, 0.13 mmol) and BOP (75 mg, 0.17 mmol) were dissolved in DMF 1 mL. After stirring for 10 minutes at room temperature, TEA (26 mg, 0.26 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, $MeOH/CH_2Cl_2$) to yield the title compound as white solid (17 mg, 40%).

1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 6 H), 6.96 (d, 2 H, J = 6.8 Hz), 3.82 (m, 4 H), 3.42 (m, 3 H), 2.99 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 (m, 2 H), 1.71 (m, 11 H), 1.64 (m, 2 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 497 (M + H).

[0208] According to the above-described synthesis process of comparative compound 809, the compounds of Table 104 were synthesized using 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 103.

Table 103. (* marks comparative compound)

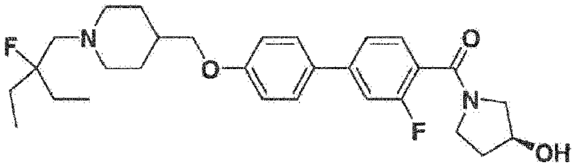
Compound No.	Reactant	Yield (%)
891	(S)-pyrrolidine-2-carboxamide	51
892*	(R)-pyrrolidine-2-ylmethanol	63
893*	(S)-pyrrolidine-3-ol	51
894*	(R)-pyrrolidine-3-ol	61

Table 104. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
891	(S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 3 H), 7.52 (d, 2 H, J = 8.6 Hz), 7.01 (s, 1 H), 6.99 (d, 2 H, J = 6.5 Hz), 5.48 (s, 1 H), 4.82 (t, 1 H, J = 6.2 Hz), 3.84 (d, 2 H, J = 5.7 Hz), 3.63 (m, 2 H), 2.99 (m, 2 H), 2.46 (m, 2 H), 2.07 (m, 2 H), 2.02 - 1.42 (m, 12 H), 0.90 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 510 (M + H).
892*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	MS (ESI) m/z 497 (M + H).
893*	(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 6 H), 6.96 (d, 2 H, J = 8.7 Hz), 4.58 - 4.45 (m, 1 H), 3.84 (m, 2 H), 3.66 (m, 4 H), 3.02 (m, 2 H), 2.48 (m, 2 H), 2.46 - 1.98 (m, 7 H), 1.82 - 1.46 (m, 7 H), 0.90 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 483 (M + H).
894*	(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 6 H), 6.97 (d, 2 H, J = 8.8 Hz), 3.84 (m, 4 H), 3.42 (m, 3 H), 2.98 (m, 2 H), 2.47 (m, 2 H), 1.92 (m, 2 H), 1.78 - 1.43 (m, 13 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 497 (M + H).

Example 99. Comparative compound 888: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone

[0209]



Step 1. ethyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine (the product of synthesis step 3 of comparative compound 809; 130 mg, 0.35 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (345 mg, 1.63 mmol), Pd(dppf)Cl_2 (60 mg, 0.07 mmol) and Na_2CO_3 (313 mg, 2.95 mmol) were dissolved in DME 12 mL and water 3 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (390 mg, 54%).

Step 2. 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid: Ethyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylate (390 mg, 0.85 mmol) was dissolved in THF/MeOH/water = 6/3/2 mL. $LiOH \cdot H_2O$ (71 mg, 1.70 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using 1 N HCl. The resulting precipitate was filtered to yield the title compound as white solid (340 mg, 92%).

Step 3. Comparative compound 888: 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid (0.03 g, 0.07 mmol), EDC (0.03 g, 0.14 mmol), HOBt (0.02 g, 0.14 mmol) and DIPEA (0.036 mL, 0.209 mmol) were dissolved in DMF (1 mL). At room temperature, (S)-pyrrolidine-3-ol (0.01 g, 0.10 mmol) was added thereto, following with stirring at 50 °C for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (22 mg, 63%).
1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 3 H), 7.39 (m, 1 H), 7.28 (m, 1 H), 6.98 (d, 2 H, J = 8.7 Hz), 4.62 (s, 0.5 H), 4.49 (s, 0.5 H), 3.86 (m, 2 H), 3.70 (m, 2 H), 3.46 (m, 1 H), 2.96 (m, 2 H), 2.43 (m, 2 H), 1.97 - 1.65 (m, 11 H), 0.91 (t, 6 H, J = 7.4 Hz); MS (ESI) m/z 501 (M + H).

[0210] According to the above-described synthesis process of comparative compound 888, the compounds of Table 106 were synthesized using 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid and the reactant of Table 105.

Table 105. (* marks comparative compound)

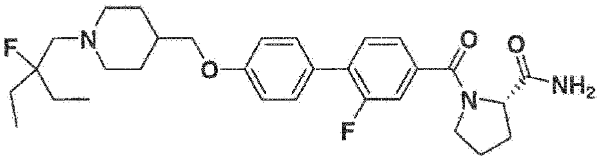
Compound No.	Reactant	Yield (%)
810*	(R)-pyrrolidine-2-ylmethanol	44
814	piperidin-4-carboxamide hydrochloride	47
866	(S)-pyrrolidine-2-carboxamide	
889*	(S)-piperidin-3-ol	63
890*	(R)-piperidin-3-ol	67

Table 106. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
810*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.47 (m, 3 H), 7.33 (m, 2 H), 6.96 (m, 2 H), 5.74 (s, 1 H), 4.42 (m, 1 H), 3.84 (d, 2 H, J = 5.9 Hz), 3.74 (m, 2 H), 3.59 (m, 2 H), 2.98 (m, 2 H), 2.48 (s, 1 H), 2.42 (s, 1 H), 1.92 (m, 11 H), 1.72 (m, 11 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 515 (M + H).
814	1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenylcarbonyl)piperidin-4-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.32 (m, 2 H), 7.27 (m, 1 H), 6.98 (m, 2 H), 5.49 (m, 1 H), 4.73 (m, 1 H), 3.84 (m, 2 H), 3.72 (m, 1 H), 3.02 (m, 4 H), 2.46 (m, 3 H), 2.04 (m, 2 H), 1.83 (m, 1 H), 1.68 (m, 12 H), 0.91 (t, 6 H, J = 7.5 Hz)
866	(S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide
	MS (ESI) m/z 528 (M + H).
889*	(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 2 H), 7.41 (m, 2 H), 7.27 (m, 1 H), 6.98 (d, 2 H, J = 8.7 Hz), 4.00 (m, 2 H), 3.85 (d, 2 H, J = 5.9 Hz), 3.36 (m, 1 H), 3.26 (m, 2 H), 2.95 (m, 2 H), 2.37 (m, 2 H), 2.16 (m, 2 H), 1.82 - 1.26 (m, 14 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 515 (M + H).
890*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 2 H), 7.42 (m, 2 H), 7.27 (m, 1 H), 6.98 (d, 2 H, J = 6.9 Hz), 4.01 (m, 2 H), 3.85 (d, 2 H, J = 5.9 Hz), 3.57 (m, 1 H), 3.33 (m, 2 H), 3.01 (m, 2 H), 2.48 (m, 2 H), 2.18 (m, 2 H), 1.94 - 1.48 (m, 14 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 515 (M + H).

Example 100. Compound 895: (S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

[0211]



Step 1. methyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine (the product of synthesis step 3 of comparative compound 809; 550 mg, 1.48 mmol), 2-fluoro-4-(methoxycarbonyl) phenylboronic acid (322 mg, 1.63 mmol), Pd(dppf)Cl_2 (60 mg, 0.07 mmol), Na_2CO_3 (313 mg, 2.95 mmol) were dissolved in DME 12 mL and water 3 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure.
The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (350 mg, 53%).

Step 2. 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid: Methyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylate (350 mg, 0.79 mmol) was dissolved in THF/MeOH/water = 6/3/2 mL. LiOH·H_2O (66 mg, 1.57 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using 1 N HCl. The resulting precipitate was filtered to yield the title compound as white solid (310 mg, 91%).

Step 3. Compound 895: 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid (0.03 g, 0.07 mmol), EDC (0.03 g, 0.14 mmol), HOBt (0.02 g, 0.14 mmol) and DIPEA (0.04 mL, 0.21 mmol) were dissolved in DMF (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (12 mg, 0.10 mmol) was added thereto, following with stirring at 50 °C for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (23 mg, 62%).
1H NMR (400 MHz, $CDCl_3$) δ 7.48 (m, 3 H), 7.35 (m, 2 H), 6.97 (d, 2 H, J = 8.7 Hz), 6.91 (s, 1 H), 5.56 (s, 1 H), 4.78 (m, 1 H), 3.84 (d, 2 H, J = 5.9 Hz), 3.61 (m, 2 H), 3.00 (m, 2 H), 2.44 (m, 2 H), 2.03 (m, 4 H), 1.89 - 1.44 (m, 12 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 528 (M + H).

[0212] According to the above-described synthesis process of compound 895, the compounds of Table 108 were synthesized using 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid and the reactant of Table 107.

Table 107. (* marks comparative compound)

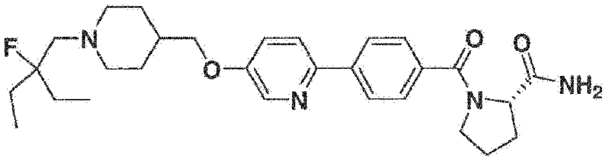
Compound No.	Reactant	Yield (%)
811*	(R)-pyrrolidine-2-ylmethanol	67
812*	(R)-piperidin-3-ol hydrochloride	57

Table 108. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
811*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 3 H), 7.37 (m, 2 H), 7.28 (m, 1 H), 6.95 (m, 2 H), 4.78 (s, 1 H), 4.37 (m, 1 H), 3.78 (m, 4 H), 3.45 (m, 2 H), 2.98 (m, 2 H), 2.47 (s, 1 H), 2.41 (s, 1 H), 2.17 (m, 3 H), 1.87 (m, 1 H), 1.75 (m, 10 H), 0.89 (t, 6 H, J = 7.5 Hz)
812*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.45 (m, 3 H), 7.21 (m, 2 H), 6.97 (m, 2 H), 3.91 (m, 4 H), 3.56 (m, 3 H), 2.99 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 (m, 2 H), 1.71 (m, 13 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 515 (M + H).

Example 101. Compound 896: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0213]



Step 1. 3-((4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: 2-chloro-5-(piperidin-4-ylmethoxy)pyridine hydrochloride (the product of synthesis step 2 of compound 691; 1.4 g, 5.32 mmol) was dissolved in EtOH 6 mL. 2,2-diethyloxirane (the product of synthesis step 1 of compound 809; 1.60 g, 15.96 mmol), K_2CO_3 (1.47 g, 10.64 mmol) and water 3 mL were added thereto, With a microwave radiation, the mixture was stirred at 110 °C for 20 minutes. Ethanol was evaporated from the reaction mixture under reduced pressure, and water was added thereto. The resulting precipitate was filtered, and dried under reduced pressure to yield the title compound as white solid (1.61 g, 92%).

Step 2. 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine: 3-((4-((6-chloropyridine-3-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (1.61 g, 4.93 mmol) was dissolved in CH_2Cl_2 10 mL. DAST (873 mg, 5.42 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (40 g ISCO silica gel cartridge, 15 - 20 % Hexane/EtOAc) to yield the title compound as white solid (1.24 g, 76%).

Step 3. methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine (550 mg, 1.67 mmol), 4-(methoxycarbonyl)phenylboronic acid (331 mg, 1.84 mmol), Pd(dppf)Cl_2 (68 mg, 0.08 mmol) and Na_3CO_3 (354 mg, 3.35 mmol) were dissolved in DME 12 mL and water 3 mL, and then refluxed with heating and stirring for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (310 mg, 43%).

Step 4. 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid: methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate (310 mg, 0.98 mmol) was dissolved in THF/MeOH/water = 6/3/2 mL. $LiOH \cdot H_2O$ (61 mg, 1.45 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using 1 N HCl. The resulting precipitate was filtered to yield the title compound as white solid (210 mg, 70%).

Step 5. Compound 896: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid (0.05 g, 0.12 mmol), EDC (0.05 g, 0.24 mmol), HOBt (0.03 g, 0.24 mmol) and DIPEA (0.06 mL, 0.36 mmol) were dissolved in CH_2Cl_2 (3 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.02 g, 0.18 mmol) was added thereto, following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (0.04 g, 61%).
1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.6 Hz), 7.97 (d, 2 H, J = 8.2 Hz), 7.62 (m, 3 H), 7.26 (m, 1 H), 7.06 (s, 1 H), 5.78 (s, 1 H), 4.78 (m, 1 H), 3.88 (d, 2 H, J = 5.9 Hz), 3.61 (m, 2 H), 3.00 (d, 2 H, J = 10.7 Hz), 2.49 - 2.43 (m, 2 H), 2.38 (m, 1 H), 2.08 (m, 4 H), 1.80 (m, 8 H), 1.42 (m, 2 H), 0.88 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 511 (M + H).

[0214] According to the above-described synthesis process of compound 896, the compounds of Table 110 were synthesized using 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoic acid and the reactant of Table 109.

Table 109. (* marks comparative compound)

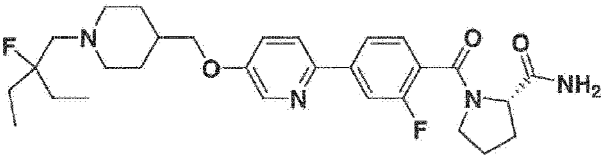
Compound No.	Reactant	Yield (%)
897*	(R)-piperidin-3-ol	51

Table 110. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
897	(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.8 Hz), 7.94 (d, 2 H, J = 8.1 Hz), 7.65 (d, 1 H, J = 8.7 Hz), 7.49 (d, 2 H, J = 8.0 Hz), 7.26 (dd, 1 H, J = 8.7, 2.8 Hz), 3.88 (m, 5 H), 3.26 (m, 3 H), 3.00 (d, 2 H, J = 10.4 Hz), 2.48 - 2.42 (m, 2 H), 2.14 (m, 2 H), 1.81 (m, 3 H), 1.74 (m, 7 H), 1.45 (m, 3 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 498 (M + H).

Example 102. Compound 898: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoyl)pyrrolidine-2-carboxamide

[0215]



Step 1. ethyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoate: 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 2 of compound 896; 550 mg, 1.67 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (390 mg, 1.84 mmol), $Pd(dppf)Cl_2$ (68 mg, 0.08 mmol) and Na_2CO_3 (354 mg, 3.35 mmol) were dissolved in DME 12 mL and water 3 mL, and then refluxed with heating for a day. The reaction mixture was filtered through Celite. The filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as white solid (290 mg, 37%).

Step 2. 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoic acid: Ethyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoate (290 mg, 0.63 mmol) was dissolved in THF/MeOH/water = 6/3/2 mL. $LiOH\cdot H_2O$ (53 mg, 1.26 mmol) was added thereto. And then, the mixture was refluxed with heating for 3 hours. After the completion of the reaction, the solvent was dried under reduced pressure, following with adjusting pH to below 6 using 1 N HCl. The resulting precipitate was filtered to yield the title compound as white solid (220 mg, 80%).

Step 3. Compound 898: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoic acid (0.05 g, 0.12 mmol), EDC (0.05 g, 0.24 mmol), HOBt (0.03 g, 0.24 mmol) and DIPEA (0.06 mL, 0.36 mmol) were dissolved in CH_2Cl_2 (3 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.02 g, 0.18 mmol) was added thereto, following with stirring with at the same temperature for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (0.04 g, 61%).

1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, 1 H, J = 2.9 Hz), 7.75 (m, 2 H), 7.67 (d, 1 H, J = 8.8 Hz), 7.49 (t, 1 H, J = 7.6 Hz), 7.27 (dd, 1 H, J = 8.5, 3.1 Hz), 6.93 (s, 1 H), 5.64 (s, 1 H), 4.81 (m, 1 H), 3.89 (d, 2 H, J = 6.0 Hz), 3.50 (m, 1 H), 3.40 (m, 1 H), 3.00 (m, 2 H), 2.43 (m, 3 H), 2.08 (m, 4 H), 1.92 - 1.46 (m, 10 H), 0.89 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 529 (M + H).

[0216] According to the above-described synthesis process of compound 898, the compounds of Table 112 were synthesized using 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorobenzoic acid and the reactant of Table 111.

Table 111. (* marks comparative compound)

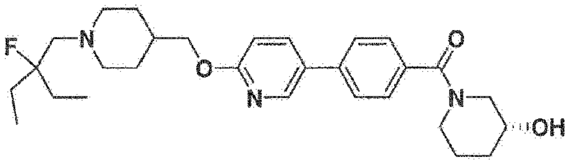
Compound No.	Reactant	Yield (%)
899*	(S)-pyrrolidine-3-ol	51
900*	(R)-piperidin-3-ol	58

Table 112. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
899*	(S)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorophenyl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, 1 H, J = 2.7 Hz), 7.75 (m, 2 H), 7.66 (d, 1 H, J = 8.7 Hz), 7.51 (m, 1 H), 7.27 (m, 1 H), 4.61 (s, 0.5 H), 4.49 (s, 0.5 H), 3.91 (d, 2 H, J = 5.8 Hz), 3.77 (m, 1 H), 3.59 (m, 2 H), 3.35 (m, 1 H), 3.02 (m, 2 H), 2.43 (m, 2 H), 2.07 (m, 5 H), 1.98 (m, 9 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 502 (M + H).
900*	(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (m, 1 H), 7.65 (m, 3 H), 7.45 (t, 1 H, J = 7.5 Hz), 7.26 (dd, 1 H, J = 9.1, 2.5 Hz), 4.07 (m, 1 H), 3.89 (d, 2 H, J = 6.0 Hz), 3.52 (m, 2 H), 3.23 (m, 2 H), 3.00 (m, 2 H), 2.49 - 2.43 (m, 2 H), 2.15 (m, 2 H), 1.91 - 1.59 (m, 13 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 516 (M + H).

Example 103. Comparative compound 954: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

[0217]



Step 1. 3-((4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: To 5-bromo-2-(piperidin-4-ylmethoxy)pyridine hydrochloride (the product of synthesis step 3 of comparative compound 784; 2.70 g, 8.77 mmol), 2,2-diethyloxirane (the product of synthesis step 1 of compound 809; 4.39 g, 43.88 mmol) and K_2CO_3 (2.42 g, 17.55 mmol), EtOH (6 mL) / H_2O (3 mL) was added. With a microwave radiation, the mixture was heated at 115 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (1.50 g, 46%, yellow oil).

Step 2. 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine: 3-((4-((5-bromopyridine-2-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (1.50 g, 4.04 mmol) was dissolved in CH_2Cl_2 (8 mL). At 0 °C, DAST (0.58 mL, 4.44 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.95 g, 63%, yellow oil).

Step 3. methyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine (0.30 g, 0.80 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.17 g, 0.96 mmol), $Pd(dppf)Cl_2$ (0.06 g, 0.08 mmol) and Na_3CO_3 (0.17 g, 1.60 mmol) were dissolved in DME (12 mL) / water (3 mL). With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated $NaHCO_3$ aqueous solution was added thereto, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.21 g, 61%).

Step 4. 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid: Methyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (0.18 g, 0.39 mmol) and $LiOH \cdot H_2O$ (0.03 g, 0.78 mmol) were dissolved in THF / MeOH (6 mL / 3 mL) / water (2 mL). The mixture was refluxed with heating for 10 hours, and then cooled to room temperature, following with concentrating under reduced pressure. After the addition of water to the concentrate, the resulting precipitate was filtered, and dried to yield the title compound as yellow solid (0.15 g, 88%).

Step 5. Comparative compound 954: 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid (0.04 g, 0.09 mmol), EDC (0.03 g, 0.19 mmol), HOBt (0.02 g, 0.19 mmol) and DIPEA (0.03 g, 0.28 mmol) were dissolved in DMF (1 mL). At room temperature, (R)-piperidin-3-ol (0.02 g, 0.15 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography

(SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 5 %), and concentrated to yield the title compound as white solid (0.02 g, 31%).
1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1 H, J = 2.5 Hz), 7.78 (dd, 1 H, J = 8.6, 2.6 Hz), 7.52 (m, 4 H), 6.81 (d, 1 H, J = 8.6 Hz), 4.17 (d, 2 H, J = 6.2 Hz), 3.98 - 3.05 (m, 6 H), 2.96 (m, 2 H), 2.46 - 2.39 (m, 2 H), 2.11 (m, 2 H), 1.95 (m, 3 H), 1.69 (m, 8 H), 1.43 (m, 3 H), 0.88 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 498 (M + H).

[0218] According to the above-described synthesis process of comparative compound 954, the compounds of Table 114 were synthesized using 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid and the reactant of Table 113.

Table 113. (* marks comparative compound)

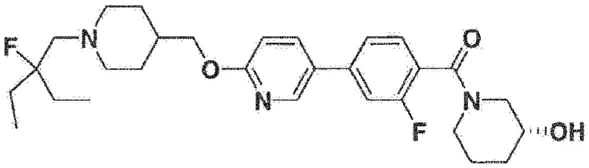
Compound No.	Reactant	Yield (%)
955*	(S)-piperidin-3-ol	37

Table 114. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
955*	(S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, 1 H, J = 2.5 Hz), 7.77 (dd, 1 H, J = 8.6, 2.5 Hz), 7.52 (m, 4 H), 6.81 (d, 1 H, J = 8.6 Hz), 4.17 (d, 2 H, J = 6.2 Hz), 4.01 - 3.08 (m, 5 H), 2.96 (m, 2 H), 2.46 - 2.40 (m, 2 H), 2.11 (m, 2 H), 1.93 - 1.63 (m, 12 H), 1.42 (m, 2 H), 0.88 (t, 6 H, J = 7.5 Hz)(S)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-2-yl)-2-fluorophenyl)(3-hydroxypyrrolidine-1-yl)methanone

Example 104. Comparative compound 956: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

[0219]



__Step 1.__ ethyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoate: To 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 2 of comparative compound 954; 0.30 g, 0.80 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.18 g, 0.88 mmol), $Pd(dppf)Cl_2$ (0.06 g, 0.08 mmol) and Na_2CO_3 (0.17 g, 1.60 mmol), DME (12 mL) / water (3 mL) was added. With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated $NaHCO_3$

aqueous solution was added thereto, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.18 g, 48%).

Step 2. 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid: Ethyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoate (0.18 g, 0.39 mmol) and $LiOH \cdot H_2O$ (0.03 g, 0.78 mmol) were dissolved in THF / MeOH (6 mL / 3 mL) / water (2 mL). The mixture was refluxed with heating for 10 hours, and then cooled to room temperature, following with concentrating under reduced pressure. After the addition of water to the concentrate, the resulting precipitate was filtered, and dried to yield the title compound as yellow solid (0.15 g, 88%).

Step 3. Comparative compound 956: 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid (0.04 g, 0.08 mmol), EDC (0.03 g, 0.16 mmol), HOBt (0.02 g, 0.16 mmol) and DIPEA (0.03 g, 0.24 mmol) were dissolved in DMF (1 mL). At room temperature, (R)-piperidin-3-ol (0.01 g, 0.12 mmol) was added thereto, following with stirring at 50 °C for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 5 %), and concentrated to yield the title compound as white solid (17 mg, 40%).
1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1 H), 7.75 (m, 1 H), 7.44 (m, 1 H), 7.35 (m, 1 H), 7.24 (m, 1 H), 6.81 (d, 1 H, J = 8.6 Hz), 4.17 (d, 2 H, J = 6.1 Hz), 3.92 (m, 2 H), 3.33 (m, 3 H), 2.96 (m, 2 H), 2.46 - 2.40 (m, 2 H), 1.96 (m, 6 H), 1.69 (m, 8 H), 1.39 (m, 2 H), 0.88 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 516 (M + H).

[0220] According to the above-described synthesis process of comparative compound 956, the compounds of Table 116 were synthesized using 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorobenzoic acid and the reactant of Table 115.

Table 115. (* marks comparative compound)

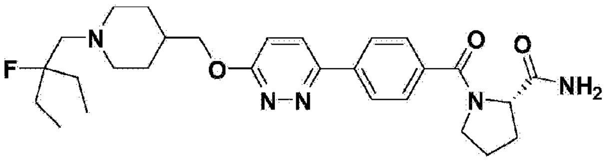
Compound No.	Reactant	Yield (%)
957*	(S)-piperidin-3-ol	35

Table 116. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
957*	(S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.33 (m, 1 H), 7.74 (m, 1 H), 7.43 (m, 1 H), 7.34 (m, 1 H), 7.24 (m, 1 H), 6.81 (d, 1 H, J = 8.6 Hz), 4.17 (d, 2 H, J = 6.2 Hz), 4.08 - 3.63 (m, 2 H), 3.58 - 3.02 (m, 3 H), 2.96 (m, 2 H), 2.45 - 2.39 (m, 2 H), 2.08 (m, 2 H), 1.95 (m, 3 H), 1.68 (m, 10 H), 1.42 (m, 2 H), 0.88 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 516 (M + H).

Example 105. Comparative Compound 953: (S)-1-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoyl)pyrrolidine-2-carboxamide

[0221]



Step 1. t-butyl 4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-carboxylate: t-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (the product of synthesis step 1 of comparative compound 686; 3.00 g, 13.94 mmol) and NaH (0.50 g, 20.90 mmol) were dissolved in DMF (100 ml). At 0 °C, 3,6-dichloropyridazine (2.49 g, 16.72 mmol) was added thereto, following with stirring at room temperature for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 0% to 50 %), and concentrated to yield the title compound as white solid (2.60 g, 56%).

Step 2. 3-chloro-6-(piperidin-4-ylmethoxy)pyridazine: t-butyl 4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-carboxylate (2.60 g, 7.93 mmol) and HCl in 1,4-dioxane (4 M solution in 1,4-dioxane, 9.91 mL, 39.66 mmol) were dissolved in MeOH (30 mL) at room temperature. The solution was stirred at the same temperature for 3 hours, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (1.80 g, 85%).

Step 3. 3-((4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: 3-chloro-6-(piperidin-4-ylmethoxy)pyridazine (1.20 g, 5.27 mmol) and Et_3N (7.31 mL, 52.70 mmol) were dissolved in EtOH (10 mL). 2,2-diethyloxirane (the product of synthesis step 1 of compound 809; 1.06 g, 10.54 mmol) was added thereto. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (0.30 g, 17%, white solid).

Step 4. 3-chloro-6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine: 3-((4-((6-chloropyridazine-3-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (0.30 g, 0.91 mmol) was dissolved in dichloromethane (20 mL). At 0 °C, DAST (0.16 g, 1.00 mmol) was added thereto, following with stirring at room temperature for 1 hour. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 50 %), and concentrated to yield the title compound as yellow solid (0.14 g, 46%).

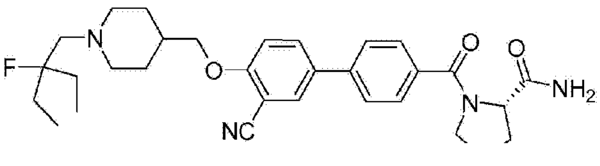
Step 5. methyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate: 3-chloro-6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine (0.14 g, 0.42 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.08 g, 0.42 mmol), Pd(dbpf)Cl_2 (0.01 g, 0.02 mmol) and Cs_2CO_3 (0.27 g, 0.85 mmol) were added to 1,4-dioxane (12 mL) / H_2O (3 mL). With a microwave radiation, the mixture was heated at 115 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 80 %), and concentrated to yield the title compound as white solid (0.05 g, 37%).

Step 6. 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid: methyl 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoate (0.05 g, 0.12 mmol) and LiOH·H_2O (0.02 g, 0.58 mmol) were dissolved in THF (2 mL) / H_2O /MeOH (3 mL) at room temperature. The solution was stirred at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as yellow solid (0.05 g, 93%).

Step 7. Comparative Compound 953: 4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoic acid (0.02 g, 0.05 mmol), EDCI (0.02 g, 0.10 mmol), HOBt (0.01 g, 0.10 mmol) and DIPEA (0.03 g, 0.24 mmol) were dissolved in DMF (2 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.01 g, 0.10 mmol) was added thereto, following with stirring at 60 °C for 12 hours. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated yield the title compound as light-yellow solid (0.01 g, 44%).
1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, 2 H, J = 8.1 Hz), 7.79 (d, 1 H, J = 9.3 Hz), 7.64 (d, 2 H, J = 10.0 Hz), 7.04 (d, 2 H, J = 9.3 Hz), 6.95 (brs, 1 H), 4.81 - 4.80 (m, 1 H), 4.42 (d, 2 H, J = 6.4 Hz), 3.59 - 3.53 (m, 2 H), 2.96 (d, 2 H, J = 11.2 Hz), 2.44 - 2.38 (m, 3 H), 2.13 - 1.62 (m, 11 H), 1.46 - 1.23 (m, 3 H), 0.87 (t, 6 H, J = 7.4 Hz); MS (ESI) m/z 512 (M+ + H).

Example 106. Compound 1004 : (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0222]



Step 1. methyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 1000; 400 mg, 1.01 mmol), 4-(methoxycarbonyl)phenylboronic acid (199 mg, 1.11 mmol), Pd(dppf)Cl_2 (82 mg, 0.10 mmol) and Cs_2CO_3 (656 mg, 2.01 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (184 mg, 40%).

Step 2. 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (184 mg, 0.41 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (85 mg, 2.03 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (158 mg, 88%).

Step 3. Compound 1004: 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (35 mg, 0.08 mmol), (S)-pyrrolidine-2-carboxamide (18 mg, 0.16 mmol), EDC (31 mg, 0.16 mmol) and HOBt (22 mg, 0.16 mmol) was added thereto, DIPEA (28 μL, 0.16 mmol) was dissolved in CH_2Cl_2 (1 mL). After stirring at room temperature for a day, the reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (22 mg, 51%).
1H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.70 (m, 2 H), 7.63 - 7.60 (m, 2 H), 7.54 - 7.52 (m, 2 H), 7.34 - 7.27 (m, 1 H), 7.02 - 6.99 (m, 1 H), 5.72 (brs, 1 H), 4.80 - 4.78 (m, 1 H), 3.94 (d, 2 H, J = 6.3 Hz), 3.66 - 3.63 (m, 1 H), 3.52 - 3.48 (m, 3 H), 3.00 (s, 1 H), 2.95 (s, 1 H), 2.71 - 2.60 (m, 2 H), 2.48 - 2.37 (m, 1 H), 2.10 - 1.99 (m, 5 H), 1.82 - 1.69 (m, 7 H), 0.87 - 0.83 (m, 6 H); MS (ESI) m/z 535 (M+ + H).

