(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 December 2013 (19.12.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/187646 A1

(51) **International Patent Classification**:
C07D 401/12 (2006.01) *A61K 31/444* (2006.01)
C07D 401/14 (2006.01) *A61P 3/10* (2006.01)

(21) **International Application Number**:
PCT/KR2013/005096

(22) **International Filing Date**:
11 June 2013 (11.06.2013)

(25) **Filing Language**: English

(26) **Publication Language**: English

(30) **Priority Data**:
10-2012-0062784 12 June 2012 (12.06.2012) KR

(71) **Applicant**: **CHONG KUN DANG PHARMACEUTICAL CORP.** [KR/KR]; 8, Chungjeong-ro, Seodaemun-gu, Seoul, 120-756 (KR).

(72) **Inventors**: **LEE, ChangSik**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **JANG, TaegSu**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **CHOI, DaeKyu**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **KO, MoonSung**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **KIM, DoHoon**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **KIM, SoYoung**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **MIN, JaeKi**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **KIM, WooSik**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). **LIM, YoungTae**; 464-3, Jung-dong, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR).

(74) **Agent**: **SUH, Jong Wan**; J.W.SUH & Partners, 4th Fl., Sungwoon Bldg., 22, Seocho-daero 56-gil, Seocho-Gu, Seoul 137-881 (KR).

(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

WO 2013/187646 A1

(54) **Title**: PIPERIDINE DERIVATIVES FOR GPR119 AGONIST

(57) **Abstract**: The present invention relates to novel piperidine derivatives, stereoisomers thereof or pharmaceutically acceptable salts thereof; methods for preparing the compound; and pharmaceutical compositions comprising the compound. The novel piperidine derivatives, according to the present invention, having an effect as GPR119 agonist can be used for treatment of metabolic disorders, including diabetes mellitus (especially type II) and related disorders.

Piperidine Derivatives for GPR119 agonist

Technical Field

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

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].

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.

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.

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].

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. 2007, 1-6].

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]

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

Disclosure

Technical Problem

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

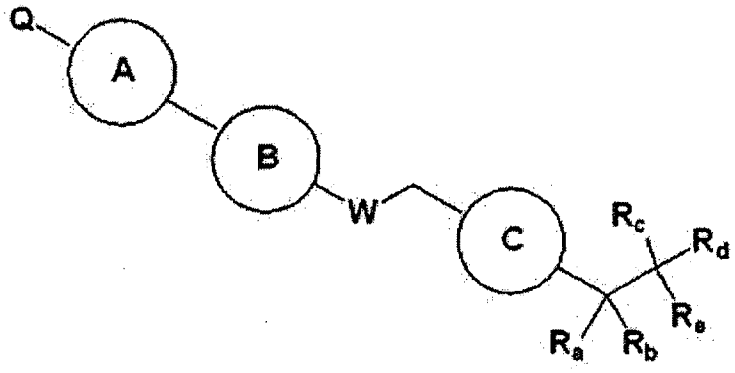
The other object of this invention is to provide a novel piperidine derivative being able to control GPR119 activity with low adverse effect, stereoisomers thereof, pharmaceutically acceptable salts thereof, and a preparing method thereof.

Technical Solution

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

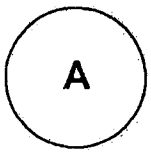
W is O or N-R_h;

R_a, R_b and R_h are each independently H or C_{1-3} alkyl;

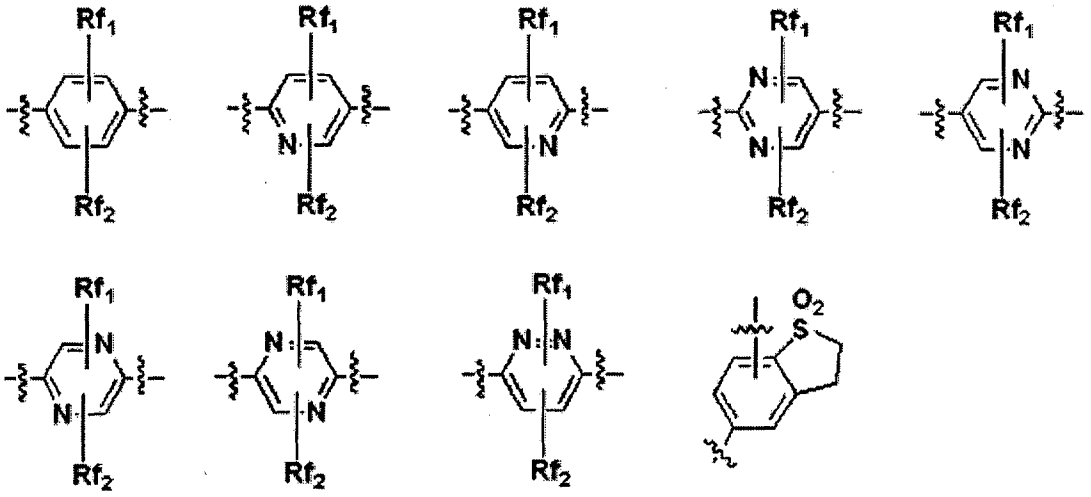
R_c is -F or -C_{1-3} hyperfluoride alkyl;

R_d and R_e are each independently selected from the group consisting of H, halogen, -C_{1-5} alkyl and -C_{3-7} cycloalkyl, wherein -C_{1-5} alkyl and -C_{3-7} cycloalkyl are each independently unsubstituted or substituted with halogen, -CN, -OC_{1-5} alkyl or -C_{1-5} alkyl;

or R_d and R_e are combined to form a -C_{3-7} cycloalkyl, wherein the -C_{3-7} cycloalkyl is unsubstituted or substituted with halogen, -OC_{1-5} alkyl or -C_{1-5} alkyl;

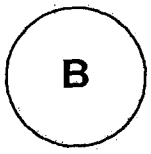


is selected from the group consisting of:

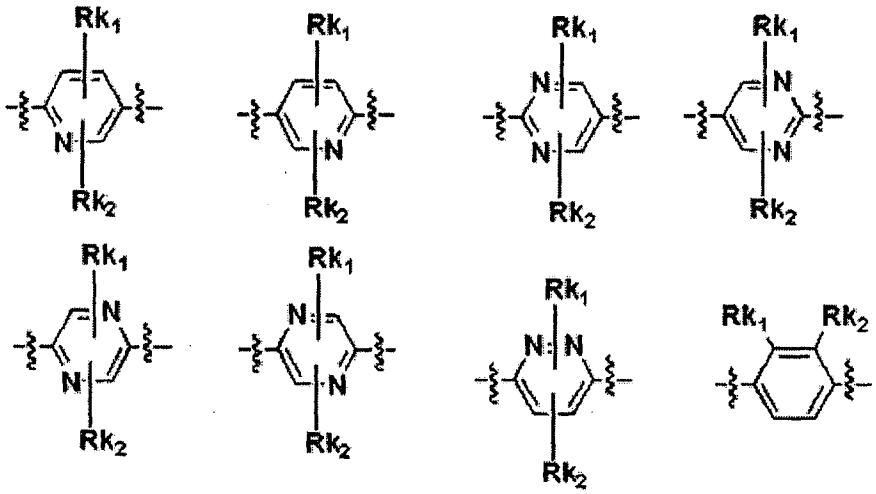


, wherein

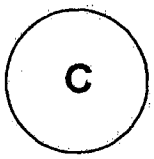
Rf_1 and Rf_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl (OH), -OC_{1-5} alkyl or -CN;

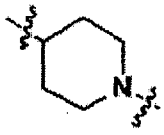


is selected from the group consisting of:

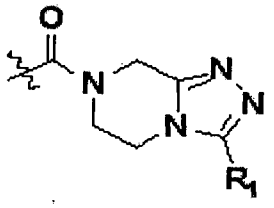


, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl (OH), -OC_{1-5} alkyl or -CN;



is  ;

Q is H, -S(O)R_1, -S(O)$_2R_1$, -C(O)R_1, -C(O)OR_1, -C(O)NHR_1, -C(O)NR_2R_3, -S(O)$_2$NHR_1,



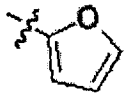
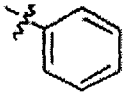
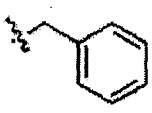
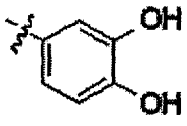
-S(O)$_2$NR_2R_3 or , wherein

R_1 is H, -CF_3, -C_{1-5} alkyl, 3 to 7-membered heterocyclic ring, C_{3-7} cycloalkyl, or Ar,

R_2 and R_3 are each independently C_{1-5} alkyl, C_{3-7} cycloalkyl, 3 to 7-membered heterocyclic ring or Ar (in R_1, R_2 and R_3, -C_{1-5} alkyl, 3 to 7-membered heterocyclic ring, C_{3-7} cycloalkyl and Ar may be each independently substituted with Rx_1 and Rx_2.),

or R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C (O), wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Ar is C6 monocyclic aromatic compound; or 5- or 6-membered heteroaryl group comprising 1 to 3 members selected from the group consisting of N, O and S,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, $-CF_3$, 3- to 7-membered heterocyclic ring, $-C_{1-5}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-5}$ alkyl(OH), $-C_{1-5}$ alkyl(OR_4), $-C_{1-5}$ alkyl(halogen), $-C(O)NR_4R_5$, $-C(O)R_4$, $-C(O)OR_4$, $-S(O)_2R_4$, $-OR_4$,  ,  ,  or  [wherein R_4 and R_5 are each independently H, $-C_{1-5}$ alkyl or $-C_{3-7}$ cycloalkyl.].

In addition, preferably,

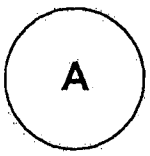
W is O;

R_a and R_b are each independently H;

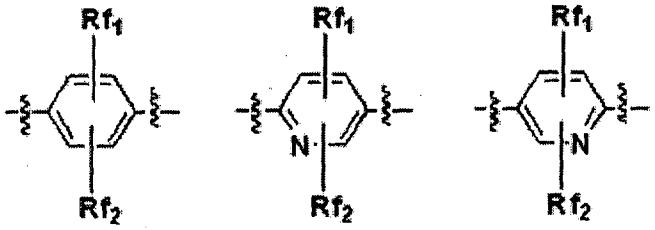
R_c is -F or $-CF_3$;

R_d and R_e are each independently $-C_{1-5}$ alkyl,

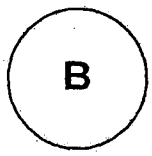
or R_d and R_e are combined to form a $-C_{3-7}$ cycloalkyl, wherein the $-C_{3-7}$ cycloalkyl is unsubstituted or substituted with halogen, $-OC_{1-5}$ alkyl or $-C_{1-5}$ alkyl;



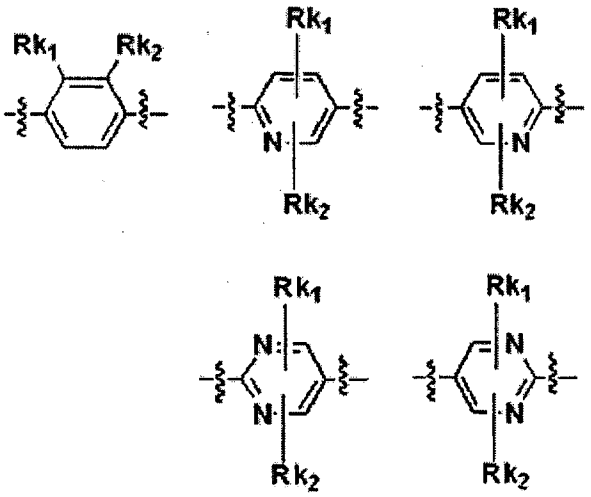
is selected from the group consisting of:



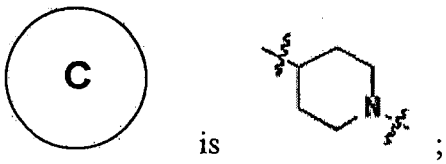
, wherein Rf_1 and Rf_2 are each independently H, halogen, $-C_{1-5}$ alkyl, $-C_{1-5}$ alkyl(OH), $-OC_{1-5}$ alkyl or –CN;



is selected from the group consisting of:



, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;



;

Q is -$S(O)_2R_1$, -$C(O)NR_2R_3$ or -$S(O)_2NR_2R_3$,

wherein R_1, R_2 and R_3 are each independently C_{1-5} alkyl substituted with Rx_1 and Rx_2, or R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C(O),

wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, -CF_3, 3- to 7-membered heterocyclic ring, -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{1-5} alkyl(OH), -C_{1-5} alkyl(OR_4), -C_{1-5} alkyl(halogen), -$C(O)NR_4R_5$, -$C(O)R_4$, -$C(O)OR_4$, -$S(O)_2R_4$ or -OR_4 [wherein R_4 and R_5 are each independently H, -C_{1-5} alkyl or -C_{3-7} cycloalkyl.].

In addition, more preferably,

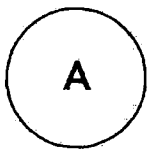
W is O;

R_a and R_b are each independently H;

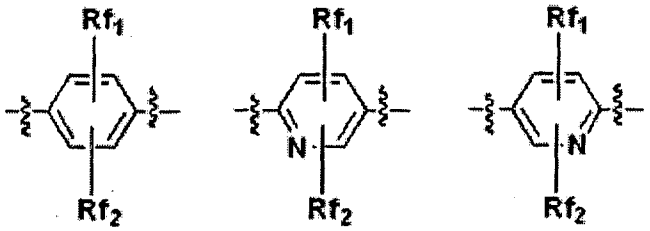
R_c is -F or -CF_3;

R_d and R_e are each independently -C_{1-5} alkyl,

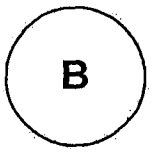
or R_d and R_e are combined to form -C_{3-7} cycloalkyl, wherein the -C_{3-7} cycloalkyl is unsubstituted or substituted with halogen, -OC_{1-5} alkyl or -C_{1-5} alkyl;



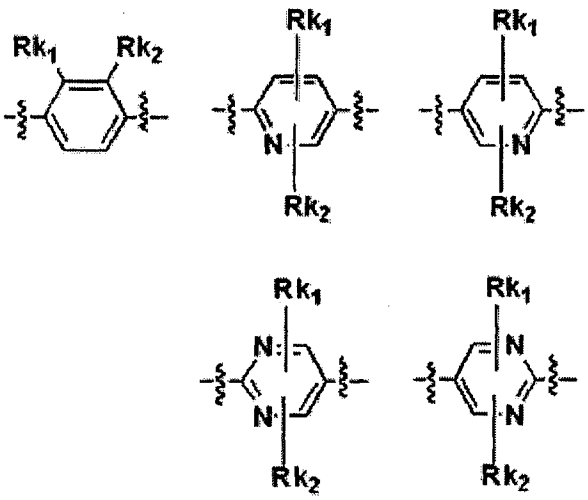
is selected from the group consisting of:



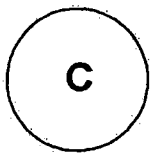
, wherein Rf_1 and Rf_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;

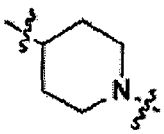


is selected from the group consisting of:



, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;



is 

;

Q is -$C(O)NR_2R_3$,

wherein R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C(O),

wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, $-CF_3$, 3- to 7-membered heterocyclic ring, $-C_{1-5}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-5}$ alkyl(OH), $-C_{1-5}$ alkyl(OR_4), $-C_{1-5}$ alkyl(halogen), $-C(O)NR_4R_5$, $-C(O)R_4$, $-C(O)OR_4$, $-S(O)_2R_4$ or $-OR_4$ [wherein R_4 and R_5 are each independently H, $-C_{1-5}$ alkyl or $-C_{3-7}$ cycloalkyl.].

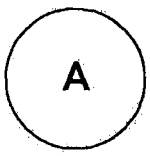
Also, alternatively,

W is O;

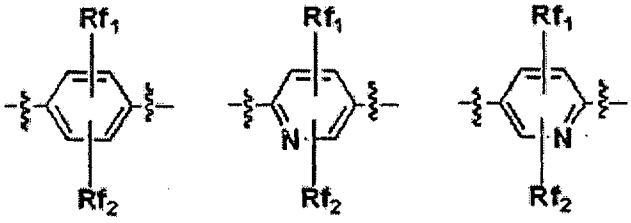
R_a and R_b are each independently H;

R_c is –F or $-CF_3$;

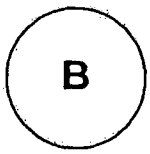
R_d and R_e are each independently selected from the group consisting of $-CH_3$ and $-CH_2CH_3$.



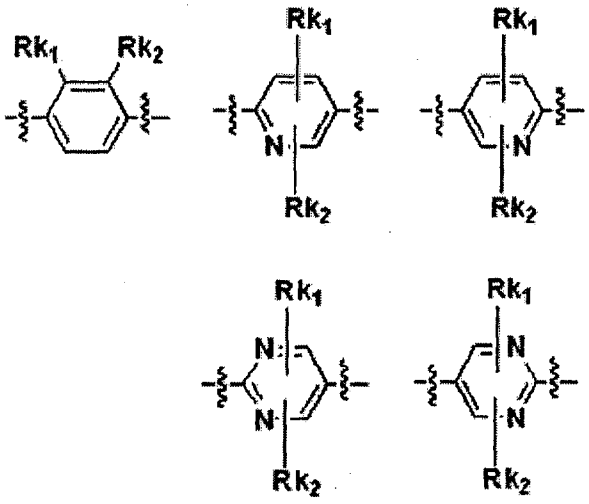
is selected from the group consisting of:



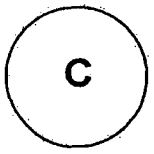
, wherein Rf_1 and Rf_2 are each independently H, -F or –CN;

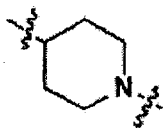


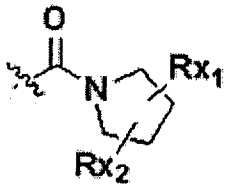
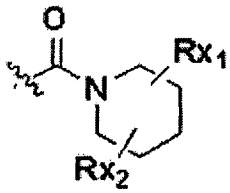
is selected from the group consisting of:



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



is  ;

Q is selected from the group consisting of:   ,

wherein Rx_1 and Rx_2 are each independently H, OH, -F, -CN, $-CF_3$, $-CH_2OH$ or $-C(O)NH_2$.

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.

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

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

Compound 431: 1-(2-fluoro-2-methylpropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 470: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide

Compound 498: methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate

Compound 499: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(2,2,2-trifluoroethyl)piperidine

Compound 500: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine

Compound 515: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 516: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide

Compound 517: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(morpholino)methanone

Compound 524: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(3,3,3-trifluoropropyl)piperidine

Compound 526: N-cyclopropyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 527: N-cyclobutyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 528: N-cyclopentyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 529: N-cyclohexyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 530: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(pyrrolidin-1-yl)methanone

Compound 531: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperidin-1-yl)methanone

Compound 533: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(4-hydroxybutyl)biphenyl-4-carboxamide

Compound 534: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide

Compound 540: 5-(4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide

Compound 542: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine

Compound 546: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidine

Compound 547: 1-(2,2-difluoropropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 548: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid

Compound 549: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide

Compound 550: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(3-hydroxypropyl)biphenyl-4-carboxamide

Compound 551: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)-N-methylbiphenyl-4-carboxamide

Compound 552: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 553: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 554: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 555: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 556: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 557: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone

Compound 558: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone

Compound 559: N-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide

Compound 560: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(furan-2-ylmethyl)biphenyl-4-carboxamide

Compound 561: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide

Compound 562: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide

Compound 563: N-benzyl-N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 564: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(trifluoromethyl)pyrrolidin-1-yl)methanone

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

Compound 566: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone

Compound 567: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone

Compound 568: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-hydroxypiperidin-1-yl)methanone

Compound 569: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 570: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone

Compound 571: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone

Compound 574: 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoic acid

Compound 575: 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanone

Compound 576: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzamide

Compound 578: (S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 579: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 580: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzamide

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

Compound 582: morpholino(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 583: piperidin-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 584: pyrrolidin-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 585: (S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

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

Compound 587: (4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 588: (4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 589: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine

Compound 593: 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)ethanone

Compound 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]pyrazin-7(8H)-yl)methanone

Compound 595: (3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 596: 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)phenyl)pyridine

Compound 597: 5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-2-(4-(methylsulfonyl)phenyl)pyridine

Compound 598: N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide

Compound 599: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropyl-N-methylbiphenyl-4-carboxamide

Compound 600: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxyazetidin-1-yl)methanone

Compound 601: (3,3-difluoroazetidin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 602: N-tert-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 603: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropylbiphenyl-4-carboxamide

Compound 604: N,N-diethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 605: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide

Compound 606: (S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxypropan-2-yl)biphenyl-4-carboxamide

Compound 607: (R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxybutan-2-yl)biphenyl-4-carboxamide

Compound 608: (R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide

Compound 609: (S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide

Compound 610: N-(1,3-dihydroxypropan-2-yl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 611: N-(2,3-dihydroxypropyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 612: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 613: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 614: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-sulfonamide

Compound 615: 1-(2-fluoro-2-methylpropyl)-4-((4'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 616: 1-(2-fluoro-2-methylpropyl)-4-((4'-(piperidin-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 617: 2-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-5-(methylsulfonyl)pyridine

Compound 618: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2-(methylsulfonyl)pyridine

Compound 619: (R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate

Compound 620: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid

Compound 621: 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-ylcarboxamido)acetic acid

Compound 622: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(thiazolidin-3-yl)methanone

Compound 623: (4-(cyclopropanecarbonyl)piperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 624: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone

Compound 625: (S)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate

Compound 626: tert-butyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazine-1-carboxylate

Compound 627: (4-benzylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 628: 1-(4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone

Compound 629: (3,3-difluoropyrrolidin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 630: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperazin-1-yl)methanone

Compound 631: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 632: (S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 633: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 634: (3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

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

Compound 636: N-(2-hydroxyethyl)-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 637: N-(2-hydroxyethyl)-N-methyl-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 638: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide

Compound 639: N,N-diethyl-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

Compound 640: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 641: (R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 642: (3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 643: 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide

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

Compound 645: methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)acetate

Compound 646: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(oxetan-3-yl)biphenyl-4-carboxamide

Compound 647: methyl 3-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)propanoate

Compound 648: (R)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydroxypropanoate

Compound 649: (S)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydroxypropanoate

Compound 650: ethyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)piperidin-1-carboxylate

Compound 651: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-pentylbiphenyl-4-carboxamide

Compound 652: (R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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

Compound 654: (S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 655: (R)-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 656: (S)-1-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 657: (R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 659: (S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 666: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidin-3-ol

Compound 667: (R)-(1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidin-2-yl)methanol

Compound 668: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidine-2-carboxamide

Compound 669: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol

Compound 670: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol

Compound 671: (R)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 672: (R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 673: (S)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 674: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-sulfonamide

Compound 675: 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-sulfonamide

Compound 676: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine

Compound 677: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxylate

Compound 678: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxylate

Compound 679: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxylate

Compound 680: (4-ethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 681: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-isopropylpiperazin-1-yl)methanone

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

Compound 683: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N,N-dimethylpyrrolidine-2-carboxamide

Compound 684: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N-methylpyrrolidine-2-carboxamide

Compound 685: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-methylpiperazin-1-yl)methanone

Compound 686: (3,5-dimethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 687: (2,6-dimethylmorpholino)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 688: 4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide

Compound 689: (4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 690: (4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 692: (R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 693: (S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 694: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 695: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

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 697: (R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 698: (R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 699: (S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 700: (R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 701: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 702: (R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 703: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 704: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 707: (R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 708: (R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 709: (R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 711: (R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 712: (R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 713: (R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 714: 1-(2-fluoro-2-methylpropyl)-4-((2-fluoro-4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 715: (S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 716: (R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 718: (R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 719: (S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 720: (S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 721: (R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 723: (R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 724: (S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 725: (S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 726: (R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 727: (R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 728: (S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 729: (R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

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

Compound 731: (S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 732: (S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 733: (R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 734: (R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 735: (S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 736: (R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 737: (S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 738: (S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 739: (S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 740: (S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 741: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone

Compound 742: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone

Compound 743: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypyrrolidin-1-yl)methanone

Compound 744: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 745: (2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone

Compound 746: (S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 747: (S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 748: (S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 749: (R)-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 751: (R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 752: (S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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

Compound 754: (R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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 758: (R)-(6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-3-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 759: (R)-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 761: (R)-(4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 763: (R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 764: (S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 765: (S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 766: (R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 767: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 768: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 769: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 771: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 772: (S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 773: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

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

Compound 775: (R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 776: (S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 777: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

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

Compound 779: (R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

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

Compound 783: (R)-(5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 784: (R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 785: (R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 786: (S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 787: (S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 789: 1-((1-fluorocyclohexyl)methyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

Compound 790: 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-2-one

Compound 791: 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carbonitrile

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

Compound 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]pyrazin-7(8H)-yl)methanone

Compound 794: (R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 795: (S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 796: (R)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

Compound 797: (S)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone

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 809: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 810: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 811: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 812: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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 815: (S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 829: (R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone

Compound 830: N-(3,4-dihydroxyphenethyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-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 834: (R)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 835: (S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 836: (S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 838: (R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 839: (S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 840: (R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 842: (S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 844: (R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 845: (S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 846: (R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 848: (R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 849: (R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 850: (S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 851: (S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 852: (R)-(4'-(((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)(methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 853: (R)-(4'-(ethyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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 857: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-2-carboxamide

Compound 858: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 859: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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 867: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 868: (S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 869: (S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 870: (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 871: (R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-3-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 883: (S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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 888: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 889: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 890: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 892: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 893: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 894: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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 897: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 899: (S)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorophenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 900: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 902: (R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 903: (R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 904: (S)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 905: (S)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

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

Compound 907: (R)-(5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 908: (2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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

Compound 910: (2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone

Compound 911: (2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone

Compound 912: (R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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

Compound 914: (R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 915: (S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 916: (S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 917: (R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

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

Compound 919: (R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 920: (S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 921: (S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

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

Compound 923: (R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 924: (S)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 925: (R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 926: (R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

Compound 927: (R)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

Compound 928: (R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone

Compound 929: (R)-(4'-(ethyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 931: (2S,4R)-methyl 4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylate

Compound 932: (2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate

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 936: 1-(4-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone

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 939: (R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 940: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 941: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 942: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone

Compound 943: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 944: (S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 945: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 947: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5'-(hydroxymethyl)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 948: (R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 949: (S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 950: (S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 951: (S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 953: (S)-1-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 954: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 955: (S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 956: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 957: (S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 963: (R)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 964: (S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

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

Compound 966: (S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 967: (R)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 968: (S)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

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

Compound 970: (S)-(3-hydroxypyrrolidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone

Compound 971: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone

Compound 972: (R)-(3-hydroxypiperidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone

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

Compound 974: (S)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 975: (R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 976: (R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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 978: (S)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 979: (R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 980: (R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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 982: (R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 983: (S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 984: (S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 985: (R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 986: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 987: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 988: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 989: (S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 990: (R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 991: (S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 992: (R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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

Compound 1001: (R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1002: (R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1003: (S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

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

Compound 1005: (R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1006: (S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1007: (R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)methanone

Compound 1008: (R)-(3-hydroxypiperidin-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)methanone

Compound 1009: (S)-1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1010: (R)-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 1011: (S)-1-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1012: (R)-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone

Compound 1013: (R)-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 1014: (S)-1-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)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 1016: (S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1017: (S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1018: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1020: (S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

Compound 1021: (S)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1022: (S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

Compound 1023: (R)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-2-carboxamide

Compound 1024: (S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

Compound 1025: (S)-1-(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide

Compound 1026: (S)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone

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

Compound 1029: (R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile

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 1033: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 1034: (S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

Compound 1035: (R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

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 1038: (S)-1-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidine-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 1052: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone

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 1056: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone

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 1072: (S)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide

Compound 1073: (R)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)piperidine-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 1077: (R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

Compound 1078: (S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone

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

Compound 1080: (R)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)piperidine-2-carboxamide

Compound 1081: (S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-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 1097: (2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carbonitrile

Compound 1098: (2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carbonitrile

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 1115: 3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(4-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile

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 1121: (S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile

Compound 1123: (R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile

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

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

Compound 1126: (R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile.

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.

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.

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

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

Advantageous Effects

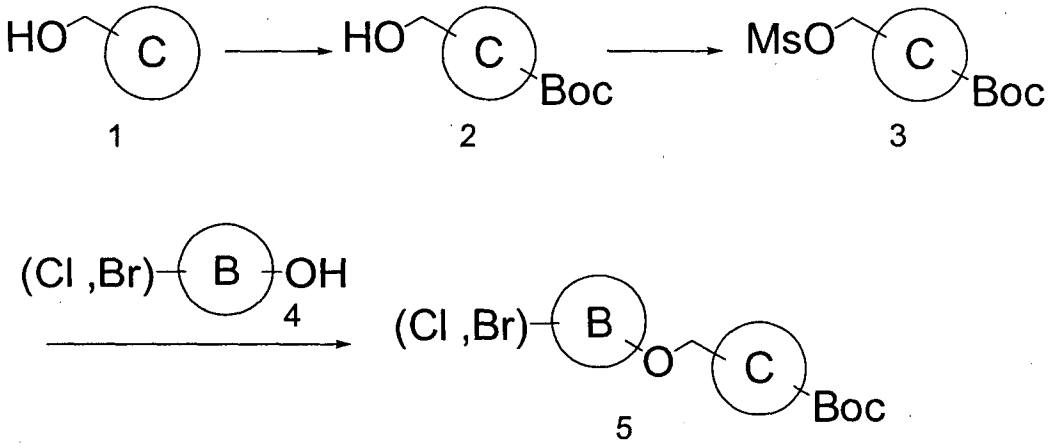
The present invention can provide a novel piperidine derivative, stereoisomers thereof, and pharmaceutically acceptable salts thereof.

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

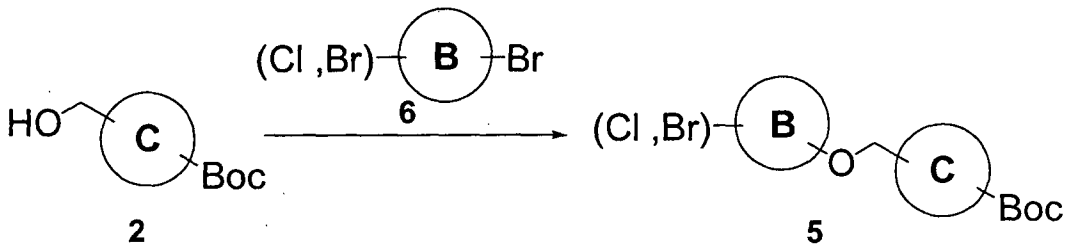
The intermediate 5 can be synthesized according to the following reaction schemes 1 and 2.

[Reaction Scheme 1]



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.

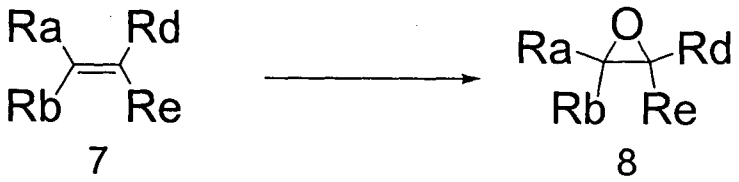
[Reaction Scheme 2]



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

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

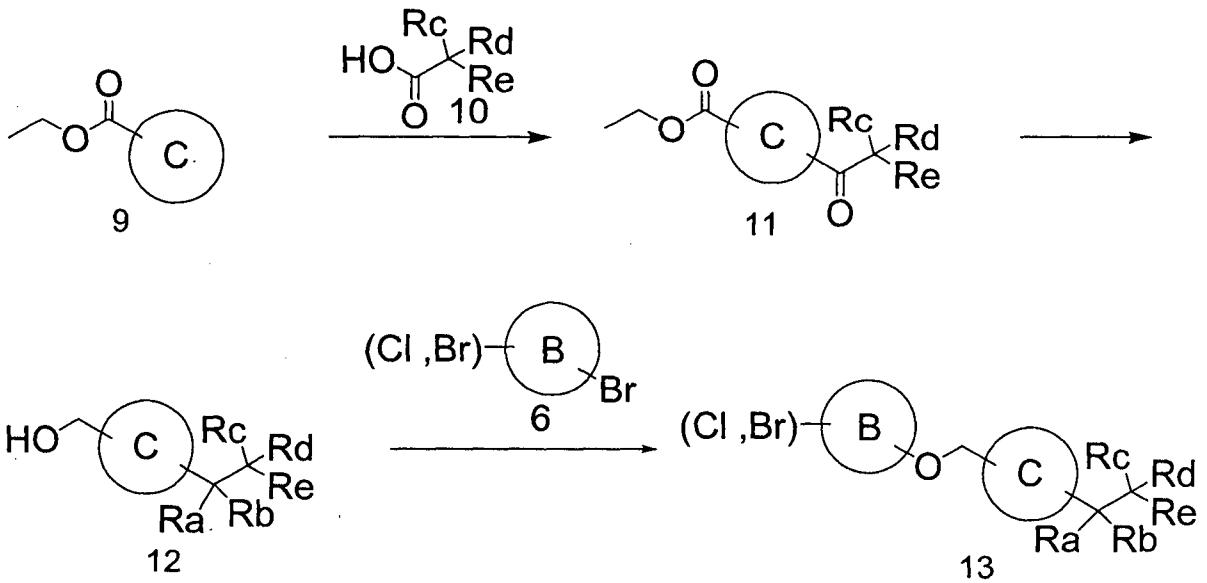
[Reaction Scheme 3]



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

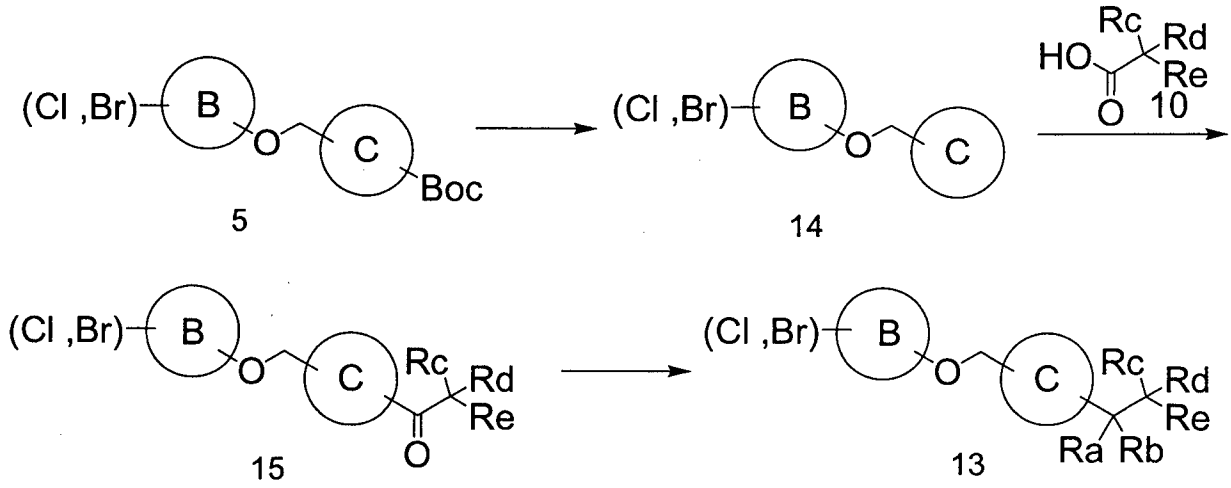
The intermediate 13 can be synthesized according to the following reaction schemes 4, 5 and 6.

[Reaction Scheme 4]



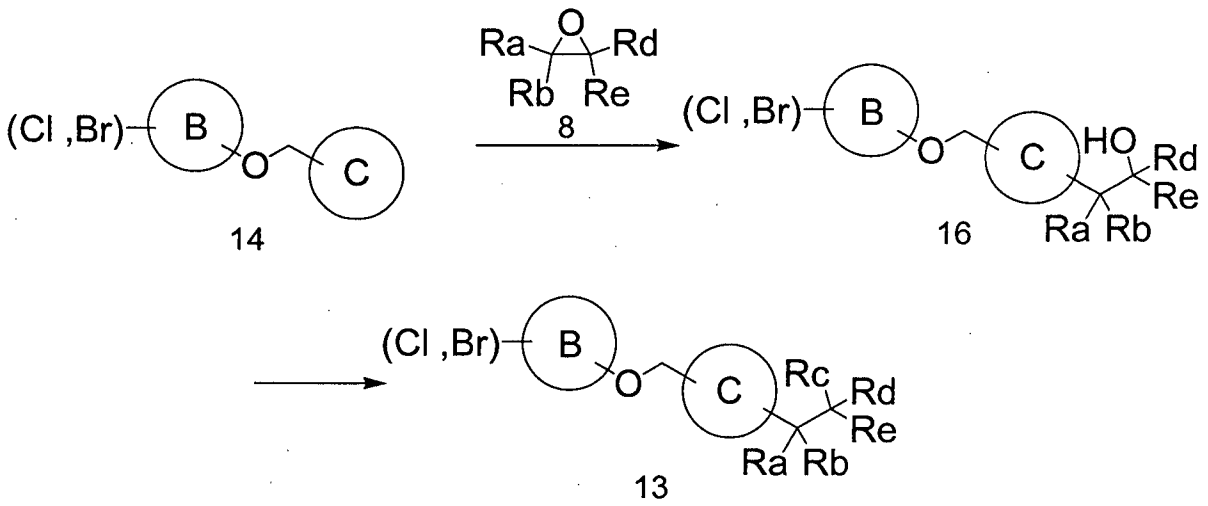
As shown in the reaction scheme 4, compound 11 is prepared by amide bond formation of compound 9 with compound 10, and then subjected to reduction thereby to obtain compound 12. Finally, the intermediate 13 is prepared through the substitution reaction of compound 12.

[Reaction Scheme 5]



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.

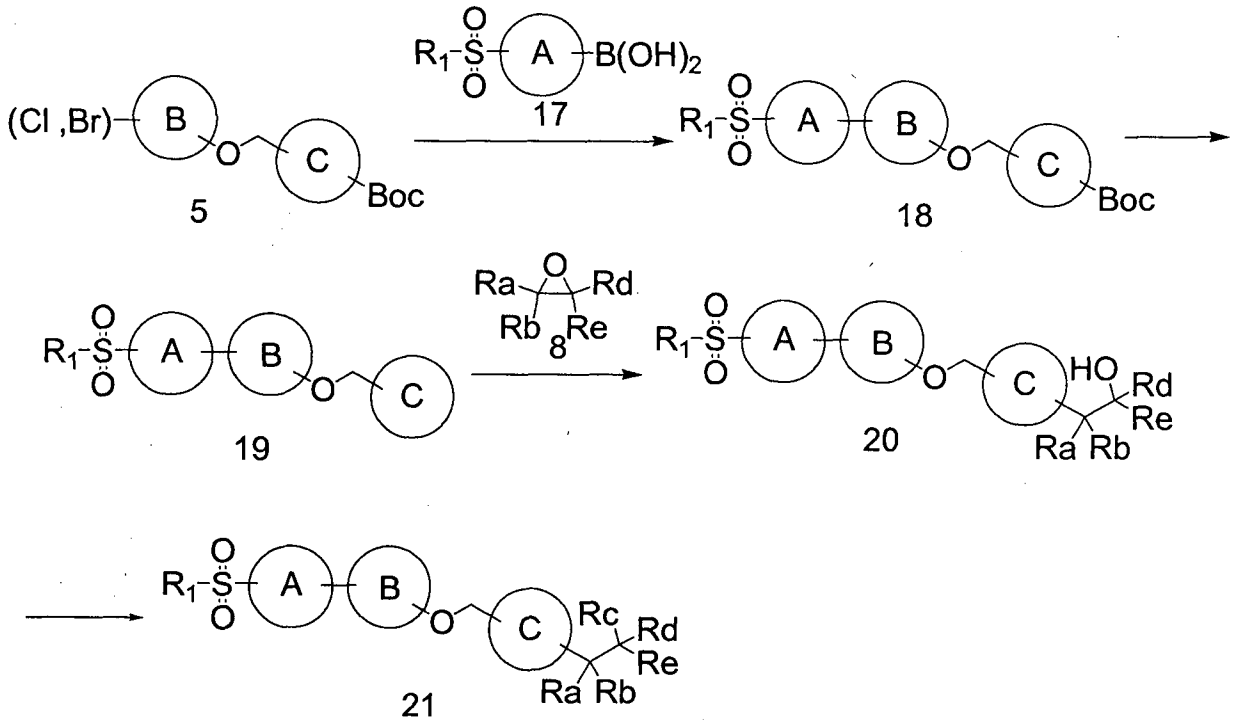
[Reaction Scheme 6]



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.

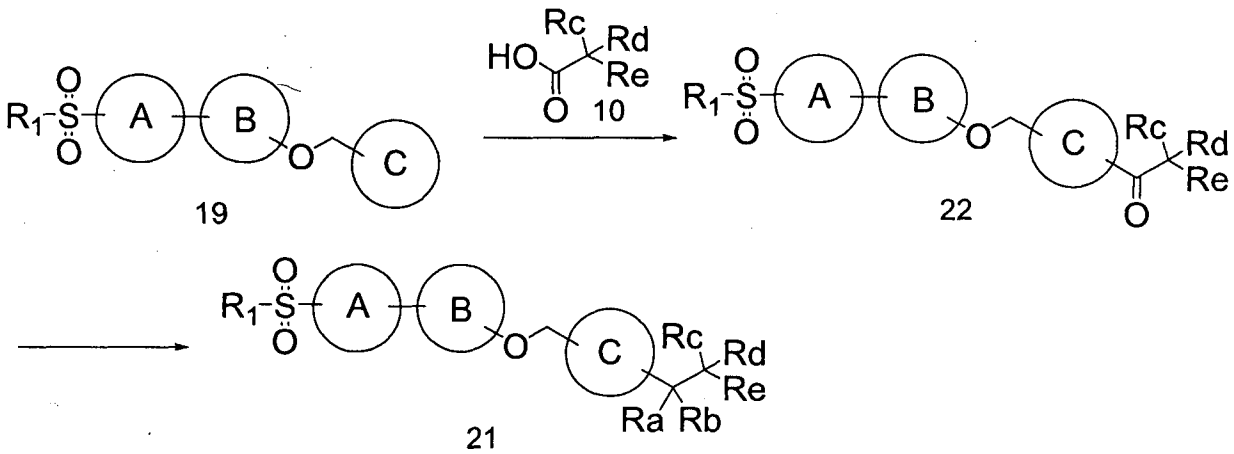
The compounds 21 and 23 that Q is $-S(O)_2R_1$ in formula 1 can be synthesized according to the following reaction schemes 7, 8, 9, 10, 11 and 12.

[Reaction Scheme 7]



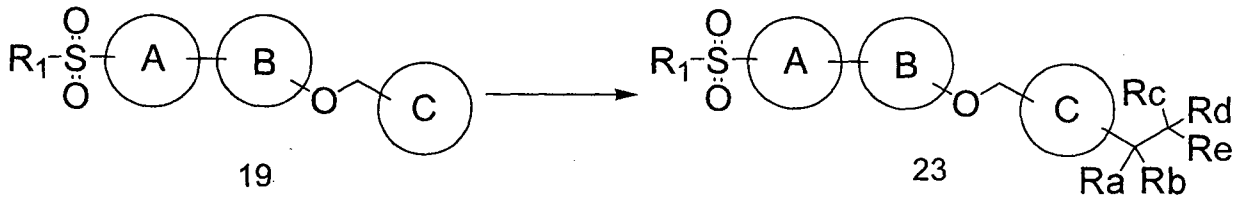
As shown in the reaction scheme 7, compound 18 is prepared through the Suzuki coupling reaction of compound 5 with boronic acid compound 17. The protection group of compound 18 is removed using acid, and reacted with oxirane compound 8 to obtain compound 20. Finally, hydroxyl group of compound 20 is substituted with fluoride to prepare compound 21.

[Reaction Scheme 8]



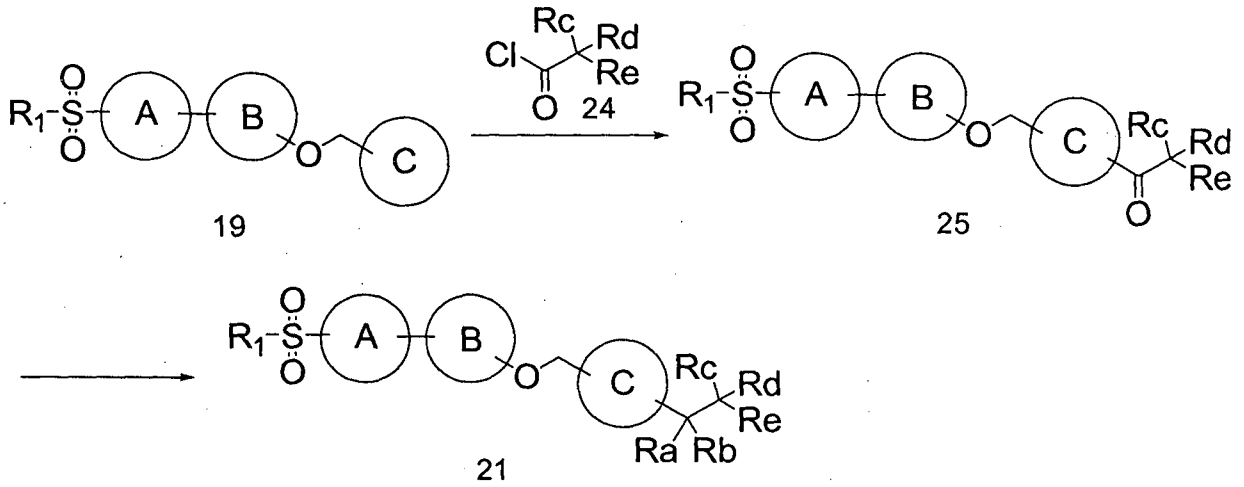
As shown in the reaction scheme 8, compound 22 is prepared by amide bond formation of compounds 19 and 10, and then subjected to reduction to prepare compound 21.

[Reaction Scheme 9]



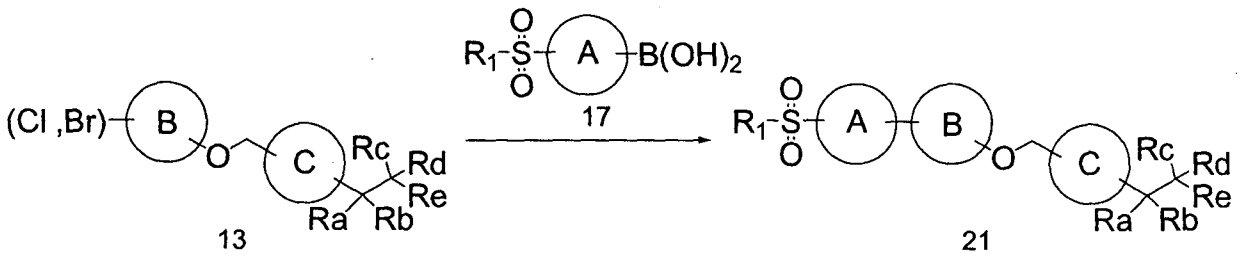
As shown in the reaction scheme 9, compound 19 is reacted with 2,2,2-trifluoroethyl trifluoromethanesulfonate to obtain compound 23.