[0223] According to the above-described synthesis process of compound 1004, the compounds of Table 118 were synthesized using 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 117.

Table 117. (* marks comparative compound)

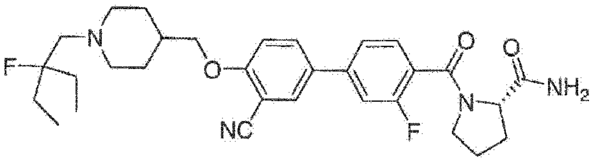
Compound No.	Reactant	Yield (%)
1005*	(R)-pyrrolidine-2-ylmethanol	48
1006*	(S)-pyrrolidine-3-ol	71

Table 118. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1005*	(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.79 - 7.74 (m, 2 H), 7.63 - 7.56 (m, 4 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.43 - 4.39 (m, 1 H), 3.96 (d, 2 H, J = 6.2 Hz), 3.84 - 3.77 (m, 2 H), 3.62 - 3.49 (m, 4 H), 3.10 (s, 1 H), 3.05 (s, 1 H), 2.80 - 2.74 (m, 2 H), 2.23 - 2.18 (m, 1 H), 2.17 - 2.02 (m, 4 H), 1.92 - 1.86 (m, 3 H), 1.81 - 1.67 (m, 6 H), 0.86 - 0.82 (m, 6 H); MS (ESI) m/z 522 (M+ + H).
1006*	(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.76 - 7.72 (m, 2 H), 7.63 - 7.58 (m, 2 H), 7.54 - 7.51 (m, 2 H), 7.03 (d, 1 H, J = 8.8 Hz), 4.60 (brs, 0.5 H), 4.48 (brs, 0.5 H), 3.94 (d, 2 H, J = 6.4 Hz), 3.82 - 3.78 (m, 2 H), 3.71 - 3.62 (m, 1 H), 3.54 - 3.50 (m, 1 H), 3.02 (brs, 2 H), 2.63 - 2.46 (m, 3 H), 2.18 - 2.11 (m, 2 H), 2.04 - 2.00 (m, 2 H), 1.99 - 1.86 (m, 3 H), 1.76 - 1.66 (m, 4 H), 1.47 (brs, 2 H), 0.92 - 0.88 (m, 6 H); MS (ESI) m/z 508 (M+ + H).

Example 107. Compound 1000 : (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

[0224]



Step 1. 5-bromo-2-((1-(2-ethyl-2-hydroxybutyl)piperidin-4-yl)methoxy)benzonitrile: To 5-bromo-2-(piperidin-4-ylmethoxy)benzonitrile hydroxychloride (the product of synthesis step 2 of compound 938; 1.00 g, 3.39 mmol), 2,2-diethyloxirane (1.70 g, 16.94 mmol) and K_2CO_3 (937 mg, 6.78 mmol), EtOH (5 mL) / H_2O (5 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material, which is the title compound as white solid (1.33 g, 99%), was used without further purification.

Step 2. 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)benzonitrile: 5-bromo-2-((1-(2-ethyl-2-hydroxybutyl)piperidin-4-yl)methoxy)benzonitrile (1.33 g, 3.36 mmol) was dissolved in CH_2Cl_2 (10 mL). At 0 °C, DAST (444 µL, 3.36 mmol) was added thereto, following with stirring at room temperature for 1 hour. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material, which is the title compound as yellow oil (800 mg, 59%), was used without further purification.

Step 3. ethyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylate: 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)benzonitrile (400 mg, 1.01 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (235 mg, 1.11 mmol), Pd(dppf)Cl_2 (82 mg, 0.10 mmol) and Cs_2CO_3 (656 mg, 2.01 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (189 mg, 38%).

Step 4. 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid: Ethyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylate (189 mg, 0.39 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH \cdot H_2O$ (82 mg, 1.95 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (161 mg, 90%).

Step 5. Compound 1000: 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid (35 mg, 0.08 mmol), (S)-pyrrolidine-2-carboxamide (18 mg, 0.15 mmol), EDC (29 mg, 0.15 mmol) and HOBt (21 mg, 0.15 mmol) was added thereto, DIPEA (27 µL, 0.15 mmol) was dissolved in CH_2Cl_2 (1 mL). After stirring at room temperature for a day, the reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (25 mg, 59%).
1H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.71 (m, 2 H), 7.51 (t, 1 H, J = 7.5 Hz), 7.38 (d, 1 H, J = 8.0 Hz), 7.30 - 7.26 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 6.90 (brs, 1 H), 5.57 (brs, 1 H), 4.83 - 4.80 (m, 1 H), 3.96 (d, 2 H, J = 6.2 Hz), 3.56 - 3.39 (m, 2 H), 3.02 (brs, 2 H), 2.50 - 2.43 (m, 2 H), 2.18 - 2.03 (m, 4 H), 1.95 - 1.87 (m, 4 H), 1.74 - 1.68 (m, 5 H), 1.45 (brs, 2 H), 0.92 - 0.88 (m, 6 H); MS (ESI) m/z 553 (M+ + H).

[0225] According to the above-described synthesis process of compound 1000, the compounds of Table 120 were synthesized using 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-carboxylic acid and the reactant of Table 119.

Table 119. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
1001*	(R)-piperidin-3-ol hydrochloride	65
1002*	(R)-pyrrolidine-2-ylmethanol	62
1003*	(S)-pyrrolidine-3-ol	47

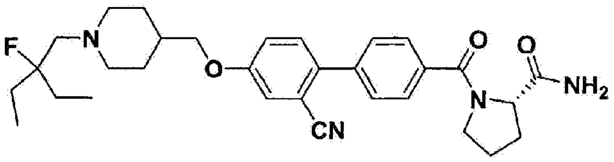
Compound No.	Reactant	Yield (%)

Table 120. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1001*	(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, CDCl$_3$) δ 7.75 - 7.69 (m, 2 H), 7.47 (t, 1 H, J = 7.4 Hz), 7.37 - 7.33 (m, 1 H), 7.27 - 7.22 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.14 - 4.07 (m, 1 H), 3.95 (d, 2 H, J = 6.3 Hz), 3.58 - 3.55 (m, 1 H), 3.34 - 3.25 (m, 1 H), 3.15 - 3.02 (m, 2 H), 2.51 - 2.46 (m, 2 H), 2.31 - 2.01 (m, 6 H), 1.99 - 1.87 (m, 6 H), 1.48 (brs, 2 H), 1.28 - 1.24 (m, 2 H), 0.92 - 0.88 (m, 6 H); MS (ESI) m/z 540 (M+ + H).
1002*	(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, CDCl$_3$) δ 7.77 - 7.71 (m, 2 H), 7.52 (t, 1 H, J = 7.5 Hz), 7.37 (d, 1 H, J = 8.0 Hz), 7.28 - 7.25 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.69 - 4.67 (m, 1 H), 4.42 - 4.39 (m, 1 H), 3.96 (d, 2 H, J = 6.2 Hz), 3.84 - 3.78 (m, 2 H), 3.47 - 3.44 (m, 2 H), 3.01 (brs, 2 H), 2.47 (brs, 2 H), 2.24 - 2.18 (m, 2 H), 1.93 - 1.82 (m, 5 H), 1.81 - 1.71 (m, 6 H), 1.43 (brs, 2 H), 0.93 - 0.89 (m, 6 H); MS (ESI) m/z 540 (M+ + H).
1003*	(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, CDCl$_3$) δ 7.76 - 7.70 (m, 2 H), 7.55 - 7.50 (m, 1 H), 7.36 - 7.34 (m, 1 H), 7.27 - 7.22 (m, 1 H), 7.05 (d, 1 H, J = 8.8 Hz), 4.63 (brs, 0.5 H), 4.50 (brs, 0.5 H), 3.96 (d, 2 H, J = 6.0 Hz), 3.84 - 3.74 (m, 2 H), 3.67 - 3.57 (m, 1 H), 3.45 - 3.33 (m, 1 H), 3.01 (brs, 2 H), 2.43 (brs, 3 H), 2.09 - 2.02 (m, 2 H), 1.89 - 1.87 (m, 3 H), 1.73 - 1.68 (m, 5 H), 1.44 (brs, 2 H), 0.92 - 0.87 (m, 6 H); MS (ESI) m/z 526 (M+ + H).

Example 108. Compound 1124 : (S)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0226]



__Step 1.__ 2-bromo-5-((1-(2-ethyl-2-hydroxybutyl)piperidin-4-yl)methoxy)benzonitrile: 5-bromo-2-(piperidin-4-ylmethoxy)benzonitrile hydroxychloride (the product of synthesis step 2 of compound 1028; 3.00 g, 9.05 mmol) was dissolved in EtOH 6 mL. 2,2-diethyloxirane (the product of synthesis step 1 of compound 809; 2.72 g, 27.14 mmol), K$_2$CO$_3$ (2.50 g, 18.09 mmol) and water 3 mL were added thereto, With a microwave radiation, the mixture was stirred at 110 °C for 15 minutes. Ethanol was evaporated from the reaction mixture under reduced pressure. After the addition of

water thereto, the resulting precipitated was filtered, and dried under reduced pressure to yield the title compound as white solid (2.9 g, 81%).

Step 2. 2-bromo-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)benzonitrile: 2-bromo-5-((1-(2-ethyl-2-hydroxybutyl)piperidin-4-yl)methoxy)benzonitrile (2.90 g, 7.34 mmol) was dissolved in CH_2Cl_2 (10 mL). At room temperature, DAST (1.30 g, 8.07 mmol) was added thereto, following with stirring at the same temperature for 3 hours. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material (yellow oil) was used without further purifying process (2.20 g, 75%).

Step 3. methyl 2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 2-bromo-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)benzonitrile (700 mg, 1.76 mmol), 4-(methoxycarbonyl)phenylboronic acid (381 mg, 2.11 mmol), Pd(dbpf)Cl_2 (57 mg, 0.09 mmol) and Cs_2CO_3 (1.15 g, 3.52 mmol) were dissolved in 1,4-dioxane (3 mL) / H_2O (1 mL). At 120 °C, the mixture was stirred for 15 minutes. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; ethyl acetate / hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.52 g, 65%).

Step 4. 2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.52 g, 1.15 mmol) and $LiOH \cdot H_2O$ (0.10 g, 2.30 mmol) were dissolved in THF / MeOH (6 mL / 3 mL) / Water (2 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with a little of conc.HCl to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.45 g, 89%).

Step 5. Compound 1124: 2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.60 g, 0.14 mmol), EDC (0.05 g, 0.27 mmol), HOBt (0.04 g, 0.27 mmol) and DIPEA (0.05 g, 0.41 mmol) were dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.02 g, 0.16 mmol) was added thereto, following with stirring at the same temperature for 8 hours. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (0.05 g, 61%).

1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2 H, J = 8.2 Hz), 7.58 (d, 2 H, J = 8.2 Hz), 7.41 (d, 1 H, J = 8.6 Hz), 7.20 (m, 2 Hz), 7.07 (s, 1 H), 5.82 (s, 1 H), 4.80 (m, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.66 (m, 2 H), 3.01 - 2.98 (m, 2 H), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.40 (m, 1 H), 2.09 (m, 4 H), 1.88 - 1.65 (m, 8 H), 1.41 (m, 2 H), 0.90 (t, 6 H, J = 7.5 Hz)

[0227] According to the above-described synthesis process of compound 1124, the compounds of Table 122 were synthesized using 2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 121.

Table 121. (* marks comparative compound)

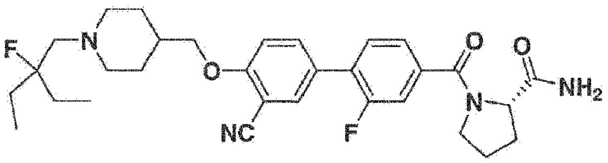
Compound No.	Reactant	Yield (%)
1125	(R)-piperidin-2-carboxamide hydrochloride	55
1126*	(R)-piperidin-3-ol hydrochloride	67

Table 122. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1125	(R)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 4 H), 7.39 (d, 1 H, J = 8.6 Hz), 7.15 (m, 2 H), 6.53 (s, 1 H), 5.90 (s, 1 H), 5.28 (m, 1 H), 3.81 (m, 3 H), 3.15 (m, 1 H), 2.97 - 2.95 (m, 2 H), 2.45 (s, 1 H), 2.39 (s, 1 H), 2.29 (m, 1 H), 2.11 (t, 2 H, J = 11.0 Hz), 1.77 - 1.62 (m, 10 H), 1.43 (m, 4 H), 0.90 (t, 6H, J = 8.8 Hz)
1126*	(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-2-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 4 H), 7.38 (d, 1 H, J = 8.6 Hz), 7.22 (m, 1 H), 7.16 (dd, 1 H, J = 8.7, 2.6 Hz), 4.07 - 3.62 (m, 4 H), 3.60 - 3.01 (m, 4 H), 2.98 - 2.95 (m, 2 H), 2.45 (s, 1 H), 2.39 (s, 1 H), 2.11 (t, 2 H, J = 10.9 Hz), 1.92 - 1.62 (m, 11 H), 1.41 (m, 2 H), 0.90 (t, 6 H, J = 7.5 Hz)

Example 109. Compound 1119 : (S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

[0228]



Step 1. methyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)2-fluorobiphenyl-4-carboxylate: 5-bromo-2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy) benzonitrile(the product of synthesis step 4 of compound 1000; 850 mg, 2.14 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (508 mg, 2.57 mmol), Pd(dbpf)Cl_2 (70 mg, 0.11 mmol) and Cs_2CO_3 (1.39 g, 4.28 mmol) were added to 1,4-dioxane (3 mL) / H_2O (1 mL). With a microwave radiation, the mixture was heated at 120 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was added with saturated $NaHCO_3$ aqueous solution, and extracted with ethyl acetate. The organic

layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; ethyl acetate/hexane = 20 % to 30 %), and concentrated to yield the title compound as white solid (0.71 g, 70%).

Step 2. 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid: Methyl 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)2-fluorobiphenyl-4-carboxylate (710 mg, 1.51 mmol) and $LiOH{\cdot}H_2O$ (0.13 g, 3.02 mmol) were dissolved in THF / MeOH (6 mL / 3 mL) / water (2 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with a little of conc.HCl to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.62 g, 90%).

Step 3. Compound 1119: 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid (0.06 g, 0.13 mmol), EDC (0.05 g, 0.26 mmol), HOBt (0.04 g, 0.26 mmol) and DIPEA (0.05 g, 0.39 mmol) were dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.02 g, 0.16 mmol) was added thereto, following with stirring at the same temperature for 8 hours. The reaction mixture was added with water, and extracted with dichloromethane. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 2 % to 5 %), and concentrated to yield the title compound as white solid (0.04 g, 53%).
1H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.70 (d, 2 H, J = 8.9 Hz), 7.38 (m, 3 H), 7.03 (d, 1 H, J = 8.8 Hz), 6.90 (s, 1 H), 5.75 (s, 1 H), 4.75 (m, 1 H), 3.93 (d, 2 H, J = 6.4 Hz), 3.62 (m, 2 H), 3.54 (m, 2 H), 2.98 - 2.95 (m, 2 H), 2.38 (m, 2 H), 2.06 (m, 5 H), 1.88 (m, 4 H), 1.70 (m, 4 H), 1.41 (m, 2 H), 0.90 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 553 (M+ + H).

[0229] According to the above-described synthesis process of compound 1119, the compounds of Table 124 were synthesized using 3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-carboxylic acid and the reactant of Table 123.

Table 123. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
1120	(S)-pyrrolidine-3-ol	53
1121*	(R)-piperidin-2-carboxamide hydrochloride	50
1123*	(R)-piperidin-3-ol hydrochloride	59

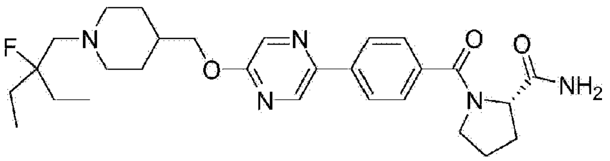
Table 124. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1120	(R)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2 H), 7.37 (m, 3 H), 7.03 (d, 1 H, J = 8.8 Hz), 4.82 (m, 1 H), 4.39 (m, 2 H), 3.92 (d, 2 H, J = 6.4 Hz), 3.73 (m, 2 H), 3.52 (m, 2 H), 2.98 - 2.95 (m, 2 H), 2.45 (s, 1 H), 2.39 (s,

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	1 H), 2.12 (m, 3 H), 1.90 - 1.61 (m, 10 H), 1.38 (m, 2 H), 0.91 (t, 6 H, J = 7.5 Hz)
1121*	(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.70 (m, 2 H), 7.37 (m, 3 H), 7.03 (d, 1 H, J = 8.8 Hz), 4.60 - 4.48 (s, 1 H), 3.93 (d, 2 H, J = 6.4 Hz), 3.82 - 3.46 (m, 4 H), 2.98 - 2.96 (m, 2 H), 2.48 (m, 3 H), 2.03 (m, 4 H), 1.99 (m, 3 H), 1.71 (m, 4 H), 1.42 (m, 2 H), 0.90 (t, 6 H, J = 7.5 Hz)
1123*	(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile
	1H NMR (400 MHz, $CDCl_3$) δ 7.72 (m, 2 H), 7.42 (t, 1 H, J = 7.8 Hz), 7.30 (m, 2 H), 7.05 (d, 1 H, J = 8.8 Hz), 3.95 (m, 3 H), 3.82 - 3.25 (m, 5 H), 3.01 - 2.98 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 (m, 2 H), 1.88 (m, 5 H), 1.71 (m, 5 H), 1.43 (m, 2 H), 0.91 (t, 6 H, J = 7.5 Hz)

Example 110. Comparative Compound 1018: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0230]



Step 1. 3-((4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: To 2-iodo-5-(piperidin-4-ylmethoxy)pyrazine hydrochloride (the product of synthesis step 2 of comparative compound 944 ; 1.00 g, 2.81 mmol), 2,2-diethyloxirane (1.01 g, 14.06 mmol) and K_2CO_3 (1.94 g, 14.06 mmol), EtOH (8 mL) / H_2O (2 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (1.15 g, 97%).

Step 2. 2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-5-iodopyrazine: 3-((4-((5-iodopyrazine-2-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (2.00 g, 5.44 mmol) was dissolved in CH_2Cl_2 (20 mL). At 0 °C, DAST (0.87 mL, 6.53 mmol) was added thereto, following with stirring at room temperature for 2 hours. After the completion of the reaction, the reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.41 g, 17%).

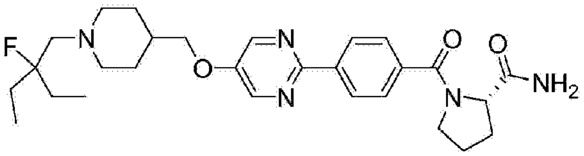
Step 3. methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate: To 2-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-5-iodopyrazine (0.40 g, 0.94 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.20 g, 1.13 mmol), Pd(dppf)Cl_2 (0.03 g, 0.04 mmol) and Cs_2CO_3 (0.61 g, 1.89 mmol), DME (3 mL) / H_2O (1 mL) was added. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.08 g, 19%).

Step 4. 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid: Methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoate (0.08 g, 0.18 mmol) and $LiOH \cdot H_2O$ (0.03 g, 0.93 mmol) were dissolved in THF / MeOH (8 mL) / H_2O (1 mL) at 60 °C, following with stirring at the same temperature for 18 hours. The reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.04 g, 54%).

Step 5. Comparative Compound 1018: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoic acid (0.04 g, 0.10 mmol), L-prolinamide (0.01 g, 0.12 mmol), HOBt (0.02 g, 0.20 mmol), EDC (0.03 g, 0.20 mmol) and DIPEA (0.03 mL, 0.20 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours, the reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; dichloromethane / methanol = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.01 g, 34%).
1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1 H), 8.30 (s, 1 H), 7.98 (d, 2 H, J = 8.3 Hz), 7.65 (d, 2 H, J = 8.2 Hz), 6.69 (s, 1 H), 5.46 (s, 1 H), 4.83 (dd, 1 H, J = 7.4, 4.7 Hz), 4.22 (d, 2 H, J = 6.2 Hz), 3.54 - 4.03 (m, 2H), 2.98 - 3.00 (m, 2 H), 2.48 - 2.51 (m, 2 H), 2.43 (s, 1 H), 2.03 - 2.16 (m, 3 H), 1.65 - 1.89 (m, 7 H), 1.39 - 1.48 (m, 2 H), 1.26 - 1.31 (m, 2H), 0.90 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 512.3 (M+ + H).

Example 111. Compound 1051: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidine-2-carboxamide

[0231]



<u>**Step 1.**</u> 3-((4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: EtOH (4 mL) / H_2O (1 mL) was added to 2-chloro-5-(piperidin-4-ylmethoxy)pyrimidine hydrochloride (the product of synthesis step 2 of compound 1032 ; 1.20 g, 4.54 mmol), 2,2-diethyloxirane (3.18 g, 31.80 mmol) and K_2CO_3 (1.25 g, 9.08 mmol). With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material was used without further purifying process (1.47 g, 98%, white solid).

<u>**Step 2.**</u> 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidine: 3-((4-((2-chloropyrimidin-5-yloxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (1.47 g, 4.48 mmol) was dissolved in CH_2Cl_2 (20 mL). At 0 °C, DAST (0.70 mL, 5.38 mmol) was added thereto, following with stirring at room temperature for 3 hours. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.71 g, 48%).

<u>**Step 3.**</u> methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoate: DME (4 mL) / H_2O (1 mL) was added to 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidine (0.20 g, 0.60 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.13 g, 0.72 mmol), Pd(dppf)Cl_2 (0.02 g, 0.03 mmol) and Cs_2CO_3 (0.39 g, 1.21 mmol). With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.20 g, 76%).

<u>**Step 4.**</u> 4-(5-((1-(2-ethyl-2-fluorobutyl)pipendin-4-yl)methyloxy)pyrimidin-2-yl)benzoic acid: Methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoate (0.20 g, 0.46 mmol) and $LiOH{\cdot}H_2O$ (0.09 g, 2.32 mmol) were dissolved in THF (4 mL) / MeOH (4 mL) / H_2O (1 mL) at room temperature. The solution was stirred at the same temperature for 5 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (20 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.15 g, 77%).

<u>**Step 5.**</u> Compound 1051: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methyloxy)pyrimidin-2-yl)benzoic acid (0.04 g, 0.10 mmol), L-prolinamide (0.01 g, 0.13 mmol), HOBt (0.02 g, 0.21 mmol), EDC (0.04 g, 0.21 mmol) and DIPEA (0.03 mL, 0.21 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was

concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.05 g, 93%).

1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2 H), 8.41 (d, 2 H, J = 8.4 Hz),7.64 (d, 2 H, J = 8.3 Hz), 7.08 (s, 1 H), 5.71 (s, 1 H), 4.82 (dd, 1 H, J = 7.3, 5.1 Hz), 3.95 (d, 2 H, J = 6.0 Hz), 3.50 - 3.66 (m, 2 H), 2.99 - 3.02 (m, 2 H), 2.40 - 2.49 (m, 3 H), 2.05 - 2.17 (m, 4 H), 1.65 - 1.91 (m, 4 H), 1.41 - 1.49 (m, 4 H), 1.20 - 1.26 (m, 2 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 512.3 (M+ + H).

[0232] According to the above-described synthesis process of compound 1051, the compounds of Table 126 were synthesized using 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methyloxy)pyrimidin-2-yl)benzoic acid and the reactant of Table 125.

Table 125. (* marks comparative compound)

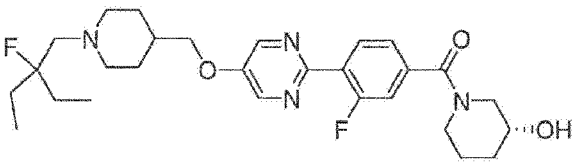
Compound No.	Reactant	Yield (%)
1052*	(R)-piperidin-3-ol hydrochloride	50
1053	(R)-piperidin-2-carboxamide hydrochloride	77

Table 126. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1052*	(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2 H), 8.39 (d, 2 H, J = 8.3 Hz), 7.52 (d, 2 H, J = 8.2 Hz), 3.95 - 4.01 (m, 3 H), 3.33 - 3.88 (m, 4 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 (t, 2 H, J = 11.0 Hz), 1.27 - 2.06 (m, 14 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 499.3 (M+ + H).
1053	(R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2 H), 8.42 (d, 2 H, J = 7.8 Hz), 7.56 (d, 2 H, J = 8.0 Hz), 6.53 (s, 1 H), 5.63 (s, 1 H), 5.31 (s, 1 H), 3.96 (d, 2 H, J = 5.8 Hz), 3.75 - 3.78 (m, 1 H), 3.09 - 3.15 (m, 1 H), 2.99 - 3.02 (m, 2 H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.33 - 2.36 (m, 1 H), 2.15 (t, 2 H, J = 11.4 Hz), 1.19 - 2.06 (m, 14 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 526.3 (M+ + H).

Example 112. Comparative compound 1056: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

[0233]



Step 1. methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoate: To 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidine (the product of synthesis step 2 of compound 1051; 0.25 g, 0.75 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (0.16 g, 0.83 mmol), Pd(dppf)Cl_2 (0.03 g, 0.03 mmol) and Cs_2CO_3 (0.49 g, 1.51 mmol), DME (4 mL) / H_2O (1 mL) was added. With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.21 g, 61%).

Step 2. 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoic acid: Methyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoate (0.21 g, 0.46 mmol) and $LiOH \cdot H_2O$ (0.09 g, 2.34 mmol) were dissolved in THF (4 mL) / MeOH (4 mL) / H_2O (1 mL) at room temperature. The solution was stirred at the same temperature for 5 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (30 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.14 g, 71%).

Step 3. Comparative compound 1056: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoic acid (0.04 g, 0.10 mmol), (R)-piperidin-3-ol hydrochloride(0.01 g, 0.12 mmol), HOBt (0.02 g, 0.20 mmol), EDC (0.04 g, 0.20 mmol) and DIPEA (0.02 g, 0.20 mmol) were dissolved in CH_2Cl_2 (1 mL) at room temperature. The solution was stirred at the same temperature for 18 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_3, 4 g cartridge; methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.02 g, 42%).
1H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 2 H), 8.06 (t, 1 H, J = 7.8 Hz), 7.24 - 7.33 (m, 2H), 3.97 (d, 2 H, J = 6.0 Hz), 3.29 - 3.79 (m, 4H), 3.00 - 3.02 (m, 2H), 2.49 (s, 1 H), 2.43 (s, 1 H), 2.15 (t, 2 H, J = 11.0 Hz), 1.27- 2.06 (m, 15 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 517.3 (M+ + H).

[0234] According to the above-described synthesis process of comparative compound 1056, the compounds of Table 128 were synthesized using 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoic acid and the reactant of Table 127.

Table 127.

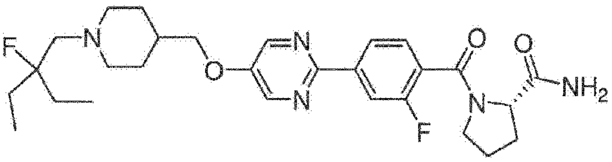
Compound No.	Reactant	Yield (%)
1057	(R)-piperidin-2-carboxamide hydrochloride	14

Table 128.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1057	(R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorobenzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 2 H), 8.10 (t, 1 H, J = 7.4 Hz), 7.23 ~ 7.36 (m, 2 H), 6.39 (s, 1 H), 5.41 (s, 1 H), 5.28 ~ 5.29 (m, 1 H), 3.98 (d, 2 H, J = 6.1 Hz), 3.78 ~ 3.97 (m,1 H), 3.11 ~ 3.18 (m, 1 H), 2.94 ~ 3.04 (m, 2 H), 2.50 (s, 1 H), 2.43 (s, 1 H), 2.28 ~ 2.37 (m, 1 H), 2.13 ~ 2.18 (m, 2 H), 1.42 ~ 1.87 (m, 14 H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 544.3 (M+ + H).

Example 113. Compound 1054: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoyl)pyrrolidine-2-carboxamide

[0235]



<u>**Step 1.**</u> ethyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoate: DME (4 mL) / H_2O (1 mL) was added to 2-chloro-5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidine (the product of synthesis step 2 of compound 1051; 0.25 g, 0.75 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.17 g, 0.83 mmol), Pd(dppf)Cl_2 (0.03 g, 0.03 mmol) and Cs_2CO_3 (0.49 g, 1.51 mmol). With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The filtrate was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; EtOAc / hexane = 0 % to 30 %), and concentrated to yield the title compound as white solid (0.26 g, 74%).

<u>**Step 2.**</u> 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoic acid: Ethyl 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoate (0.26 g, 0.60 mmol) and LiOH·H_2O (0.12 g, 3.02 mmol) were dissolved in THF (4 mL) / MeOH (4 mL) / H_2O (1 mL) at room temperature. The solution was stirred at the same temperature for 5 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (20 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.19 g, 72%).

<u>**Step 3.**</u> Compound 1054: 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoic acid (0.04 g, 0.10 mmol), L-prolinamide (0.01 g, 0.12 mmol), HOBt (0.02 g, 0.20 mmol), EDC (0.04 g, 0.20 mmol) and DIPEA (0.03 mL, 0.20 mmol) were dissolved in CH_2Cl_2 (1 mL)

at room temperature. The solution was stirred at the same temperature for 18 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with EtOAc. The organic layer was washed with water, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 4 g cartridge; methanol / dichloromethane = 0 % to 15 %), and concentrated to yield the title compound as white solid (0.05 g, 90%).