[Reaction Scheme 10]



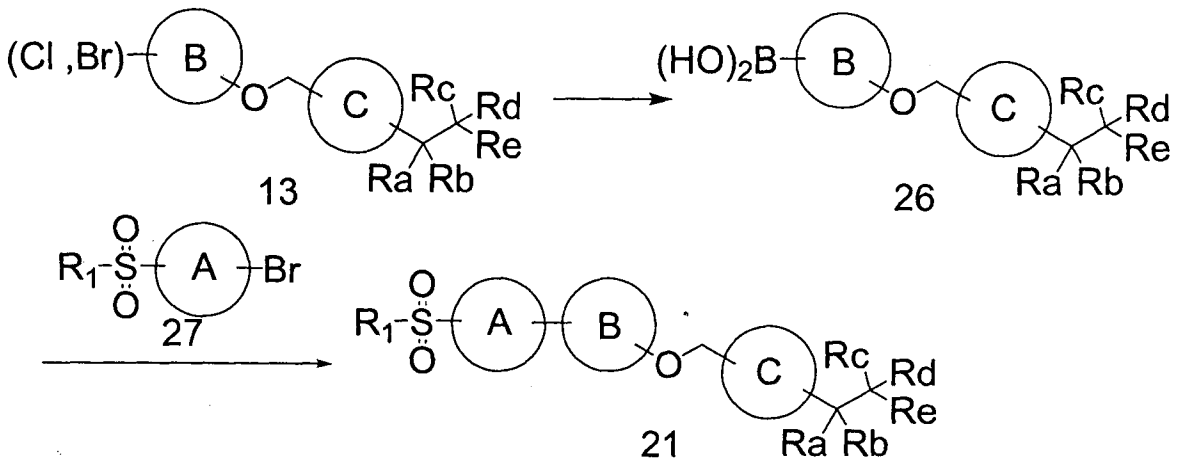
As shown in the reaction scheme 10, compound 25 is prepared by amide bond formation of compounds 19 and 24, and subjected to the reduction to prepare compound 21.

[Reaction Scheme 11]



As shown in the reaction scheme 11, compound 13 is subjected to Suzuki coupling reaction with boronic acid compound 17 to prepare compound 21.

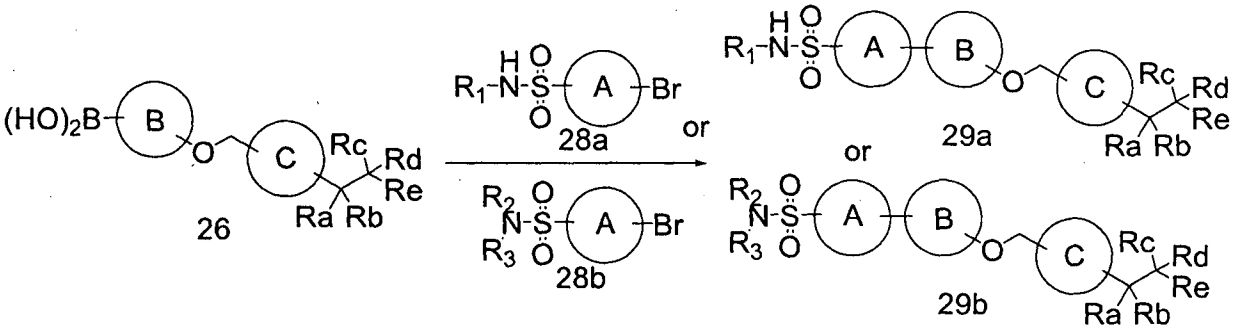
[Reaction Scheme 12]



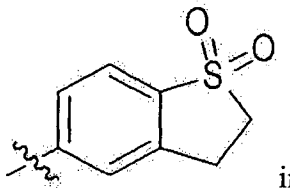
As shown in the reaction scheme 12, boronic acid compound 26 is prepared using compound 13 as a starting compound, and then subjected to Suzuki coupling reaction with compound 27 to prepare compound 21.

The compound 29 that Q is $-S(O)_2NHR_1$ or $-S(O)_2NR_2R_3$ in formula 1 can be synthesized according to the following reaction scheme 13.

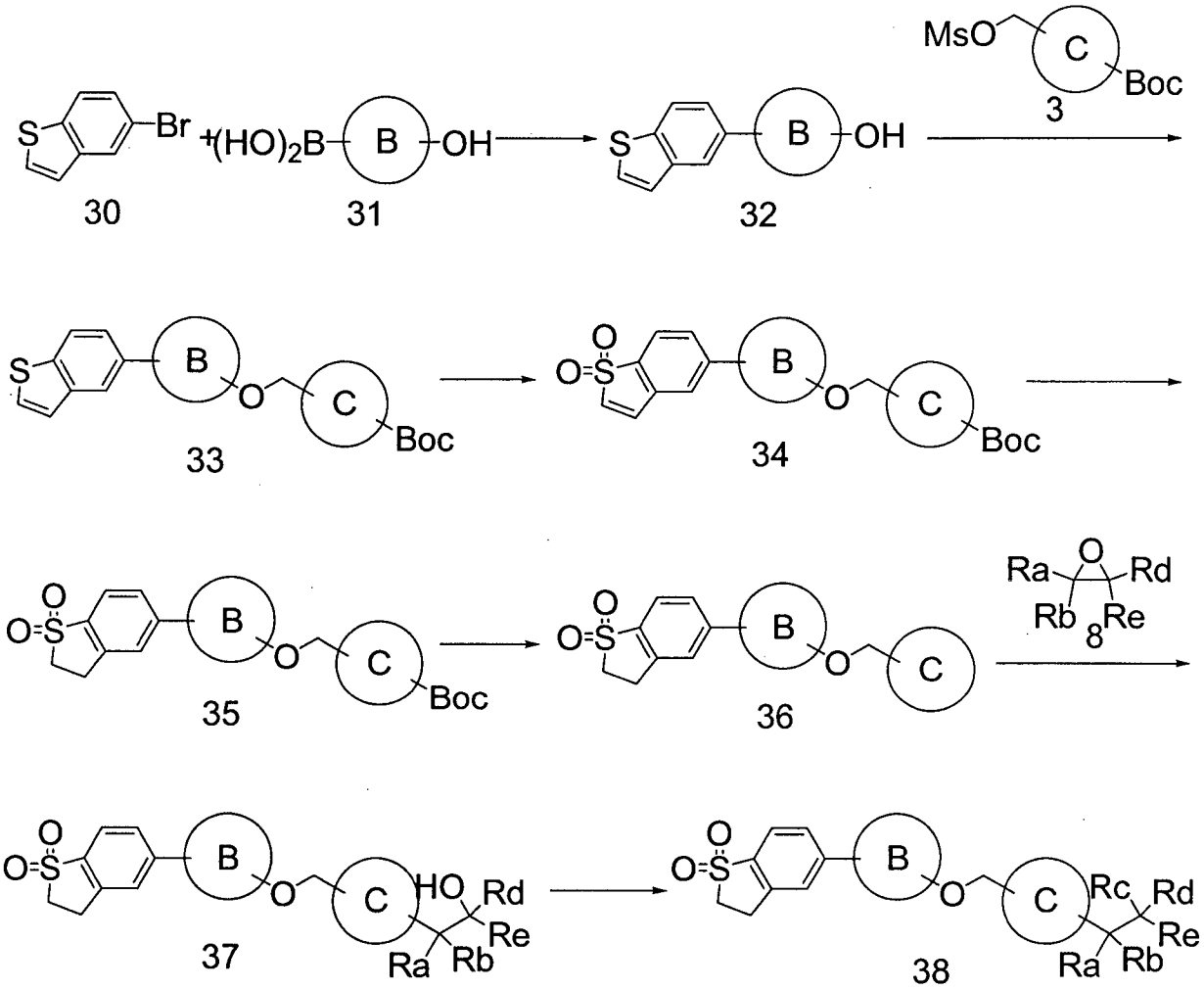
[Reaction Scheme 13]



As shown in the reaction scheme 13, compound 26 is subjected to Suzuki coupling reaction with compound 28 to prepare compound 29.

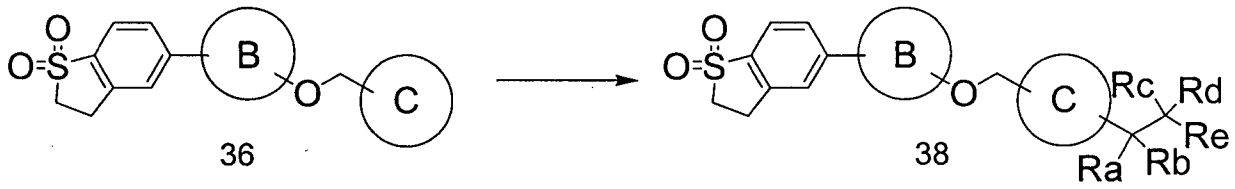
The compound 38 that the ring **A** is  in formula 1 can be synthesized according to the following reaction schemes 14 and 15.

[Reaction Scheme 14]



As shown in the reaction scheme 14, compound 30 is subjected to Suzuki coupling reaction with compound 31 to prepare compound 32. Compound 33 is prepared through the substitution reaction of compound 32 with compound 3, and subjected to the oxidation and hydrogenation reactions to prepare compound 35. The protecting group of compound 35 is removed with acid, following with reaction with oxirane compound 8 to prepare compound 37. Finally, hydroxyl group of compound 37 is substituted with fluoride to obtain compound 38.

[Reaction Scheme 15]

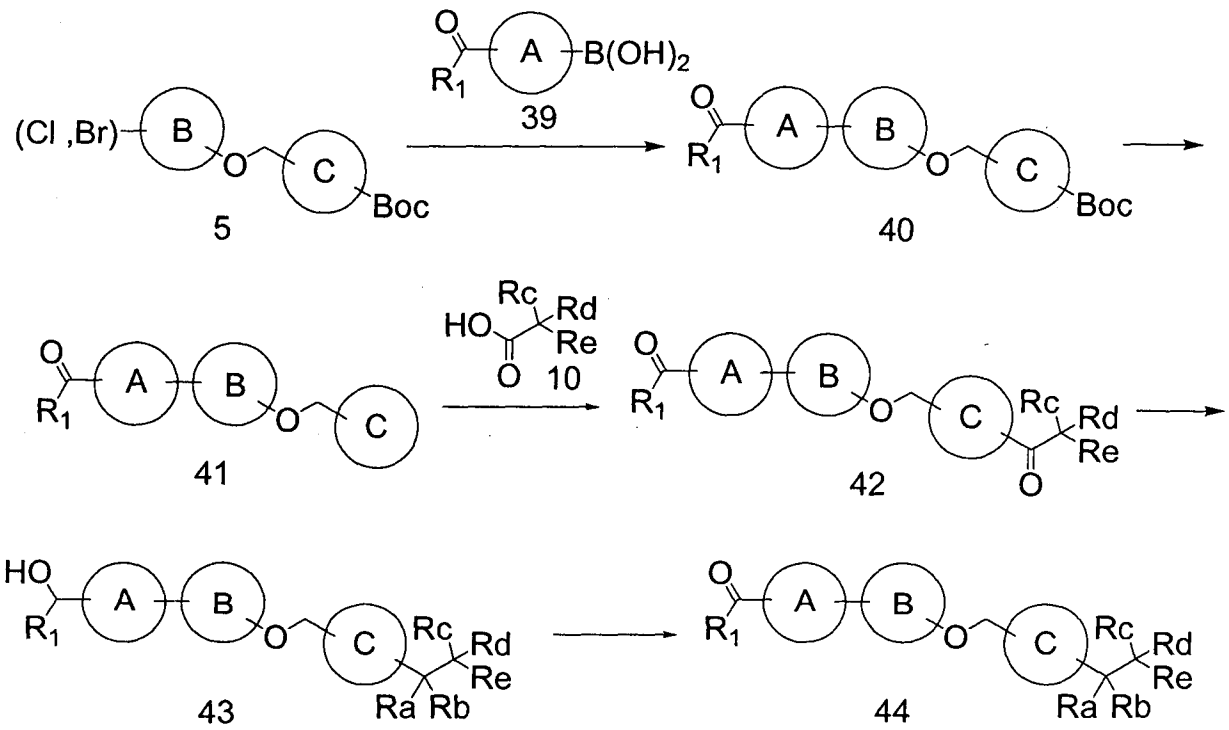


As shown in the reaction scheme 15, compound 36 is reacted with 2,2,2-trifluoroethyl trifluoromethanesulfonate to prepare compound 38.

The compound 44 that Q is $-C(O)R_1$ in formula 1 can be synthesized according to the

following reaction scheme 16.

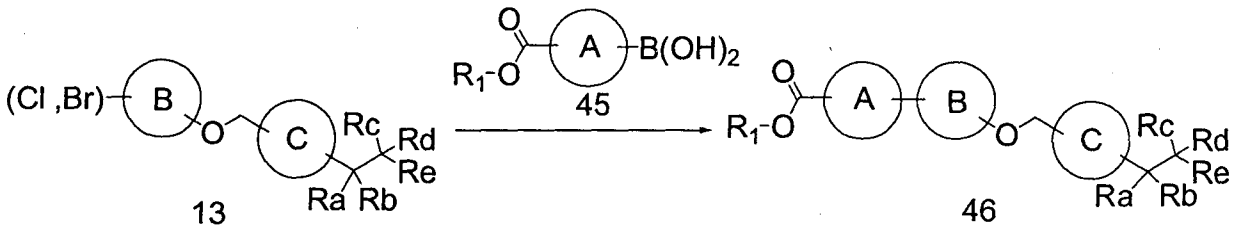
[Reaction Scheme 16]



As shown in the reaction scheme 16, compound 5 is subjected to Suzuki coupling reaction with compound 39 to prepare compound 40. The protecting group of compound 40 is removed using acid, following with the formation of amide bond with compound 10 to prepare compound 42. The carbonyl group of amide in compound 42 is removed through reduction, and then, in order to re-introducing the undesired reduced keton group, following with oxidation to obtain compound 44.

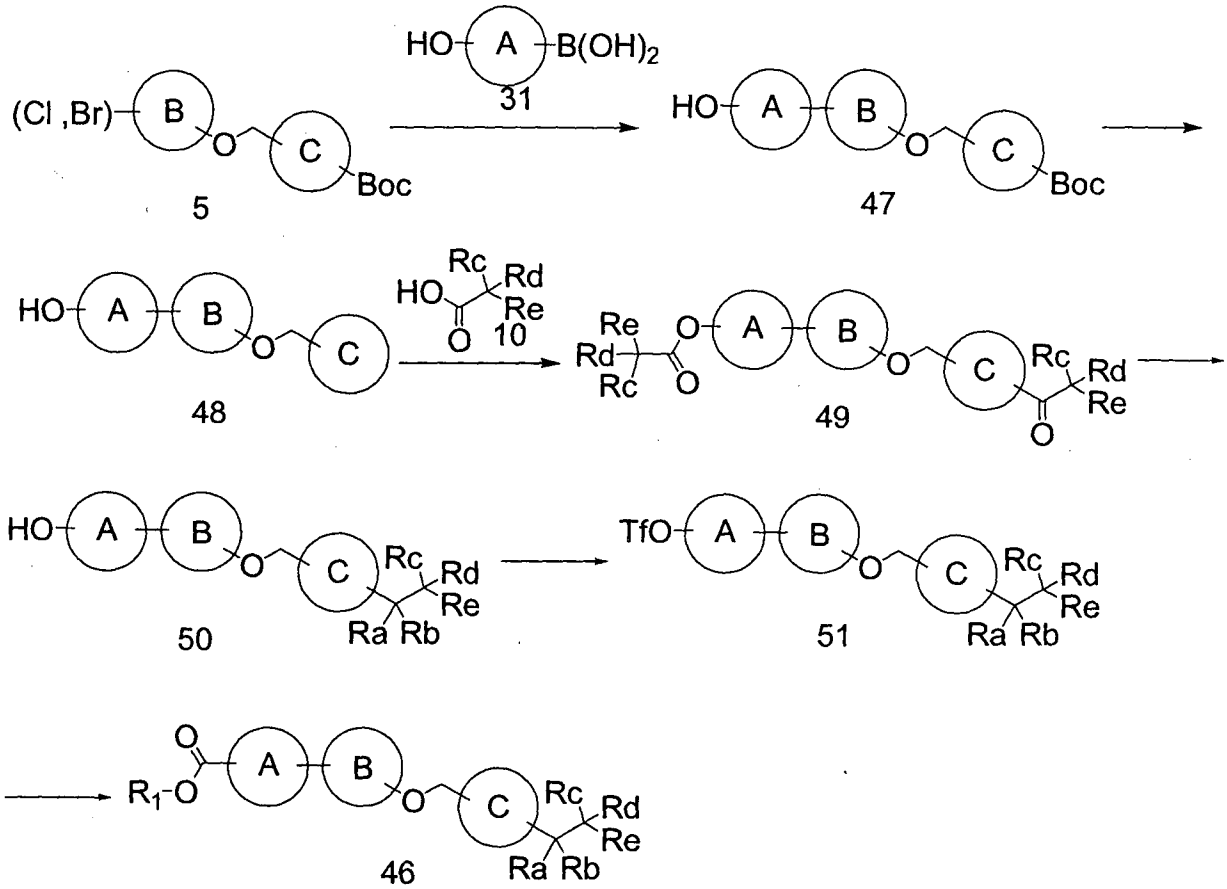
The intermediate 46 can be synthesized according to the following reaction schemes 17, 18, 19 and 20.

[Reaction Scheme 17]



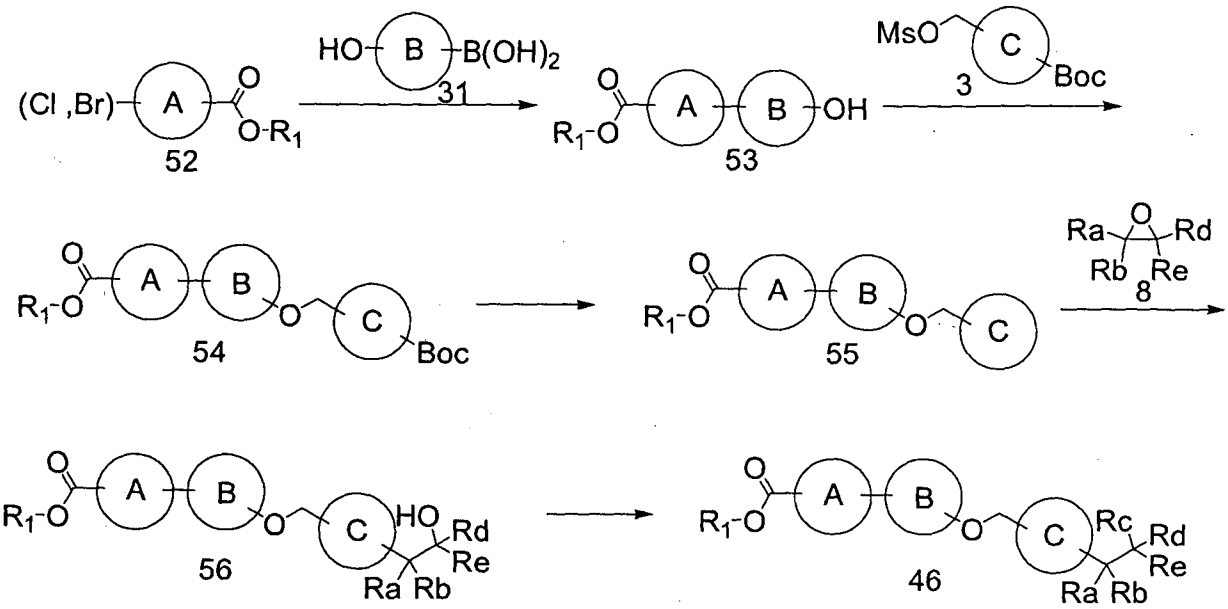
As shown in the reaction scheme 17, compound 13 is subjected to Suzuki coupling reaction with boronic acid compound 45 to prepare compound 46.

[Reaction Scheme 18]



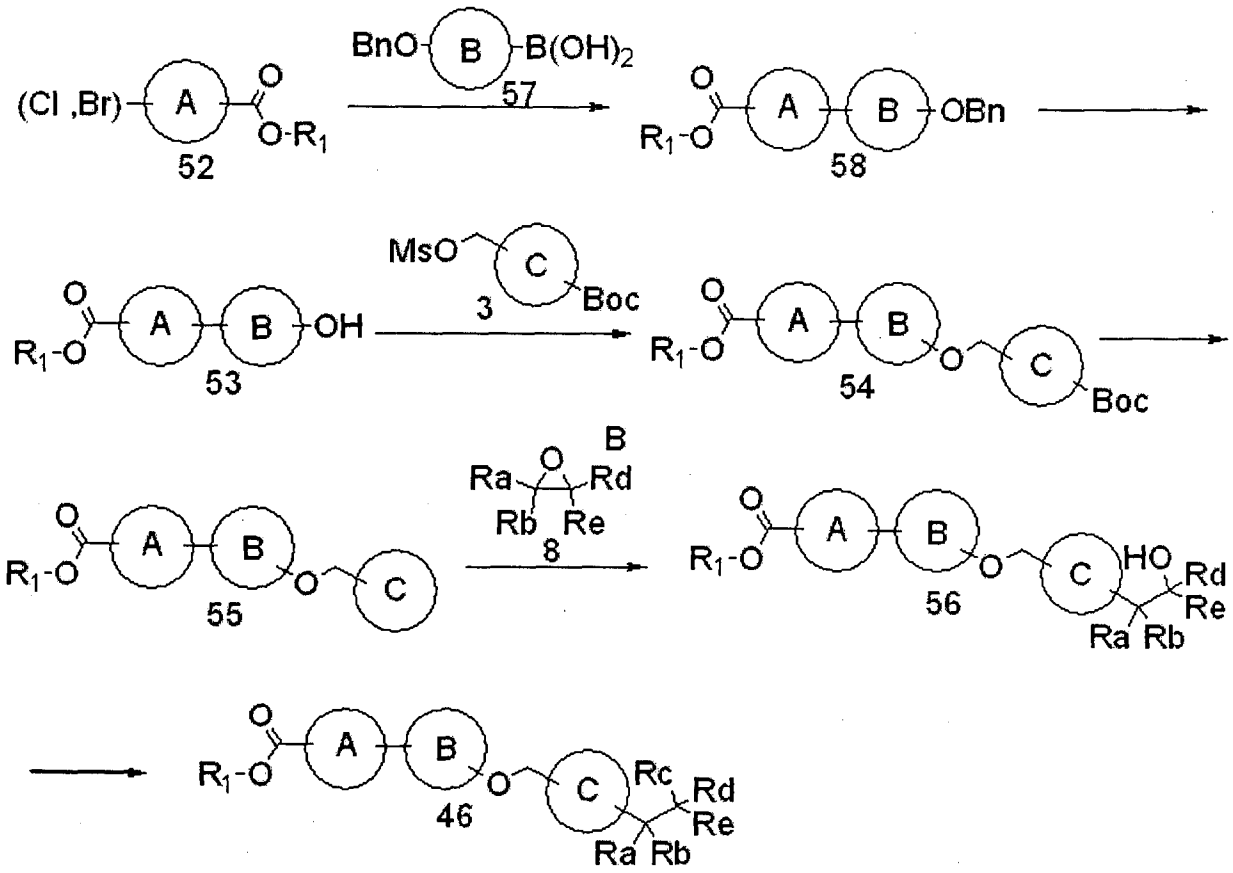
As shown in the reaction scheme 18, compound 5 is subjected to Suzuki coupling reaction with boronic acid compound 31 to prepare compound 47. The protecting group is removed using acid, following with the formation of amide bond with compound 10 to prepare compound 49. Through the reduction, the removal 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]



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.

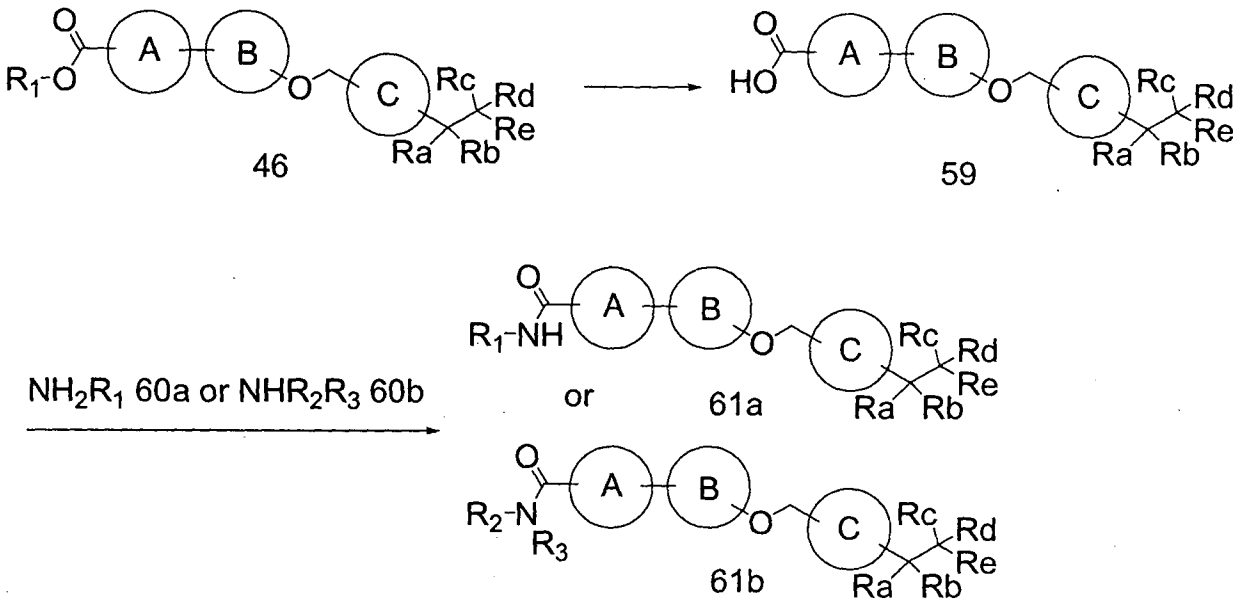
[Reaction Scheme 20]



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.

The compound 61 that Q is $-C(O)NHR_1$ or $-C(O)NR_2R_3$ in formula 1 can be synthesized according to the following reaction scheme 21.

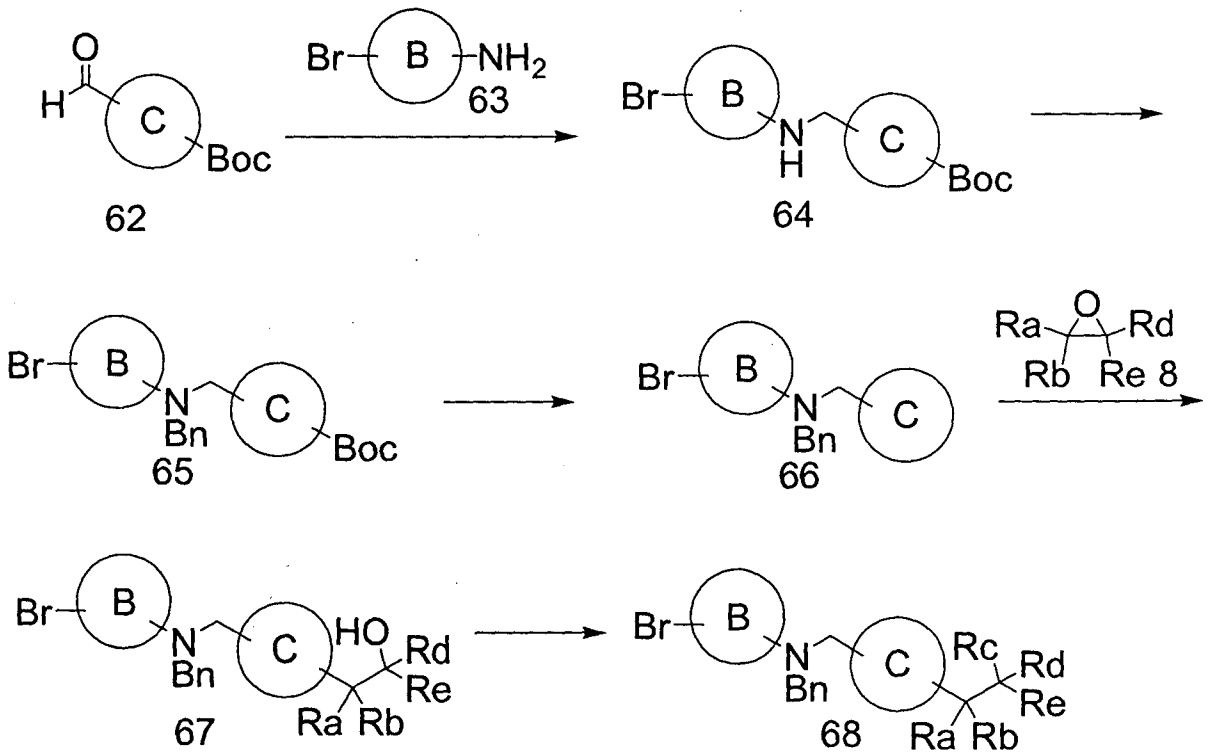
[Reaction Scheme 21]



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 61a or compound 61b.

The intermediate 68 can be synthesized according to the following reaction scheme 22 and 23.

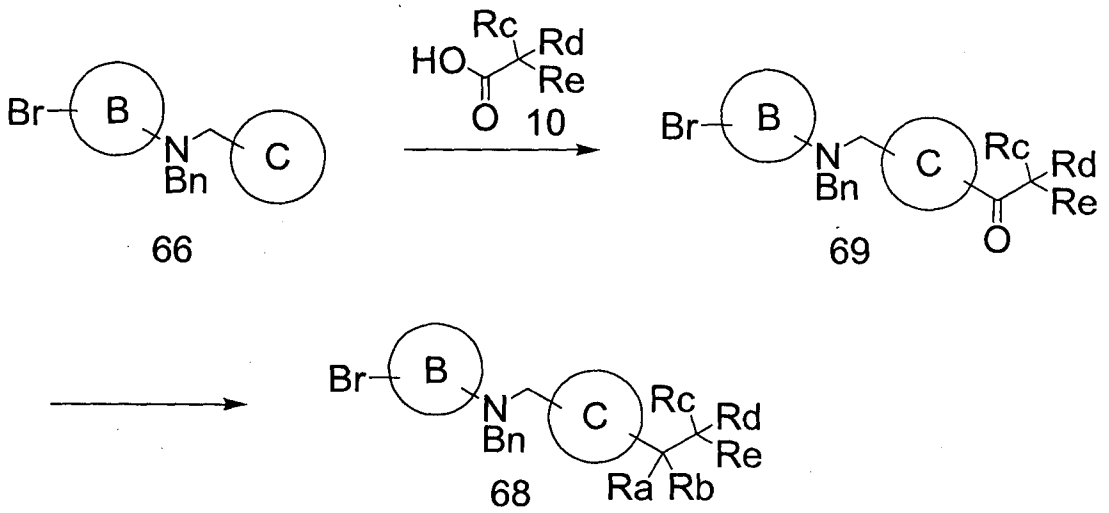
[Reaction Scheme 22]



As shown in the reaction scheme 22, compound 62 is subjected to the reduction

amination with compound 63 to prepare compound 64. Protecting group is introduced into the secondary amine of compound 64 to prepare compound 65. The protecting group of compound 65 is removed, following with the reaction with oxirane compound 8 to prepare compound 67. Finally, hydroxyl group of compound 67 is substituted with fluoride to prepare compound 68.

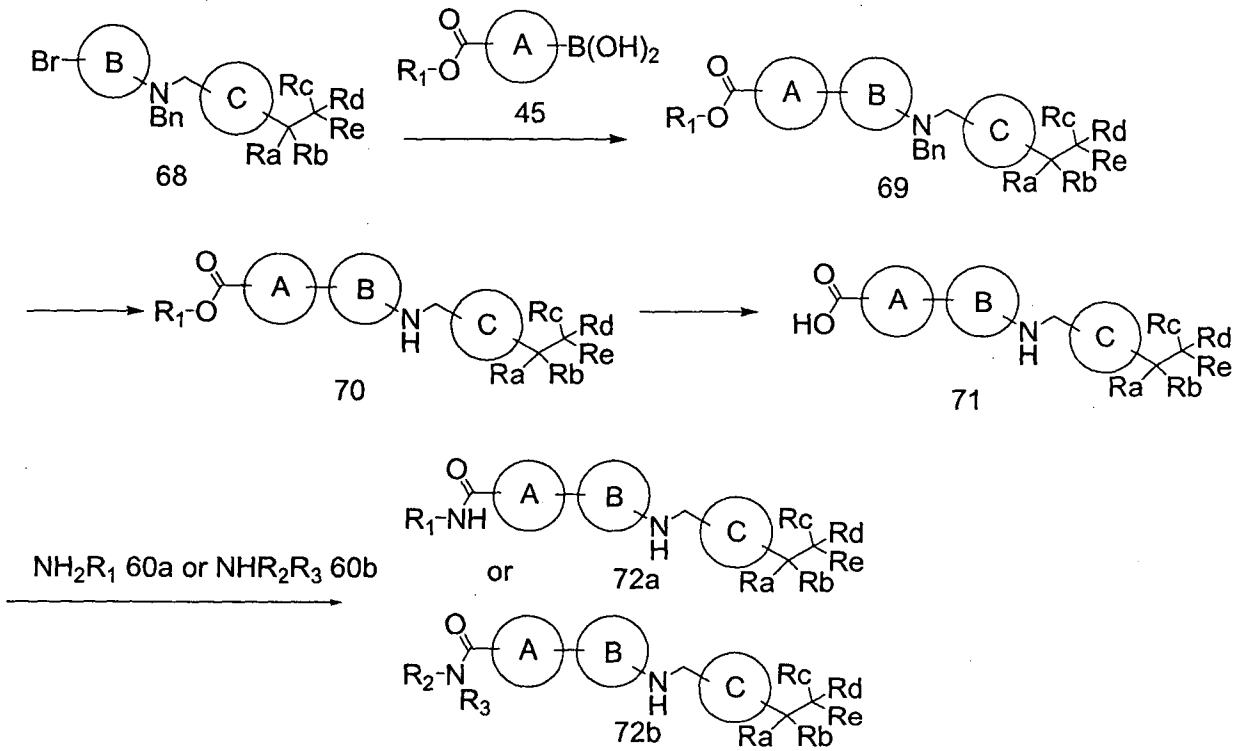
[Reaction Scheme 23]



As shown in the reaction scheme 23, compound 66 is subjected to the formation of amide bond with compound 10 to prepare compound 69, following with a reduction to obtain compound 68.

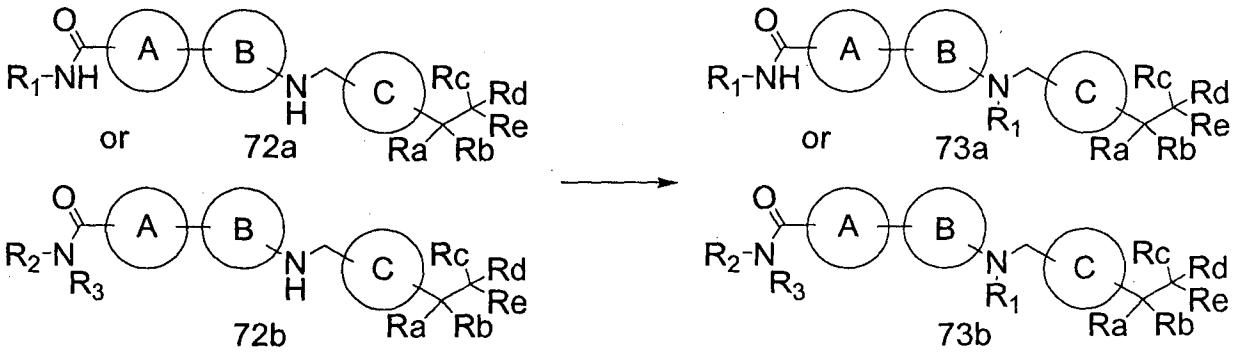
The compounds 72 and 73 that Q is $-C(O)NHR_1$ or $-C(O)NR_2R_3$ in formula 1 can be synthesized according to the following reaction schemes 24 and 25.

[Reaction Scheme 24]



As shown in the reaction scheme 24, compound 68 is subjected to Suzuki coupling reaction with boronic acid compound 45 to prepare compound 69. Secondary amine of compound 69 is removed to prepare compound 70. And then, compound 71 is prepared through the hydrolysis of compound 70, and subjected to the formation of amide bond with amine compound 60 to prepare compound 72.

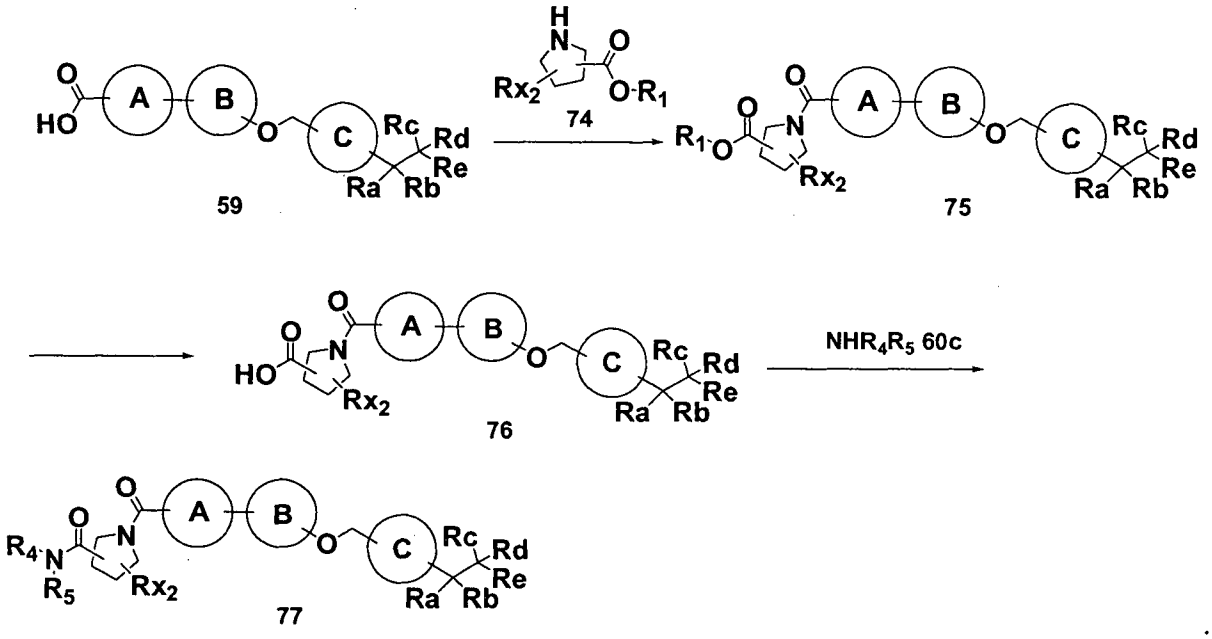
[Reaction Scheme 25]



As shown in the reaction scheme 25, compound 72 is subjected to the reduction amination with an aldehyde to prepare compound 73.

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]



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

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

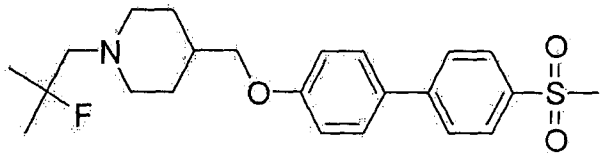
Best Mode for Carrying out the Invention

Preparation of Compounds and Preparing Method of Compounds

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

Example 1. Compound 431:

1-(2-fluoro-2-methylpropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine



5

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 10 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- 15 (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 20 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 25 (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 30 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%).

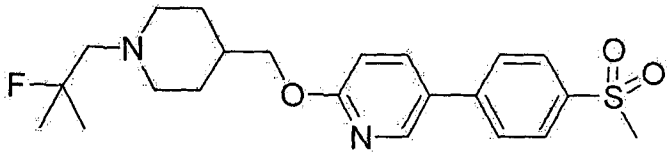
Step 6. 2-methyl-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-ol: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate (100 mg, 0.22 mmol) and K_2CO_3 (15 mg, 0.11 mmol) were suspended in EtOH 1 mL. Water 0.5 mL was added thereto, and then suspended 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. 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. Compound 596: 2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)phenyl)pyridine



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%).

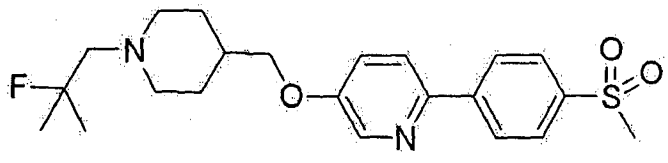
Step 3. 5-(4-(methylsulfonyl)phenyl)-2-(piperidin-4-ylmethoxy)pyridine hydrochloride: t-butyl 4-((5-(4-(methylsulfonyl)phenyl)pyridine-2-yloxy)methyl)piperidin-1-carboxylate (0.2 g, 0.45 mmol) was dissolved in MeOH. 1.25 M HCl in MeOH (2.24 mmol, 1.8 mL) was added thereto. The solvent was removed completely 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. 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. Compound 597: 5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-2-(4-(methylsulfonyl)phenyl)pyridine



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, 1.0 mmol) 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-(methylsulfonyl)phenyl)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)

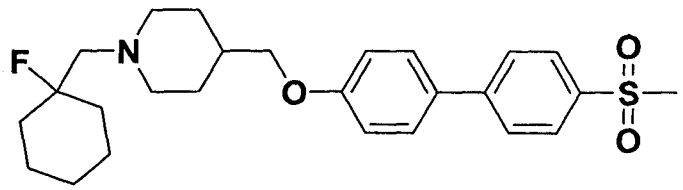
to yield the title compound as white solid (0.15 g, 92%).

Step 5. 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. Compound 789:

1-((1-fluorocyclohexyl)methyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

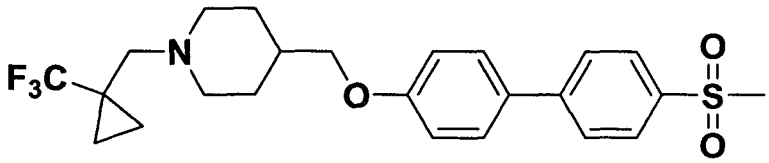


Step 1. 1-((4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)methyl)cyclohexanol: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (0.04 g, 0.11 mmol) and K_2CO_3 (0.01 g, 0.06mmol) were suspended in EtOH (1 mL). Water (0.5 mL) was added thereto, and the mixture was 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. 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. Compound 500: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine



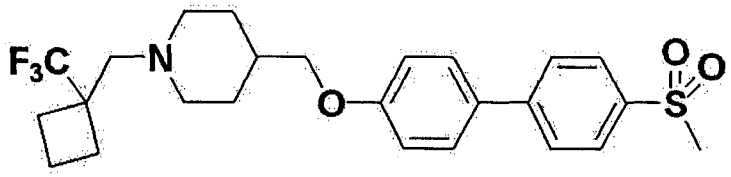
Step 1. (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclopropyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride [the product of synthesis step 5 of compound 431; 74 mg, 0.20 mmol], 1-(trifluoromethyl)cyclopropan-1-carboxylic acid (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. 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. Compound 542: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine

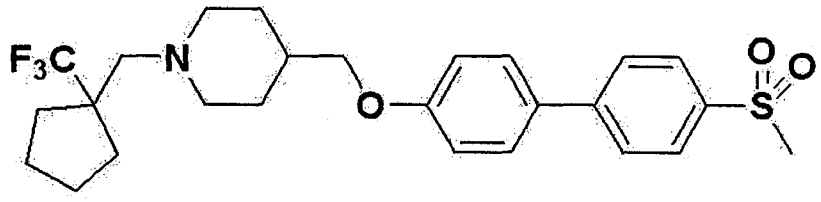


Step 1. (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl) cyclobutyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate [the product of synthesis step 5 of compound 431; 140 mg, 0.37 mmol], 1-(trifluoromethyl)cyclobutanecarboxylic 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. 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. Compound 546: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidine



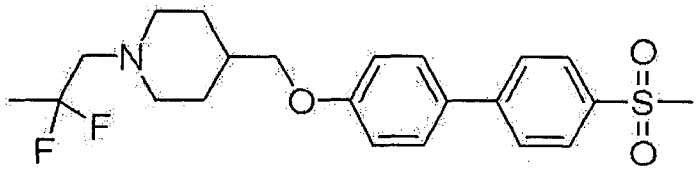
Step 1. (4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopentyl)methanone: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate [the product of synthesis step 5 of compound 431; 150 mg, 0.39 mmol], 1-(trifluoromethyl)cyclopentanecarboxylic 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%).

Step 2. 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. Compound 547:

1-(2,2-difluoropropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

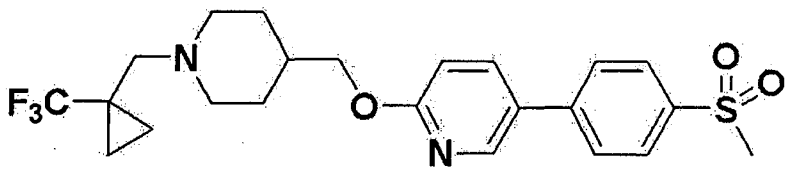


Step 1. 1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-2-one 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine 2,2,2-trifluoroacetate (the product of synthesis step 5 of compound 431; 50 mg, 0.11 mmol) and 1-chloropropan-2-one (13 μL, 0.16 mmol) were dissolved in MeCN 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. 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. Compound 589: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine



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%).

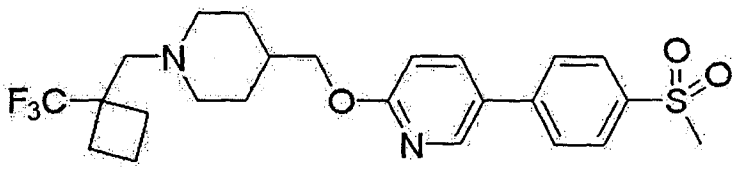
Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine: (1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methanol (577 mg, 2.43 mmol) was dissolved in THF 10 mL. At 0 °C, NaH (87 mg, 3.65 mmol) was added slowly thereto. The reaction was performed at room 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. 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. Compound 676: 5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine



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%).

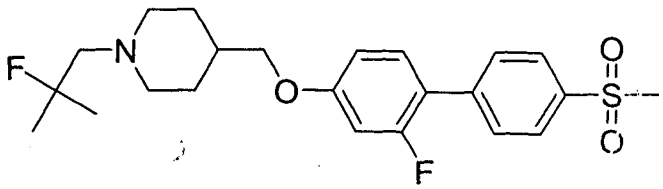
Step 3. 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy) pyridine: (1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methanol (581 mg, 2.31 mmol) were dissolved in THF 10 mL. At 0 °C, NaH (83 mg, 3.47 mmol) was added slowly thereto. The reaction was performed at room 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. 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. Compound 714: 1-(2-fluoro-2-methylpropyl)-4-((2-fluoro-4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine

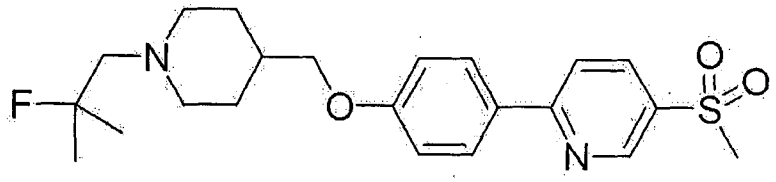


4-((4-bromo-3-fluorophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine (the product of synthesis step 4 of compound 704; 850 mg, 2.35 mmol), 4-(methylsulfonyl)phenylboronic acid (563 mg, 2.82 mmol), $Pd(dbpf)Cl_2$ (77 mg, 0.12 mmol) and Cs_2CO_3 (1.53 g, 4.69 mmol) were added to water (2 mL)/1,4-dioxane (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. Compound 617: 2-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-

yl)methoxy)phenyl)-5-(methylsulfonyl)pyridine



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 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. 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).