1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 2 H), 8.23 (d, 1 H, J = 8.0 Hz), 8.14 (d, 1 H, J = 11.1 Hz), 7.52 (t, 1 H, J = 7.5 Hz), 6.96 (s, 1 H), 5.71 (s, 1 H), 4.81 - 4.84 (m, 1 H), 3.96 (d, 2 H, J = 6.0 Hz), 3.38 - 3.56 (m, 2 H), 3.03 - 3.00 (m, 2 H), 2.44 - 2.50 (m, 3 H), 1.26 - 2.18 (m, 14 H), 0.90 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 530.3 (M+ + H).

[0236] According to the above-described synthesis process of compound 1054, the compounds of Table 130 were synthesized using 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoic acid and the reactant of Table 129

Table 129.

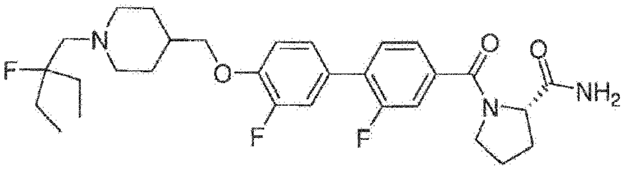
Compound No.	Reactant	Yield (%)
1055	(R)-piperidin-2-carboxamide hydrochloride	33

Table 130.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
1055	(R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorobenzoyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 2 H), 8.27 (d, 1 H, J = 8.0 Hz), 8.15 (d, 1 H, J = 11.2 Hz), 7.54 (t, 1 H, J = 7.5 Hz), 6.33 (s, 1 H), 5.47 - 5.56 (m, 2 H), 3.97 (d, 2 H, J = 6.1 Hz), 3.57 - 3.61 (m, 1 H), 3.20 - 3.22 (m, 1 H), 3.02 - 3.05 (m, 2 H), 2.45 - 2.51 (m, 2 H), 2.08 (t, 2 H, J = 19.7 Hz), 1.20 - 1.83 (m, 15H), 0.91 (t, 6 H, J = 7.5 Hz); MS (ESI) m/z 544.3 (M+ + H).

Example 114. Compound 937:(S)-1-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenylcarbonyl)pyrrolidine-2-carboxamide

[0237]



Step 1. 3-((4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)methyl)pentane-3-ol: EtOH (5 mL) / H_2O (5 mL) was added to 4-((4-bromo-2-fluorophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 2 of comparative compound 725; 500 mg, 1.54 mmol), 2,2-diethyloxirane (771 mg, 7.70 mmol) and K_2CO_3 (426 mg, 3.08 mmol). With a microwave radiation, the mixture was

heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained material, which is the title compound as white solid (542 mg, 90%), was used without further purification.

Step 2. 4-((bromo-2-fluorophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine: 3-((4-((4-bromo-2-fluorophenoxy)methyl)piperidin-1-yl)methyl)pentane-3-ol (524 mg, 1.40 mmol) was dissolved in CH_2Cl_2 (10 mL). At 0 °C, DAST (184 μL, 1.40 mmol) was added thereto, following with stirring at room temperature for 1 hour. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (371 mg, 68%).

Step 3. ethyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-carboxylate: 4-((bromo-2-fluorophenoxy)methyl)-1-(2-ethyl-2-fluorobutyl)piperidine (371 mg, 0.95 mmol), 2-fluoro-4-(methoxycarbonyl)phenylboronic acid (188 mg, 0.95 mmol), Pd(dppf)Cl_2 (78 mg, 0.10 mmol) and Cs_2CO_3 (619 mg, 1.90 mmol) were added to water (2 mL)/DME (6 mL). With a microwave radiation, the mixture was heated at 110 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (EtOAc/hexane = 30 % ~ 70 %) to yield the title compound as white solid (242 mg, 53%).

Step 4. 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-carboxylic acid: Ethyl 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-carboxylate (242 mg, 0.51 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH{\cdot}H_2O$ (106 mg, 2.53 mmol) was added thereto little by little at room temperature, following with stirring for 1 hour. After the completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting precipitate was filtered, and dried to yield the title compound as white solid (200 mg, 87%).

Step 5. Compound 937: 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-carboxylic acid (40 mg, 0.09 mmol), EDC (34 mg, 0.18 mmol) and HOBt (24 mg, 0.18 mmol) was added thereto, DIPEA (32 μL, 0.18 mmol) was dissolved in CH_2Cl_2 (1 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (20 mg, 0.18 mmol) was added thereto, following with stirring for a day. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, and then. The organic layer was dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The concentrate was purified by silica gel column chromatography (CH_2Cl_2 /MeOH = 95 % ~ 5 %) to yield the title compound as white solid (35 mg, 87%).
1H NMR (400 MHz, $CDCl_3$) δ 7.47 (t, 1 H, J = 7.8 Hz), 7.40 - 7.27 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 6.89 (brs, 0.5 H), 5.47 (brs, 0.5 H), 4.82 - 4.79 (m, 1 H), 3.92 (d, 2 H, J = 6.2 Hz), 3.66 - 3.57 (m, 2 H), 3.00 (d, 2 H, J = 10.4 Hz), 2.49 - 2.43 (m, 2 H), 2.18 - 2.06 (m, 4 H), 1.92 - 1.66 (m, 10 H), 1.47 - 1.41 (m, 2 H), 0.92 (s, 3 H), 0.88 (s, 3 H); MS (ESI) m/z 546 (M+ + H).

[0238] According to the above-described synthesis process of compound 937, the compounds of Table 132 were synthesized using 4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-carboxylic acid and the reactant of Table 131.

Table 131. (* marks comparative compound)

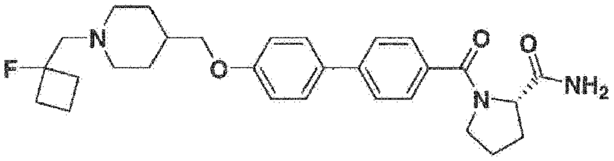
Compound No.	Reactant	Yield (%)
940*	(R)-piperidin-3-ol hydrochloride	71
941*	(R)-pyrrolidine-2-ylmethanol	65
942*	(S)-piperidin-3-ol hydrochloride	69
943*	(S)-pyrrolidine-3-ol	67

Table 132. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
940*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, 1 H, J = 7.6 Hz), 7.34 - 7.22 (m, 4 H), 6.98 (t, 1 H, J = 8.6 Hz), 4.02 - 3.91 (m, 1 H), 3.89 (d, 2 H, J = 6.3 Hz), 3.84 - 3.75 (m, 1 H), 3.49 (brs, 1 H), 3.48 (d, 2 H, J = 11.8 Hz), 3.40 - 3.21 (m, 1 H), 2.97 - 2.91 (m, 2 H), 2.58 (t, 2 H, J = 11.8 Hz), 2.05 - 1.71 (m, 12 H), 1.28 - 1.25 (m, 2 H), 0.89 - 0.81 (m, 6 H); MS (ESI) m/z 533 (M+ + H).
941*	(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.46 (t, 1 H, J = 7.8 Hz), 7.38 - 7.27 (m, 4 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.44 - 4.42 (m, 1 H), 3.92 (d, 2 H, J = 6.2 Hz), 3.86 - 3.74 (m, 2 H), 3.61 - 3.53 (m, 2 H), 2.99 (d, 2 H, J = 11.2 Hz), 2.48 (s, 1 H), 2.12 (s, 1 H), 2.23 - 2.12 (m, 3 H), 1.93 - 1.88 (m, 1 H), 1.83 (d, 3 H, J =11.9 Hz), 1.75 - 1.63 (m, 6 H), 1.47 - 1.41 (m, 2 H), 1.38 - 1.26 (m, 1 H), 0.93 - 0.79 (m, 6 H); MS (ESI) m/z 533 (M+ + H).
942*	(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, 1 H, J = 7.6 Hz), 7.34 - 7.22 (m, 4 H), 6.98 (t, 1 H, J = 8.6 Hz), 4.02 - 3.91 (m, 1 H), 3.89 (d, 2 H, J = 6.3 Hz), 3.84 - 3.75 (m, 1 H), 3.49 (brs, 1 H), 3.48 (d, 2 H, J = 11.8 Hz), 3.40 - 3.21 (m, 1 H), 2.97- 2.91 (m, 2 H), 2.58 (t, 2 H, J = 11.8 Hz), 2.05 - 1.71 (m, 12 H), 1.28 - 1.25 (m, 2 H), 0.89 - 0.81 (m, 6 H); MS (ESI) m/z 533 (M+ + H).
943*	(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.26 (m, 5 H), 7.03 (t, 1 H, J = 8.6 Hz), 4.62 - 4.61 (m, 1 H), 3.91 (d, 2 H, J = 6.2 Hz), 3.83 - 3.82 (m, 2 H), 3.80 - 3.79 (m, 1 H), 3.71 - 3.67 (m, 1 H), 2.99 (d, 2 H, J = 11.5 Hz), 2.48 (s, 1 H), 2.42 (s, 1 H), 2.17 - 2.12 (m, 2 H), 2.02 - 1.85 (m, 3 H), 1.82 - 1.81 (m, 3 H), 1.75 - 1.65 (m, 4 H), 1.44 - 1.40 (m, 2 H), 0.92 - 0.88 (m, 6 H); MS (ESI) m/z 519 (M+ + H).

Example 115. Compound 922: (S)-1-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0239]



__Step 1.__ 1-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)cyclobutanol: 4-((4-bromophenoxy)methyl)piperidine (the product of synthesis step 4 of comparative compound 686; 0.10 g, 0.33 mmol), 1-oxaspiro[2,3]hexane (55 mg, 0.65 mmol) and Et_3N (0.23 μL, 1.63 mmol) were dissolved in EtOH 2 mL. With a microwave radiation, the reaction was performed at 110 °C for 20 minutes. The reaction mixture was diluted with water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (90 mg, 78%).

__Step 2.__ 4-((4-bromophenoxy)methyl)-1-((1-fluorocyclobutyl)methyl)piperidine: 1-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)cyclobutanol (0.61 g, 1.72 mmol) was dissolved in CH_2Cl_2 10 mL. DAST (0.23 μl, 1.72 mmol) was added thereto. After stirring for 1 hour at room temperature, a saturated $NaHCO_3$ aqueous solution was added thereto, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (12 g, ISU silica gel cartridge, 0-5 % MeOH/CH_2Cl_2) to yield the title compound as white solid (234 mg, 38%).

__Step 3.__ methyl 4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-((1-fluorocyclobutyl)methyl)piperidine (234 mg, 0.66 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.14 g, 0.79 mmol), Pd(dbpf)Cl_2 (13 mg, 0.02 mmol) and Cs_2CO_3 (0.64 g, 1.97 mmol) were added to the mixed solvents of 1,4-dioxane/H_2O 3 mL/l mL. With a microwave radiation, the mixture was heated at 140 °C for 15 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, filtered through Celite to remove a solid, and then concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, methanol/dichloromethane = 0 % to 5 %), and concentrated to yield the title compound as light-yellow solid (194 mg, 72%).

__Step 4.__ 4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (0.19 g, 0.47 mmol) and LiOH·H_2O (0.1 g, 2.35 mmol) were dissolved in THF/MeOH/H_2O 6 mL/2 mL/2 mL, and then refluxed with heating and stirring for 4 hours. The reaction mixture was cooled to room temperature, and added with water. The resulting precipitate was filtered, and dried to yield the title compound as light-brown solid (0.18 g, 94%).

Step 5. Compound 922: 4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (0.04 g, 0.10 mmol), EDCI (0.04 g, 0.20 mmol), HOBt (0.03 g, 0.20 mmol) and DIPEA (0.09 mL, 0.50 mmol) were dissolved in DMF (2 mL). At room temperature, (0.02 g, 0.20 mmol) was added thereto, following with stirring at 60 °C for 12 hours. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2; methanol/dichloromethane = 0 % to 10 %), and concentrated yield the title compound as light-yellow solid (0.03 g, 58%).

1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 4 H), 7.53 (d, 2 H, J = 8.8 Hz), 7.04 (brs, 1 H), 6.98 (d, 2 H, J = 9.0 Hz), 5.65 (brs, 1 H), 4.81 (brs, 1 H), 3.85 (d, 2 H, J = 6.0 Hz), 3.63 - 3.59 (m, 2 H), 3.01 (d, 2 H, J = 11.4 Hz), 2.66 (s, 1 H), 2.60 (s, 1 H), 2.28 - 2.00 (m, 10 H), 1.87 - 1.81 (m, 3 H), 1.50 - 1.44 (m, 4 H); MS (ESI) m/z 494 (M+ + H).

[0240] According to the above-described synthesis process of compound 922, the compounds of Table 134 were synthesized using 4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 133.

Table 133. (* marks comparative compound)

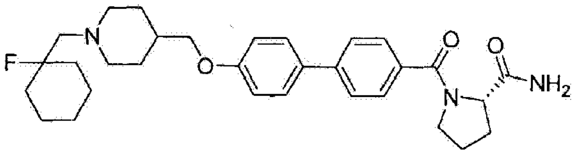
Compound No.	Reactant	Yield (%)
923*	(R)-pyrrolidine-2-ylmethanol	38
924*	(S)-pyrrolidine-3-ol	70
925*	(R)-piperidin-3-ol	46

Table 134. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
923*	(R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.53 (m, 4 H), 7.51 (d, 2 H, J = 12.0 Hz), 6.96 (d, 2 H, J = 8.8 Hz), 4.52 - 4.48 (m, 1 H), 3.83 - 3.59 (m, 6 H), 2.98 (d, 2 H, J = 11.6 Hz), 2,64 (s, 1 H), 2.57 (s, 1 H), 2.26 - 2.12 (m, 8 H), 1.86 - 1.78 (m, 6 H), 1.48 - 1.41 (m, 5 H); MS (ESI) m/z 481 (M+ + H).
924*	(S)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.49 (m, 6 H), 6.96 (d, 2 H, J = 11.6 Hz), 4.49 (d, 1 H, J = 49.6 Hz), 3.84 - 3.47 (m, 6 H), 3.01 (d, 2 H, J = 11.2 Hz), 2.66 (s, 1 H), 2.60 (s, 1 H), 2.34 - 2.03 (m, 8 H), 1.96 - 1.80 (m, 3 H), 1.55 - 1.26 (m, 4 H); MS (ESI) m/z 467 (M+ + H).
925*	(R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 - 7.45 (m, 6 H), 6.98 - 6.96 (m, 2 H), 4.02 - 3.41 (m, 7 H), 4.02 - 3.41 (m, 7 H), 3.01 (d, 2 H, J = 11.2 Hz), 2.66 (s, 1 H), 2.60 (s, 1 H), 2.34 - 2.03 (m, 7 H), 1.95 - 1.64 (m, 8 H), 1.55 - 1.41 (m, 4 H); MS (ESI) m/z 481 (M+ + H).

Example 116. Compound 760: (S)-1-(4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0241]



Step 1. 1-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)cyclohexanol: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (500 mg, 1.63 mmol), 1-oxaspiro[2.5]octane (274 mg, 2.45 mmol) and K_2CO_3 (113 mg, 0.82 mmol) were added into a microwave reactor, and then ethanol 4 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. After removing ethanol, a little of water was added to the reaction mixture. The resulting precipitate was washed thoroughly with water, and dried to yield the title compound as white solid (520 mg, 83%).

Step 2. 4-((4-bromophenoxy)methyl)-1-((1-fluorocyclohexyl)methyl)piperidine: 1-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)cyclohexanol (400 mg, 1.05 mmol) was dissolved in CH_2Cl_2 10 ml. Deoxo-Fluor® (0.23 mL, 1.26 mmol) was added thereto., following with stirring at room temperature for 5 hours. A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-50 % EtOAc/hexane) to yield the title compound as white solid (100 mg, 25%).

Step 3. methyl 4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-((1-fluorocyclohexyl)methyl)piperidine (115 mg, 0.30 mmol), 4-(methoxycarbonyl)phenylboronic acid (60 mg, 0.33 mmol), Pd(dbpf)Cl_2 (6 mg, 0.01 mmol), Cs_2CO_3 (291 mg, 0.90 mmol) were added into a microwave reactor, and then 1,4-dioxane 4 mL and water 2 mL were added thereto. With a microwave radiation, the reaction was performed at 110 °C for 30 minutes. The reaction mixture was filtered through a Celite pad. The filtrate was added with water, and then extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (100 mg, 76%).

Step 4. 4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate(100 mg, 0.23 mmol) was dissolved in the mixed solvents of THF 2 mL / water 2 mL. $LiOH \cdot H_2O$ (20 mg, 0.46 mmol) was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl thereto, the resulting precipitate was filtered to yield the title compound as white solid (95 mg, 98%).

Step 5. Compound 760: 4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid(50 mg, 0.12 mmol), L-prolinamide (20 mg, 0.18 mmol), EDC (45 mg, 0.24 mmol) and HOBt (32 mg, 0.24 mmol) were dissolved in DMF 2 mL. DIPEA (30 mg, 0.24 mmol) was added thereto, and the reaction was performed at 60 °C for 10 hours. The reaction mixture was cooled to room temperature, and added with water. The formed solid was filtered, washed with water thoroughly, and dried to yield the title compound as yellow solid (15 mg, 25%).

1H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.52 (m, 5 H), 7.02 - 6.97 (m, 3 H), 5.42 (s, 1 H), 4.85 (t, 1 H, J = 6.2 Hz), 3.86 (s, 2 H), 3.61 (m, 2 H), 3.01 (m, 2 H), 2.53 (m, 3 H), 2.21 - 2.04 (m, 4 H), 1.85 (m, 6 H), 1.65 - 1.24 (m, 11 H); MS (ESI) m/z 522 (M+ + H).

[0242] According to the above-described synthesis process of compound 760, the compounds of Table 136 were synthesized using 4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 135.

Table 135. (* marks comparative compound)

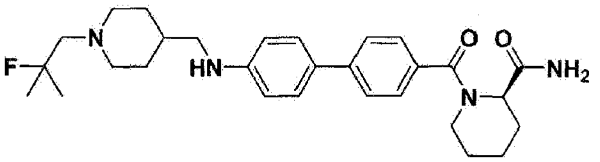
Compound No.	Reactant	Yield (%)
761*	(R)-piperidin-3-ol hydrochloride	28

Table 136. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
761*	(R)-(4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin- 1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.2 Hz), 7.53 (d, 2 H, J = 8.8 Hz), 7.48 (d, 2 H, J = 8.3 Hz), 6.98 (d, 2 H, J = 8.0 Hz), 4.02 - 3.42 (m, 7 H), 3.07 (m, 2 H), 2.59 - 2.06 (m, 5 H), 2.00 - 1.80 (m, 8 H), 1.80 - 1.24 (m, 11 H); MS (ESI) m/z 509 (M+ + H).

Example 117. Comparative Compound 857: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidin-2-carboxamide

[0243]



Step 1. t-butyl 4-((4-bromophenylamino)methyl)piperidin-1-carboxylate: 4-bromobenzeneamine (4.00 g, 18.76 mmol) was dissolved in MeOH 100 mL. Acetic acid (1.03 mL, 18.76 mmol) and t-butyl 4-formylpiperidin-1-carboxylate (3.38 g, 19.69 mmol) were added thereto, following with stirring at room temperature for 5 hours. $NaCNBH_3$ (1.17 g, 18.75 mmol) was added thereto slowly at 0 °C, following with stirring at room temperature for 3 hours and extracting with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution three times. The obtained organic layer was dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (4 g ISCO silica gel cartridge, 0

- 30 % EtOAc/hexane) to yield the title compound as light-yellow solid (3.00 g, 43%).

Step 2. t-butyl 4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-carboxylate: t-butyl 4-((4-bromophenylamino)methyl)piperidin-1-carboxylate (3.00 g, 8.12 mmol) and NaH (0.39 g, 16.24 mmol) were dissolved in DMF (100 mL). At 0 °C, benzyl bromide (2.08 g, 12.18 mmol) was added thereto, following with stirring at room temperature for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (2.70 g, 72%).

Step 3. N-benzyl-4-bromo-N-(piperidin-4-ylmethyl)benzeneamine hydrochloride: t-butyl 4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-carboxylate (5.20 g, 14.08 mmol) was dissolved in EtOAc (100 mL). At room temperature, HCl in 1,4-dioxane (17.60 mL, 70.40 mmol) was added thereto, following with stirring at the same temperature for 2 hours. The resulting precipitate was filtered, and dried to yield the title compound as white solid (4.80 g, 86%).

Step 4. 1-(4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)-2 methylpropan-2-ol: N-benzyl-4-bromo-N-(piperidin-4-ylmethyl)benzeneamine hydrochloride (2.40 g, 6.70 mmol) and K_2CO_3 (4.63 g, 33.51 mmol) were dissolved in EtOH (10 mL) / H_2O (10 mL). 1,2-epoxy-2-methylpropane (5.95 mL, 67.02 mmol) was added thereto. With a microwave radiation, the mixture was heated at 110 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was used without further purification for the next step (2.00 g, 69%, colorless oil).

Step 5. N-benzyl-4-bromo-N-((1-(2-fluoro-2-methylpropyl)piperidin-2-yl)methyl)benzeneamine: 1-(4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)-2 methylpropan-2-ol (4.00 g, 9.27 mmol) was dissolved in CH_2Cl_2 (100 mL). At 0 °C, DAST (1.64 g, 10.19 mmol) was added thereto. Following with stirring at the same temperature for 1 hour. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as colorless oil (2.87 g, 71%).

Step 6. methyl 4'-(benzyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate: N-benzyl-4-bromo-N-((1-(2-fluoro-2-methylpropyl)piperidin-2-yl)methyl)benzeneamine (1.00 g, 2.30 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.41 g, 2.30 mmol), Pd(dbpf)Cl_2 (0.07 g, 0.11 mmol) and Cs_2CO_3 (1.50 g, 4.61 mmol) were added to 1,4-dioxane (12 mL) / H_2O (3 mL). With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as yellow oil

(0.89 g, 78%).

Step 7. methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate: Methyl 4'-(benzyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate (0.89 g, 1.82 mmol) was dissolved in MeOH (3 mL) / EtOAc (5 mL). At room temperature, NH_4COOH (1.14 g, 18.21 mmol) was added thereto, following with stirring at 80 °C for 2 hours. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with dichloromethane.. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 30 %), and concentrated yield the title compound as light-yellow solid (0.40 g, 55%).

Step 8. 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid: Methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate (0.40 g, 1.0 mmol) was dissolved in THF (3 mL) / H_2O /MeOH (2 mL). At room temperature, $LiOH{\cdot}H_2O$ (0.21 g, 5.01 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.32 g, 84%).

Step 9. Comparative Compound 857: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid (0.10 g, 0.23 mmol), EDCI (0.09 g, 0.47 mmol), HOBt (0.06 g, 0.47 mmol) and DIPEA (0.15 g, 1.18 mmol) were dissolved in DMF (2 mL). At room temperature, (R)-piperidin-2-carboxamide (0.06 g, 0.47 mmol) was added thereto, following with stirring at 60 °C for 5 hours. The concentrate was added with water (6 mL), and stirred. The resulting precipitate was filtered, dried, and purified by column chromatography (SiO_2, dichloromethane / methanol = 0 % to 5 %), and concentrated to yield the title compound as light-yellow solid (0.06 g, 51%).
1H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.27 (m, 6 H), 6.67 - 6.61 (m, 3 H), 5.92 (brs, 1 H), 5.28 (brs, 1 H), 3.83 (d, 1 H, J = 12.0 Hz), 3.13 - 2.94 (m, 5 H), 2.45 (s, 1 H), 2.39 (s, 1 H), 2.33 (d, 1 H, J = 12.0 Hz), 2.12 (t, 2 H, J = 11.4 Hz), 1.75 - 1.55 (m, 8 H), 1.38 - 1.23 (m, 8 H); MS (ESI) m/z 495 (M+ + H)

[0244] According to the above-described synthesis process of comparative compound 857, the compounds of Table 138 were synthesized using 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid and the reactant of Table 137.

Table 137. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
858*	(S)-pyrrolidine-2-ylmethanol	78
859*	(R)-pyrrolidine-2-ylmethanol	69
867*	(R)-piperidin-3-ol	54
868*	(S)-pyrrolidine-2-carboxamide	68

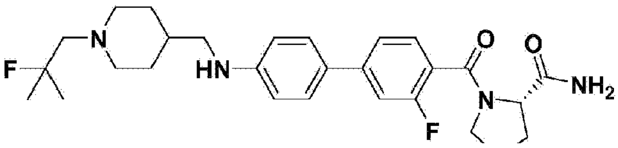
Compound No.	Reactant	Yield (%)
869*	(S)-pyrrolidine-3-ol	66

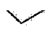
Table 138. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
858*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.50 (m, 4 H), 7.43 (d, 2 H, J = 8.0 Hz), 6.65 (d, 2 H, J = 8.5 Hz), 4.37 (m, 1 H), 3.75 - 3.57 (m, 4 H), 3.03 (d, 2 H, J = 6.4 Hz), 2.95 (d, 2 H, J = 11.6 Hz), 2.13 - 2.07 (m, 3 H), 1.73 - 1.70 (m, 6 H), 1.37 - 1.31 (m, 8 H); MS (ESI) m/z 468 (M+ + H).
859*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.50 (m, 4 H), 7.42 (d, 2 H, J = 8.0 Hz), 6.65 (d, 2 H, J = 8.3 Hz), 4.38 - 4.36 (m, 1 H), 3.75 - 3.73 (m, 2 H), 3.58 - 3.53 (m, 2 H), 3.03 (d, 2 H, J = 6.4 Hz), 2.95 (d, 2 H, J = 11.6 Hz), 2.44 - 2.38 (m, 3 H), 2.13 - 2.07 (m, 3 H), 1.92 - 1.56 (m, 5 H), 1.36 - 1.31 (m, 8 H); MS (ESI) m/z 468 (M+ + H).
867*	(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	; MS (ESI) m/z 468 (M+ + H).
868*	(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.52 (m, 4 H), 7.42 (d, 2 H, J = 8.2 Hz), 6.64 (d, 2 H, J = 8.2 Hz), 4.68 (t, 1 H, J = 6.9 Hz), 3.67 - 3.55 (m, 2 H), 3.02 (d, 2 H, J = 6.5 Hz), 2.95 (d, 2 H, J = 11.4 Hz), 2.43 (s, 1 H), 2.38 (s, 1 H), 2.21 - 2.00 (m, 5 H), 1.72 - 1.69 (m, 4 H), 1.56 - 1.23 (m, 8 H); MS (ESI) m/z 482 (M+ + H).
869*	(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.50 - 7.37 (m, 4 H), 7.36 (d, 2 H, J = 6.8 Hz), 6.60 (d, 2 H, J = 8.8 Hz), 4.43 - 4.26 (m, 1 H), 3.72 - 3.53 (m, 5 H), 2.97 (d, 2 H, J = 6.4 Hz), 2.90 (d, 2 H, J = 11.6 Hz), 2.39 (s, 1 H), 2.33 (s, 1 H), 2.06 - 1.87 (m, 4 H), 1.67 (d, 2 H, J = 12.4 Hz), 1.59 - 1.56 (m, 1 H), 1.33 - 1.25 (m, 8 H); MS (ESI) m/z 454 (M+ + H).

Example 118. Comparative Compound 870: (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide

[0245]





Step 1. ethyl 4'-(benzyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)-3-fluorobiphenyl-4-carboxylate: N-benzyl-4-bromo-N-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)benzeneamine (0.80 g, 1.84 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.36 g, 1.84 mmol), Pd(dbpf)Cl_2 (0.06 g, 0.09 mmol) and Cs_2CO_3 (1.20 g, 3.69 mmol) were added to 1,4-dioxane (12 mL) / H_2O (3 mL). With a microwave radiation, the mixture was heated at 120 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was added with saturated aqueous brine solution was added thereto, and then extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as yellow oil (0.74 g, 79%).

Step 2. ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate: Ethyl 4'-(benzyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)-3-fluorobiphenyl-4-carboxylate (0.74 g, 1.41 mmol) was dissolved in MeOH (3 mL) / EtOAc (5 mL). At room temperature, NH_4COOH (0.89 g, 14.15 mmol) was added thereto, following with stirring at 80 °C for 2 hours. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was diluted with water, and extracted with dichloromethane.. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as light-yellow solid (0.40 g, 67%).

Step 3. 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid: Ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate (0.37 g, 0.88 mmol) was dissolved in THF (3 mL) / H_2O /MeOH (2 mL). At room temperature, $LiOH \cdot H_2O$ (0.18 g, 4.44 mmol) was added thereto, following with stirring at the same temperature for 1 hour. The reaction mixture was concentrated under reduced pressure. The concentrate was added with water (10 mL), and stirred. The resulting precipitate was filtered, and dried to yield the title compound as white solid (0.35 g, 97%).

Step 4. Comparative Compound 870: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid (0.06 g, 0.14 mmol), EDCI (0.05 g, 0.29 mmol), HOBt (0.04 g, 0.29 mmol) and DIPEA (0.13 mL, 0.74 mmol) were dissolved in DMF (2 mL). At room temperature, (S)-pyrrolidine-2-carboxamide (0.03 g, 0.29 mmol) was added thereto, following with stirring at 60 °C for 5 hours. The concentrate was added with water (5 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2, dichloromethane / methanol = 0 % to 10 %), and concentrated yield the title compound as light-yellow solid (0.04 g, 61%).
1H NMR (400 MHz, $CDCl_3$) δ 7.57 - 7.37 (m, 4 H), 7.27 (t, 1 H, J = 5.6 Hz), 6.95 (brs, 1 H), 6.67 (d, 2 H, J = 8.8 Hz), 5.59 (brs, 1 H), 4.83 - 4.80 (m, 1 H), 3.55 - 3.42 (m, 2 H), 3.06 (d, 2 H, J = 6.8 Hz), 2.98 (d, 2 H, J = 11.2 Hz), 2.46 - 2.40 (m, 3 H), 2.15 - 1.86 (m, 5 H), 1.74 (d, 2 H, J = 12.4 Hz), 1.60 - 1.56 (m, 1 H), 1.39 - 1.26 (m, 8 H); MS (ESI) m/z 499 (M+ + H).

[0246] According to the above-described synthesis process of comparative compound 870, the compounds of Table 140 were synthesized using 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid and the reactant of Table 139.

Table 139.

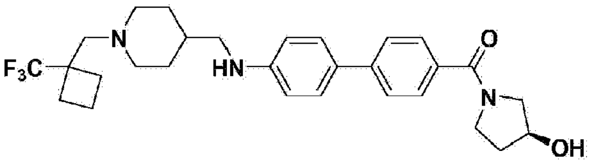
Compound No.	Reactant	Yield (%)
871*	(R)-piperidin-3-carboxamide	40

Table 140.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
871*	(R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidin-3-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, 2 H, J = 8.4 Hz), 7.37 (s, 1 H), 7.27 - 7.21 (m, 3 H), 6.66 (d, 2 H, J = 8.0 Hz), 5.54 (brs, 1 H), 4.17 - 4.14 (m, 1 H), 3.79 - 3.74 (m, 1 H), 3.48 - 3.32 (m, 2 H), 3.06 (d, 2 H, J = 6.4 Hz), 2.98 (d, 2 H, J = 11.2 Hz), 2.58 (brs, 1 H), 2.46 (s, 1 H), 2.41 (s, 1 H), 2.15 - 1.46 (m, 9 H), 1.39 - 1.18 (m, 8 H); MS (ESI) m/z 513 (M+ + H).

Example 119. Comparative compound 1020: (S)-(3-hydroxypyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

[0247]



Step 1. (4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclobutyl)methanone: N-benzyl-4-bromo-N-(piperidin-4-ylmethyl)benzeneamine hydrochloride(the product of synthesis step 3 of comparative compound 857; 0.80 g, 4.75 mmol), EDCI (1.82 g, 9.51 mmol), HOBt (1.28 g, 9.51 mmol) and DIPEA (4.15 mL, 23.79 mmol) were dissolved in DMF (20 mL). At room temperature, 1-(trifluoromethyl)cyclobutanecarboxylic acid (1.97 g, 4.99 mmol) was added thereto, following with stirring at the same temperature for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as yellow oil (1.30 g, 53%).

Step 2. N-benzyl-4-bromo-N-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)benzeneamine: (4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclobutyl)methanone (1.30 g, 2.55 mmol) was dissolved in THF (15 mL) and then cooled to room temperature, following with concentrating under reduced pressure. The concentrate with heating and stirring for 1 hour, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.96 g, 75%).

Step 3. methyl 4'-(benzyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate: N-benzyl-4-bromo-N-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)benzeneamine (0.96 g, 1.93 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.34 g, 1.93 mmol), Pd(dbpf)Cl_2 (0.06 g, 0.09 mmol) and Cs_2CO_3 (1.26 g, 3.87 mmol) were added to 1,4-dioxane (12 mL) / H_2O (3 mL). With a microwave radiation, the mixture was heated at 115 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (0.80 g, 75%).

Step 4. methyl 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino) biphenyl-4-carboxylate: Methyl 4'-(benzyl((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate (0.80 g, 1.45 mmol) and 10% wt Pd/C (0.3 g), NH_4COOH (0.91 g, 14.52 mmol) were dissolved in MeOH (6 mL) / EtOAc (12 mL). The reaction mixture was refluxed with heating for 3 hours, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was concentrated under reduced pressure to remove the solvent. The concentrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (0.44 g, 65%).

Step 5. 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid: Methyl 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate (0.44 g, 0.95 mmol) and $LiOH \cdot H_2O$ (0.20 g, 4.77 mmol) were dissolved in THF (2 mL) / H_2O / MeOH (3 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (20 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.42 g, 98%).

Step 6. Comparative compound 1020: 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid (0.05 g, 0.11 mmol), EDCI (0.04 g, 0.22 mmol), HOBt (0.03 g, 0.22 mmol) and DIPEA (0.09 mL, 0.56 mmol) were dissolved in DMF (2 mL). At room temperature, (S)-pyrrolidine-3-ol (0.02 g, 0.22 mmol) was added thereto, following with stirring at 60 °C for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by

column chromatography (SiO_2, 12 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as yellow solid (0.03 g, 64%).
1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2 H, J = 7.2 Hz), 7.45 (d, 2 H, J = 8.4 Hz), 6.67 (d, 2 H, J = 8.5 Hz), 4.62 (brs, 0.5 H), 4.41 (brs, 0.5 H), 3.81 - 3.43 (m, 5 H), 3.07 (d, 2 H, J = 6.6 Hz), 2.88 (d, 2 H, J = 11.6 Hz), 2.23 - 1.73 (m, 12 H), 1.39 - 1.35 (m, 3 H)); MS (ESI) m/z 516 (M+ + H).

[0248] According to the above-described synthesis process of compound 1020, the compounds of Table 142 were synthesized using 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid and the reactant of Table 141.

Table 141. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
926*	(R)-piperidin-3-ol	70
1021*	(S)-pyrrolidine-2-carboxamide	64
1022*	(S)-piperidin-3-ol	60
1023*	(R)-piperidin-2-carboxamide	61

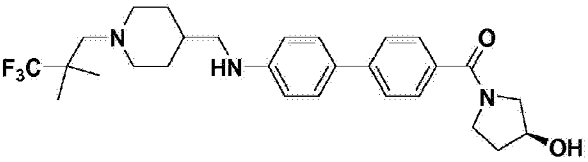
Table 142. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
926*	(R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methylamino)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2 H, J = 8.0 Hz), 7.42 (d, 4 H, J = 7.4 Hz), 6.65 (d, 2 H, J = 8.4 Hz), 3.87 - 3.22 (m, 5 H), 3.05 (d, 2 H, J = 6.4 Hz), 2.86 (d, 2 H, J = 10.8 Hz), 2.50 (s, 2 H), 2.25 - 1.58 (m, 15 H), 1.39 - 1.31 (m, 2 H); MS (ESI) m/z 530 (M+ + H).
1021*	(S)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 4 H), 7.46 (d, 2 H, J = 8.4 Hz), 7.27 (brs, 1 H), 6.67 (d, 2 H, J = 8.5 Hz), 5.59 (brs, 1 H), 4.82 (m, 1 H), 3.70 - 3.58 (m, 2 H), 3.07 (d, 2 H, J = 6.6 Hz), 2.88 (d, 2 H, J = 11.2 Hz), 2.52 (s, 2 H), 2.24 - 1.73 (m, 15 H), 1.39 - 1.35 (m, 2 H); MS (ESI) m/z 543 (M+ + H).
1022*	(S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methylamino)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ7.56 (d, 2 H, J = 8.2 Hz), 7.45 (d, 4 H, J = 8.8 Hz), 6.67 (d, 2 H, J = 8.6 Hz), 3.91 - 3.31 (m, 5 H), 3.07 (d, 2 H, J = 6.6 Hz), 2.88 (d, 2 H, J = 11.4 Hz), 2.52 (s, 2 H), 2.24 - 1.76 (m, 15 H), 1.73 - 1.36 (m, 2 H); MS (ESI) m/z 530 (M+ + H).
1023*	(R)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidin-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.58 (m, 2 H), 7.49 - 7.44 (m, 4 H), 6.68 (d, 2 H, J = 8.4 Hz), 6.58 (brs, 1 H), 5.52 (brs, 1 H), 5.29 (brs, 1 H), 3.92 - 3.80 (m, 2 H), 3.08 - 3.06 (m, 3 H), 2.88 (d, 2 H, J = 11.2 Hz), 2.52 (s, 2 H), 2.23 - 1.57 (m, 16 H), 1.39 - 1.35 (m, 2 H); MS (ESI) m/z 557 (M+

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	+ H).

Example 120. Comparative compound 1024: (S)-(3-hydroxypyrrolidine-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

[0249]



Step 1. 1-(4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)-3,3,3-trifluoro-2,2-dimethylpropan-1-one: N-benzyl-4-bromo-N-(piperidin-4-ylmethyl)benzeneamine hydrochloride (the product of synthesis step 3 of comparative compound 857; 0.80 g, 5.12 mmol), EDCI (1.96 g, 10.25 mmol), HOBt (1.38 g, 10.25 mmol) and DIPEA (4.47 mL, 25.62 mmol) were dissolved in DMF (20 mL). At room temperature, 3,3,3-trifluoro-2,2-dimethylpropanoic acid (2.13 g, 5.38 mmol) was added thereto, following with stirring at the same temperature for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0% to 20 %), and concentrated to yield the title compound as light-yellow solid (1.54 g, 60%).

Step 2. N-benzyl-4-bromo-N-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)benzeneamine: 1-(4-((benzyl(4-bromophenyl)amino)methyl)piperidin-1-yl)-3,3,3-trifluoro-2,2-dimethylpropan-1-one (1.54 g, 3.09 mmol) was dissolved in THF (15 mL) and then cooled to room temperature, following with concentrating under reduced pressure. The concentrate with heating for 1 hour, and then cooled to room temperature. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was washed with saturated $NaHCO_3$ aqueous solution. The organic layer was dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 40 g cartridge; EtOAc / hexane = 0 % to 10 %), and concentrated to yield the title compound as transparent oil (0.42 g, 28%).

Step 3. methyl 4'-(benzyl((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate: N-benzyl-4-bromo-N-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)benzeneamine (0.42 g, 0.86 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.15 g, 0.86 mmol), Pd(dppf)Cl_2 (0.02 g, 0.04 mmol) and Cs_2CO_3 (0.56 g, 1.73 mmol) were added to 1,4-dioxane (12 mL) / H_2O (3 mL). With a microwave radiation, the mixture was heated at 115 °C for 20 minutes, and then cooled to room temperature. The reaction mixture was added with water, and extracted with dichloromethane. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0% to 20 %), and concentrated to yield the title compound as white solid (0.37 g, 79%).

Step 4. methyl 4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino) biphenyl-4-carboxylate: Methyl 4'-(benzyl((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-carboxylate (0.37 g, 0.68 mmol), 10% Pd/C (0.15 g) and NH_4COOH (0.43 g, 6.86 mmol) were added to MeOH (3 mL) / EtOAc (6 mL). The mixture was refluxed with heating for 5 hours, and then cooled to room temperature. The reaction mixture was filtered through a Celite pad to remove a solid. The obtained filtrate was concentrated under reduced pressure. The obtained concentrate was diluted with water, and extracted with EtOAc. The obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 20 %), and concentrated to yield the title compound as white solid (0.24 g, 77%).

Step 5. 4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid: Methyl 4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylate (0.24 g, 0.53 mmol) and $LiOH\cdot H_2O$ (0.11 g, 2.67 mmol) were dissolved in THF (2 mL) / H_2O / MeOH (3 mL) at room temperature. The solution was stirred at the same temperature for 12 hours, the reaction mixture was concentrated under reduced pressure. The concentrate was added with water (20 mL) to be suspended, and filtered. The obtained solid was dried to yield the title compound as white solid (0.22 g, 94%).

Step 6. Comparative compound 1024: 4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid (0.06 g, 0.13 mmol), EDCI (0.05 g, 0.27 mmol), HOBt (0.03 g, 0.27 mmol) and DIPEA (0.12 mL, 0.69 mmol) were dissolved in DMF (2 mL). At room temperature, (S)-pyrrolidine-3-ol (0.02 g, 0.27 mmol) was added thereto, following with stirring at 60 °C for 12 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as yellow solid (0.04 g, 67%).
1H NMR (400 MHz, $CDCl_3$) δ 7.55 - 7.53 (m, 4 H), 7.44 (d, 2 H, J = 8.4 Hz), 6.66 (d, 2 H, J = 8.5 Hz), 4.58 (brs, 0.5 H), 4.41 (brs, 0.5 H), 3.82 - 3.43 (m, 5 H), 3.05 (d, 2 H, J = 6.4 Hz), 2.82 (d, 2 H, J = 11.6 Hz), 2.39 (s, 2 H), 2.29 (t, 2 H, J = 11.0 Hz), 1.95 - 1.70 (m, 5 H), 1.37 - 1.31 (m, 2 H), 1.10 (s, 6 H); MS (ESI) m/z 504 (M+ + H).

[0250] According to the above-described synthesis process of comparative compound 1024, the compounds of Table 144 were synthesized using 4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-carboxylic acid and the reactant of Table 143.
Table 143. (* marks comparative compound)

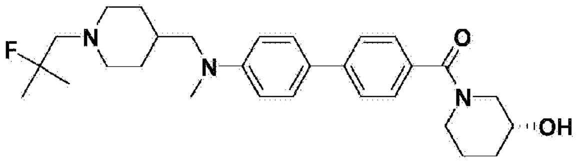
Compound No.	Reactant	Yield (%)
927*	(R)-piperidin-3-ol	34
1025*	(S)-pyrrolidine-2-carboxamide	67
1026*	(S)-piperidin-3-ol	72

Table 144. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
927*	(R)-(3-hydroxypiperidin-1-yl)(4'-(((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2 H, J = 8.0 Hz), 7.43- 7.41 (m, 4 H), 7.07 (d, 2 H, J = 8.4 Hz), 3.87- 3.40 (m, 5 H), 3.04 (d, 2 H, J = 6.6 Hz), 2.81 - 2.78 (m, 2 H), 2.37 (s, 2 H), 2.28 (t, 2 H, J = 11.4 Hz), 1.93 - 1.52 (m, 7 H), 1.36 - 1.24 (m, 2 H), 1.08 (d, 6 H); MS (ESI) m/z 518 (M+ + H).
1025*	(S)-1-(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 4 H), 7.46 (d, 2 H, J = 8.0 Hz), 7.07 (brs, 1 H), 6.67 (d, 2 H, J = 8.4 Hz), 5.66 (brs, 1 H), 5.66 (brs, 1 H), 4.82 - 7.80 (m, 1 H), 3.92 (brs, 1 H), 3.65 - 3.60 (m, 2 H), 3.06 (d, 2 H, J = 6.8 Hz), 2.82 (d, 2 H, J = 11.2 Hz), 2.43 - 2.38 (m, 3 H), 2.29 (t, 2 H, J = 11.4 Hz), 2.13 - 1.57 (m, 7 H), 1.37 - 1.26 (m, 2 H), 1.10 (s, 6 H); MS (ESI) m/z 531 (M+ + H).
1026*	(S)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2 H, J = 8.4 Hz), 7.45 (d, 4 H, J = 8.4 Hz), 6.67 (d, 2 H, J = 8.4 Hz), 3.90 - 3.32 (m, 5 H), 3.06 (d, 2 H, J = 6.6 Hz), 2.82 (d, 2 H, J = 11.6 Hz), 2.39 (s, 2 H), 2.28 (t, 2 H, J = 12.2 Hz), 2.05 - 1.57 (m, 6 H), 1.35 - 1.26 (m, 3 H), 1.10 (s, 6 H); MS (ESI) m/z 518 (M+ + H).

Example 121. Comparative compound 852: (R)-(4'-(((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)(methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0251]



[0252] (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone (comparative compound 867, 0.02 g, 0.05 mmol) was dissolved in acetonitrile 5 mL. Formaldehyde (0.01 mL, 0.27 mmol) and acetic acid (0.30 mL, 0.05 mmol) were added thereto, following with stirring for a day and then cooling the temperature. At 0 °C, $NaCNBH_3$

(0.30 mg, 0.05 mmol) was added slowly thereto, following with increasing the temperature and stirring at room temperature for 2 hours. After the reaction was quenched by addition of a little of water, the reaction mixture was added with water, and then extracted with CH_2Cl_2. The obtained organic layer was washed several times with H_2O, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as yellow solid (0.01 g, 62%).

1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2 H, J = 8.0 Hz), 7.47 (dd, 4 H, J = 20.7, 8.7 Hz), 6.74 (d, 2 H, J = 8.8 Hz), 3.98 (brs, 2 H), 3.24 (d, 2 H, J = 6.8 Hz), 3.02 - 2.96 (m, 5 H), 2.50 - 2.41 (m, 5 H), 2.13 - 1.65 (m, 9 H), 1.39 - 1.26 (m, 8 H); MS (ESI) m/z 482 (M+ + H).

[0253] According to the above-described synthesis process of comparative compound 852, the compounds of Table 146 were synthesized using (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino) biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone and the reactant of Table 145.

Table 145. (* marks comparative compound)

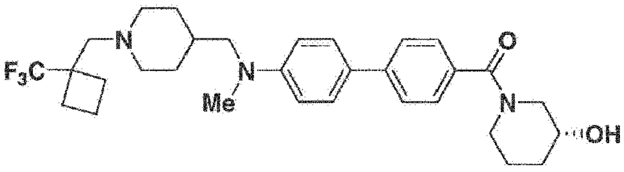
Compound No.	Reactant	Yield (%)
853*	Acetaldehyde	45

Table 146. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
853*	(R)-(4'-(ethyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2 H, J = 8.4 Hz), 7.49 - 7.27 (m, 4 H), 6.73 (d, 2 H, J = 8.8 Hz), 4.21 - 3.87 (m, 3 H), 3.46 - 3.41 (m, 4 H), 3.18 (d, 2 H, J = 8.0 Hz), 2.97 (d, 2 H, J = 12.0 Hz), 2.46 (s, 1 H), 2.40 (s, 1 H), 2.12 - 1.96 (m, 6 H), 1.72 - 1.69 (m, 3 H), 1.39 - 1.26 (m, 8 H), 1.17 (t, 3 H, J = 7.0 Hz); MS (ESI) m/z 496 (M+ + H).

Example 122. Comparative compound 928: (R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone

[0254]



[0255] (R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone (comparative compound 926, 0.03 g, 0.05 mmol), formaldehyde (8 µL, 0.28 mmol) and AcOH (3 µL, 0.05 mmol) were dissolved in Acetonitrile (3 mL), following with stirring with at 12 hours at room temperature and cooling the temperature slowly to 0 °C. $NaCNBH_3$ (4 mg, 0.05 mmol) was added thereto at 0 °C, following with stirring at room temperature for 1 hour. The concentrate was added with water (10 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2, 12 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.02 g, 81%).

1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.0 Hz), 7.51 (d, 2 H, J = 8.8 Hz), 7.45 (d, 2 H, J = 8.0 Hz), 6.75 (d, 2 H, J = 8.8 Hz), 4.03 - 3.42 (m, 5 H), 3.25 (d, 2 H, J = 7.1 Hz), 3.02 (s, 3 H), 2.86 (d, 2 H, J = 11.2 Hz), 2.51 (s, 2 H), 2.24 - 1.65 (m, 15 H), 1.38 - 1.34 (m, 2 H); MS (ESI) m/z 544 (M+ + H).

[0256] According to the above-described synthesis process of comparative compound 928, the compounds of Table 148 were synthesized using (R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone and the reactant of Table 147.

Table 147. (* marks comparative compound)

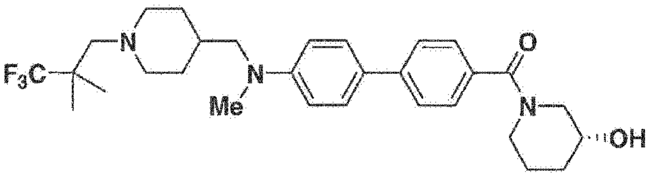
Compound No.	Reactant	Yield (%)
929*	Acetaldehyde	72

Table 148. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
929*	(R)-(4'-(ethyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, 2 H, J = 8.0 Hz), 7.48 - 7.42 (m, 4 H), 6.72 (d, 2 H, J = 7.2 Hz), 3.98 - 3.67 (m, 2 H), 3.45 - 3.39 (m, 5 H), 3.17 (d, 2 H, J = 6.6 Hz), 2.86 (d, 2 H, J = 11.2 Hz), 2.500 (s, 2 H), 2.25 - 1.67 (m, 15 H), 1.43 - 1.17 (m, 5 H); MS (ESI) m/z 558 (M+ + H).

Example 123. Comparative compound 930: (R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone

[0257]

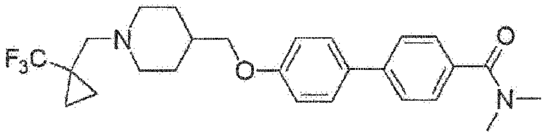


[0258] (R)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone (the product of synthesis of comparative compound 927; 0.03 g, 0.05 mmol), formaldehyde (8 µL, 0.29 mmol) and AcOH (3 µL, 0.05 mmol) were dissolved in Acetonitrile (3 mL). At 0 °C, $NaCNBH_3$ (4.00 mg, 0.05 mmol) was added thereto, , following with stirring at room temperature for 2 hours. The concentrate was added with water (8 mL) to be suspended, and filtered. The obtained solid was dried, and purified by column chromatography (SiO_2, 12 g cartridge; methanol / dichloromethane = 0 % to 10 %), and concentrated to yield the title compound as white solid (0.01 g, 48%).

1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2 H, J = 8.4 Hz), 7.48 (dd, 4 H, J = 20.3, 8.5 Hz), 6.74 (d, 2 H, J = 8.9 Hz), 4.17 - 3.42 (m, 5 H), 3.24 (d, 2 H, J = 7.2 Hz), 3.02 (s, 3 H), 2.80 (d, 2 H, J = 11.4 Hz), 2.37 (s, 2 H), 2.27 (t, 2 H, J = 5.9 Hz), 2.23 - 1.50 (m, 7 H), 1.37 - 1.24 (m, 2 H), 1.51 (s, 6 H); MS (ESI) m/z 532 (M+ + H).

Example 124. Comparative compound 552: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

[0259]



Step 1. (4-((4-bromophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopropyl) methanone: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 1of comparative compound 498; 200 mg, 0.65 mmol) and 1-(trifluoromethyl)cyclopropanecarboxylic acid (101 mg, 0.65 mmol) were dissolved in CH_2Cl_2 4 mL. EDC (250 mg, 1.31 mmol) and HOBt (176 mg, 1.31 mmol) were added thereto. Lastly, DIPEA (0.57 mL, 3.26 mmol) was added thereto, following with stirring at room temperature for 15 hours. The reaction mixture was diluted with water, and extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-50% EtOAc/Hexane) to yield the title compound as white solid (239 mg, 90%).

Step 2. 4-((4-bromophenoxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine: (4-((4-bromophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopropyl)methanone (239 mg, 0.59 mmol) was dissolved in dry THF 10 mL, and then cooled with ice bath. 1 M LAH in THF (1.77 mL, 1.77 mmol) was added dropwise slowly thereto, following with increasing the temperature to room temperature slowly and stirring for 1 hour. The reaction was quenched by addition of water. After the addition of EtOAc thereto, the resulting precipitate was filtered, and extracted with EtOAc. The organic layer was dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-40 % EtOAc/hexane) to yield the title compound as colorless liquid (64 mg, 28%).

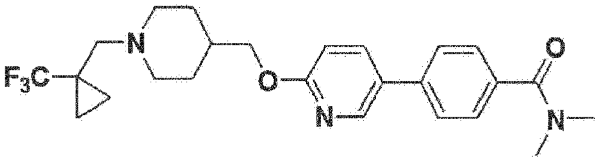
Step 3. methyl 4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy) biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidine (50 mg, 0.127 mmol) and 4-(methoxycarbonyl)phenylboronic acid(28 mg, 0.15 mmol) were dissolved in dioxane 1 mL. Water 0.3 mL was added thereto. $Pd(dbpf)Cl_2$ (30 µg, 0.01 mmol) and Cs_2CO_3 (125 mg, 0.38 mmol) were added thereto. With a microwave radiation, the reaction was performed at 140 °C for 15 minutes. The reaction mixture was diluted with water, and extracted with CH_2Cl_2 three times. The organic layer was dried over $MgSO_4$, filtered through Celite to remove solid, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (0-40 % EtOAc/Hexane) to yield the title compound as light-yellow solid (30 mg, 53%).

Step 4. 4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (30 mg, 0.07 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 1 mL were added thereto. LiOH (14 mg, 0.34 mmol) was added thereto, following with stirring at room temperature for 15 hours. After acidification with 1N HCl, the resulting precipitate was filtered to yield the title compound as white solid (28 mg, 97%).

Step 5. Comparative compound 552: 4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (28 mg, 0.07 mmol) and dimethylamine hydrochloride (11 mg, 0.13 mmol) were dissolved in DMF 1 mL. EDC (25 mg, 0.13 mmol) and HOBt (18 mg, 0.13 mmol) were added thereto. Lastly, DIPEA (57 µL, 0.26 mmol) was added thereto, following with stirring at room temperature for 15 hours. Water 5 mL was added thereto, and filtered to give a solid. The residue was purified by silica gel column chromatography (0-5 % MeOH/CH_2Cl_2) to yield the title compound as white solid (23 mg, 76%).
1H NMR (400 MHz, $CDCl_3$) δ7.60 - 7.55 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.50 - 7.45 (m, 2 H), 7.00 - 6.93 (m, 2 H), 3.83 (d, 2 H, J = 6.0 Hz), 3.13 (s, 3 H), 3.04 (s, 3 H), 2.98 (d, 2 H, J = 11.3 Hz), 2.54 (s, 2 H), 2.03 - 1.94 (m, 2 H), 1.86 - 1.74 (m, 3 H), 1.40 (dd, 2 H, J = 12.2, 2.6 Hz), 1.02 - 0.95 (m, 2 H), 0.65 (s, 2 H); MS (ESI) m/z 461 (M+ + H).

Example 125. Comparative compound 580: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzamide

[0260]



Step 1. methyl 4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy) pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine (the product of synthesis step 3 of comparative compound 589; 0.50 g, 1.27 mmol), 4-(methoxycarbonyl)phenylboronic acid (0.25 g, 1.40 mmol), Pd(dbpf)Cl_2 (24 mg, 0.04 mmol), Cs_2CO_3 (1.24 g, 3.81 mmol) were added into a microwave reactor, and then dioxane 6 mL and water 3 mL were added thereto. With a microwave radiation, the reaction was performed at 100 °C for 30 minutes. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (20-70 % EtOAc/hexane) to yield the title compound as white solid (0.40 g, 70%).

Step 2. 4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid: Methyl 4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate (0.40 g, 0.89 mmol) was dissolved in THF 10 mL. LiOH·HiO (0.07 g, 1.78 mmol) in water 10 mL was added thereto, and the reaction was performed at 60 °C for 4 hours. The solvent was concentrated under reduced pressure. After the addition of 1M HCl 5 mL thereto, the resulting precipitate was filtered to yield the title compound as white solid (0.37 g, 96%).

Step 3. Comparative compound 580: 4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (0.05 g, 0.12 mmol), dimethylamine hydrochloride(0.02 g, 0.23 mmol), EDC (0.04 g, 0.23 mmol) and HOBt (0.03 g, 0.23 mmol) were dissolved in DMF 2 mL. DIPEA (0.04 mL, 0.23 mmol) was added thereto, following with stirring at room temperature for 10 hours. The reaction mixture was added with saturated NH_4Cl aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (10-70 % EtOAc/hexane) to yield the title compound as white solid (0.01 g, 19%). 1H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.54 (dd, 4 H, J = 19.3, 8.3 Hz), 6.83 (d, 1 H, J = 8.7 Hz), 4.26 - 4.19 (m, 2 H), 3.14 - 2.98 (m, 8 H), 2.54 (m, 2 H), 2.19 - 1.80 (m, 5 H), 1.52 - 1.26 (m, 2 H), 1.03 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 462.2 (M+ + H); MS (ESI) m/z 462 (M+ + H).

[0261] According to the above-described synthesis process of comparative compound 580 (Step 3), the compounds of Table 150 were synthesized using 4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 149.

Table 149. (* marks comparative compound)

Compound No.	Reactant	Yield (%)
582*	morpholine	22
583*	piperidine	26
584*	pyrrolidine	32
585*	(S)-3-pyrrolidinol	29
586	L-prolinamide	41
587*	4-piperidinemethanol	65

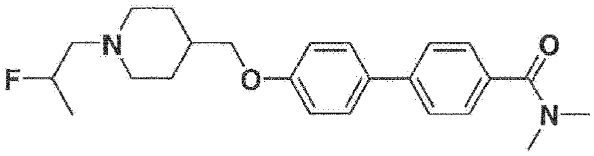
Table 150. (* marks comparative compound)

Compound No.	Compound Name, ^1H-NMR, MS (ESI)
582*	morpholino(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ8.37 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.54 (dd, 4 H, J = 19.3, 8.3 Hz), 6.83 (d, 1 H, J = 8.7 Hz), 4.21 - 4.18 (m, 2 H), 3.82 - 3.25 (m, 9 H), 3.09 - 2.40 (m, 4 H), 2.25 - 1.25 (m, 6 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 504 (M+ + H).
583*	piperidin-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ8.37 (s, 1H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.52 (dd, 4 H, J = 19.3, 8.3 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 4.21 - 4.18 (m, 2

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
	H), 3.80-3.60 (m, 2 H), 3.50 - 3.30 (m, 2 H), 2.97 (m, 2 H), 2.54 (m, 2 H), 2.10 - 1.25 (m, 13 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 502 (M+ + H).
584*	pyrrolidine-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ8.37 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.58 (dd, 4 H, J = 19.3, 8.3 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 4.29 - 4.20 (m, 2 H), 3.68 (t, 2 H, J = 6.9 Hz), 3.50 (t, 2 H, J = 6.5 Hz), 2.99 (m, 2 H), 2.11 (m, 2 H), 2.08 - 1.26 (m, 11 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 488 (M+ + H).
585*	(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ8.37 (s, 1 H), 7.79 (m, 1 H), 7.58 (m, 4 H), 6.82 (m, 1 H), 4.61 - 4.48 (m, 1 H), 4.20 (m, 2 H), 3.86 - 3.48 (m, 4 H), 2.99 (m, 2 H), 2.54 (m, 2 H), 2.22 - 1.63 (m, 8 H), 1.57 - 1.38 (m, 2 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 504 (M+ + H).
586	(S)-1-(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxamide
	1H NMR (400 MHz, $CDCl_3$) δ8.38 (s, 1 H), 7.80 (dd, 1 H, J = 8.4, 2.3 Hz), 7.60 (dd, 4 H, J = 19.3, 8.3 Hz), 7.00 (m, 1 H), 6.83 (d, 1 H, J = 8.7 Hz), 5.43 (m, 1 H), 4.83 (m, 1 H), 4.21 (m, 2 H), 3.65 - 3.54 (m, 2 H), 3.01 - 2.90 (m, 2 H), 2.79 - 2.42 (m, 2 H), 2.22 - 1.65 (m, 9 H), 1.42 (m, 2 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 531 (M+ + H).
587*	(4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ8.38 (d, 1 H, J = 2.2 Hz), 7.79 (dd, 1 H, J = 8.4, 2.3 Hz), 7.51 (dd, 4 H, J = 19.3, 8.3 Hz), 6.82 (d, 1 H, J = 8.7 Hz), 4.77 (m, 1 H), 4.20 (m, 2 H), 3.87 (m, 1 H), 3.55 (m, 2 H), 3.20 - 2.70 (m, 4 H), 2.54 (m, 2 H), 2.05 - 1.65 (m, 9 H), 1.42 - 1.11 (m, 4 H), 0.98 (m, 2 H), 0.66 (m, 2 H); MS (ESI) m/z 532 (M+ + H).