According to the above-described synthesis process of 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.

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.

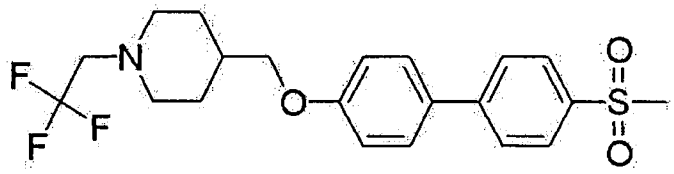
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
618	5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2-(methylsulfonyl)pyridine 1H NMR (400 MHz, $CDCl_3$) δ 8.90 (m, 1 H), 8.13 (dd, 1 H, J = 8.2, 0.8 Hz), 8.08 (dd, 1 H, J = 8.2, 2.2 Hz), 7.56 (dt, 2 H, J = 9.0, 2.5 Hz), 7.05 (dt, 2 H, 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 = 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).
669	(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, 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. Compound 499:

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(2,2,2-trifluoroethyl)piperidine

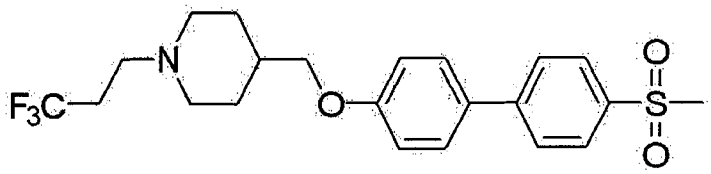


4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (the product of synthesis step 5 of compound 431; 50 mg, 0.13 mmol) was dissolved in DMSO 2 mL. 2,2,2-trifluoroethyl trifluoromethanesulfonate (30 mg, 0.13 mmol) and K_2CO_3 (91 mg, 0.66 mmol) were added thereto, following with stirring 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. Compound 524:

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(3,3,3-trifluoropropyl)piperidine



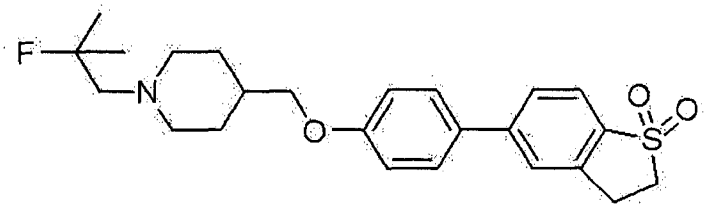
<u>Step 1.</u> 3,3,3-trifluoro-1-(4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidin-1-yl)propan-1-one: 4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine hydrochloride (the product of synthesis step 5 of compound 431; 40 mg, 0.11 mol) and CF_3CH_2COCl (16 μL, 0.16 mmol) were dissolved in 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. 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. Compound 470: 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide



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%).

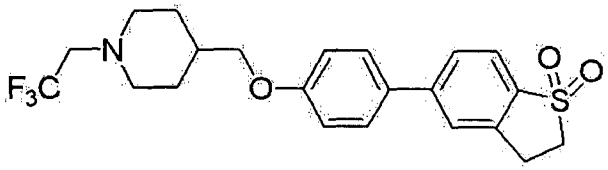
Step 5. 5-(4-(piperidin-4-ylmethoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide 2,2,2-trifluoroacetate: t-butyl 4-((4-(1,1-dioxido-2,3-dihydrobenzo[b]thiophen-5-yl)phenoxy) methyl)piperidin-1-carboxylate (800 mg, 1.75 mmol) was dissolved in CH_2Cl_2 6 mL. TFA 161 μL was added thereto, following 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. 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).

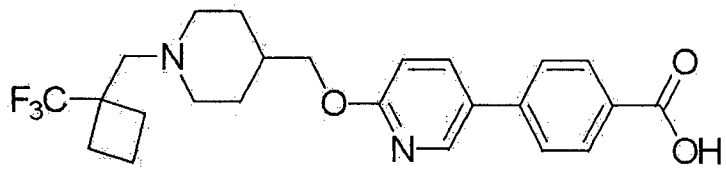
Example 16. Compound 540: 5-(4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy) phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide



5-(4-(piperidin-4-ylmethoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide 2,2,2-trifluoroacetate (the product of synthesis step 5 of 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. Compound 574: 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid

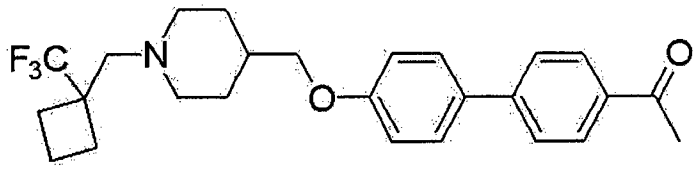


Step 1. methyl 4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoate: 5-bromo-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)pyridine (the product of synthesis step 3 of compound 676; 0.34 g, 0.85 mmol), 4-(methoxycarbonyl)phenylboronic acid (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. 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. $LiOH \cdot H_2O$ (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. Compound 575: 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanone



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 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%).

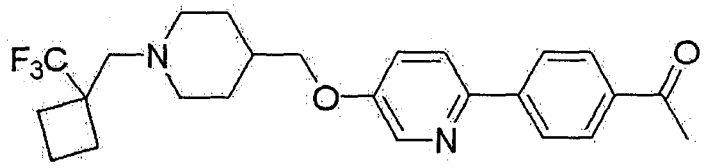
Step 4. 1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanol: 1-(4'-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy) biphenyl-4-yl)ethanone (193 mg, 0.42 mmol) was dissolved in dry THF 10 mL, and then cooled with ice bath. LAH (1 M in THF, 0.13 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. 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 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. Compound 593: 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanone



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 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%).

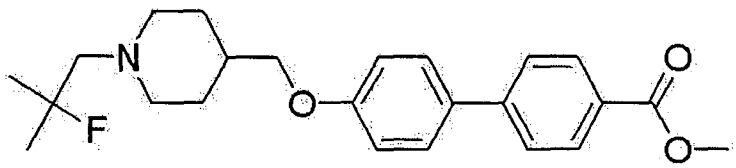
Step 4. 1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanol: 1-(4-(5-((1-(1-(trifluoromethyl)cyclobutanecarbonyl)piperidin-4-yl)methoxy)pyridine-2-yl)phenyl)ethanone (148 mg, 0.32 mmol) was dissolved in dry THF 7 mL, and then cooled with ice bath. LAH (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. 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. Compound 498:

methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate



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%).

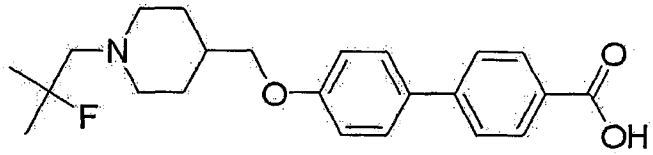
Step 3. 4-((4-bromophenoxy)methyl)-1-(2-fluoro-2-methylpropyl)piperidine: 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)-2-methylpropan-2-ol(1.10 g, 3.21 mmol) was dissolved in CH_2Cl_2 10 mL. DAST (0.43 mL, 3.21 mmol) was added thereto, following with stirring with at room temperature for 1 hour. A saturated $NaHCO_3$ 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. 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. Compound 548:

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid

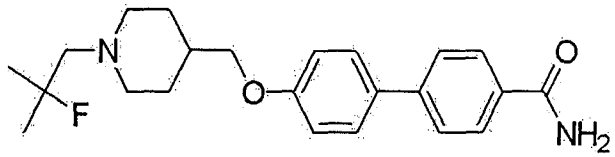


Methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (682 mg, 1.71 mmol) was dissolved in THF 6 mL. MeOH 2 mL and H_2O 2 mL were added thereto. LiOH (358 mg, 8.53 mmol) was added thereto, following with stirring at room temperature and refluxing with heating and stirring 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. Compound 515:

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide

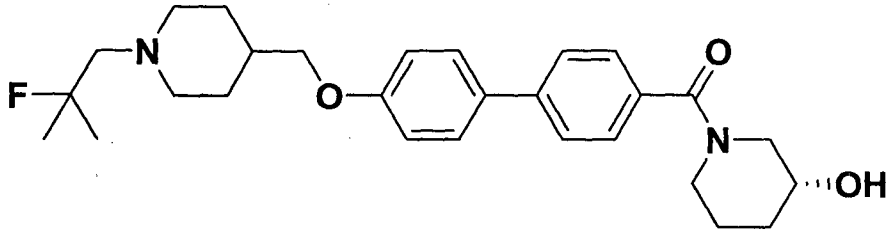


4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (compound 548, 15 mg, 0.04 mmol) and NH_4Cl (4 mg, 0.08 mmol) were dissolved in DMF 1 mL. EDC (15 mg, 0.08 mmol) and HOBt (11 mg, 0.08 mmol) were added thereto. Lastly, DIPEA (34 μL, 0.20 mmol) was added thereto, following 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. Compound 612: (R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (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).

According to the above-described synthesis process of 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.

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
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
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.

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).
528	N-cyclopentyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-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)piperidin-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).
549	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide 1H 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).
556	(S)-(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 7.61 - 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).
562	4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide 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).
568	(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-hydroxypiperidin-1-yl)methanone 1H NMR (400 MHz, $CDCl_3$) δ 7.61 - 7.56 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.45 (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).
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).
605	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 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).
611	N-(2,3-dihydroxypropyl)-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 = 8.3 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).
625	(S)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate 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

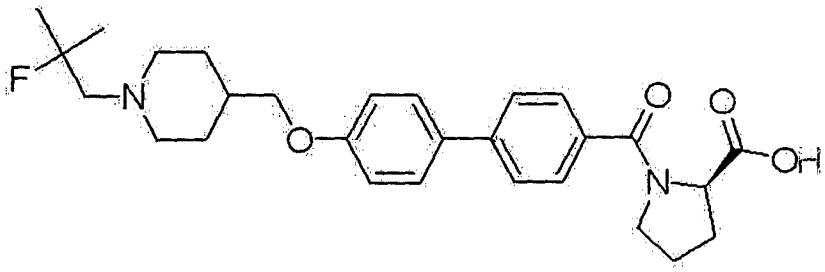
	1H NMR (400 MHz, $CDCl_3$) δ 7.62 - 7.52 (m, 6 H), 6.99 (d, 2 H, *J* = 6.5 Hz), 4.03 - 3.80 (m, 6 H), 3.10 - 3.01 (m, 2 H), 2.65 - 2.43 (m, 4 H), 2.19 - 2.05 (m, 2 H), 1.97 - 1.82 (m, 2 H), 1.59 - 1.41 (m, 2 H), 1.36 (s, 3 H), 1.27 (s, 3 H); MS (ESI) m/z 475 (M+ + H).
645	methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)acetate 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 (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-hydroxypropanoate 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).
677	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 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).
686	(3,5-dimethylpiperazin-1-yl)(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 = 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).
832	(S)-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 = 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).

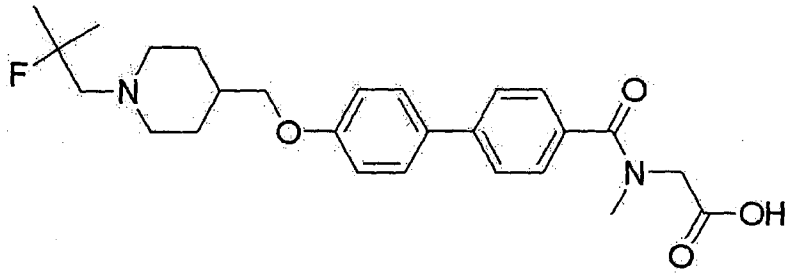
Example 24. Compound 620: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid



(R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl) pyrrolidine-2-carboxylate (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·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).

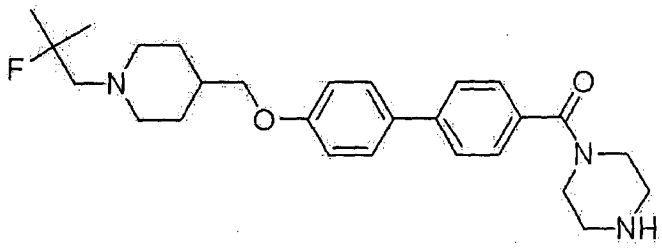
Example 25. Compound 621: 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-ylcarboxamido)acetic acid



4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (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. Compound 630: (4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperazin-1-yl)methanone

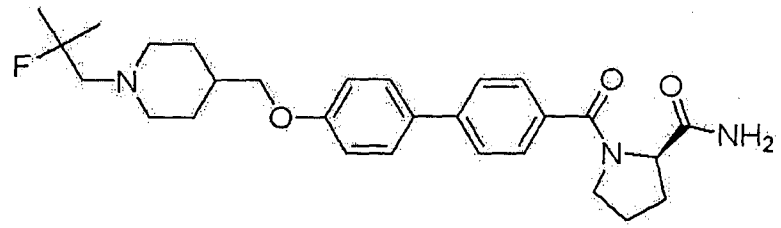


t-butyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-carboxylate (compound 626, 20 mg, 0.04 mmol) was dissolved in MeOH. trifluoroacetic

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



(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid (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 μL, 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).

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.

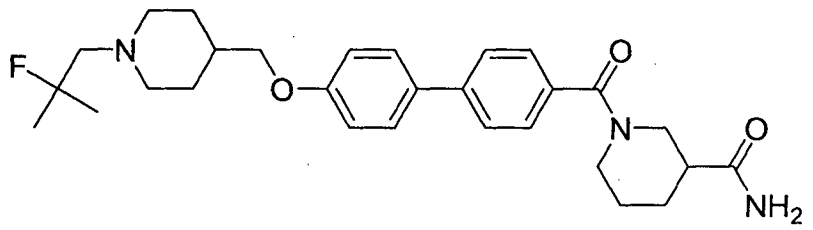
Table 5.

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

Table 6.

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



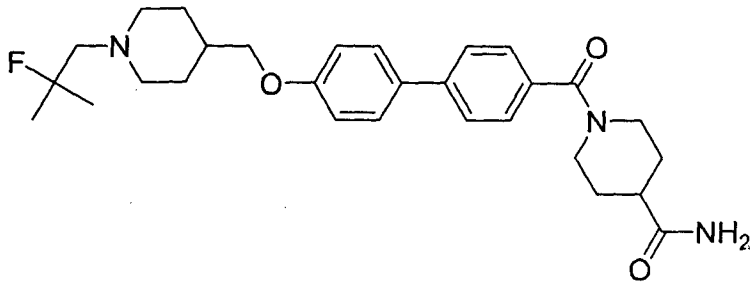
Step 1. 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-3-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-3-carboxylate (compound 677, 0.07 g, 0.14 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and 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



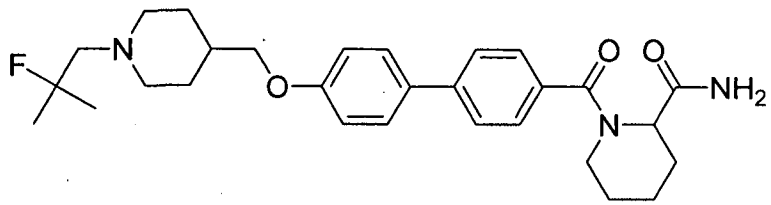
Step 1. 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-4-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-4-carboxylate (compound 678, 0.09 g, 0.17 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and 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



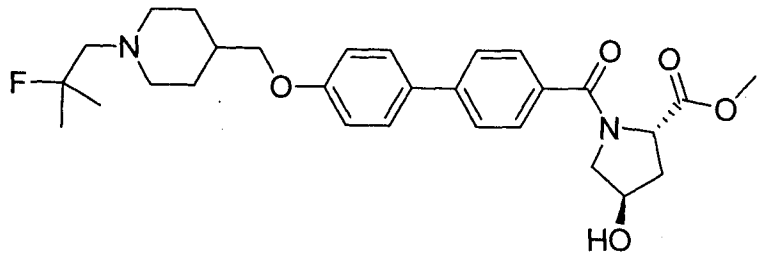
Step 1. 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidin-2-carboxylic acid: ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) biphenylcarbonyl)piperidine-2-carboxylate (compound 679, 0.09 g, 0.16 mmol) was dissolved in THF (1.5 mL). MeOH (0.5 mL) and 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).

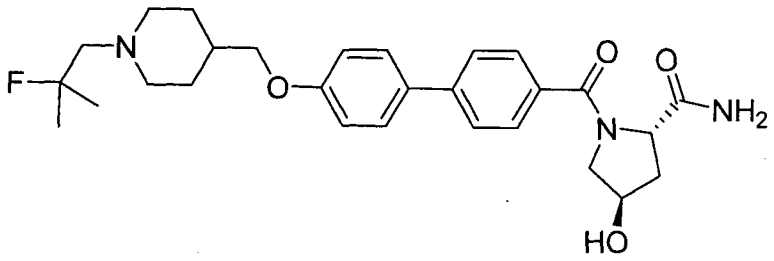
Example 31. Compound 932: (2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate



4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid (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'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxamide

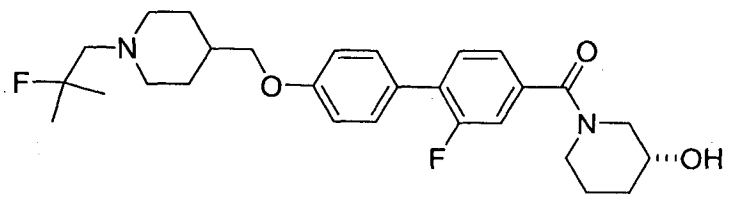


Step 1. (2S,4R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid: (2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate (400 mg, 0.78 mmol) and $LiOH \cdot H_2O$ (65 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. Compound 749: (R)-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



Step 1. 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%).

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 (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 1N HCl. The resulting precipitate was filtered, and dried to yield the title compound as white solid (90 mg, 81%).

Step 3. 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).

According to the above-described synthesis process of 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.

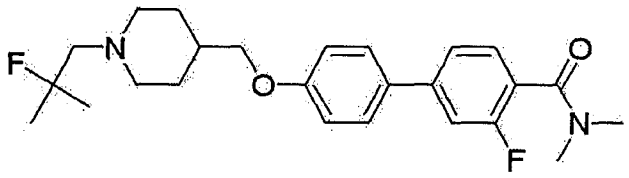
Table 7.

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



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%).

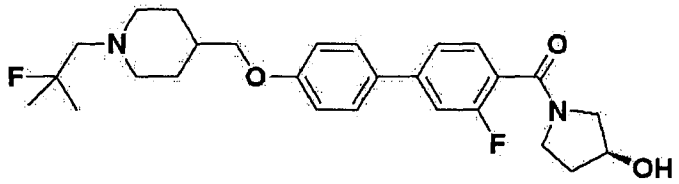
Step 2. 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: ethyl 3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (350 mg, 0.84 mmol) was dissolved in THF 2 mL. MeOH 1 mL and H_2O 0.5 mL were added thereto. LiOH (70 mg, 1.68 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. 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. Compound 640: (S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone



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).

According to the above-described synthesis process of 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.

Compound No.	Reactant	Yield (%)
639	dimethylamine hydrochloride	44
641	(R)-prolinol	55

642	3-hydroxypiperidine	38
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

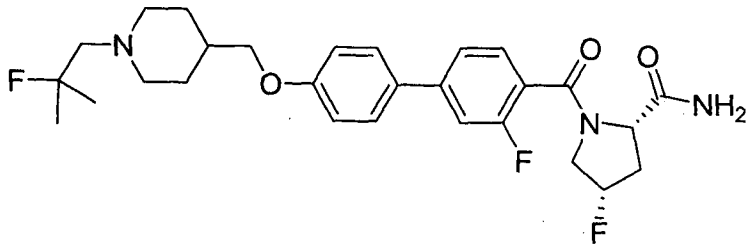
Table 10.

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-1-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 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(8H)-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).
872	(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), 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



Step 1. (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_2, 4 g cartridge; ethyl acetate / hexane = 10 % to 50 %), and concentrated

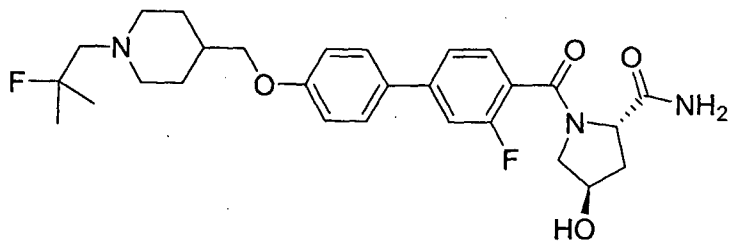
to yield the title compound as colorless oil (0.12 g, 61%).

Step 2. (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.

Step 3. 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



Step 1. (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

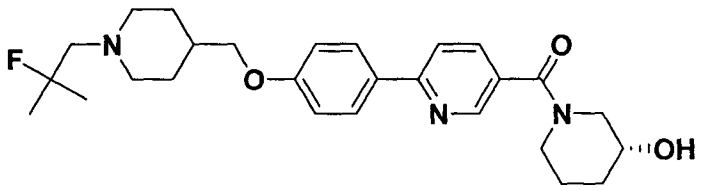
column chromatography (SiO_2, 4 g cartridge; ethyl acetate / hexane = 10 % to 80 %), and concentrated to yield the title compound as colorless oil (70 mg, 53%).

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



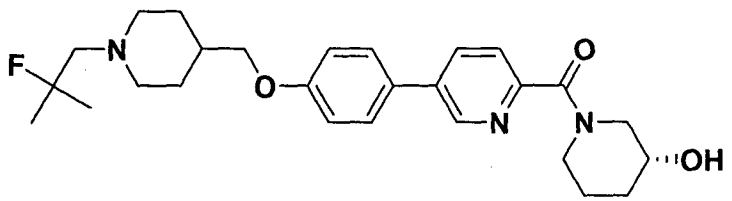
Step 1. methyl 6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)nicotinate: Methyl 6-bromonicotinate (0.07 g, 46%) was dissolved in 1,4-dioxane 2 mL and H_2O 1 mL. 4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenylboronic acid (the product of synthesis step 1 of compound 617; 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. 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. Compound 759: (R)-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridine-2-yl)(3-hydroxypiperidin-1-yl)methanone



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 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

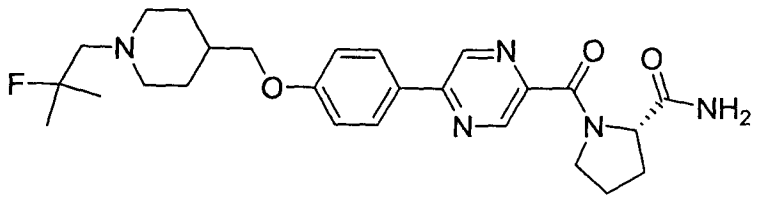
30 minutes. After the completion of the reaction, the reaction mixture was filtered through Celite. The filtrate was added with water, and extracted with CH_2Cl_2. The obtained organic layer was washed with saturated aqueous brine solution, dried over $MgSO_4$, and concentrated under reduced pressure. 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. 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. Compound 1038: (S)-1-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carbonyl)pyrrolidine-2-carboxamide



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%).