Example 126. Comparative compound 688: 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide

[0262]



Step 1. 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)propan-2-ol: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 2 of comparative compound 686; 200 mg, 0.65 mmol) was dissolved in EtOH 1 mL. 2-methyloxirane (379 mg, 6.52

mmol), K_2CO_3 (180 mg, 1.31 mmol) and water 1 mL were added thereto. With a microwave radiation, the mixture was stirred at 110 °C for 20 minutes. After the completion of the reaction, EtOH was evaporated from the reaction mixture under reduced pressure, and then a little of water was added to thereto. The resulting precipitate was filtered, and dried under reduced pressure to yield the title compound as red oil (190 mg, 88%).

Step 2. 4-((4-bromophenoxy)methyl)-1-(2-fluoropropyl)piperidine: 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)propan-2-ol (190 mg, 0.58 mmol) was dissolved in CH_2Cl_2 2 mL. Deoxo-fluor (141 mg, 0.64 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer washed with saturated aqueous brine solution, dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as yellow oil (180 mg, 94%).

Step 3. methyl 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-fluoropropyl)piperidine (190 mg, 0.58 mmol), 4-(methoxycarbonyl)phenylboronic acid (124 mg, 0.69 mmol), Pd(dbpf)Cl_2 (19 mg, 0.03 mmol) and Cs_2CO_3 (375 mg, 1.15 mmol) were dissolved in 1,4-dioxane 2 mL and water 0.5 mL. With a microwave radiation, the mixture was stirred at 120 °C for 20 minutes. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CH_2Cl_2) to yield the title compound as yellow solid (87 mg, 39%).

Step 4. 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: methyl 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (87 mg, 0.23 mmol) was dissolved in THF:MeOH:water =4:2:1. $LiOH\cdot H_2O$ (19 mg, 0.45 mmol) was added thereto, and refluxed with heating for 7 hours. After the reaction was complete, the solvent was evaporated under reduced pressure. After adjusting pH to below 6 using 1 N HCl, the resulting precipitate was washed with EtOAc thoroughly, and filtered to yield the title compound as gray solid (80 mg, 95%).

Step 5. Comparative compound 688: 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (40 mg, 0.11 mmol), dimethylamine hydrochloride (18 mg, 0.22 mmol) and PyBOP (84 mg, 0.16 mmol) were dissolved in CH_2Cl_2 1 mL. After stirring at room temperature for 10 minutes, DIPEA (28 mg, 0.22 mmol) was added thereto, following with stirring at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, EA) to yield the title compound as white solid (17 mg, 45%).
1H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 6 H), 6.98 (d, 2 H, J = 8.8 Hz), 4.71 (m, 0.5 H), 4.58 (m, 0.5 H), 3.86 (d, 2 H, J = 6.0 Hz), 3.01 (m, 6 H), 2.66 (m, 1 H), 2.47 (m, 1 H), 2.14 (m, 2 H), 1.81 (m, 3 H), 1.66 (m, 2 H), 1.57 (m, 2 H), 1.01 (t, 3 H, J = 7.5 Hz); MS (ESI) m/z 413 (M+ + H).

[0263] According to the above-described synthesis process of comparative compound 688, the compounds of Table 152 were synthesized using 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 151.

Table 151. (* marks comparative compound)

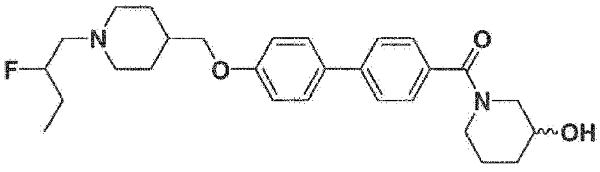
Compound No.	Reactant	Yield (%)
689*	(R)-pyrrolidine-2-ylmethanol	30

Table 152. (* marks comparative compound)

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
689*	(4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone
	1H NMR (400 MHz, $CDCl_3$) δ 7.51 (m, 6 H), 6.98 (d, 2 H, J = 8.8 Hz), 4.99 (m, 0.5 H), 4.72 (m, 0.5 H), 3.86 (m, 4 H), 3.46 (m, 2 H), 3.04 (m, 2 H), 2.68 (m, 1 H), 2.52 (m, 1 H), 2.13 (m, 2 H), 1.85 (m, 7 H), 1.61 (m, 2 H), 1.51 (m, 2 H) 1.30 (m, 3 H); MS (ESI) m/z 455 (M+ + H).

Example 127. Compartive compound 690: (4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

[0264]



__Step 1.__ 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)butan-2-ol: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 2 of comparative compound 686; 200 mg, 0.65 mmol) was dissolved in EtOH 1 mL. 2-ethyloxirane (470 mg, 6.52 mmol), K_2CO_3 (180 mg, 1.31 mmol) and water 1 mL were added thereto. With a microwave radiation, the mixture was stirred at 110 °C for 20 minutes. After the completion of the reaction, EtOH was evaporated from the reaction mixture under reduced pressure, and then a little of water was added to thereto. The resulting precipitate was filtered, and dried under reduced pressure to yield the title compound as red oil (134 mg, 88%).

__Step 2.__ 4-((4-bromophenoxy)methyl)-1-(2-fluorobutyl)piperidine: 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)butan-2-ol (134 mg, 0.39 mmol) was dissolved in CH_2Cl_2 2 mL. Deoxo-fluor (95 mg, 0.43 mmol) was added thereto, following with stirring at room temperature for 3 hours. After the completion of the reaction, the reaction mixture was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer washed with saturated aqueous brine solution, dried over $MgSO_4$ and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography

(ISCO silica gel cartridge, EtOAc/Hexane) to yield the title compound as yellow oil (120 mg, 89%).

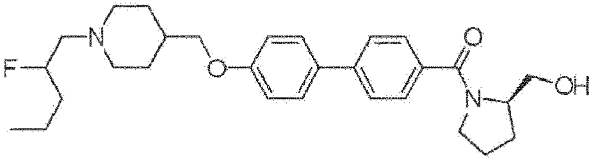
<u>**Step 3.**</u> methyl 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-fluorobutyl)piperidine (150 mg, 0.44 mmol), 4-(methoxycarbonyl) phenylboronic acid (94 mg, 0.52 mmol), Pd(dbpf)Cl_2 (14 mg, 0.02 mmol), Cs_2CO_3 (284 mg, 0.87 mmol) was dissolved in 1,4-dioxane 2 mL and water 0.5 mL. With a microwave radiation, the mixture was stirred at 120 °C for 20 minutes. The reaction mixture was added with saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The obtained organic layer was dried over $MgSO_4$, and filtered to remove the solid residue. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CH_3Cl_3) to yield the title compound as yellow solid (30 mg, 17%).

<u>**Step 4.**</u> 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (30 mg, 0.08 mmol) was dissolved in THF:MeOH: water =4:2:1. LiOH·H_2O (6 mg, 0.15 mmol) was added thereto, and refluxed with heating for 7 hours. After the reaction was complete, the solvent was evaporated under reduced pressure. After adjusting pH to below 6 using 1 N HCl, the resulting precipitate was washed with EtOAc thoroughly, and filtered to yield the title compound as gray solid (21 mg, 72%).

<u>**Step 5.**</u> Comparative compound 690: 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)-biphenyl-4-carboxylic acid (21 mg, 0.05 mmol), piperidin-3-ol (11 mg, 0.11 mmol) and PyBOP (43 mg, 0.08 mmol) were dissolved in CH_2Cl_2 1 mL. After stirring at room temperature for 10 minutes, DIPEA (14 mg, 0.11 mmol) was added thereto, following with stirring at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, filtered to remove the solid residue, and the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (ISCO silica gel cartridge, MeOH/CH_2Cl_2) to yield the title compound as white solid (14 mg, 54%).
1H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 6 H), 6.97 (d, 2 H, J = 6.8 Hz), 4.60 (m, 0.5 H), 3.86 (m, 0.5 H), 3.08 (m, 4 H), 3.45 (m, 2 H), 2.66 (m, 2 H), 2.53 (m, 1 H), 2.45 (m, 1 H), 2.13 (m, 2 H), 1.82 (m, 6 H), 1.64 (m, 3 H), 1.59 (m, 3 H), 1.01 (t, 3 H, J = 7.4 Hz); MS (ESI) m/z 469 (M+ + H).

Example 128. Comparative compound 655: (R)-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone

[0265]



<u>**Step 1.**</u> 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)pentane-2-ol: 4-((4-bromophenoxy) methyl)piperidine hydrochloride (the product of synthesis step 1 of comparative compound 498; 500

mg, 1.63 mmol) and K_2CO_3 (450 mg, 3.26 mmol) were suspended in EtOH 2 mL. Water 2 mL was added thereto, and the mixture was suspended with a little heating. 2-propyloxirane (1.40 g, 16.31 mmol) was added thereto. With a microwave radiation, the reaction was performed at 110 °C for 20 minutes. The reaction mixture was diluted with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to yield the title compound as white solid (510 mg, 88%).

Step 2. 4-((4-bromophenoxy)methyl)-1-(2-fluoropentyl)piperidine: 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)pentane-2-ol (510 mg, 1.43 mmol) was dissolved in CH_2Cl_2 4 mL. Deoxo-Fluor (348 mg, 1.58 mmol) was added thereto. After stirring for 3 hours at room temperature, A saturated $NaHCO_3$ aqueous solution was added thereto, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and filtered to remove a solid. The filtrate was concentrated under reduced pressure to yield the title compound as yellow oil (395 mg, 77%).

Step 3. methyl 4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4-((4-bromophenoxy)methyl)-1-(2-fluoropentyl)piperidine(250 mg, 0.70 mmol) and 4-(methoxycarbonyl)phenylboronic acid (151 mg, 0.84 mmol) were dissolved in dioxane 2 mL. Water 0.5 mL was added thereto. Pd(dbpf)Cl_2 (23 mg, 0.04 mmol) and Cs_2CO_3 (455 mg, 1.40 mmol) were added thereto. With a microwave radiation, the reaction was performed at 120 °C for 20 minutes. The reaction mixture was filtered through Celite. The filtrate was added with a saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and then concentrated under reduced pressure. The obtained concentrate was purified by silica gel column chromatography (MeOH/CH_2Cl_2) to yield the title compound as white solid (115 mg, 40%).

Step 4. 4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (115 mg, 0.28 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 0.5 mL were added thereto. The mixture was added with $LiOH \cdot H_2O$ (23 mg, 0.56 mmol), and then refluxed with heating and stirring for a day. After acidification with 1 N HCl, the resulting precipitate was filtered to yield the title compound as white solid (100 mg, 90%).

Step 5. Comparative compound 655: 4'-((1-(2-fluoropentyi)piperidin-4-yl)methoxy)-biphenyl-4-carboxylic acid (40 mg, 0.10 mmol), (R)-pyrrolidine-2-ylmethanol (15 mg, 0.15 mmol) and PyBOP (78 mg, 0.15 mmol) were dissolved in DMF 1 mL. DIPEA (26 mg, 0.20 mmol) was added thereto. The reaction was performed at room temperature for 8 hours. The reaction mixture was added with water, and extracted with EtOAc. The obtained organic layer was dried over $MgSO_4$, and filtered. The obtained concentrate was purified by silica gel column chromatography (MeOH/CH_2Cl_2) to yield the title compound as light-yellow solid (21mg, 43%).
1H NMR (400 MHz, $CDCl_3$) δ 7.57 (m, 4 H), 7.52 (d, 2 H, J = 8.7 Hz), 6.97 (d, 2 H, J = 8.7 Hz), 4.78 (m, 0.5 H), 4.64 (m, 0.5 H), 4.42 (m, 1 H), 3.75 (m, 4 H), 3.55 (m, 2 H), 3.16 (m, 2 H), 2.62 (m, 1 H), 2.53 (m, 1 H), 2.17 (m, 3 H), 1.80 (m, 5 H), 1.63 (m, 2 H), 1.47 (m, 3 H), 0.95 (t, 3 H, J = 7.1 Hz); MS (ESI) m/z 483 (M+ + H).

[0266] According to the above-described synthesis process of comparative compound 655 (Step 5), the compounds of Table 154 were synthesized using 4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid and the reactant of Table 153.

Table 153.

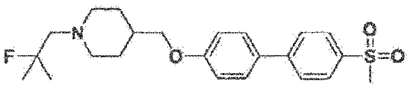
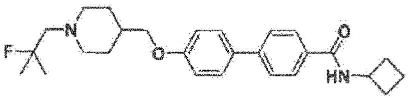
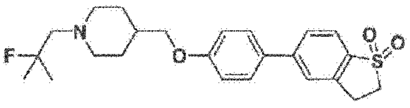
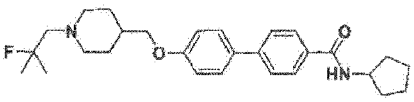
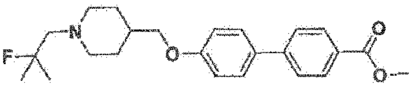
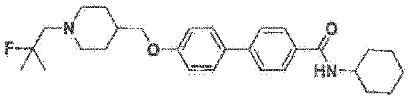
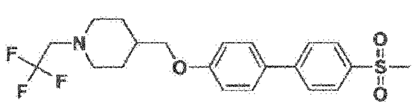
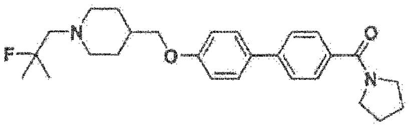
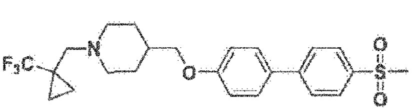
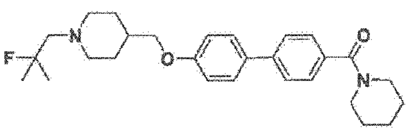
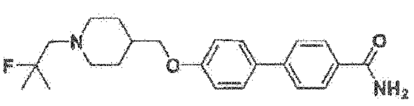
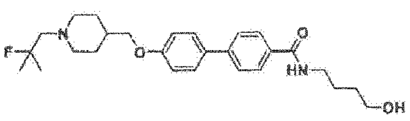
Compound No.	Reactant	Yield (%)
656*	L-prolinamide	48

Table 154.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
656*	(S)-1-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide
	^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (s, 3 H), 7.52 (d, 2 H, *J* = 8.6 Hz), 7.02 (s, 1 H), 6.96 (d, 2 H, *J* = 8.6 Hz), 5.57 (s, 1 H), 4.79 (m, 1.5 H), 4.65 (m, 0.5 H), 3.84 (d, 2 H, *J* = 5.8 Hz), 3.63 (m, 2 H), 3.15 (m, 1 H), 3.07 (m, 2 H), 2.64 (m, 1 H), 2.44 (m, 2 H), 2.08 (m, 4 H), 1.81 (m, 5 H), 1.48 (m, 4 H), 0.94 (t, 3 H, *J* = 7.1 Hz); **MS** (ESI) m/z 496 (M$^+$ + H).

[0267] The structural formulae are as following Tables 155-180.

Table 155. (* marks comparative compound)

Compound	Structure	Compound	Structure
431*		527*	
470*		528 *	
498*		529*	
499*		530*	
500*		531*	
515*		533*	

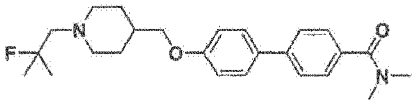
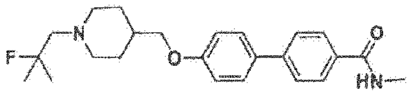
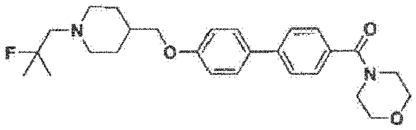
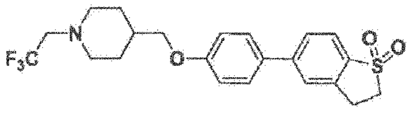
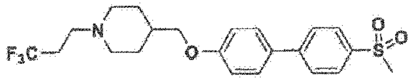
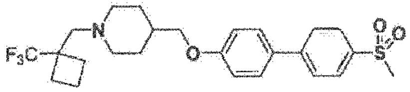
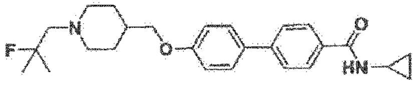
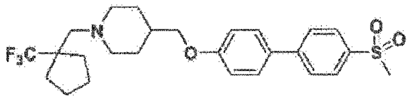
Compound	Structure	Compound	Structure
516*		534*	
517*		540*	
524*		542*	
526*		546*	

Table 156. (* marks comparative compound)

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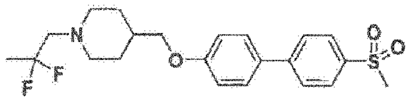
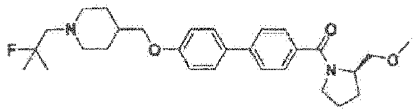
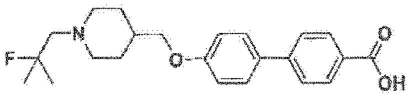
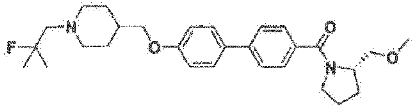
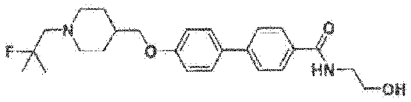
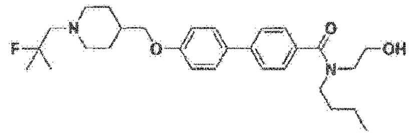
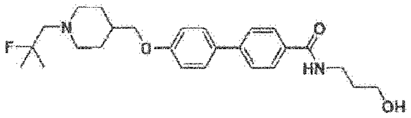
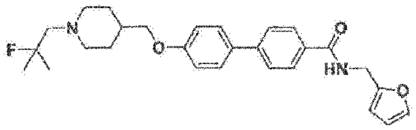
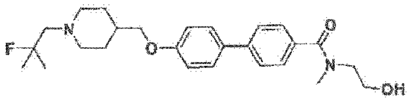
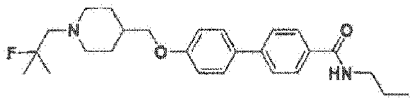
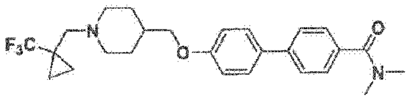
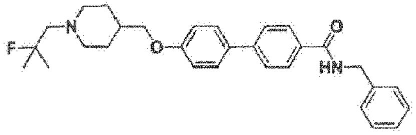
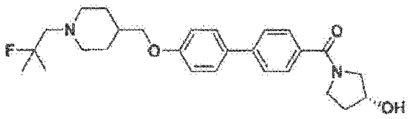
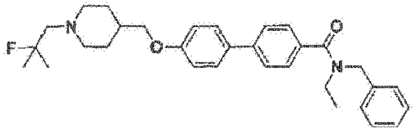
547*		557*	
548*		558*	
549*		559*	
550*		560*	
551*		561*	
552*		562*	
553*		563*	

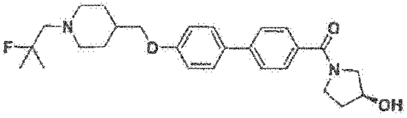
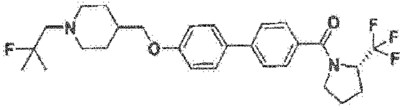
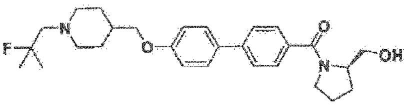
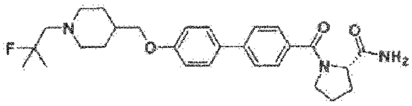
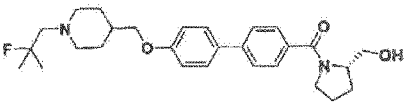
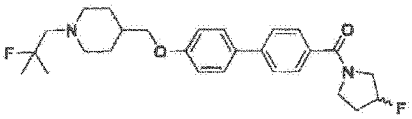
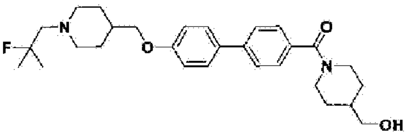
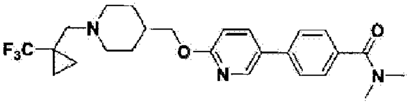
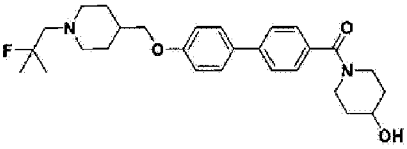
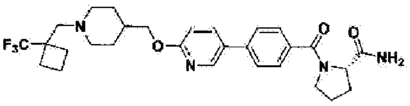
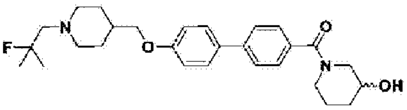
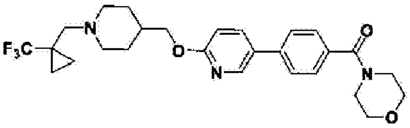
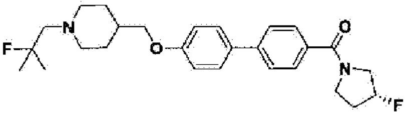
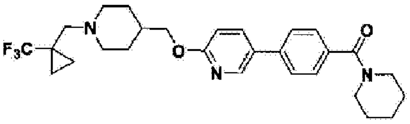
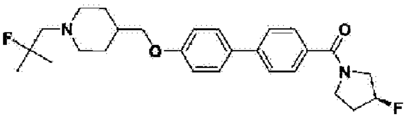
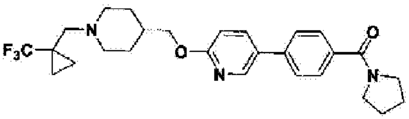
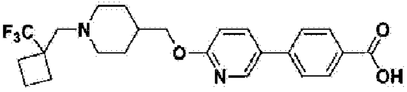
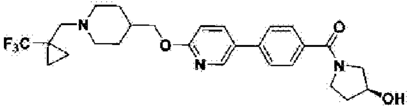
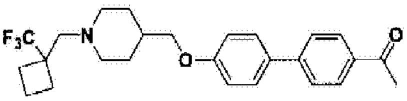
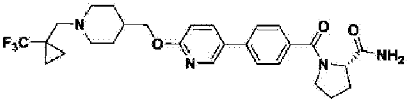
Compound	Structure	Compound	Structure
554*		564*	
555*		565	
556*		566*	

Table 157. (* marks comparative compound)

Compound	Structure	Compound	Structure
567*		580*	
568*		581	
569*		582*	
570*		583*	
571*		584*	
574*		585*	
575*		586	
			

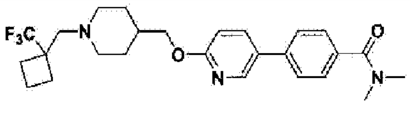
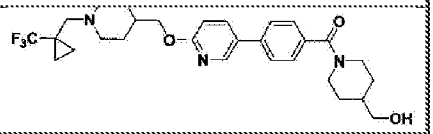
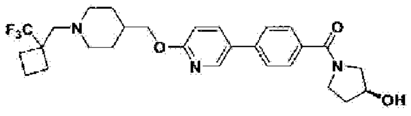
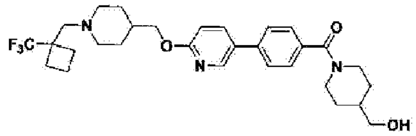
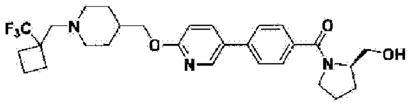
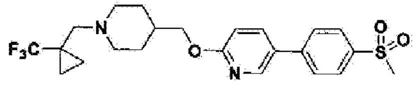
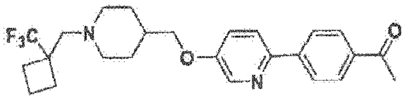
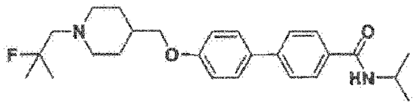
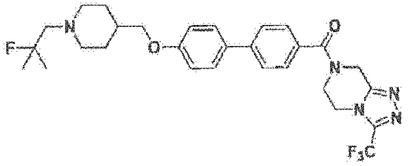
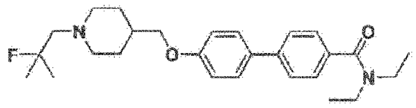
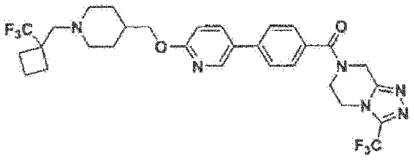
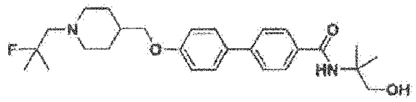
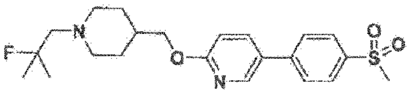
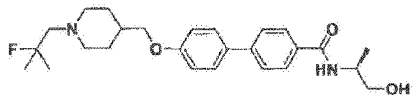
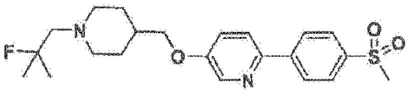
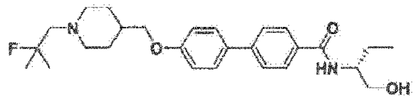
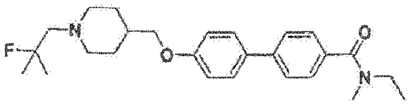
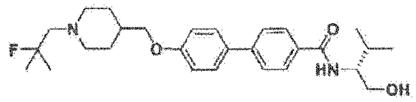
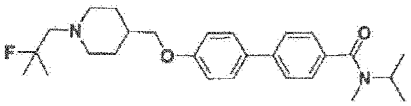
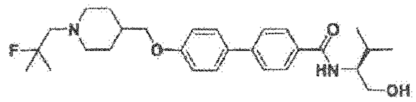
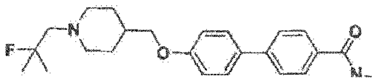
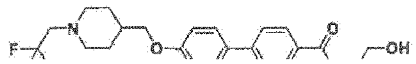
Compound	Structure	Compound	Structure
576*		587*	
578*		588*	
579*		589*	

Table 158. (* marks comparative compound)

Compound	Structure	Compound	Structure
593*		603*	
594*		604*	
595*		605*	
596*		606*	
597*		607*	
598*		608*	
599*		609*	
600*		610*	

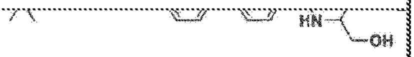
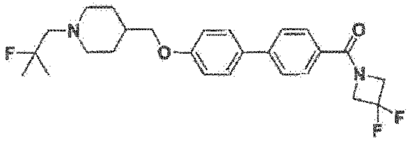
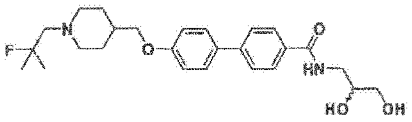
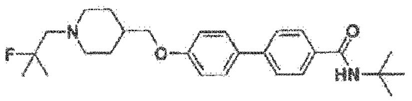
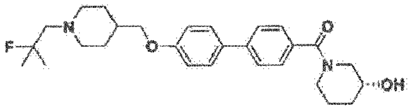
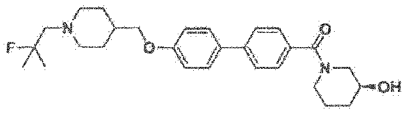
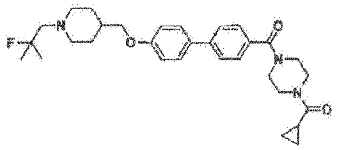
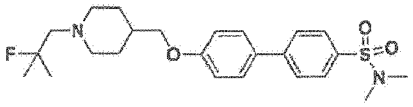
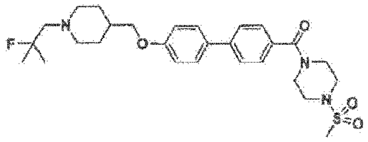
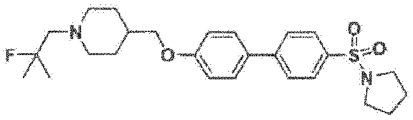
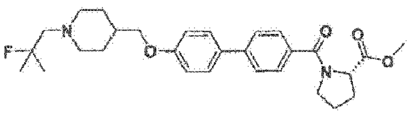
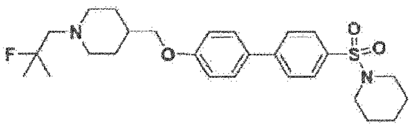
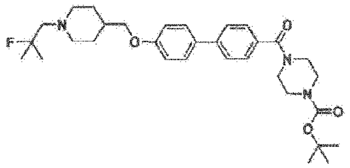
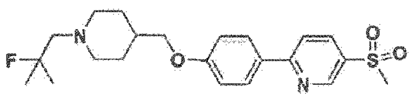
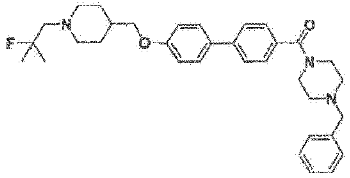
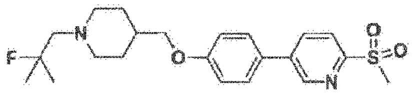
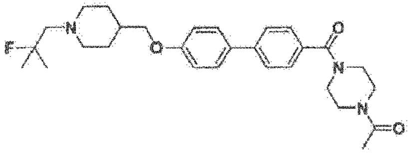
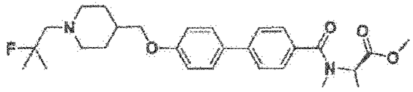
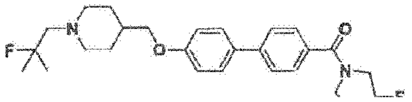
Compound	Structure	Compound	Structure
			
601*		611*	
602*		612*	

Table 159. (* marks comparative compound)

Compound	Structure	Compound	Structure
613*		623*	
614*		624*	
615*		625*	
616*		626*	
617*		627*	
618*		628*	
619*		629*	

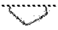
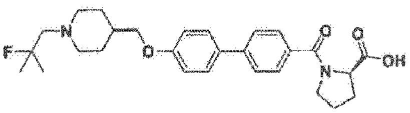
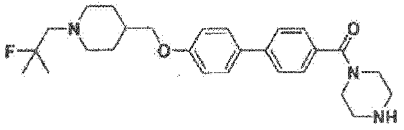
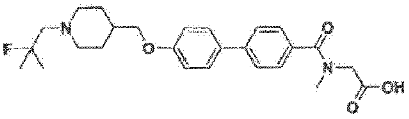
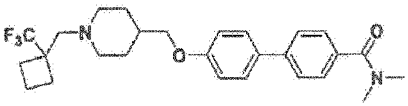
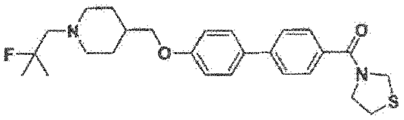
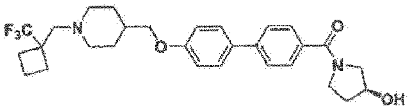
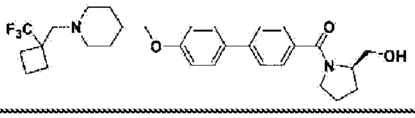
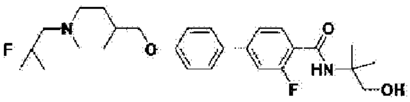
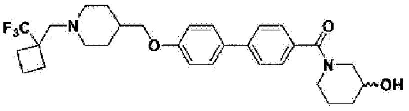
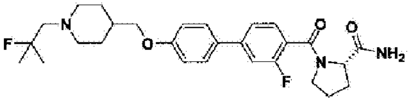
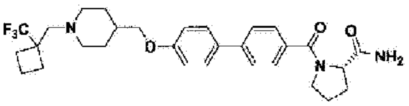
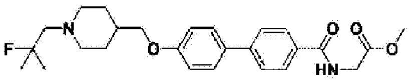
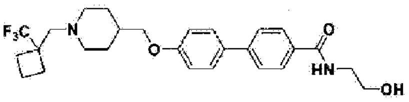
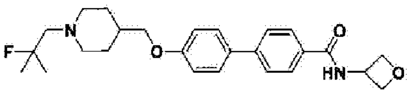
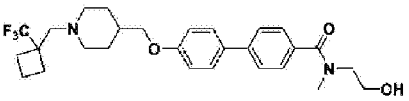
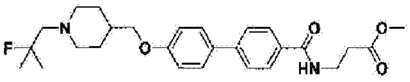
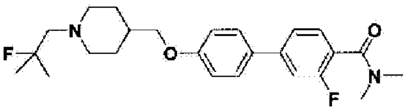
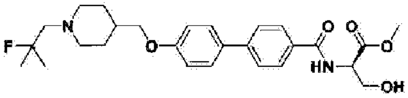
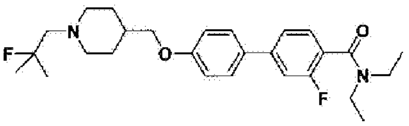
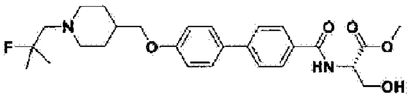
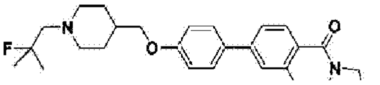
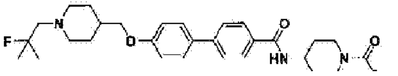
Compound	Structure	Compound	Structure
			
620*		630*	
621*		631*	
622*		632*	

Table 160. (* marks comparative compound)

Compound	Structure	Compound	Structure
633*		643*	
634*		644	
635		645*	
636*		646 *	
637*		647*	
638*		648*	
639*		649*	
640*		650*	

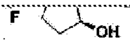
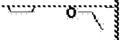
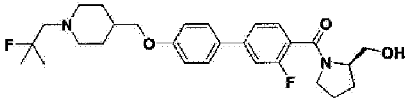
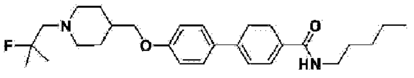
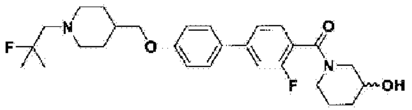
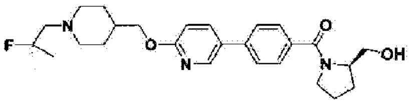
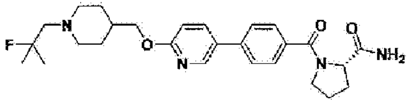
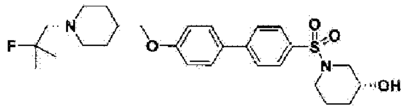
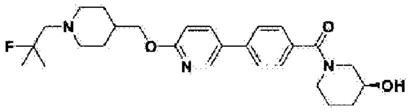
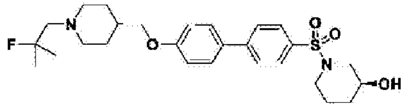
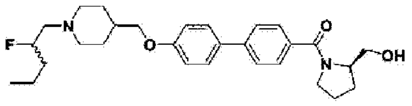
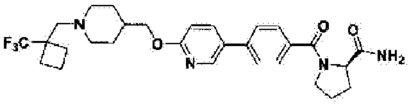
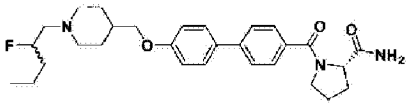
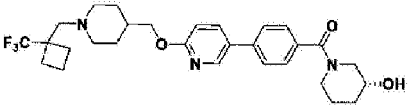
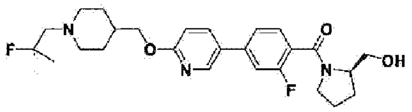
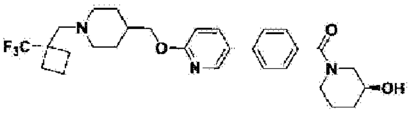
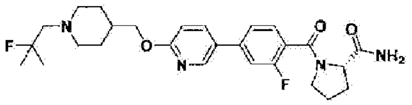
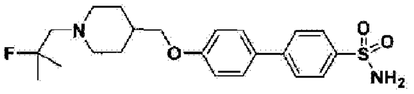
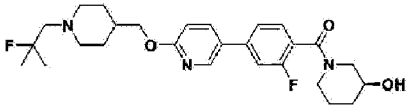
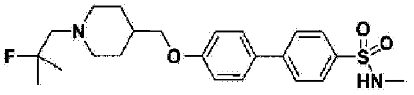
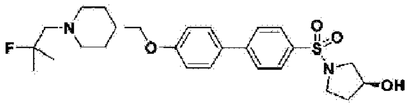
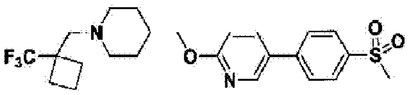
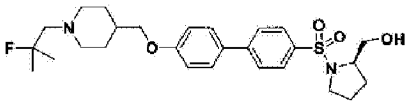
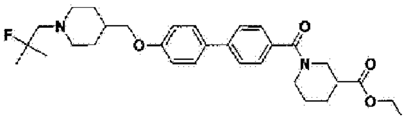
Compound	Structure	Compound	Structure
			
641*		651*	
642*		652*	

Table 161. (* marks comparative compound)

Compound	Structure	Compound	Structure
653		669*	
654*		670*	
655*		671*	
656*		672*	
657*		673*	
658		674*	
659*		675*	
666*		676*	
667*		677*	

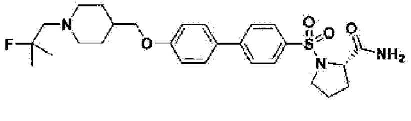
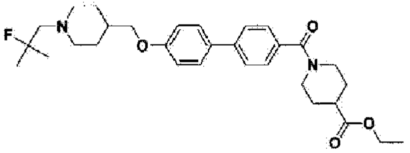
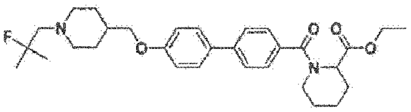
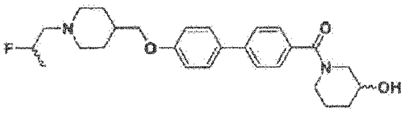
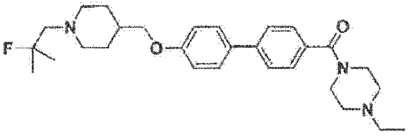
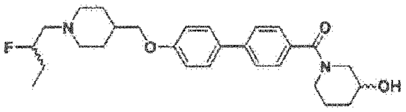
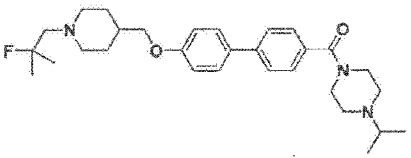
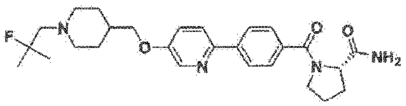
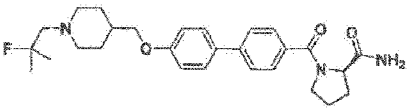
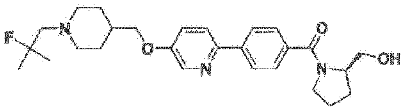
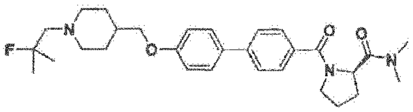
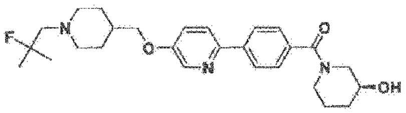
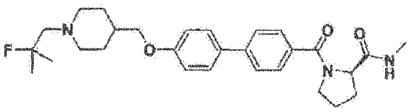
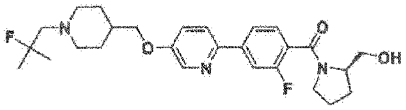
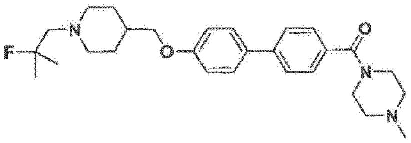
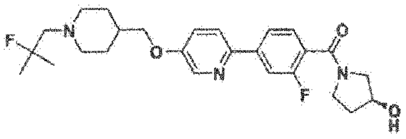
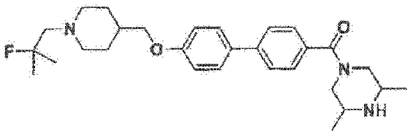
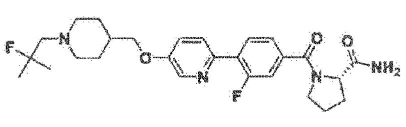
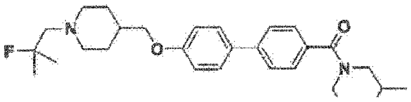
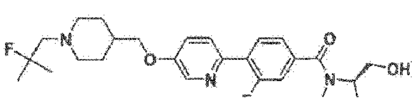
Compound	Structure	Compound	Structure
668*		678*	

Table 162. (* marks comparative compound)

Compound	Structure	Compound	Structure
679*		689*	
680*		690*	
681*		691	
682		692*	
683*		693*	
684*		694*	
685*		695*	
686*		696	
687*		697*	

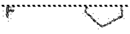
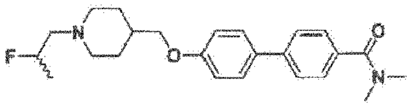
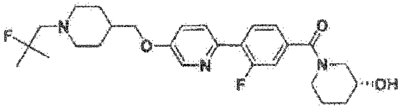
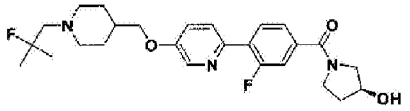
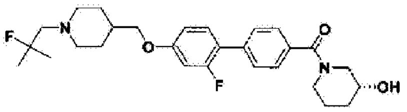
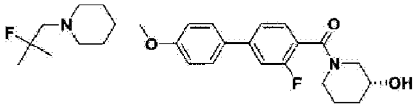
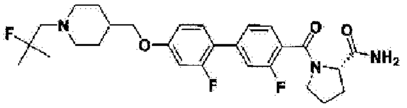
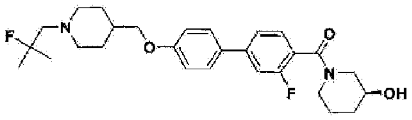
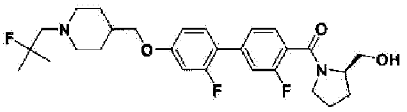
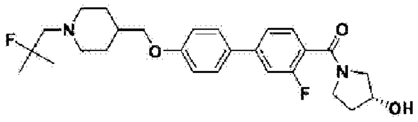
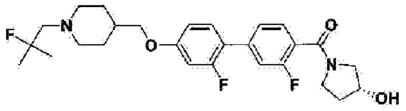
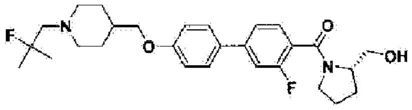
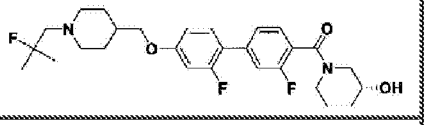
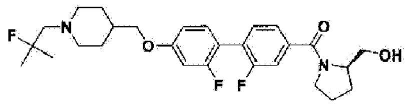
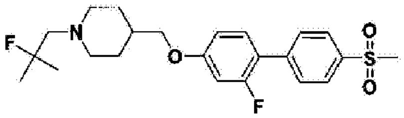
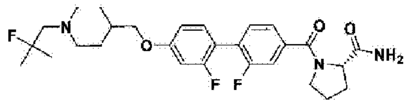
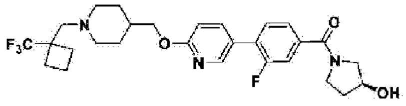
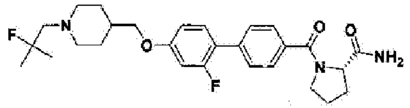
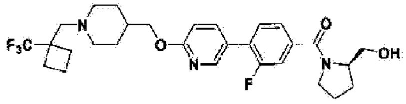
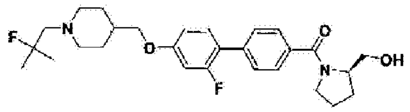
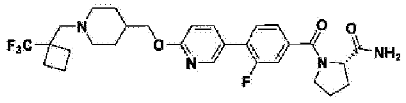
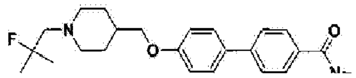
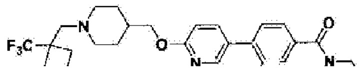
Compound	Structure	Compound	Structure
			
688*		698*	

Table 163. (* marks comparative compound)

Compound	Structure	Compound	Structure
699*		709*	
700*		710	
701*		711*	
702*		712*	
703*		713*	
704*		714*	
705		715*	
706		716*	
707*		717	
708*		718*	

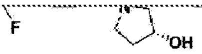
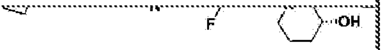
Compound	Structure	Compound	Structure
			

Table 164. (* marks comparative compound)

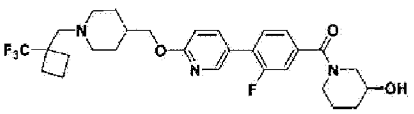
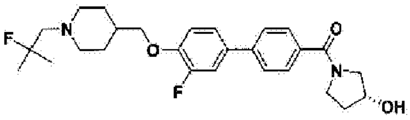
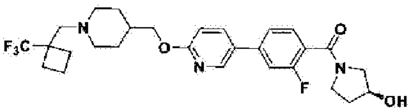
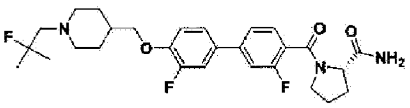
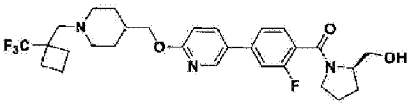
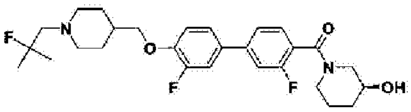
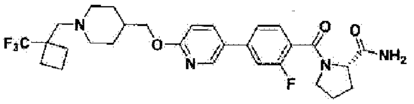
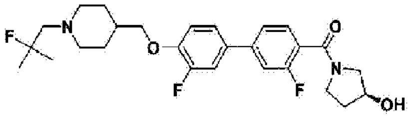
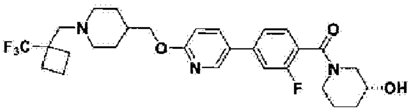
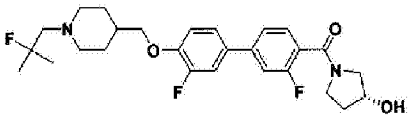
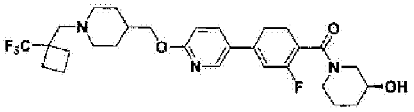
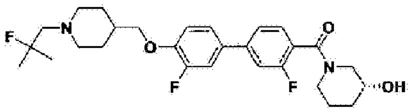
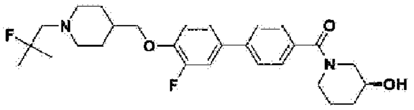
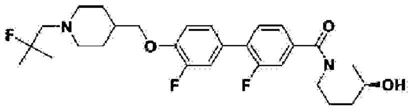
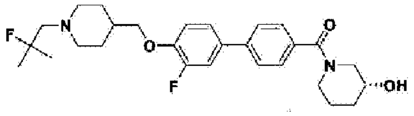
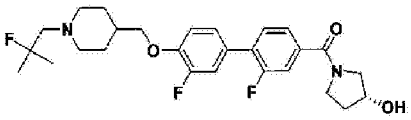
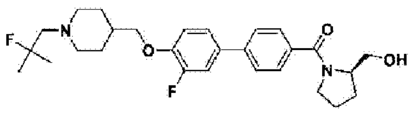
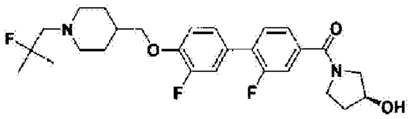
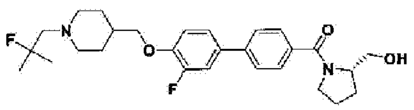
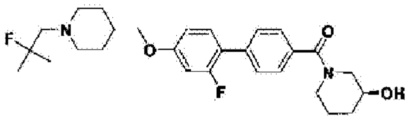
Compound	Structure	Compound	Structure
719*		729*	
720*		730	
721*		731*	
722		732*	
723*		733*	
724*		734*	
725*		735*	
726*		736*	
727*		737*	
728*		738*	

Table 165. (* marks comparative compound)

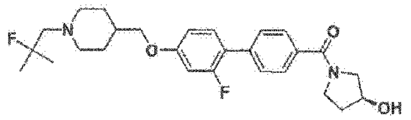
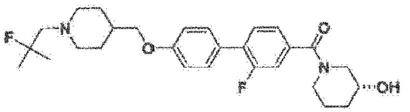
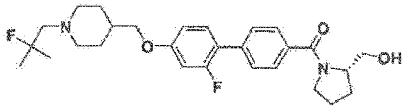
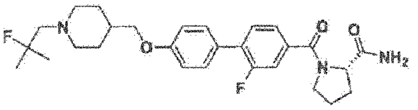
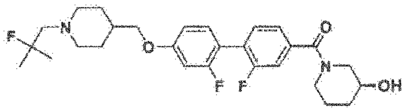
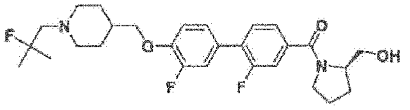
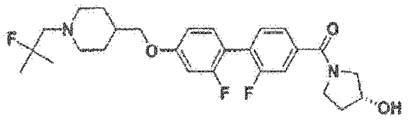
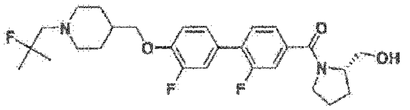
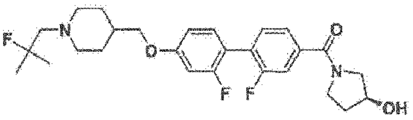
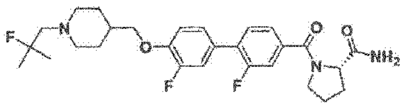
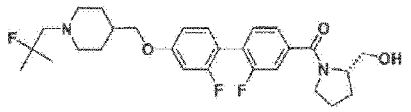
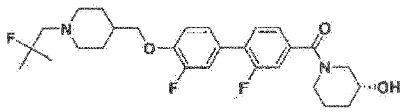
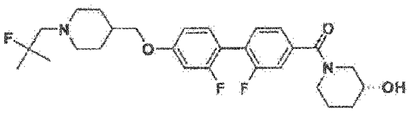
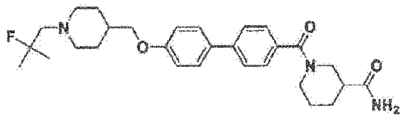
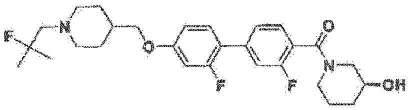
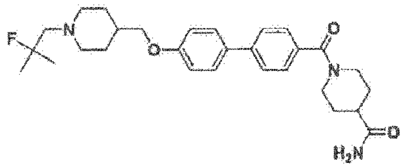
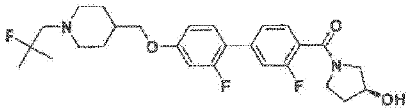
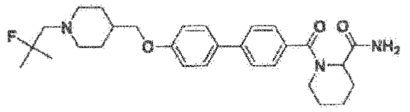
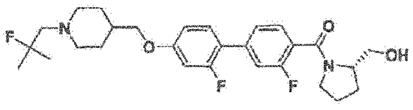
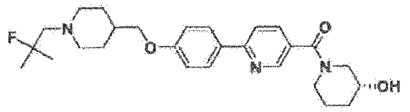
Compound	Structure	Compound	Structure
739*		749*	
740*		750	
741*		751*	
742*		752*	
743*		753	
744*		754*	
745*		755	
746*		756	
747*		757	
748*		758*	

Table 166. (* marks comparative compound)

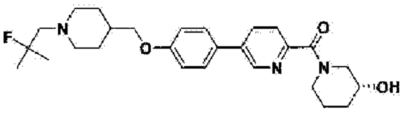
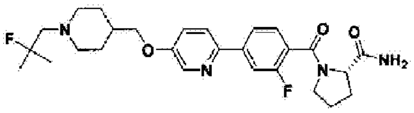
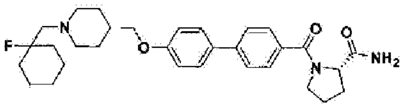
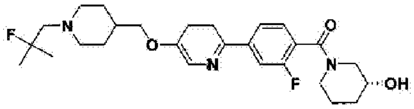
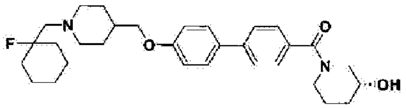
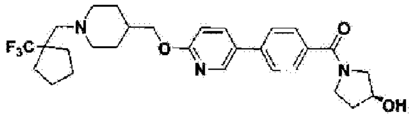
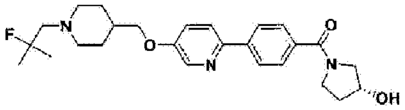
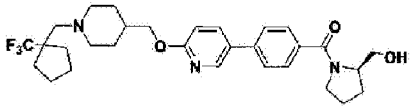
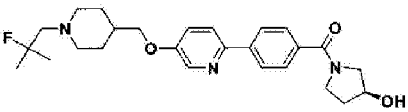
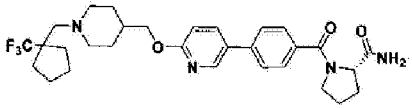
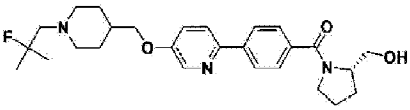
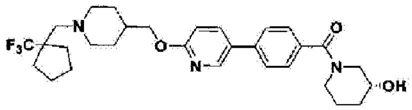
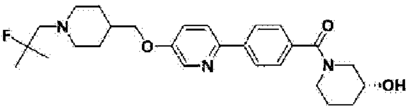
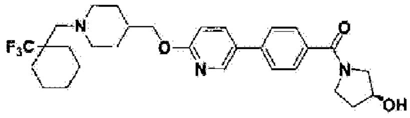
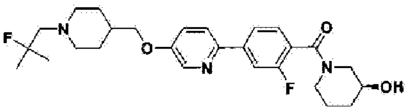
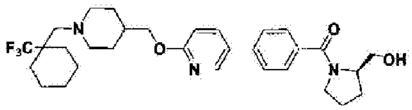
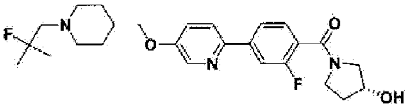
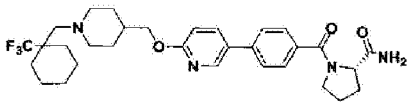
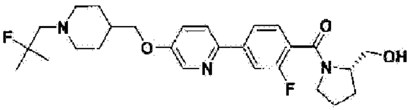
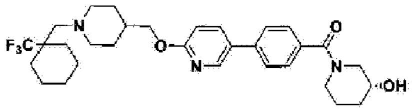
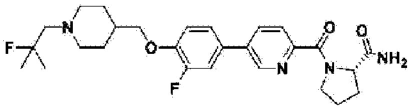
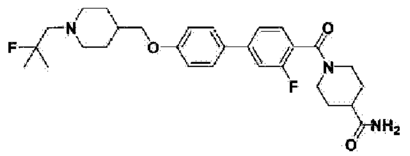
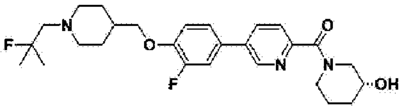
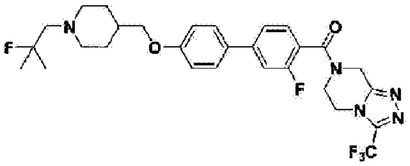
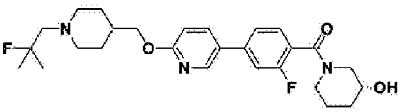
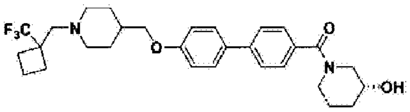
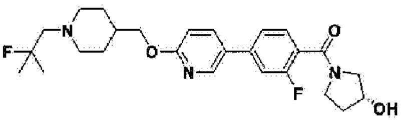
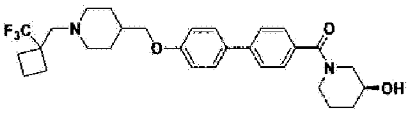
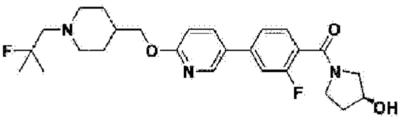
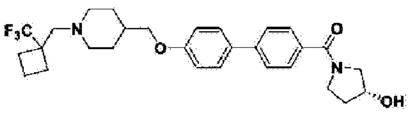
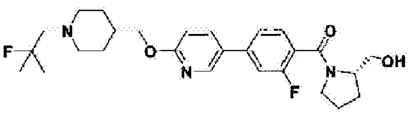
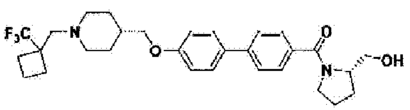
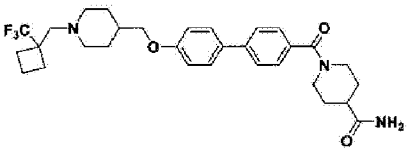
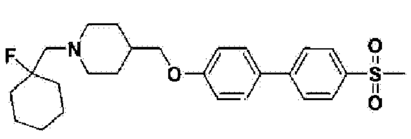
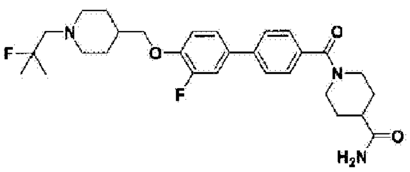
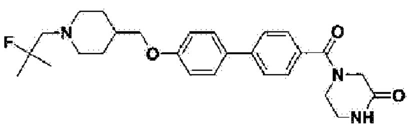
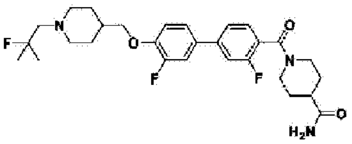
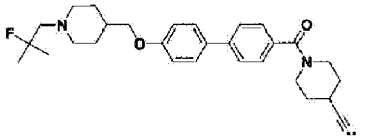
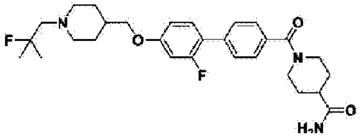
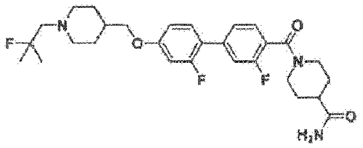
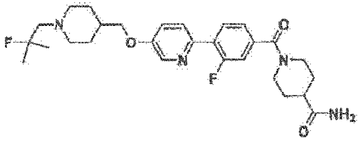
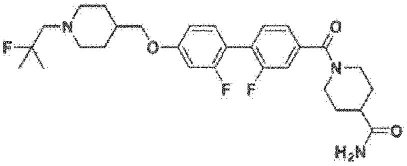
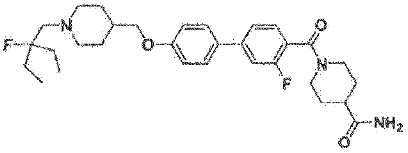
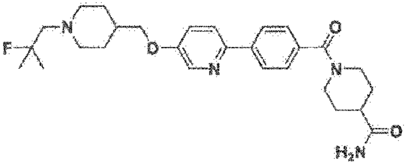
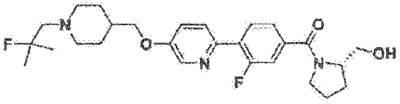
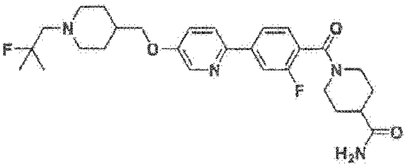
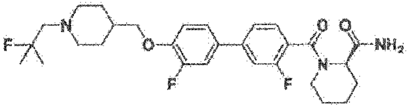
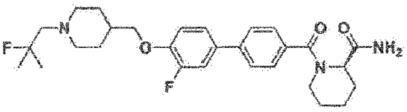
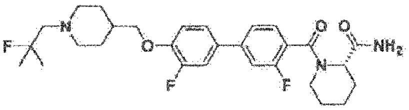
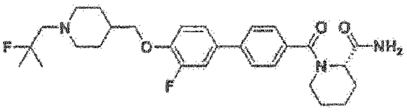
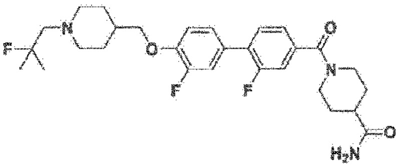
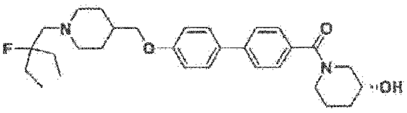
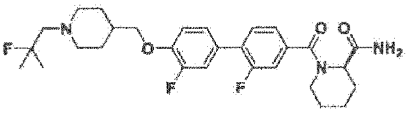
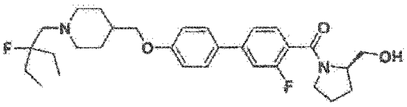
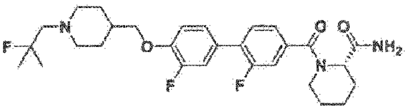
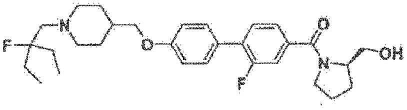
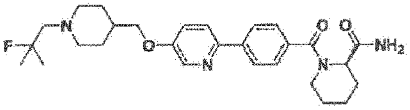
Compound	Structure	Compound	Structure
759*		770	
760		771*	
761*		772*	
763*		773*	
764*		774	
765*		775*	
766*		776*	
767*		777*	
768*		778	
769*		779*	