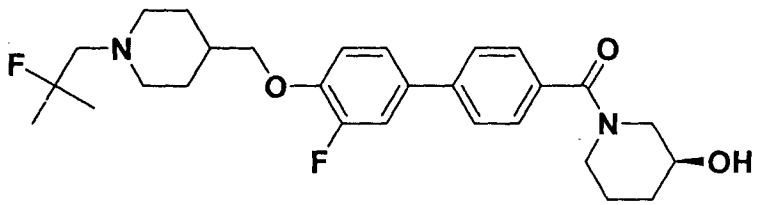
Step 5. methyl 5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate: methyl 5-(4-((1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) pyrazine-2-carboxylate (117 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (15 mL). At room

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



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)biphenyl-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. $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

Compound No.	Reactant	Yield (%)
726	(R)-piperidin-3-ol	85

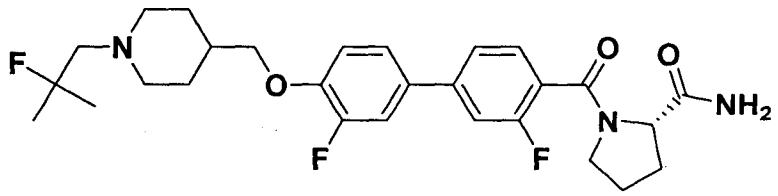
727	(R)- pyrrolidine-2-ylmethanol	3
728	(S)-pyrrolidine-2-ylmethanol	27
729	(R)-pyrrolidine-3-ol	28
799	piperidin-4-carboxamide	47
806	(R)-piperidin-2-carboxamide	47
807	(S)-piperidin-2-carboxamide	16

Table 12.

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, CDCl3) 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).
806	(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 (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



Step 1. 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 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 brown solid (0.5 g, 69%).

Step 2. 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).

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.

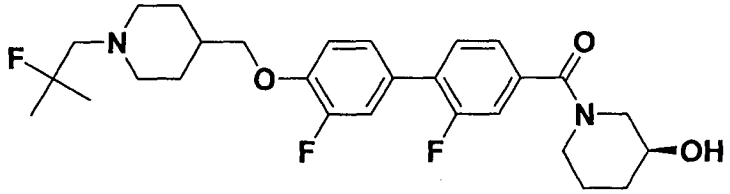
Compound No.	Reactant	Yield (%)
731	(S)-piperidin-3-ol	48
732	(S)-pyrrolidine-3-ol	22
733	(R)-pyrrolidine-3-ol	28
734	(R)-piperidin-3-ol	65
800	piperidin-4-carboxamide	53
816	(R)-piperidin-2-carboxamide	51
817	(S)-piperidin-2-carboxamide	42

Table 14.

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).
733	(R)-(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 7.59 – 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. Compound 735: (S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl) piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



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·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).

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.

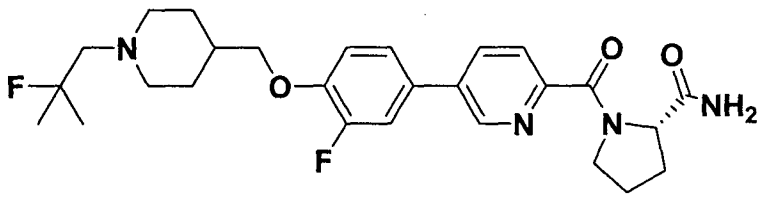
Compound No.	Reactant	Yield (%)
736	(R)-pyrrolidine-3-ol	43
737	(S)-pyrrolidine-3-ol	21
751	(R)-pyrrolidine-2-ylmethanol	10
752	(S)-pyrrolidine-2-ylmethanol	6
753	(S)-pyrrolidine-2-carboxamide	71
754	(R)-piperidin-3-ol	31
818	piperidin-4-carboxamide	41
819	(R)-piperidin-2-carboxamide	43
820	(S)-piperidin-2-carboxamide	40

Table 16.

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 (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, $CDCl_3$) δ7.47 (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



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. $LiOH \cdot H_2O$ (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).

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.

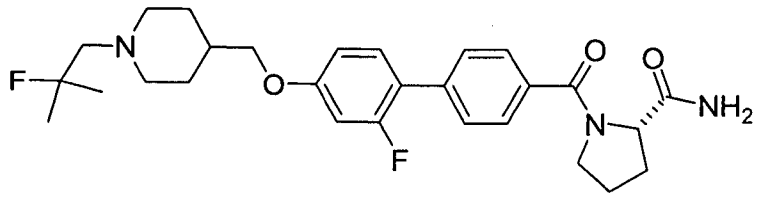
Table 17.

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

Table 18.

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), 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



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 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 1N 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_2Cl_2 /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).

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.

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

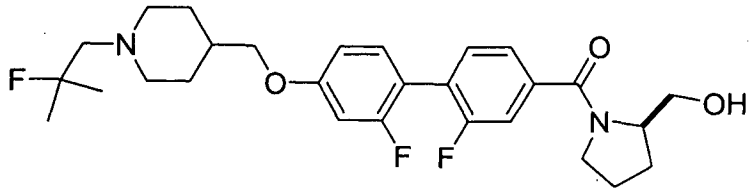
Table 20.

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 (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 = 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. 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



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. 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).

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.

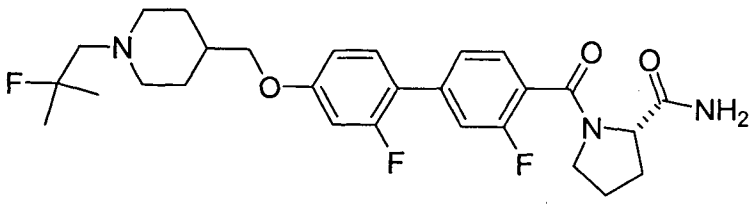
Compound No.	Reactant	Yield (%)
705	(S)-pyrrolidine-2-carboxamide	35
741	(S)-piperidin-3-ol hydrochloride	25
742	(R)-pyrrolidine-3-ol	30
743	(S)-pyrrolidine-3-ol	36
744	(S)-pyrrolidine-2-ylmethanol	33
745	(R)-piperidin-3-ol hydrochloride	31
803	piperidin-4-carboxamide	61
825	(R)-piperidin-2-carboxamide	48
860	(S)-piperidin-2-carboxamide	41

Table 22.

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 (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



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).

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.

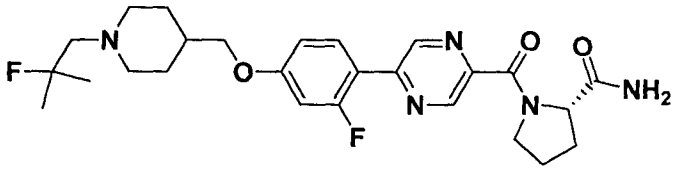
Compound No.	Reactant	Yield (%)
711	(R)-pyrrolidine-2-ylmethanol	31
712	(R)-pyrrolidine-3-ol	46
713	(R)-piperidin-3-ol hydrochloride	30
746	(S)-piperidin-3-ol hydrochloride	38
747	(S)-pyrrolidine-3-ol	30
748	(S)-pyrrolidine-2-ylmethanol	35
802	piperidin-4-carboxamide	59
823	(R)-piperidin-2-carboxamide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

Table 24.

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).
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



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).

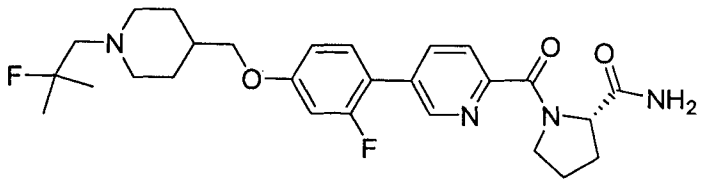
Step 7. 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylic acid: methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyrazine-2-carboxylate (0.09 g, 0.21 mmol) and $LiOH \cdot H_2O$ (0.04 g, 1.04 mmol) were dissolved in THF / MeOH (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



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 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%).

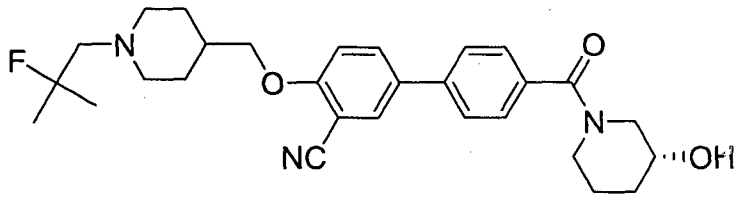
Step 2. 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinic acid: methyl 5-(2-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinate (200 mg, 0.48 mmol) was dissolved in THF (10 mL) and water (5 mL). $LiOH·H_2O$ (100 g, 2.39 mmol) was added thereto 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. Compound 963: (R)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidin-1-carbonyl)biphenyl-3-carbonitrile



Step 1. methyl 3'-cyano-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), 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 $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

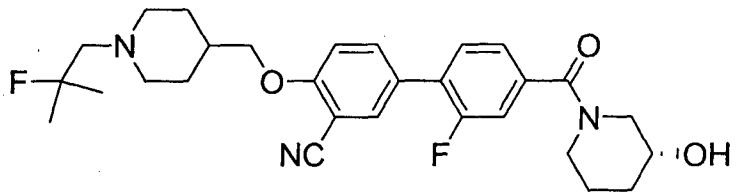
Compound No.	Reactant	Yield (%)
964	(S)-piperidin-3-ol hydrochloride	83
965	L-prolinamide	26
966	(R)-pyrrolidine-3-ol	49

Table 26.

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



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. 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).

According to the above-described synthesis process of 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.

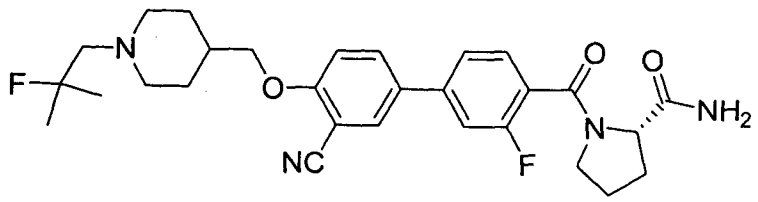
Compound No.	Reactant	Yield (%)
968	(S)-piperidin-3-ol hydrochloride	52
969	L-prolinamide	42

Table 28.

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



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 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), $Pd(dppf)Cl_2$ (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)piperidin-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). $LiOH \cdot H_2O$ (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).

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.

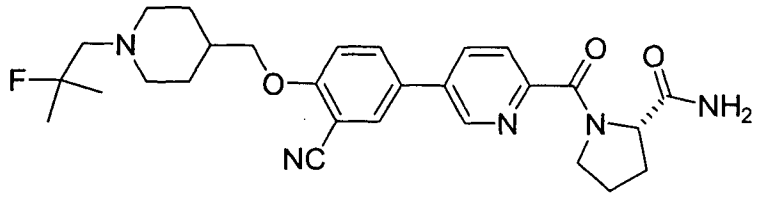
Compound No.	Reactant	Yield (%)
939	(R)-piperidin-3-ol hydrochloride	53
1015	(S)-piperidin-2-carboxamide hydrochloride	33
1016	(S)-piperidin-2-ol hydrochloride	50
1017	(S)-pyrrolidine-3-ol	46

Table 30.

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 – 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)-1-(5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide



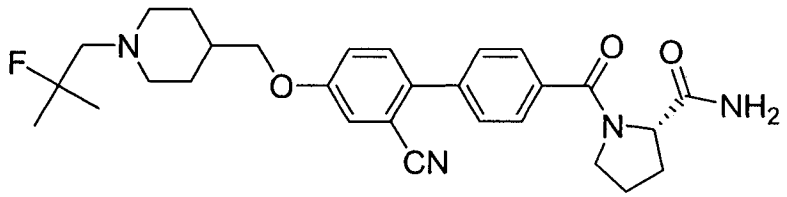
Step 1. methyl 5-(3-cyano-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl) picolinate: 5-bromo-2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)benzonitrile (the product of synthesis step 4 of compound 938; 673 mg, 1.82 mmol), 6-(methoxycarbonyl) pyridine-3-ylboronic acid (330 mg, 1.82 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



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%).

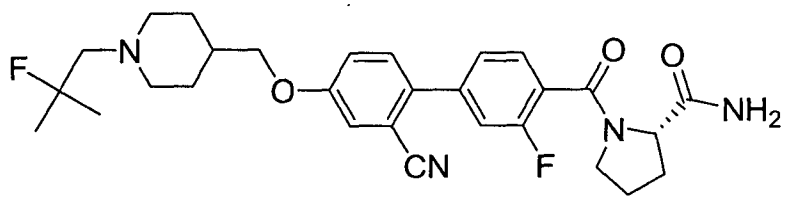
Step 2. 2'-cyano-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-

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



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 4 M HCl 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 $LiOH \cdot H_2O$ (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).

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.

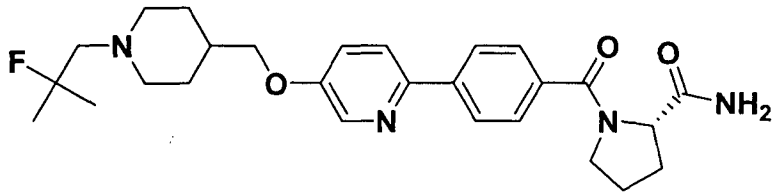
Compound No.	Reactant	Yield (%)
1029	(R)-piperidin-3-ol	89
1030	(R)-piperidin-2-carboxamide hydrochloride	60
1115	piperidin-4-ol	16

Table 32.

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



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 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. $LiOH \cdot H_2O$ (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).

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.

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

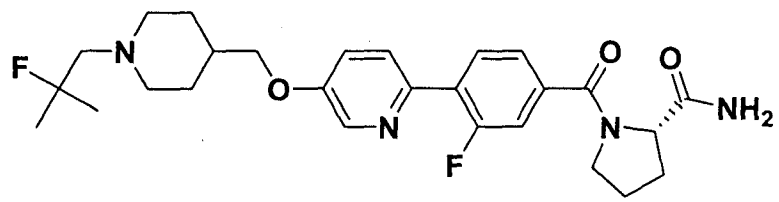
5

Table 34.

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, 1 H, 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).
763	(R)-(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).
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 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



Step 1. methyl 3-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; 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_2CO_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. $LiOH \cdot H_2O$ (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 1N 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, $MeOH/CH_2Cl_2$) 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).

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.

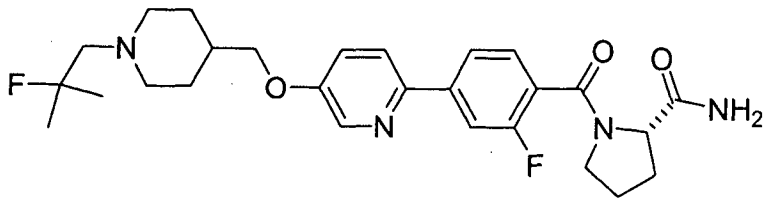
Table 35.

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.

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)
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



Step 1. 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%).

Step 2. 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%).

Step 3. 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%).

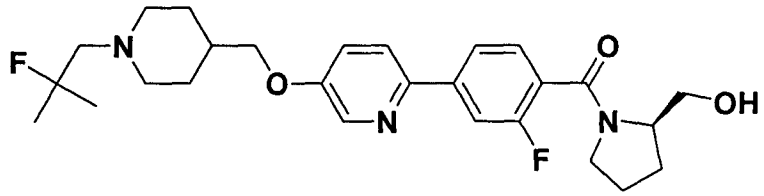
Step 7. ethyl 2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoate: 2-chloro-5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine (0.60 g, 1.99 mmol), 4-(ethoxycarbonyl)-3-fluorophenylboronic acid (0.51 g, 2.39 mmol), $Pd(dppf)Cl_2$ (0.08 g, 0.10 mmol) and 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). $LiOH \cdot H_2O$ (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 1N 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. 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



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_2CO_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. 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)

According to the above-described synthesis process of 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.

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

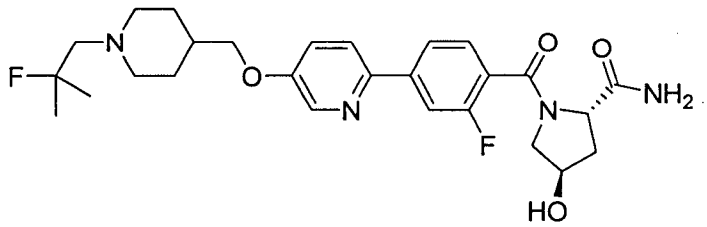
Table 38.

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+ + 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-yl)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-((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), 7.79 – 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).
824	(S)-1-(2-fluoro-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 – 8.35 (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



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 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%).

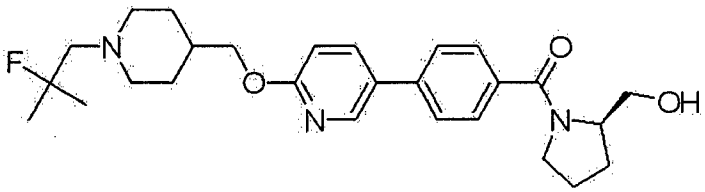
Step 2. (2S,4R)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy) pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylic acid: (2S,4R)-methyl 1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-2-yl)benzoyl)-4-hydroxypyrrolidine-2-carboxylate(230 mg, 0.43 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-((1-(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 compound 652: (R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone



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 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. 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).

According to the above-described synthesis process of 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.

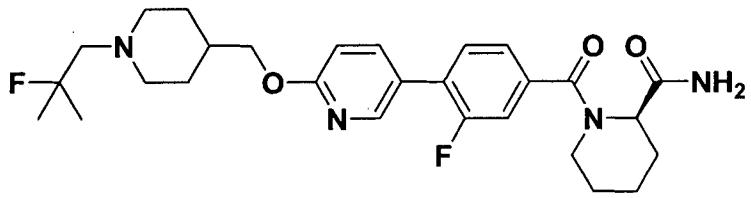
Compound No.	Reactant	Yield (%)
653	L-prolinamide	57
654	(S)-3-hydroxypiperidine	35
1076	(R)-piperidin-2-carboxamide hydrochloride	54
1077	(R)-pyrrolidine-3-ol	65
1078	(S)-pyrrolidine-3-ol	61
1079	(S)-piperidin-2-carboxamide hydrochloride	33

Table 40.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
653	(S)-1-(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 8.39 (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 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



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 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)

According to the above-described synthesis process of compound 862, the compounds of Table 42 were synthesized using 3-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid and the reactant of Table 41.

Table 41.

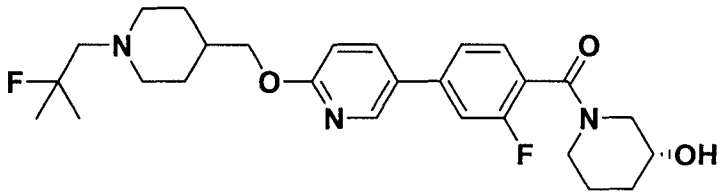
Compound No.	Reactant	Yield (%)
863	(S)-piperidin-2-carboxamide	53
864	piperidin-4-carboxamide	37

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. 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



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 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). $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

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.

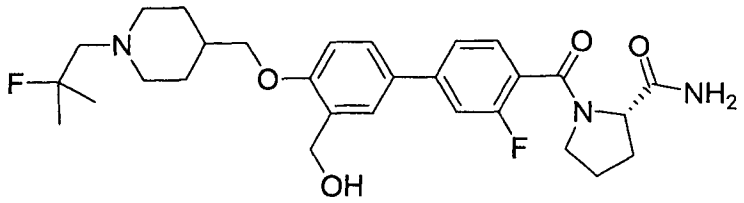
Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
785	(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypyrrolidine-1-yl)methanone 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (t, 1 H, J = 2.6 Hz), 7.76 – 7.73 (m, 1 H), 7.50 – 7.45 (m, 1 H), 7.35 – 7.21 (m, 2 H), 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).
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-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), 7.79 – 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 – 3.21 (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).
657	(R)-(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 (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. Compound 946 :

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



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 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-((1-(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. 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).

According to the above-described synthesis process of 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.

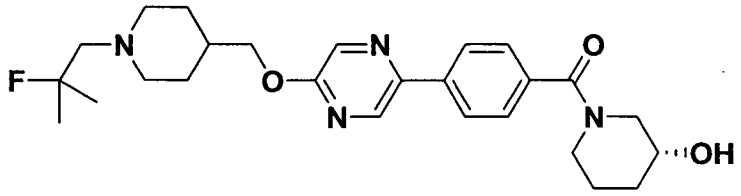
Table 45.

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

Table 46.

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



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 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. 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 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.

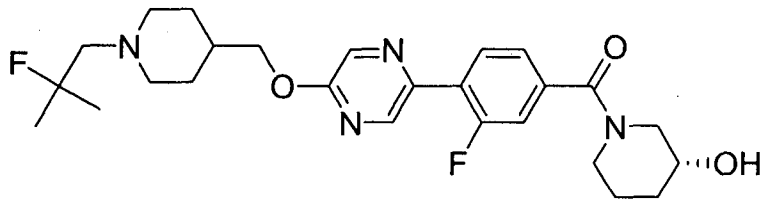
Compound No.	Reactant	Yield (%)
949	(S)-pyrrolidine-3-ol	45
950	(S)-pyrrolidine-2-carboxamide	40
951	(S)-piperidin-3-ol	52
1080	(R)-piperidin-2-carboxamide hydrochloride	62
1081	(S)-piperidin-2-carboxamide hydrochloride	70

Table 48.

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, 1 H), 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. 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



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 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. 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).

According to the above-described synthesis process of 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.

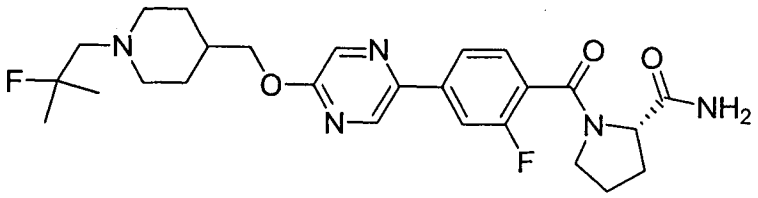
Compound No.	Reactant	Yield (%)
983	(S)-piperidin-3-ol hydrochloride	37
984	(S)-pyrrolidine-3-ol	47
985	(R)-pyrrolidine-2-ylmethanol	35
1072	(S)-pyrrolidine-2-carboxamide	57
1073	(R)-piperidin-2-carboxamide hydrochloride	27

Table 50.

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



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 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. 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).

According to the above-described synthesis process of 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.

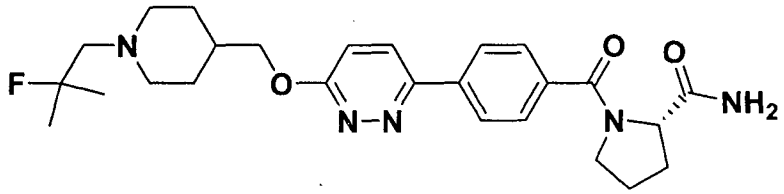
Compound No.	Reactant	Yield (%)
945	(R)-piperidin-3-ol hydrochloride	49
986	(S)-piperidin-2-ol hydrochloride	54
987	(S)-pyrrolidine-3-ol	53
988	(R)-pyrrolidine-2-ylmethanol	54

Table 52.

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



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 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. 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).

According to the above-described synthesis process of 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.

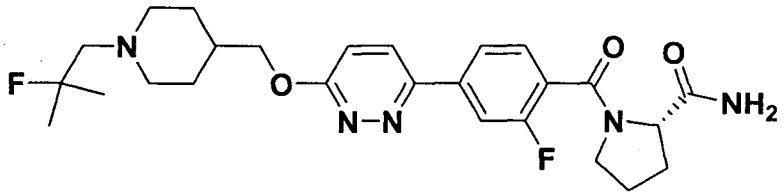
Table 53.

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

Table 54.

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. Compound 991: (S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoyl)pyrrolidine-2-carboxamide



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 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. 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 %).

According to the above-described synthesis process of 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.

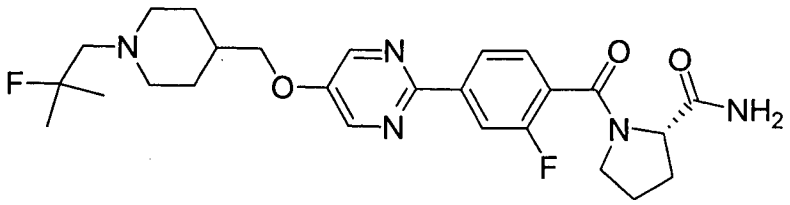
Table 55.