Table 167. (* marks comparative compound)

Compound	Structure	Compound	Structure
782		792	
783*		793*	
784*		794*	
785*		795*	
786*		796*	
787*		797*	
-	-	798	
789*		799	
790*		800	
791*		801	

Compound	Structure	Compound	Structure

Table 168. (* marks comparative compound)

Compound	Structure	Compound	Structure
802		813	
803		814	
804		815*	
805		816	
806		817	
807		818	
809*		819	
810*		820	
811*		821	

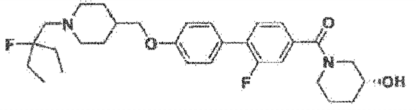
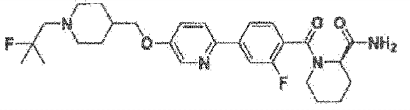
Compound	Structure	Compound	Structure
812*		822	

Table 169. (* marks comparative compound)

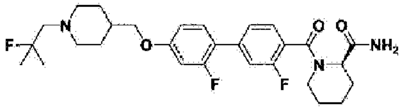
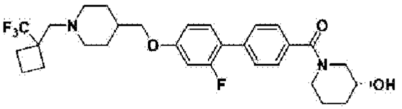
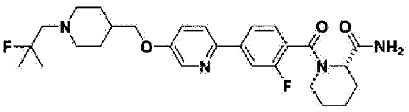
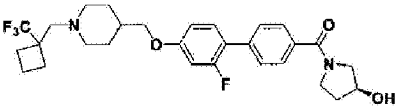
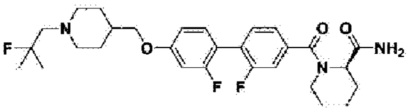
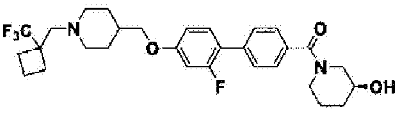
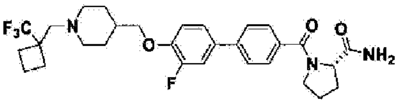
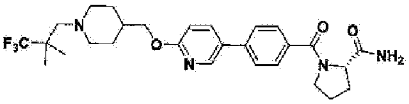
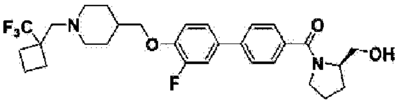
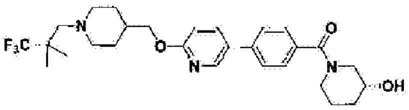
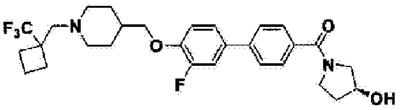
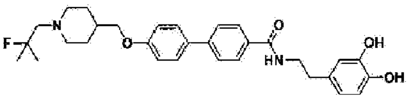
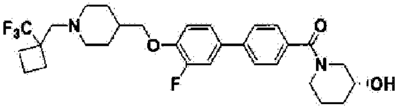
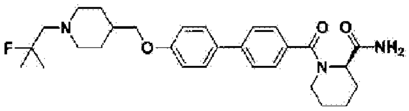
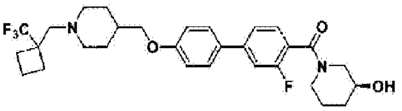
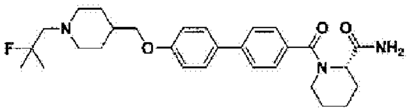
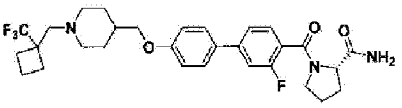
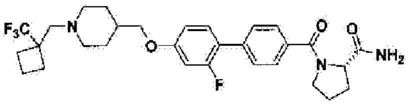
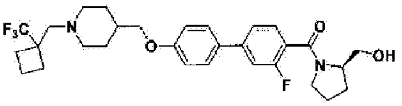
Compound	Structure	Compound	Structure
823		834*	
824		835*	
825		836*	
-	-	837	
828		838*	
829*		839*	
830*		840*	
831		842*	
832		843	
833		844*	

Table 170. (* marks comparative compound)

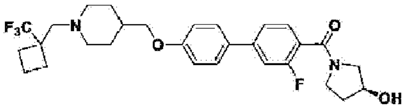
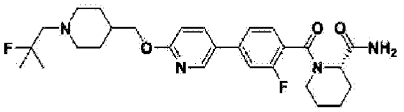
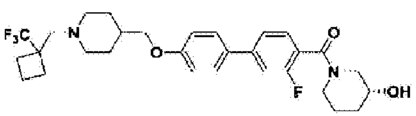
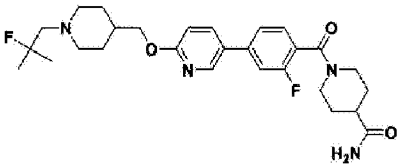
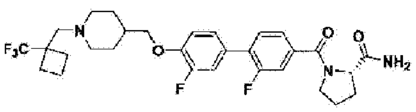
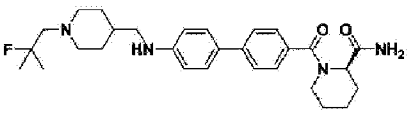
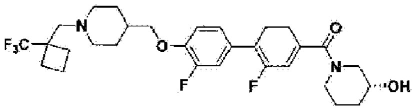
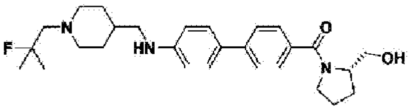
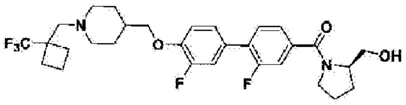
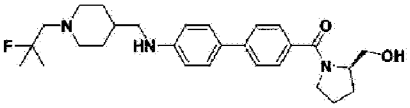
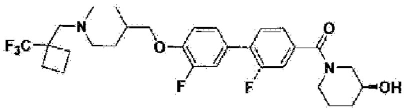
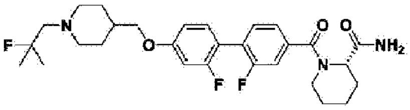
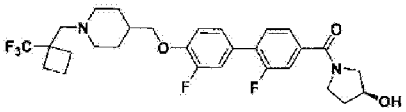
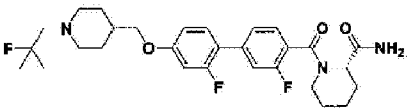
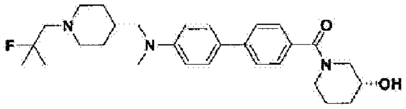
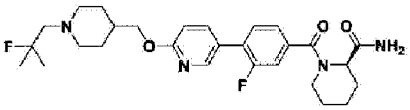
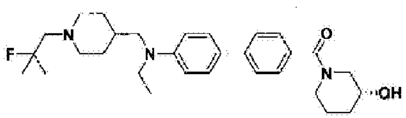
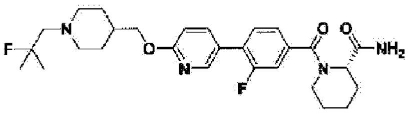
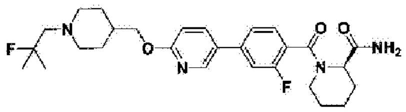
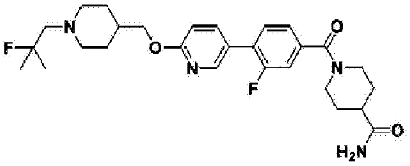
Compound	Structure	Compound	Structure
845*		855	
846*		856	
847		* 857	
848*		858*	
849*		859*	
850*		860	
851*		861	
852*		862	
853*		863	
854		864	

Table 171. (* marks comparative compound)

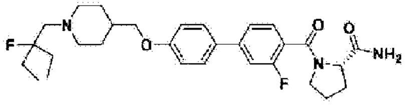
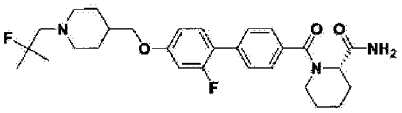
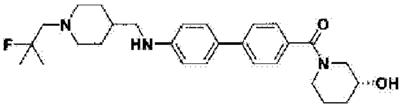
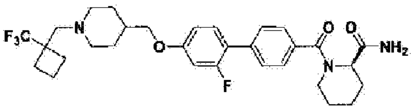
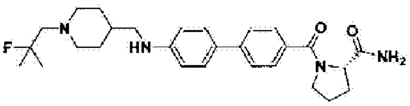
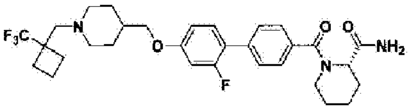
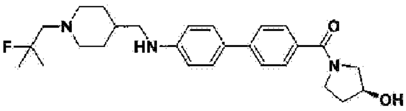
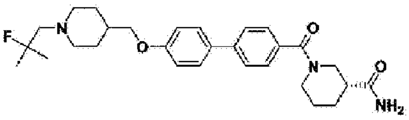
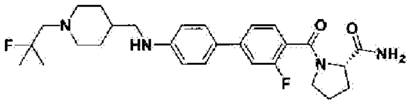
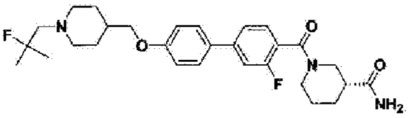
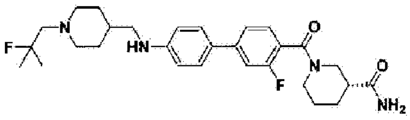
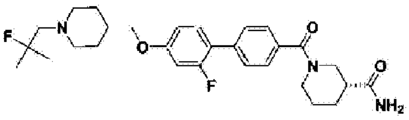
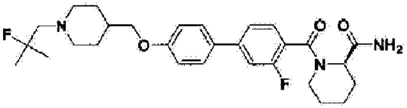
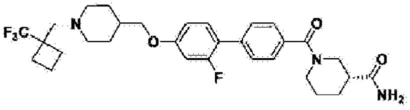
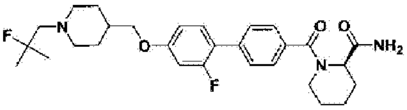
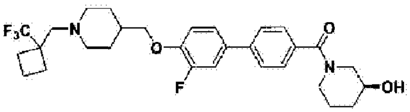
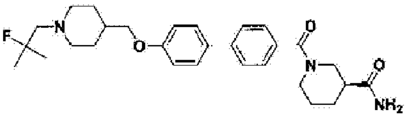
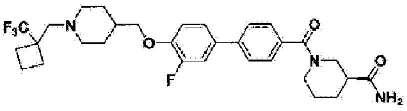
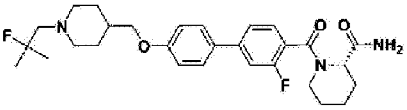
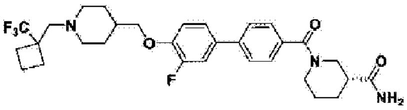
Compound	Structure	Compound	Structure
866		876	
867*		877	
868*		878	
869*		879	
870*		880	
871*		881	
872		882	
873		883*	
874		884	
875		885	

Table 172. (* marks comparative compound)

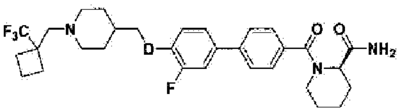
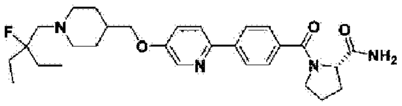
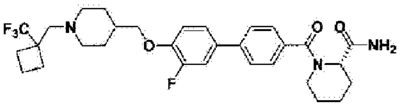
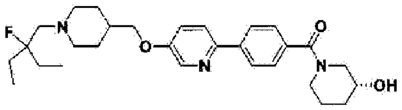
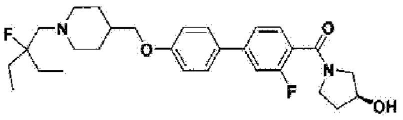
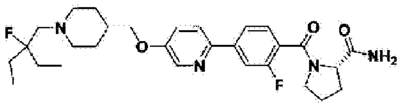
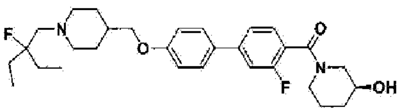
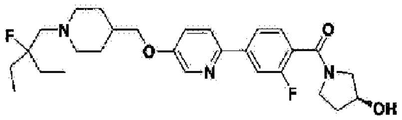
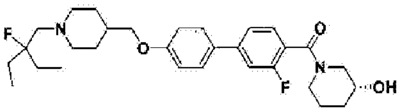
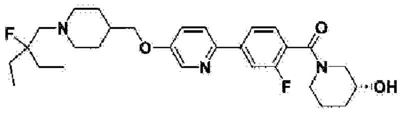
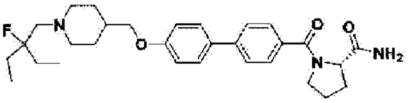
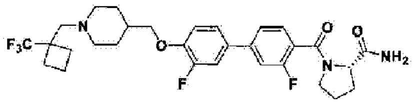
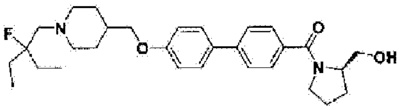
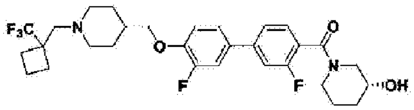
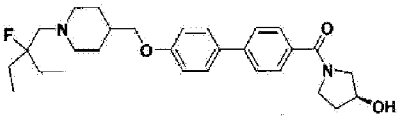
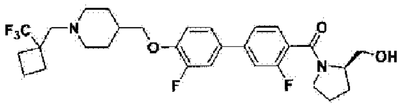
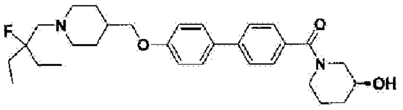
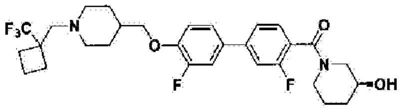
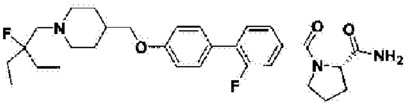
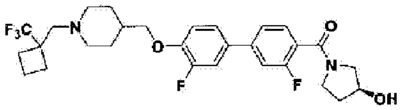
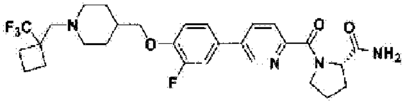
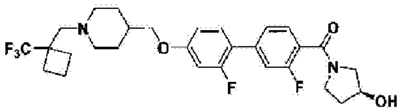
Compound	Structure	Compound	Structure
886		896	
887		897*	
888*		898	
889*		899*	
890*		900*	
891		901	
892*		902*	
893*		903*	
894*		904*	
895		905*	

Table 173. (* marks comparative compound)

Compound	Structure	Compound	Structure
906		916*	

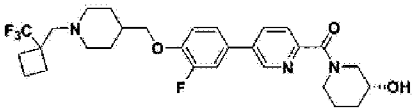
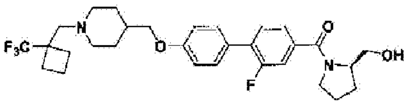
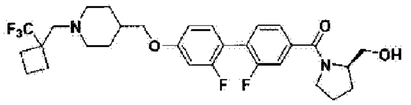
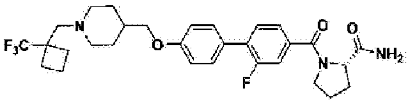
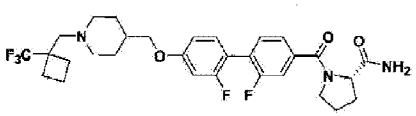
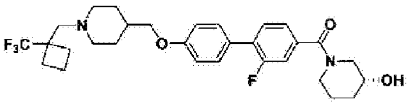
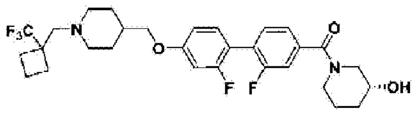
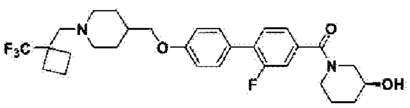
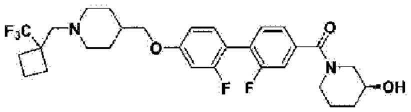
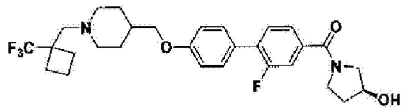
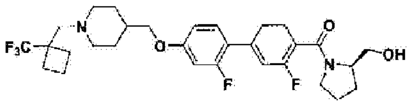
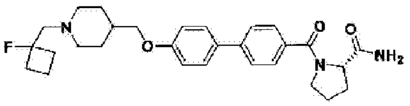
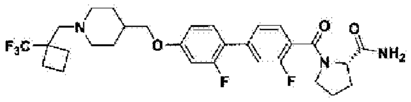
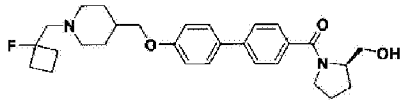
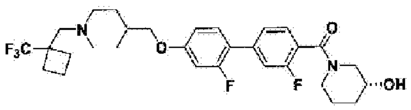
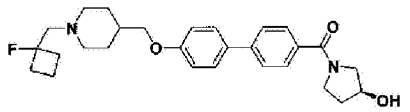
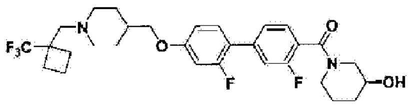
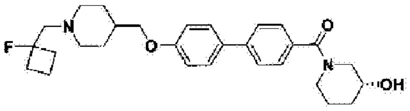
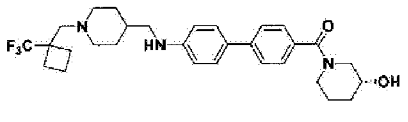
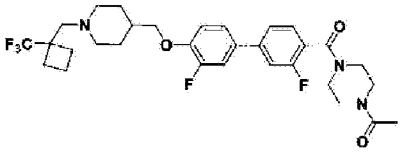
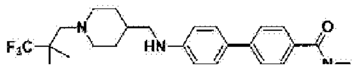
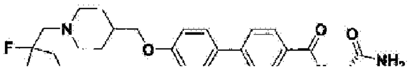
Compound	Structure	Compound	Structure
907*		917*	
908*		918	
909		919*	
910*		920*	
911*		921*	
912*		922	
913		923*	
914*		924*	
915*		925*	

Table 174. (* marks comparative compound)

Compound	Structure	Compound	Structure
926*		936*	
927*		937	

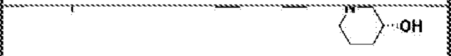
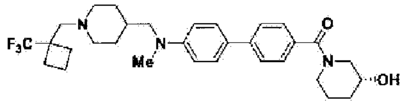
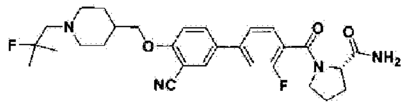
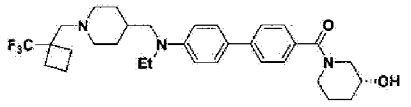
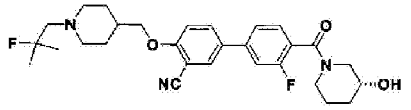
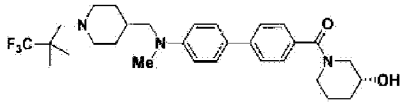
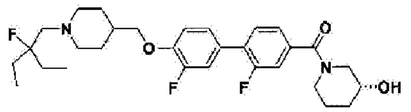
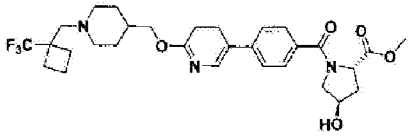
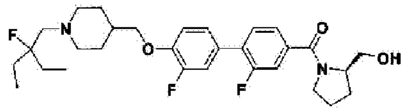
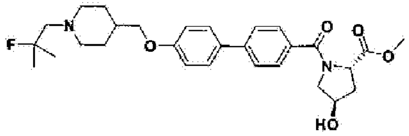
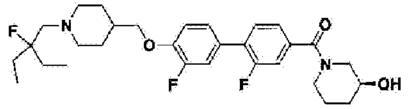
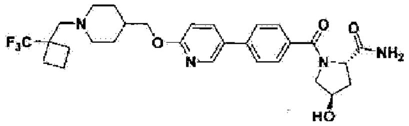
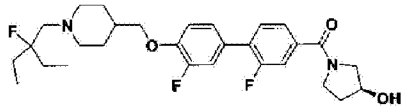
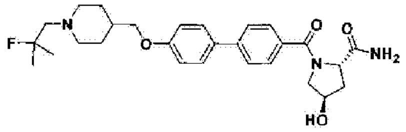
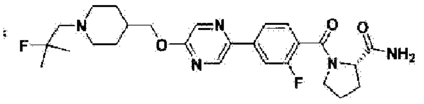
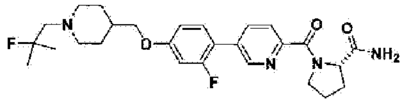
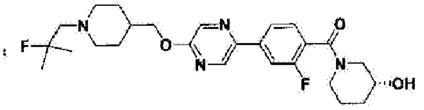
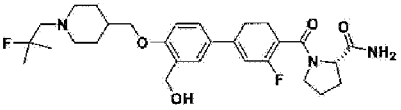
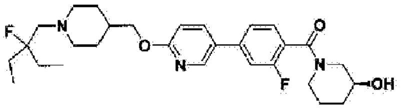
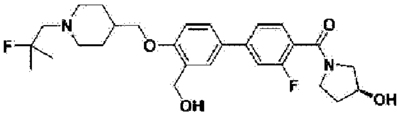
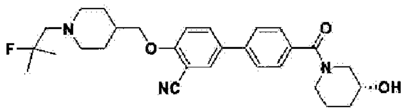
Comp-ound	Structure	Compound	Structure
			
928*		938	
929*		939*	
930*		940*	
931*		941*	
932*		942*	
933		943*	
934		944*	
935		945*	

Table 175. (* marks comparative compound)

Compound	Structure	Compound	Structu re
946*		957*	
947*		963*	

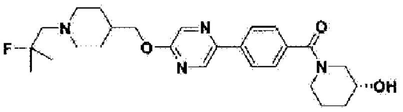
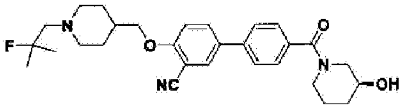
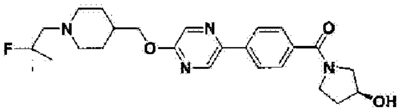
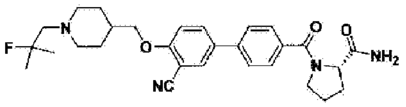
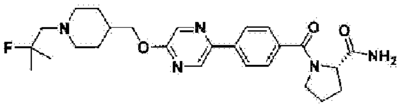
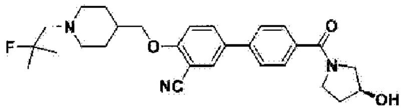
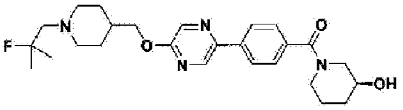
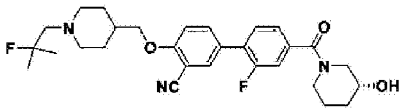
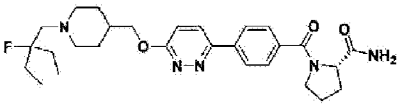
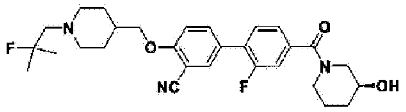
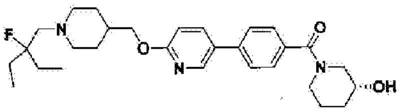
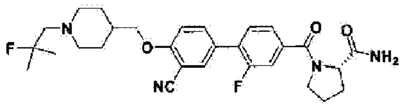
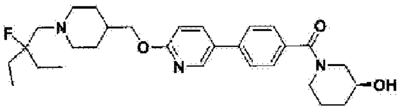
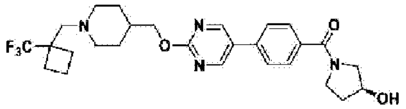
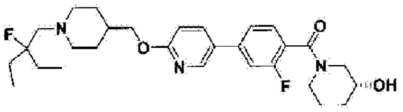
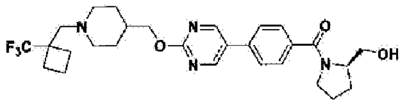
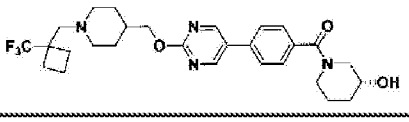
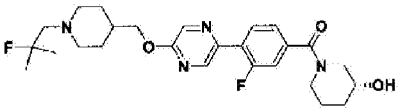
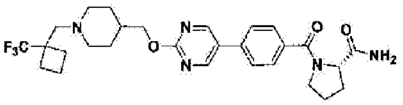
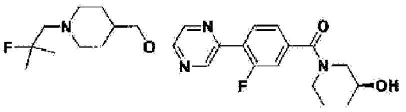
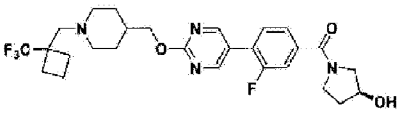
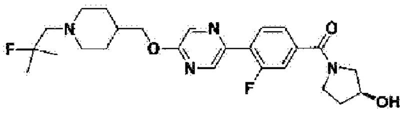
Compound	Structure	Compound	Structure
948*		964*	
949*		965	
950*		966*	
951*		967*	
953*		968*	
954*		969	
955*		970*	
956*		971*	

Table 176. (* marks comparative compound)

Compound	Structure	Compound	Structure
972*		982*	
973		983*	
974*		984*	

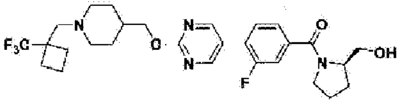
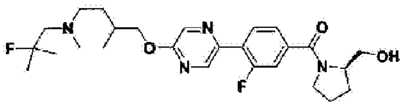
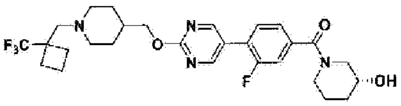
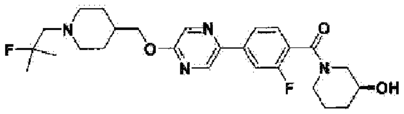
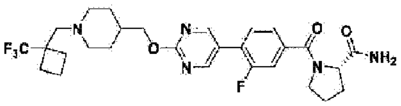
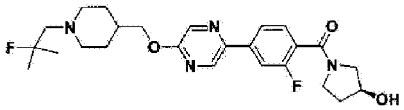
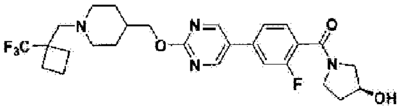
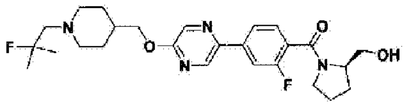
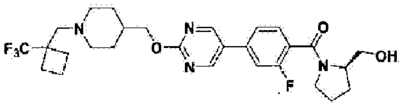
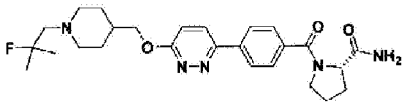
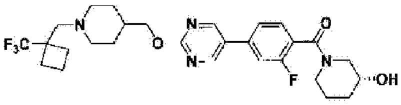
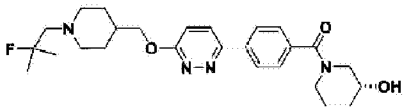
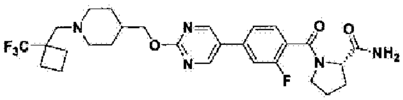
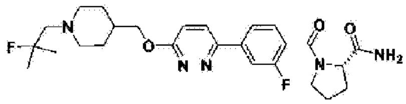
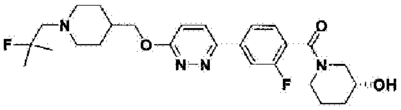
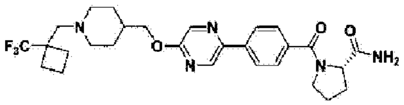
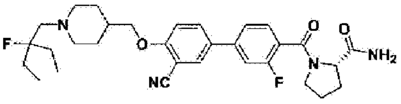
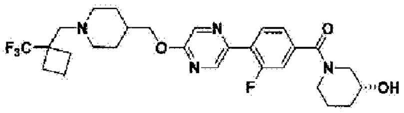
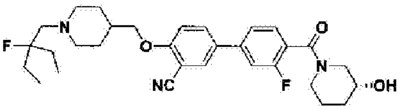
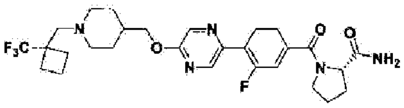
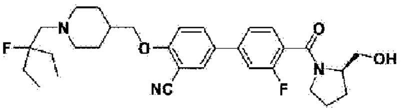
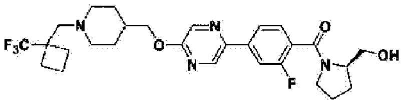
Compound	Structure	Compound	Structure
975*		985*	
976*		986*	
977		987*	
978*		988*	
979*		989*	
980*		990*	
981		991*	