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

Table 56.

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



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 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).

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.

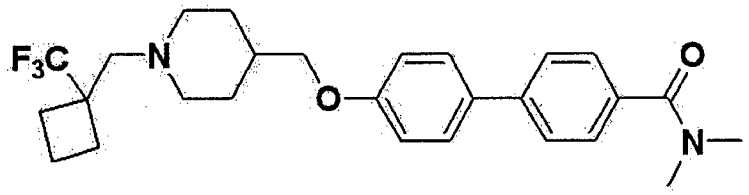
Compound No.	Reactant	Yield (%)
1033	(R)-piperidin-3-ol hydrochloride	37
1034	(S)-piperidin-3-ol hydrochloride	39
1035	(R)-pyrrolidine-3-ol	36
1037	(R)-piperidin-2-carboxamide hydrochloride	28

Table 58.

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. Compound 631: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclobutyl) methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide



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 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%).

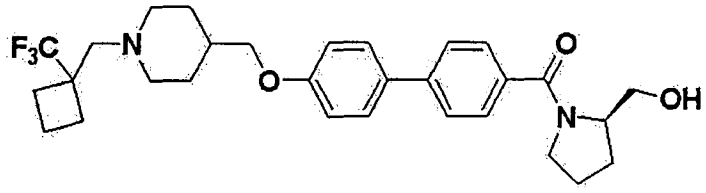
Step 6. methyl 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate: 4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl trifluoromethanesulfonate (200 mg, 0.36 mmol), $Pd(OAc)_2$ (4 mg, 0.02 mmol) and dppp (9 mg, 0.02) were dissolved 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. 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. Compound 633: (R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone



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).

According to the above-described synthesis process of 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.

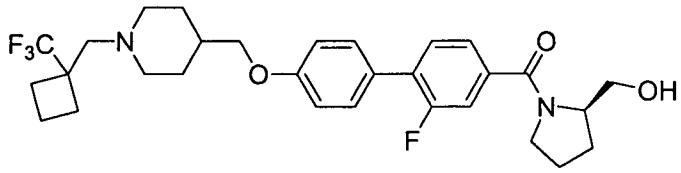
Compound No.	Reactant	Yield (%)
632	(S)-3-pyrrolidinol	46
634	3-hydroxypiperidine	45
635	L-prolinamide	43
636	2-aminoethanol	57
637	2-(methylamino)ethanol	58
794	(R)-piperidin-3-ol hydrochloride	40
795	(S)-piperidin-3-ol	40
796	(R)-pyrrolidine-3-ol	44
797	(S)-pyrrolidine-2-ylmethanol	43
798	piperidin-4-carboxamide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

Table 60.

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).
634	(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 = 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 (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. Compound 917: (R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone



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 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).

According to the above-described synthesis process of 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.

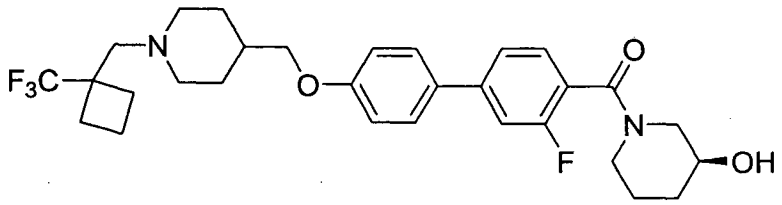
Compound No.	Reactant	Yield (%)
918	L-prolinamide	58
919	(R)-piperidin-3-ol hydrochloride	67
920	(S)-piperidin-3-ol hydrochloride	76
921	(S)-pyrrolidine-3-ol	54

Table 62.

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).
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 – 7.01 (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. Compound 842: (S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl) piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



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 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. 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).

According to the above-described synthesis process of 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.

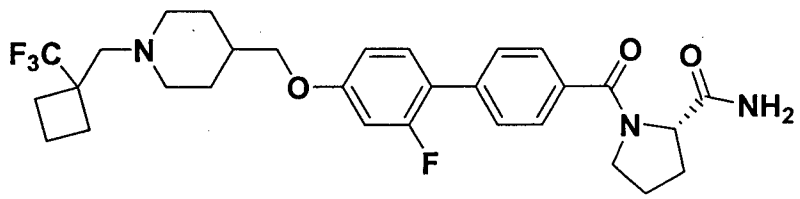
Table 63.

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.

Compound No.	Compound Name, ^{1}H-NMR, MS (ESI)
843	(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 7.53 – 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



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 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 a t 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)

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.

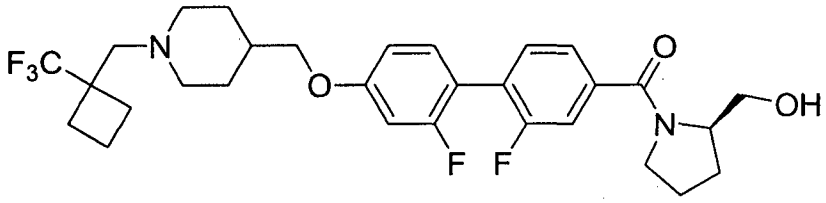
Compound No.	Reactant	Yield (%)
834	(R)-piperidin-3-ol	50
835	(S)-pyrrolidine-3-ol	41
836	(S)-piperidin-3-ol	46
877	(R)-piperidin-2-carboxamide hydrochloride	61
878	(S)-piperidin-2-carboxamide hydrochloride	55
882	(R)-piperidin-3-carboxamide hydrochloride	69

Table 66.

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. 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



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 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. 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).

According to the above-described synthesis process of 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.

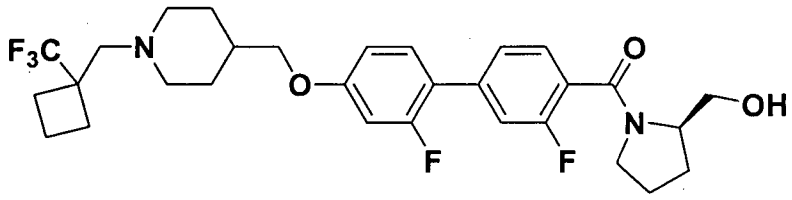
Table 67.

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

Table 68.

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 1H 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 – 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. 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



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 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 $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

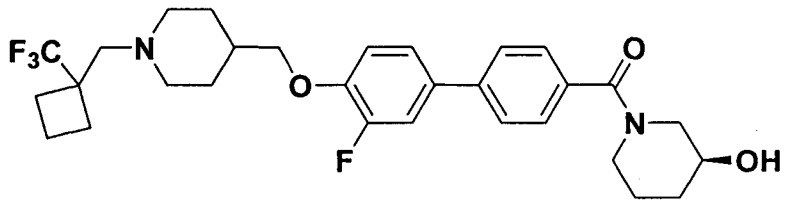
Compound No.	Reactant	Yield (%)
913	L-prolinamide	81
914	(R)-piperidin-3-ol hydrochloride	97
915	(S)-piperidin-3-ol hydrochloride	14
916	(S)-pyrrolidine-3-ol	98

Table 70.

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



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 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 1N HCl. The resulting precipitate was filtered to yield the title compound as white solid (380 mg, 93%).

Step 8. 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).

According to the above-described synthesis process of 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.

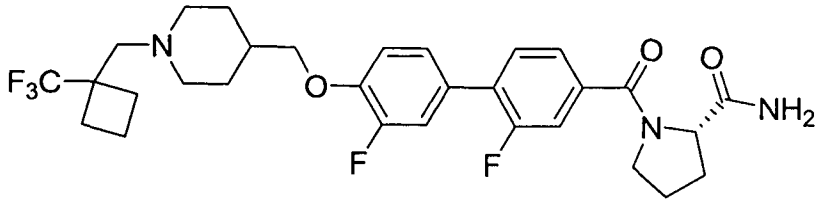
Compound No.	Reactant	Yield (%)
837	(S)-pyrrolidine-2-carboxamide	47
838	(R)-pyrrolidine-2-ylmethanol	44
839	(S)-pyrrolidine-3-ol	52
840	(R)-piperidin-3-ol	42
884	(S)-piperidin-3-carboxamide hydrochloride	48
885	(R)-piperidin-3-carboxamide hydrochloride	50
886	(R)-piperidin-2-carboxamide hydrochloride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

Table 72.

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 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



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 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).

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.

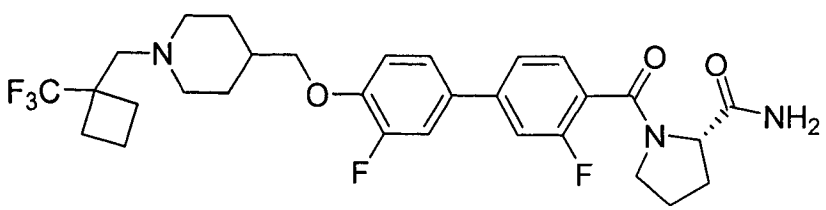
Compound No.	Reactant	Yield (%)
848	(R)-piperidin-3-ol hydrochloride	66

849	(R)-pyrrolidine-2-ylmethanol	68
850	(S)-piperidin-3-ol hydrochloride	64
851	(S)-pyrrolidine-3-ol	61

Table 74.

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).
851	(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 7.46 – 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



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, $LiOH \cdot H_2O$ (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).

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.

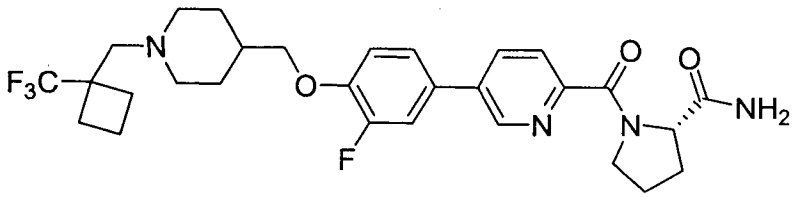
Compound No.	Reactant	Yield (%)
902	(R)-piperidin-3-ol hydrochloride	66
903	(R)-pyrrolidine-2-ylmethanol	62
904	(S)-piperidin-3-ol hydrochloride	55
905	(S)-pyrrolidine-3-ol	61
936	1-(piperazin-1-yl)ethanone	79

Table 76.

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).
905	(S)-(3,3'-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 7.51 – 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 – 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)piperidin-4-yl)methoxy)phenyl)picolinoyl)pyrrolidine-2-carboxamide



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%).

Step 3. 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).

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.

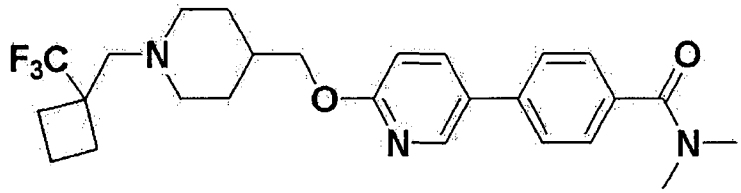
Table 77.

Compound No.	Reactant	Yield (%)
907	(R)-piperidin-3-ol hydrochloride	48

Table 78.

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. Compound 576: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzamide

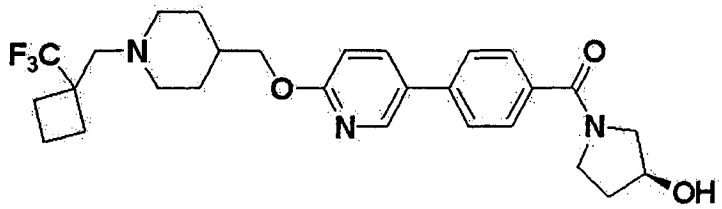


4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of compound 574; 20 mg, 0.05 mmol), dimethylamine (4 mg, 0.09 mmol), EDC (17 mg, 0.09 mmol) and HOBt (12 mg, 0.09 mmol) were dissolved in DMF 1 mL. DIPEA (11 mg, 0.09 mmol) 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).

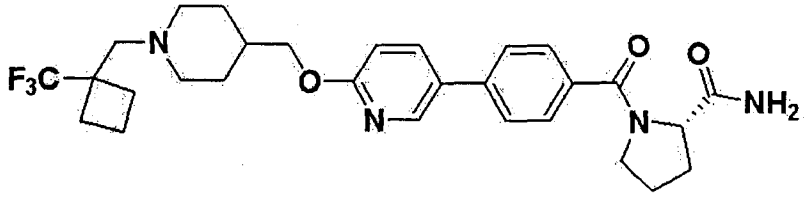
Example 83. Compound 578:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone



4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of 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



4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of 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).

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.

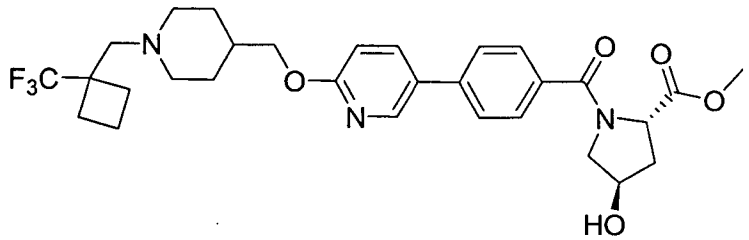
Compound No.	Reactant	Yield (%)
579	(R)-prolinol	30
588	piperidin-4-yl methanol	71
595	3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine	45
671	D-prolinamide	41
672	(S)-3-hydroxypiperidine hydrochloride	48
673	(R)-3-hydroxypiperidine hydrochloride	44

Table 80.

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, CDCl3) 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).
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. 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

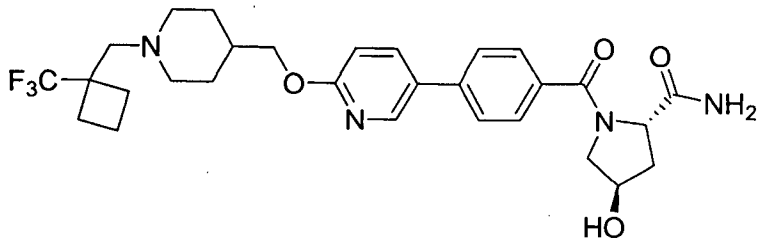


4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoic acid (the product of synthesis step 2 of compound 574; 300 mg, 0.67 mmol), (2S,4R)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (182 mg, 1.00 mmol), EDC (257 mg, 1.34 mmol), HOBt (181 mg, 1.34 mmol) 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



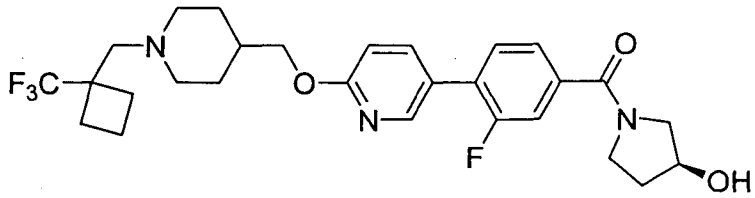
Step 1. (2S,4R)-4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxylic acid: (2S,4R)-methyl 4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzoyl)pyrrolidine-2-carboxylate(400 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. 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



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. 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).

According to the above-described synthesis process of 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.

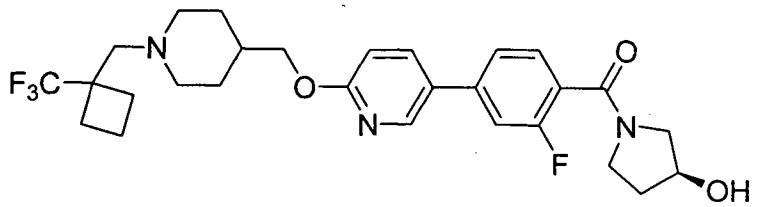
Table 81.

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.

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 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), 6.83 (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).
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. 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



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 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. 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 ($M^+ + H$).

According to the above-described synthesis process of 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.

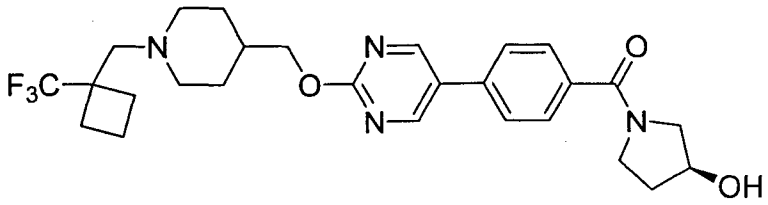
Table 83.

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.

Compound No.	Compound Name, ^{1}H-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).
722	(S)-1-(2-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 8.36 (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. Compound 970:(S)-(3-hydroxypyrrolidine-1-yl)(4-(2-((1-((1-(trifluoromethyl) cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone



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. 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).

According to the above-described synthesis process of 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.

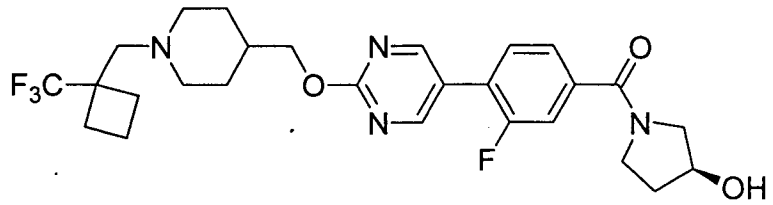
Table 85.

Compound No.	Reactant	Yield (%)
971	(R)-pyrrolidine-2-ylmethanol	34
972	(R)-piperidin-3-ol hydrochloride	34
973	L-prolinamide	33

Table 86.

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 (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. 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



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 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 $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

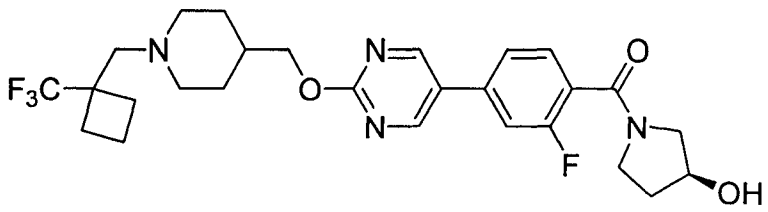
Table 87.

Compound No.	Reactant	Yield (%)
975	(R)-pyrrolidine-2-ylmethanol	34
976	(R)-piperidin-3-ol hydrochloride	34
977	L-prolinamide	33

Table 88.

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)pyrrolidine-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).
977	(S)-1-(3-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 (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. 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



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 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. 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).

According to the above-described synthesis process of 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.

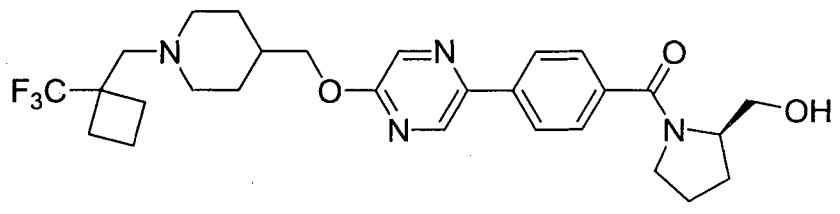
Table 89.

Compound No.	Reactant	Yield (%)
979	(R)-pyrrolidine-2-ylmethanol	36
980	(R)-piperidin-3-ol hydrochloride	34
981	L-prolinamide	33

Table 90.

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. Compound 1007: (R)-(2-(hydroxymethyl)pyrrolidine-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazine-2-yl)phenyl)methanone



Step 1. 2-iodo-5-((1-((1-(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. 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).

According to the above-described synthesis process of 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.

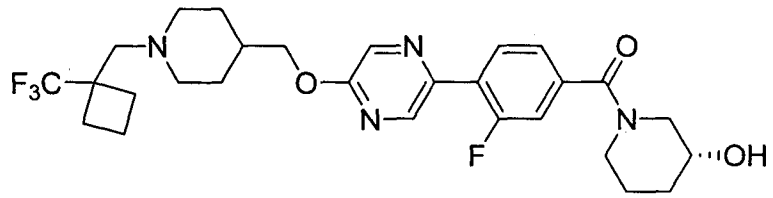
Table 91.

Compound No.	Reactant	Yield (%)
1008	(R)-piperidin-3-ol hydrochloride	37
1009	L-prolinamide	36

Table 92.

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. 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



Step 1. 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 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. 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).

According to the above-described synthesis process of 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

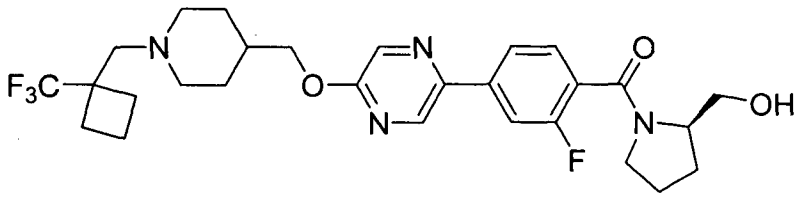
Table 94.

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. 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



<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 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> 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).

According to the above-described synthesis process of 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.

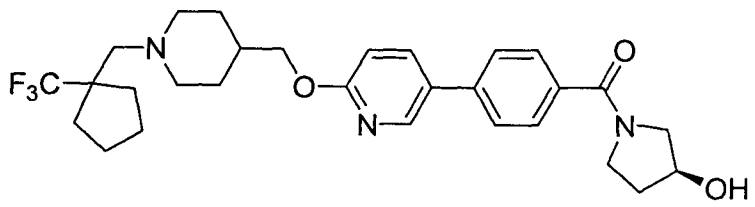
Table 95.

Compound No.	Reactant	Yield (%)
1013	(R)-piperidin-3-ol hydrochloride	43
1014	L-prolinamide	42

Table 96.

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. Compound 772:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone



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. 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, 1 H), 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).

According to the above-described synthesis process of 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.

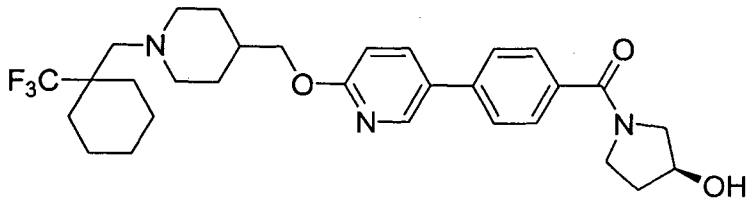
Compound No.	Reactant	Yield (%)
773	(R)-pyrrolidine-2-ylmethanol	42
774	L-prolinamide	40
775	(R)-piperidin-3-ol hydrochloride	37

Table 98.

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. Compound 776:(S)-(3-hydroxypyrrolidine-1-yl)(4-(6-((1-((1-(trifluoromethyl) cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridine-3-yl)phenyl)methanone



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. 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).

According to the above-described synthesis process of 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.

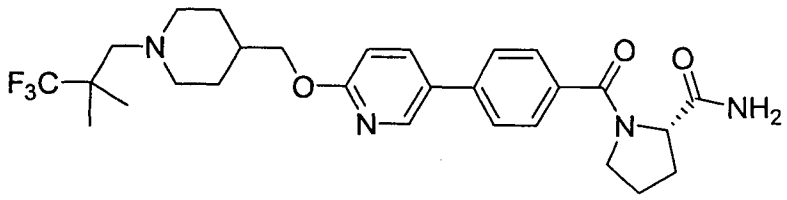
Table 99.

Compound No.	Reactant	Yield (%)
777	(R)-pyrrolidine-2-ylmethanol	42
778	L-prolinamide	28
779	(R)-piperidin-3-ol hydrochloride	38

Table 100.

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



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).

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.

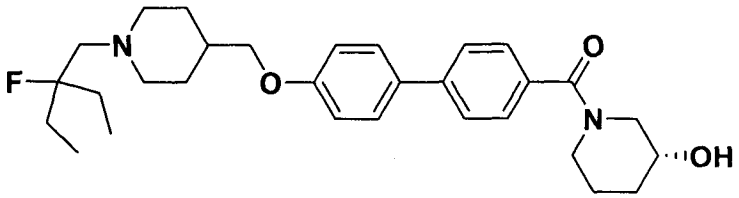
Table 101.