Table 177. (* marks comparative compound)

Compound	Structure	Compound	Structure
992*		1009*	
1000		1010*	
1001*		1011*	
1002*		1012*	

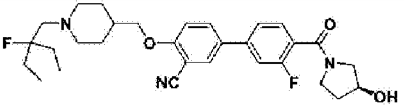
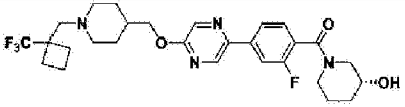
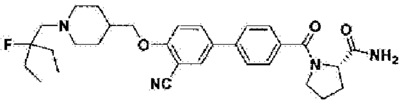
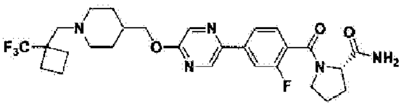
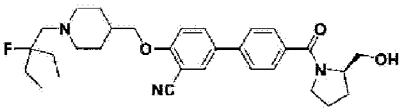
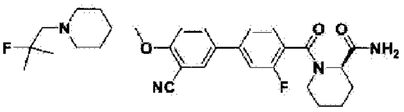
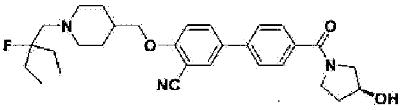
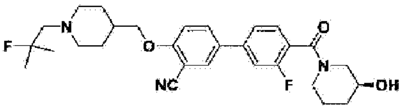
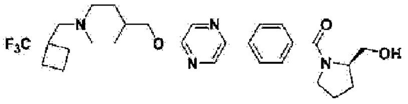
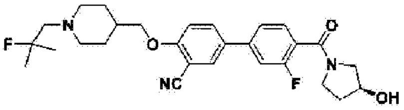
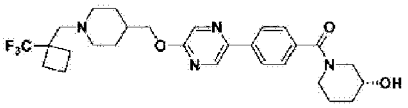
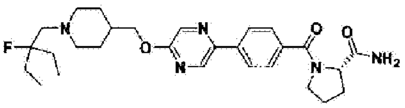
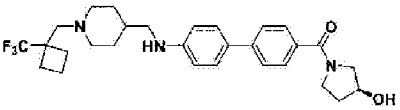
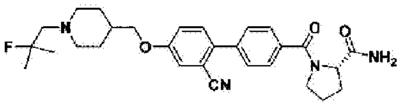
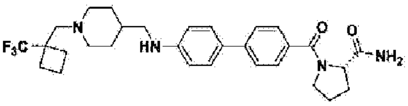
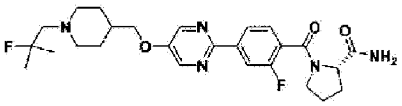
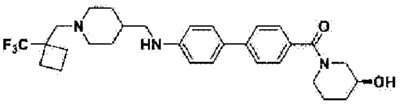
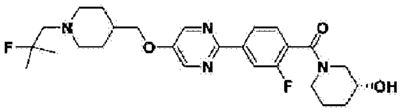
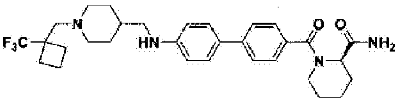
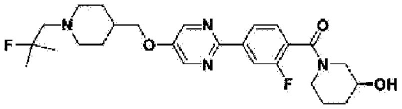
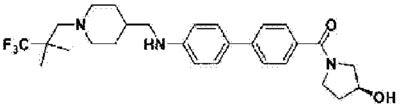
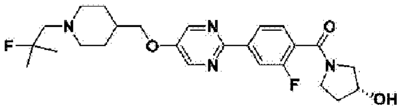
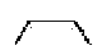
Compound	Structure	Compound	Structure
1003*		1013*	
1004		1014*	
1005*		1015	
1006*		1016*	
1007*		1017*	
1008*		1018*	

Table 178. (* marks comparative compound)

Compound	Structure	Compound	Structure
1020*		1031	
1021*		1032	
1022*		1033*	
1023*		1034*	
1024*		1035*	
			

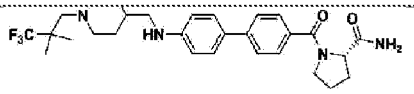
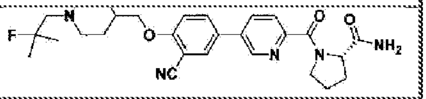
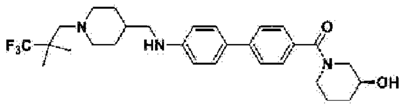
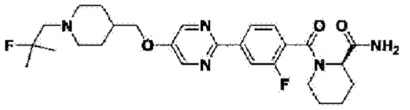
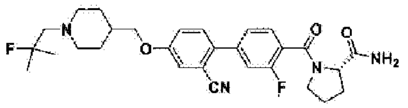
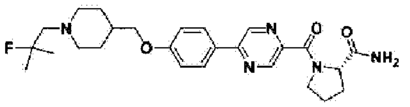
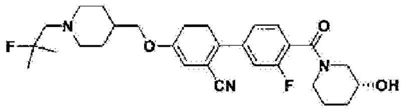
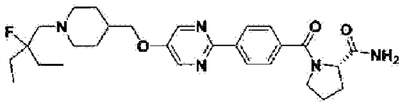
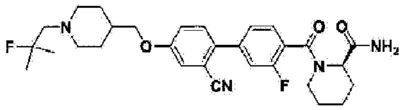
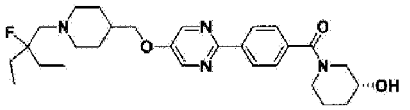
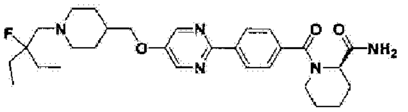
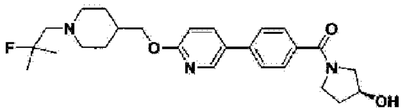
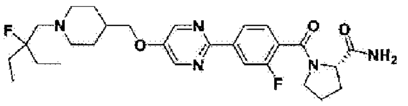
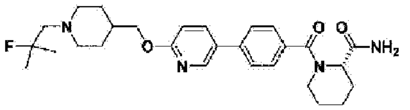
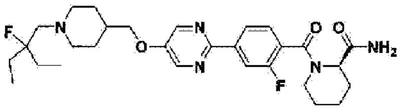
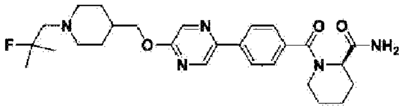
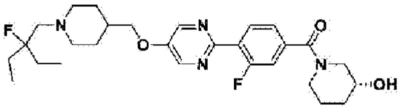
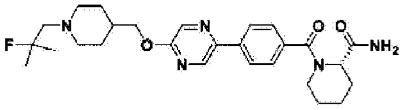
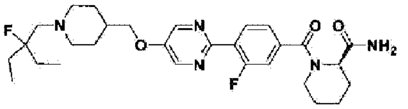
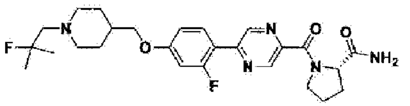
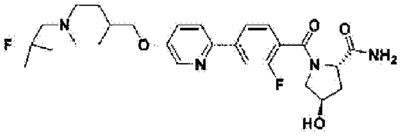
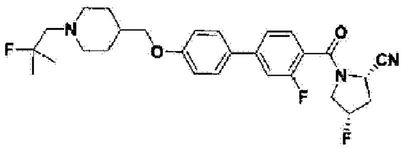
Compound	Structure	Compound	Structure
1025*		1036	
1026*		1037	
1028		1038*	
1029*		1051	
1030		1052*	

Table 179. (* marks comparative compound)

Compound	Structure	Compound	Structure
1053		1078*	
1054		1079	
1055		1080*	
1056*		1081*	
1057		1082	
1067		1097*	

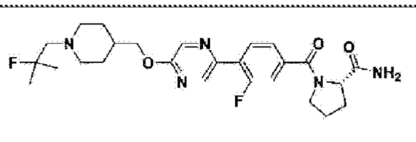
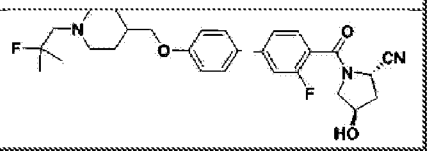
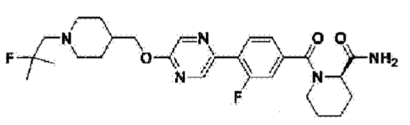
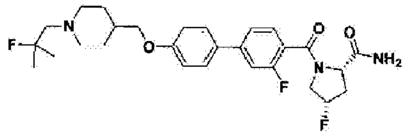
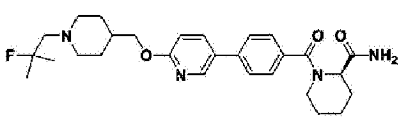
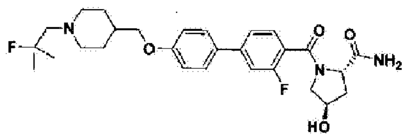
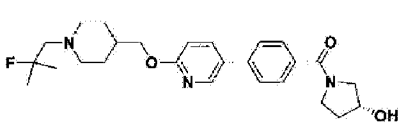
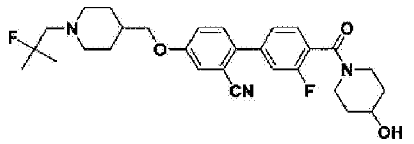
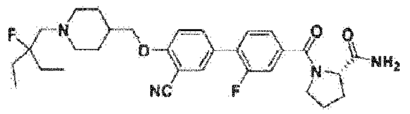
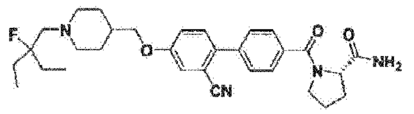
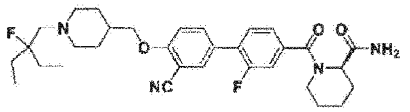
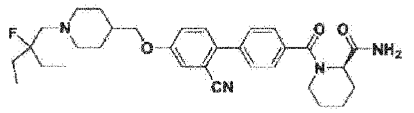
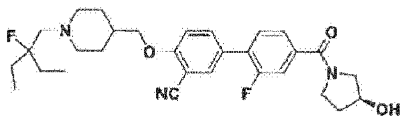
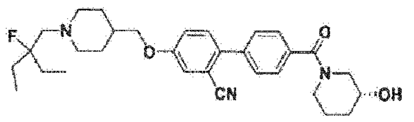
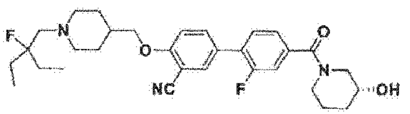
Compound	Structure	Compound	Structure
1072*		1098*	
1073*		1099	
1076		1100	
1077*		1115*	

Table 180. (* marks comparative compound)

Compound	Structure	Compound	Structure
1119		1124	
1120		1125	
1121		1126*	
1123*		-	-

Protocol of Experiment: Activity test of the compound of the present invention

[0268] Using the commercial product as a control group, the treatment activities of the compounds of formula 1 according to the present invention for type II diabetes were tested, and the safety of the compound of formula 1 was also tested.

Experimental Example 1. Activity test for the GPR 119 receptor (in vitro)

1. Human GPR119 receptor cell

[0269] As a human GPR119 receptor expression cell for this test, the cell line "GeneBLAzerTM T-Rex GPR 119 CHO-K1 DA cells" that is commercially available from Invitrogen, was used. The cell was incubated in the DMEM media containing 1% dialyzed fetal bovine serum etc.. The cell incubator was kept at constant temperature and constant humidity of 37 °C, 5% CO_2.

2. Activity test for human GPR119 receptor

[0270] The human GPR119 receptor expressing cell was used to this test. Each of test compounds was added to be final concentrations of 0.1, 1, 10 μM in 96 well and tested in duplicate. A fixed amount of cell was added to each well of 96 well separately, and then treated with the test compound for 5 hours. After treatment of color development agent for 2 hours, the fluorescence value was determined with plate reader. To the luminous wavelength of control well, which was not treated with the agonist sample, but in which only a vehicle (i.e., cell) was contained, the ratio of the luminous wavelength of test well, which was treated with the agonist sample, was calculated, and then converted to obtain % value.

3. Statistical processing

[0271] All the results were expressed as mean ± SD, and each test groups and the control group were compared using student's t-test to adjudge the effects of each test groups.

4. Result of activity test for human GPR119

[0272]

Table 181. Result of activity test for human GPR119 (* marks comparative compound)

Compound	Conc.(μM)	% Activation
MBX-2982	0.1	180
	1	206
	10	200
500*	0.1	214
	1	298
	10	310
516*	0.1	185
	1	243

Compound	Conc.(µM)	% Activation
	10	289
517*	0.1 1	192 244
	10	291
542*	0.1	256
	1	347
	10	376
551*	0.1	135
	1	232
	10	288
553*	0.1	149
	1	204
	10	253
554*	0.1	141
	1	219
	10	279
555*	0.1	190
	1	269
	10	272
581	0.1	254
	1	344
	10	273
586	0.1	213
	1	310
	10	379
587*	0.1	227
	1	288
	10	297
628*	0.1	138
	1	210
	10	257
629*	0.1	199
	1	229
	10	269
635	0.1	265
	1	305
	10	239

Compound	Conc.(µM)	% Activation
641*	0.1	167
	1	220
	10	246
644	0.1	213
	1	295
	10	294
658	0.1	289
	1	248
	10	311
720*	0.1	160
	1	228
	10	262
722	0.1	198
	1	269
	10	261
768*	0.1	162
	1	260
	10	313
770	0.1	228
	1	280
	10	310
794*	0.1	256
	1	296
	10	252
829*	0.1	257
	1	313
	10	303
837	0.1	251
	1	296
	10	306
886	0.1	164
	1	241
	10	246
944*	0.1	180
	1	291
	10	310

Compound	Conc.(μM)	% Activation
950*	0.1	191
	1	232
	10	307
999*	0.1	145
	1	264
	10	365
1000	0.1	311
	1	367
	10	374
1009*	0.1	235
	1	314
	10	340
1013*	0.1	410
	1	490
	10	426
1028	0.1	187
	1	348
	10	402
1032	0.1	321
	1	459
	10	430
1037	0.1	223
	1	478
	10	439
1055	0.1	407
	1	474
	10	408
1119	0.1	406
	1	428
	10	482

[0273] In Table 181, "% activation" shows the extent that human GPR119 receptor is activated by test compounds of each concentration. The higher value of % activation means the more excellent activity. The maximum % activation of control compound (MBX-2982) is 200, and the most of the compounds of the present invention show more than 200 of % activation. The compounds 1013 and 1028 show the excellent activity with 490 and 402 of % activation respectively.

Experimental Example 2. Animal test of activity for the GPR 119 receptor in normal mouse (in vivo)

1. Method of glucose tolerance test

[0274] Male C57/6J Jms mice of 6-7 weeks of age were fasted for 16 hours before the start of glucose tolerance test. The experimental animal groups consist of:

1. A. a vehicle group (10 % EtOH, 20 % HPBCD in saline),
2. B. a positive control group administered with MBX-2982 (10 mg/kg), and
3. C. test groups administered with compound 516, 581, 586, 612, 640, 644 or etc. (10 mg/kg). Before compound administration, that is, at 0 hour, whole blood glucose level was determined using a Glucometer (ACCU-CHEK, Roche). At 30 minutes after compound administration, whole blood glucose level was determined once again, and 20 % glucose (2 g/ kg/10 mL) was administered orally. Whole blood glucose level was determined at 20, 40, 60, 80, and 120 minutes after 20 % glucose administration. Area under the curve (AUC) of whole blood glucose level was obtained using GraphPad Prism 5.0. The effect of glucose tolerance was adjudged with the corrected area under the curve (cAUC), on which the base value of glucose area under the curve was excluded.

2. Result of glucose tolerance test

[0275] In Table 182, "Decrease % of AUC" shows the extent that whole blood glucose level is decreased by the test compounds administrated after oral administration of glucose into normal mouse. The higher value of decrease % of AUC means the more excellent drop effect in blood glucose level. The control compound (MBX-2982) shows only 24% of the excellent drop effect in blood glucose level, and some of the compounds of the present invention show more than 40% of the excellent drop effect in blood glucose level. The compounds 612 and 1028 show the very excellent drop effect in blood glucose level with 50 and 46 % respectively.

Table 182. Result of glucose tolerance test (* marks comparative compound)

	Decrease % of AUC at 10 mg/kg
MBX-2982	24
Compound 516*	43
Compound 581	50
Compound 586	34
Compound 612*	50
Compound 640*	52
Compound 644	39

	Decrease % of AUC at 10 mg/kg
Compound 658	38
Compound 768*	40
Compound 770	47
Compound 944*	32
Compound 950*	39
Compound 999*	39
Compound 1000	38
Compound 1028	46
Compound 1032	31
Compound 1037	42

Experimental Example 3. Disease model animal test of activity for the GPR 119 receptor (DIO mouse)

1. Method of glucose tolerance test

[0276] Male C57BL/6J mice of 6.5 weeks of age were taken with high fat diet (60% kcal, Research Diets) for 12 weeks. The obtained male diet induced obesity (DIO) C57BL/6J mice of 18.5 weeks of age were fasted for 16 hours before the start of glucose tolerance test. The experimental animal groups consist of:

1. A. a vehicle group (10 % EtOH, 20 % HPBCD in D.W.),
2. B. a positive control group administered with Sitagliptin (30 mg/kg), and
3. C. test groups administered with compound 770 and Compound 1028 (10, 30 mg/kg and combination administration with sitagliptin 30 mg/kg).

[0277] Each test compounds was administered at the same time of every day for 2 weeks. Before the compound administration, whole blood glucose level was determined using a Glucometer (ACCU-CHEK, Roche). At 30 minutes after compound administration, whole blood glucose level was determined once again, and 20 % glucose (2 g/ kg/10 mL) was administered orally. Whole blood glucose level was determined at 20, 40, 60, 80, and 120 minutes after 20 % glucose administration. Area under the curve (AUC) of whole blood glucose level was obtained using GraphPad Prism 5.0. The effect of glucose tolerance was adjudged with the corrected area under the curve (cAUC), on which the base value of glucose area under the curve was excluded.

2. Measurement of whole blood glucose level change

[0278] Whole blood glucose level was measured at about 1 hour after test compound administration from caudal vein of mice using Glucometer. Whole blood glucose level was determined three times totally, that is, (1) at prior to the start of drug administration, (2) after 1 week from the start of 2-weeks drug administration, and (3) after the termination of 2-weeks drug administration. Each determination was started with 20 % glucose administration, and then perfomed at 20, 40, 60, 80, and 120 minutes after 20 % glucose administration.

3. Result of glucose tolerance test (DIO)

[0279] Table 183 shows the extent that whole blood glucose level is decreased by the test compounds administrated after oral administration of glucose into disease model mouse (DIO mouse). The higher value means the more excellent drop effect in blood glucose level. The effect was tested, separately, after administration of test compound alone and after co-administration of test compound with Sitagliptin, which is a DPP IV inhibitor. As a result, the compounds alone of the present invention show more than 20% of the excellent drop effect in blood glucose level, and the co-administration of the compound of the present invention with Sitagliptin show also the excellent effect. The compound 1028 shows 28.5% for alone-administration and 32.3% for co-administration.

Table 183.

Group	Whole Blood Glucose Level Change (%) by drug administration		
	0 week	1 week	2 weeks
Sitagliptin (30 mpk)	0	25.5	31.7
Compound 770 (10 mpk)	0	22.9	24.0
Compound 770 (30 mpk)	0	25.5	26.6
Compound 770 (30 mpk) + Sitagliptin (30 mpk)	0	26.7	31.6
Compound 1028 (10 mpk)	0	22.5	26.5
Compound 1028 (30 mpk)	0	28.5	29.0
Compound 1028 (30 mpk) + Sitagliptin (30 mpk)	0	32.3	30.0

REFERENCES CITED IN THE DESCRIPTION

Patent documents cited in the description

- WO2011008663A1 [0009]
- WO2009106561A1 [0010]

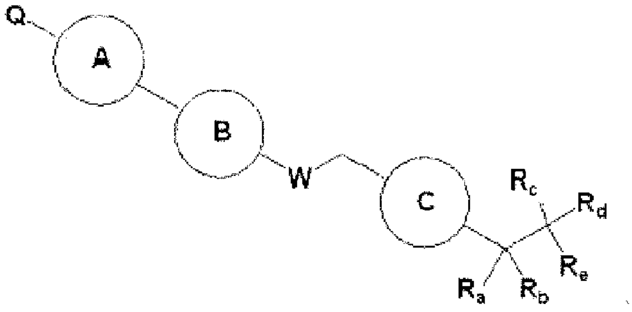
Non-patent literature cited in the description

- **B. POURCET et al.**Expert Opin. Emerging Drugs, 2006, vol. 11, 379-401 [0002]
- **R. R. HOLMAN**Metabolism, 2006, vol. 55, S2-S5 [0005]
- **Z.-L. CHU et al.**Endocrinol., 2007, vol. J 48, 2601-2609 [0006]
- **Z.-L. CHU**Endocrinol., 2008, vol. 149, 2038-2047 [0006]
- **H. A. OVERTON et al.**Brit. J. Pharmacol., 2008, vol. 513, 76-81 [0006]
- **T. SOGA et al.**Biochem. Biophys. Res. Commun., 2005, 326- [0007]

PATENTKRAV

1. Piperidinderivat med følgende formel 1, stereoisomerer deraf eller farmaceutisk acceptable salte deraf:

[Formel 1]



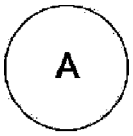
hvor

W er O;

R_a og R_b hver uafhængigt er H;

R_c er -F eller $-CF_3$;

R_d og R_e hver uafhængigt er valgt fra gruppen bestående af $-CH_3$ og $-CH_2CH_3$;



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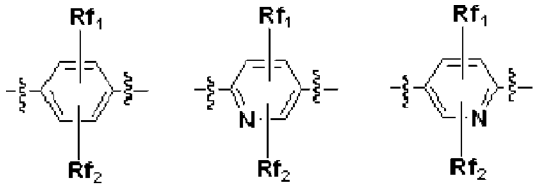

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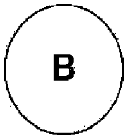
hvor Rf_1 og Rf_2 hver uafhængigt er H, -F eller -CN;



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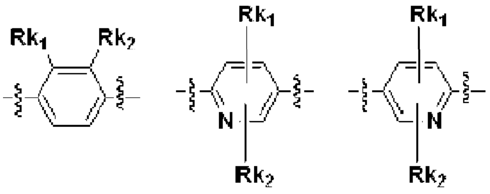

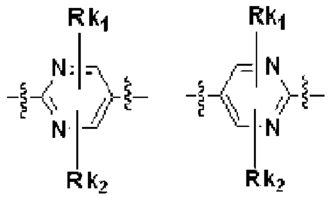

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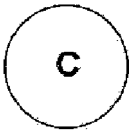
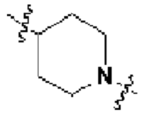
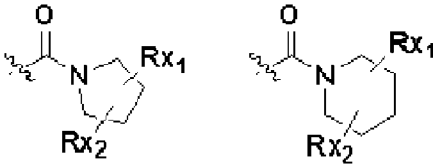


er



;

Q er valgt fra gruppen bestående af:



,

hvor Rx_1 er $-C(O)NH_2$; og

Rx_2 er H, OH, -F, -CN, $-CF_3$, $-CH_2OH$ eller $-C(O)NH_2$.

2. Piperidinderivat, stereoisomerer deraf eller farmaceutisk acceptable salte deraf ifølge krav 1, hvor piperidinderivatet er valgt fra gruppen bestående af:

(S)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(2-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(R)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(3-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;

(2S)-1-(2,2'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2',3-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(5-(3-fluor-4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidin-2-carboxamid;

1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(3'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(3,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(2'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(2',3-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(2,2'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

1-(4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-4-carboxamid;

1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-4-carboxamid;

(R)-1-(3'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(3'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

1-(3-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-4-carboxamid;

1-(4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-3-fluorbiphenylcarbonyl)piperidin-4-carboxamid;

(R)-1-(3,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(3,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

1-(2,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

(R)-1-(2,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2,3'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-2-carboxamid;

(R)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-2-carboxamid;

(R)-1-(2',3-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)piperidin-2-carboxamid;

(2R)-1-(2,2'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(4-(6-((1-(3,3,3-trifluor-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(R)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(2-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;

(S)-1-(2-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;

1-(2-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-4-carboxamid;

(2S)-1-(2,6'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(3,6'-difluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(3-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;

(S)-1-(3-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;

1-(3-fluor-4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-4-carboxamid;

(S)-1-(4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-3-fluorbiphenylcarbonyl)pyrrolidin-2-carboxamid;

(R)-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(2'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(S)-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(R)-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(R)-1-(2'-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(S)-1-(4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-2-fluorbiphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorbenzoyl)pyrrolidin-2-carboxamid;

(2S,4R)-1-(4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidin-2-carboxamid;

(S)-1-(5-(2-fluor-4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidin-2-carboxamid;

(S)-1-(4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-2,3'-difluorbiphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-cyano-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-cyano-2-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-3-fluorbiphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(R)-1-(3'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(R)-1-(2'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;
(S)-1-(2'-cyano-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;
(S)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(5-(3-cyano-4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidin-2-carboxamid;
(R)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidin-2-carboxamid;
(S)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidin-2-carboxamid;
(R)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidin-2-carboxamid;
(S)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorbenzoyl)pyrrolidin-2-carboxamid;
(R)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-2-fluorbenzoyl)piperidin-2-carboxamid;
(R)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorbenzoyl)piperidin-2-carboxamid;
(2S,4R)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)-4-hydroxypyrrolidin-2-carboxamid;
(R)-1-(4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;
(S)-1-(4-(6-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)piperidin-2-carboxamid;
(S)-1-(5-(2-fluor-4-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidin-2-carboxamid;
(2S,4S)-4-fluor-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;
(2S,4R)-1-(3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidin-2-carboxamid;
(S)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-2-fluorbiphenylcarbonyl)pyrrolidin-2-carboxamid;

(R)-1-(3'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)-2-fluorbiphenylcarbonyl)piperidin-2-carboxamid;
(S)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid; og
(R)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid.

3. Piperidinderivat, stereoisomerer deraf eller farmaceutisk acceptable salte deraf ifølge krav 2, hvor piperidinderivatet er valgt fra gruppen bestående af:

(S)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(4-(5-((1-(2-ethyl-2-fluorbutyl)piperidin-4-yl)methoxy)pyridin-2-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(3'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;
(S)-1-(2'-cyano-3-fluor-4'-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid; og
(S)-1-(2-fluor-4-(5-((1-(2-fluor-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)pyrrolidin-2-carboxamid.

4. Piperidinderivat, stereoisomerer deraf eller farmaceutisk acceptable salte deraf, hvor piperidinderivatet er valgt fra gruppen bestående af:

(S)-1-(4-(6-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(4-(6-((1-((1-(trifluormethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;
(R)-1-(4-(6-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(3-fluor-4-(6-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;
(S)-1-(2-fluor-4-(6-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(4'-((1-((1-fluorcyclohexyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(6-((1-((1-(trifluormethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(6-((1-((1 -(trifluormethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

1-(4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxamid;

(S)-1-(2'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(3-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2,3'-difluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(R)-1-(2'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(2'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(R)-1-(2'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(S)-1-(3'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(R)-1-(3'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxamid;

(R)-1-(3'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(3'-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxamid;

(S)-1-(3,3'-difluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(5-(3-fluor-4-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidin-2-carboxamid;

(2S)-1-(2,2'-difluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2',3-difluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(2-fluor-4'-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(S)-1-(4'-((1-((1-fluorcyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidin-2-carboxamid;

(2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(4-(2-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(3-fluor-4-(2-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxamid;

(S)-1-(2-fluor-4-(2-((1-((1-(trifluormethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)benzoyl)pyrrolidin-2-carboxamid;

5. Farmaceutisk sammensætning, der omfatter piperidinderivatet, stereoisomerer deraf eller farmaceutisk acceptable salte deraf ifølge et hvilket som helst af kravene 1 til 4 og farmaceutisk acceptable bærere.

6. Farmaceutisk sammensætning ifølge krav 5 til anvendelse ved behandling af en sygdom, der er forbundet med GPR119-agonist.

7. Farmaceutisk sammensætning til anvendelse ifølge krav 6, hvor sygdommen, der er forbundet med GPR119-agonist, er diabetes mellitus.