Compound No.	Reactant	Yield (%)
829	(R)-piperidin-3-ol hydrochloride	41

Table 102.

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. Compound 809: (R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



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 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. $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

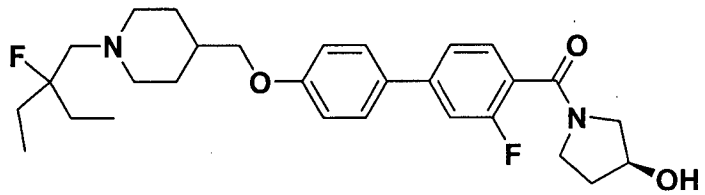
Table 103.

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.

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. Compound 888: (S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypyrrolidine-1-yl)methanone



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 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. 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).

According to the above-described synthesis process of 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.

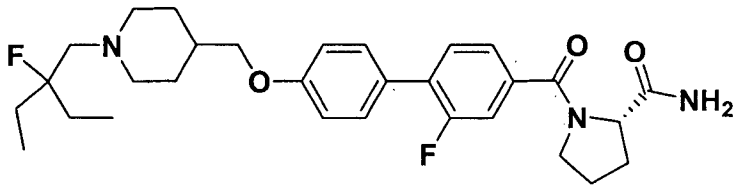
Compound No.	Reactant	Yield (%)
810	(R)-pyrrolidine-2-ylmethanol	44
814	piperidin-4-carboxamide hydrochloride	47
866	(S)-pyrrolidine-2-carboxamide	
889	(S)-piperidin-3-ol	63
890	(R)-piperidin-3-ol	67

Table 106.

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



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 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. $LiOH \cdot H_2O$ (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).

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.

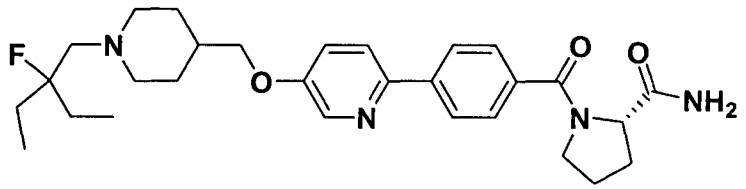
Compound No.	Reactant	Yield (%)
811	(R)-pyrrolidine-2-ylmethanol	67
812	(R)-piperidin-3-ol hydrochloride	57

Table 108.

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



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_2CO_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).

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.

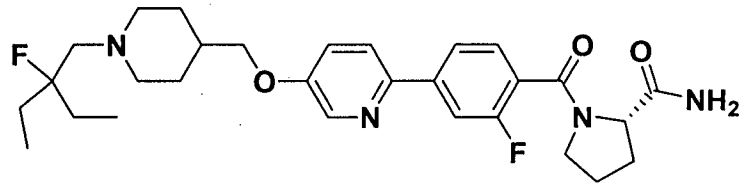
Table 109.

Compound No.	Reactant	Yield (%)
897	(R)-piperidin-3-ol	51

Table 110.

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



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. $LiOH·H_2O$ (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).

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.

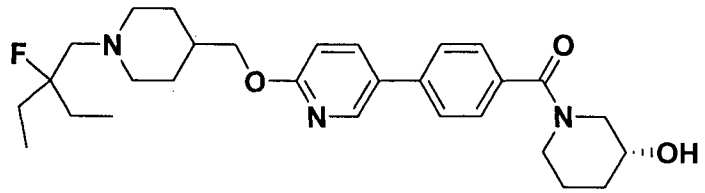
Compound No.	Reactant	Yield (%)
899	(S)-pyrrolidine-3-ol	51
900	(R)-piperidin-3-ol	58

Table 112.

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. Compound 954: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-

yl)methoxy)pyridine-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone



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 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_2CO_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. 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).

According to the above-described synthesis process of 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.

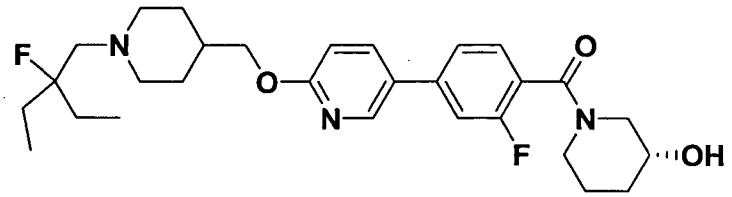
Compound No.	Reactant	Yield (%)
955	(S)-piperidin-3-ol	37

Table 114.

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. Compound 956: (R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridine-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone



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 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. 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).

According to the above-described synthesis process of 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.

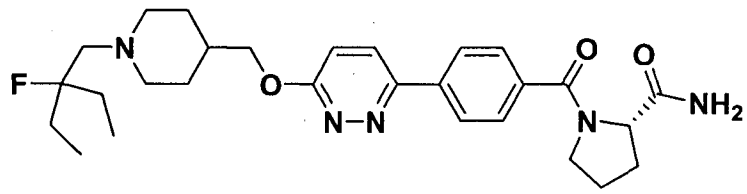
Table 115.

Compound No.	Reactant	Yield (%)
957	(S)-piperidin-3-ol	35

Table 116.

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. Compound 953: (S)-1-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazine-3-yl)benzoyl)pyrrolidine-2-carboxamide



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 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

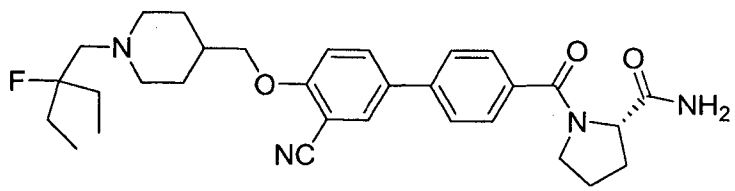
obtained organic layer was washed with saturated aqueous brine solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 g cartridge; EtOAc / hexane = 0 % to 80 %), and concentrated to 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 $LiOH \cdot H_2O$ (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. 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



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).

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.

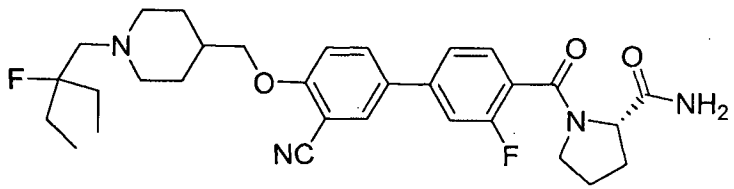
Compound No.	Reactant	Yield (%)
1005	(R)-pyrrolidine-2-ylmethanol	48

1006	(S)-pyrrolidine-3-ol	71

Table 118.

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



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).

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.

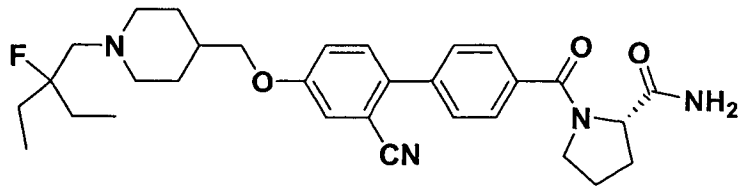
Compound No.	Reactant	Yield (%)
1001	(R)-piperidin-3-ol hydrochloride	65
1002	(R)-pyrrolidine-2-ylmethanol	62
1003	(S)-pyrrolidine-3-ol	47

Table 120.

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



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_2CO_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)

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.

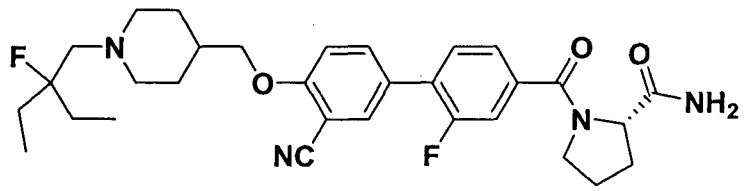
Compound No.	Reactant	Yield (%)
1125	(R)-piperidin-2-carboxamide hydrochloride	55
1126	(R)-piperidin-3-ol hydrochloride	67

Table 122.

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



<u>Step 1.</u> 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%).

<u>Step 2.</u> 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%).

<u>Step 3.</u> 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).

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.

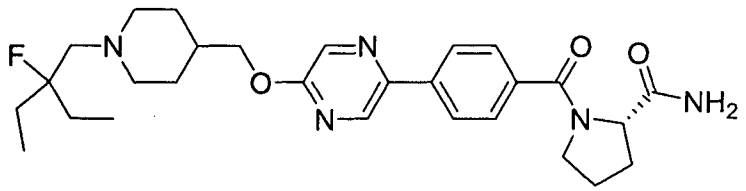
Compound No.	Reactant	Yield (%)
1120	(S)-pyrrolidine-3-ol	53
1121	(R)-piperidin-2-carboxamide hydrochloride	50
1123	(R)-piperidin-3-ol hydrochloride	59

Table 124.

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, 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. Compound 1018: (S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazine-2-yl)benzoyl)pyrrolidine-2-carboxamide



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 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

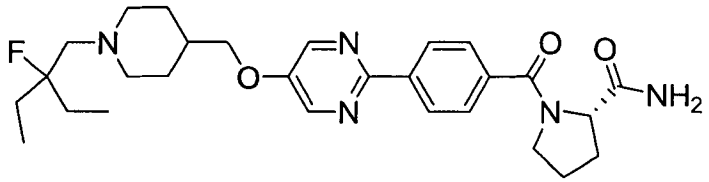
obtained filtrate was diluted with water, and extracted with EtOAc. The organic layer was washed with saturated NH_4Cl aqueous solution, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (SiO_2, 12 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. 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



Step 1. 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).

Step 2. 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%).

Step 3. 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%).

Step 4. 4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-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%).

Step 5. 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).

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.

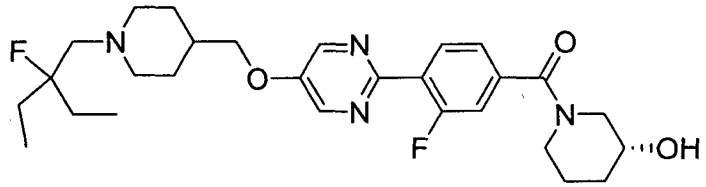
Compound No.	Reactant	Yield (%)
1052	(R)-piperidin-3-ol hydrochloride	50
1053	(R)-piperidin-2-carboxamide hydrochloride	77

Table 126.

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. Compound 1056: (R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone



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. 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_2, 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).

According to the above-described synthesis process of 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.

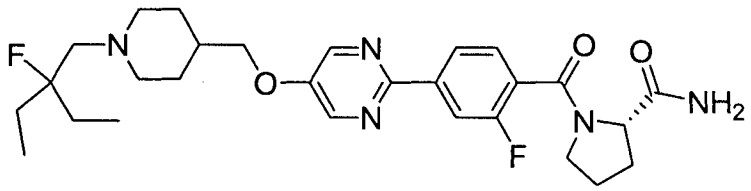
Table 127.

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



Step 1. 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%).

Step 2. 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 $LiOH \cdot H_2O$ (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%).

Step 3. 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).

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

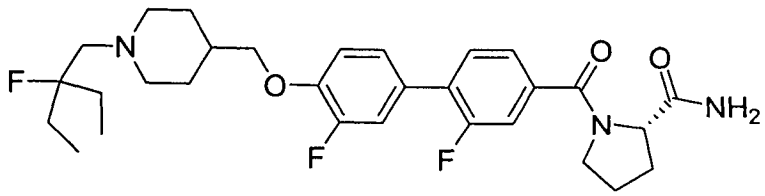
Table 129.

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



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 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).

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.

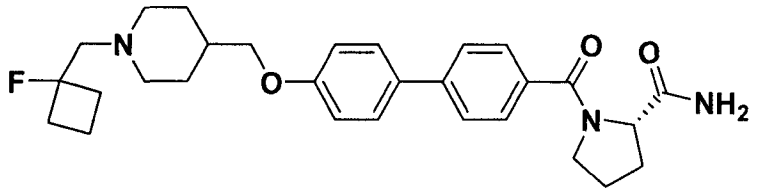
Table 131.

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.

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



Step 1. 1-((4-((4-bromophenoxy)methyl)piperidin-1-yl)methyl)cyclobutanol: 4-((4-bromophenoxy)methyl)piperidine (the product of synthesis step 4 of 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/1 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 $LiOH \cdot H_2O$ (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).

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.

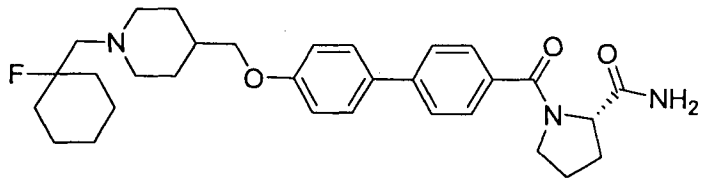
Compound No.	Reactant	Yield (%)
923	(R)-pyrrolidine-2-ylmethanol	38
924	(S)-pyrrolidine-3-ol	70
925	(R)-piperidin-3-ol	46

Table 134.

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



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).

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.

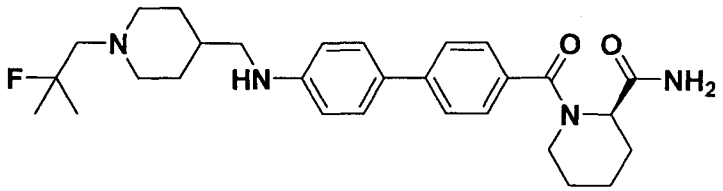
Table 135.

Compound No.	Reactant	Yield (%)
761	(R)-piperidin-3-ol hydrochloride	28

Table 136.

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. Compound 857: (R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidin-2-carboxamide



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. 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)

According to the above-described synthesis process of 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.

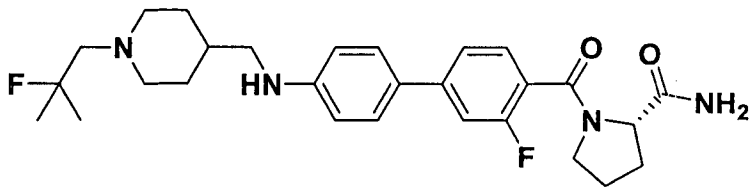
Compound No.	Reactant	Yield (%)
858	(S)-pyrrolidine-2-ylmethanol	78
859	(R)-pyrrolidine-2-ylmethanol	69
867	(R)-piperidin-3-ol	54
868	(S)-pyrrolidine-2-carboxamide	68
869	(S)-pyrrolidine-3-ol	66

Table 138.

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. Compound 870: (S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide



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. 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).

According to the above-described synthesis process of 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.

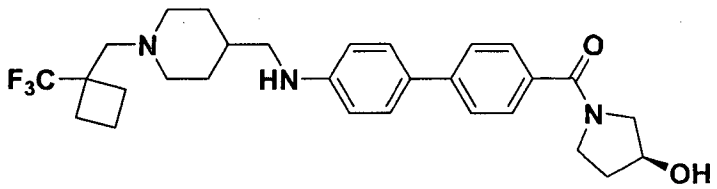
Table 139.

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, CDCl3) 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. Compound 1020: (S)-(3-hydroxypyrrolidine-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone



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 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. 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).

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.

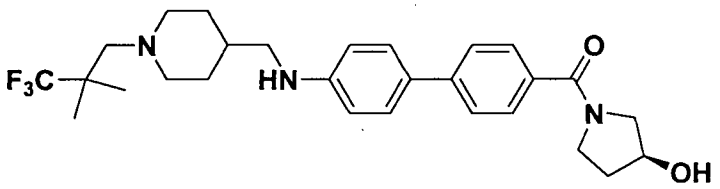
Compound No.	Reactant	Yield (%)
926	(R)-piperidin-3-ol	70
1021	(S)-pyrrolidine-2-carboxamide	64
1022	(S)-piperidin-3-ol	60
1023	(R)-piperidin-2-carboxamide	61

Table 142.

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+ + H).

Example 120. Compound 1024: (S)-(3-hydroxypyrrolidine-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone



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 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. 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).

According to the above-described synthesis process of 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.

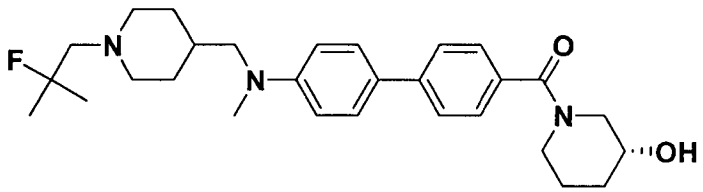
Compound No.	Reactant	Yield (%)
927	(R)-piperidin-3-ol	34
1025	(S)-pyrrolidine-2-carboxamide	67
1026	(S)-piperidin-3-ol	72

Table 144.

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. Compound 852: (R)-(4'-(((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)(methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone (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).

According to the above-described synthesis process of 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.

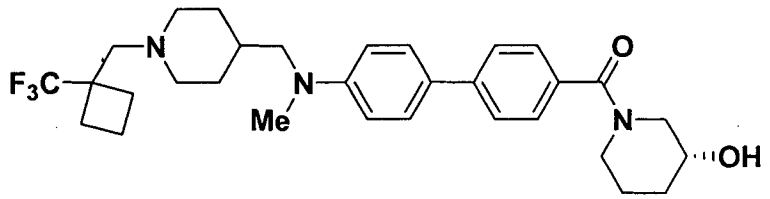
Table 145.

Compound No.	Reactant	Yield (%)
853	Acetaldehyde	45

Table 146.

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. Compound 928: (R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone



(R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone (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).

According to the above-described synthesis process of 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.

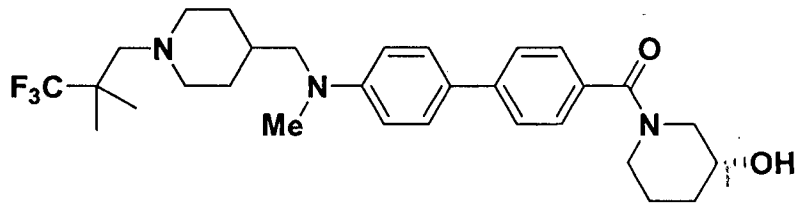
Table 147.

Compound No.	Reactant	Yield (%)
929	Acetaldehyde	72

Table 148.

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).

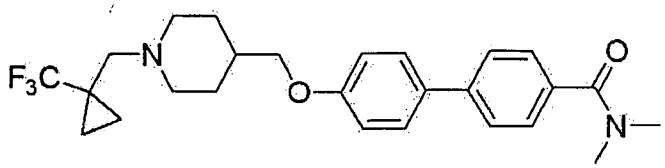
Example 123. Compound 930: (R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone



(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 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. Compound 552: N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide



Step 1. (4-((4-bromophenoxy)methyl)piperidin-1-yl)(1-(trifluoromethyl)cyclopropyl) methanone: 4-((4-bromophenoxy)methyl)piperidine hydrochloride (the product of synthesis step 1 of 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.

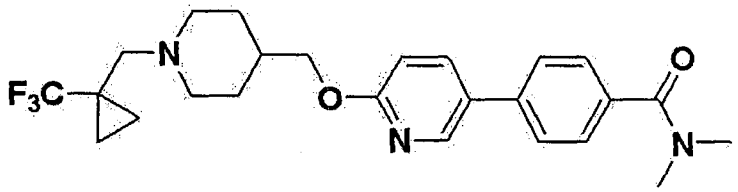
The obtained concentrate was purified by silica gel column chromatography (0-40 % EtOAc/Hexane) to yield the title compound as light-yellow solid (30 mg, 53%).

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 1 N HCl, the resulting precipitate was filtered to yield the title compound as white solid (28 mg, 97%).

Step 5. 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. Compound 580: N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclopropyl) methyl)piperidin-4-yl)methoxy)pyridine-3-yl)benzamide



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 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. $LiOH \cdot H_2O$ (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. 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).

According to the above-described synthesis process of 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.

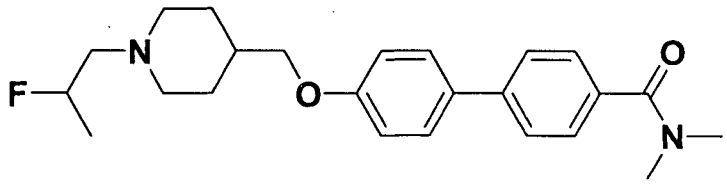
Compound No.	Reactant	Yield (%)
582	morpholine	22
583	piperidine	26
584	pyrrolidine	32
585	(S)-3-pyrrolidinol	29
586	L-prolinamide	41
587	4-piperidinemethanol	65

Table 150.

Compound No.	Compound Name, ^{1}H-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, 1 H), 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 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. Compound 688:

4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide



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 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. 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).

According to the above-described synthesis process of 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.

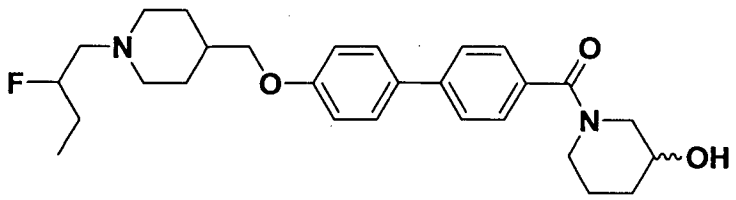
Table 151.

Compound No.	Reactant	Yield (%)
689	(R)-pyrrolidine-2-ylmethanol	30

Table 152.

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. Compound 690: (4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone



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 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%).

Step 3. 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_2Cl_2) to yield the title compound as yellow solid (30 mg, 17%).

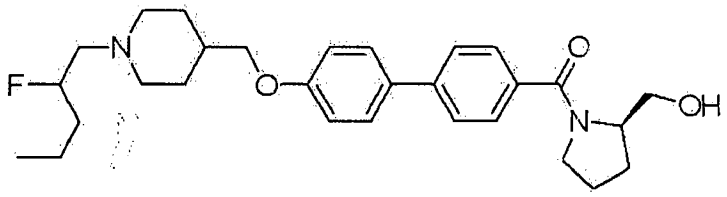
Step 4. 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid: Methyl 4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate (30 mg, 0.08 mmol) was dissolved in THF:MeOH: water =4:2:1. $LiOH \cdot H_2O$ (6 mg, 0.15 mmol) was added thereto, and refluxed with heating for 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%).

Step 5. 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. Compound 655: (R)-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidine-1-yl)methanone



Step 1. 1-(4-((4-bromophenoxy)methyl)piperidin-1-yl)pentane-2-ol: 4-((4-bromophenoxy) methyl)piperidine hydrochloride (the product of synthesis step 1 of 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. Compound 655: 4'-((1-(2-fluoropentyl)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 (21 mg, 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).

According to the above-described synthesis process of 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).

The structural formulae are as following Tables 155-180.

Table 155.

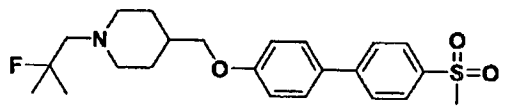
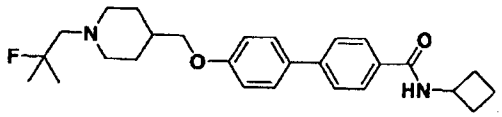
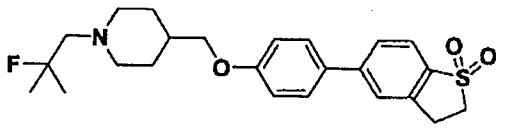
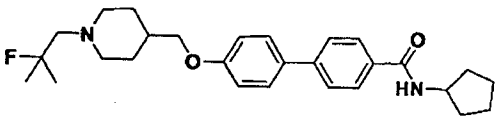
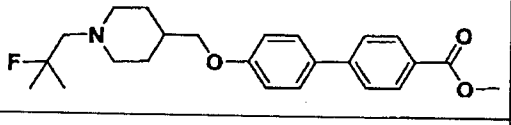
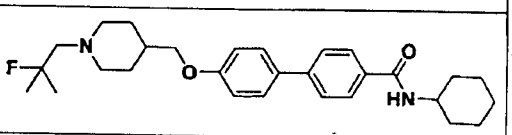
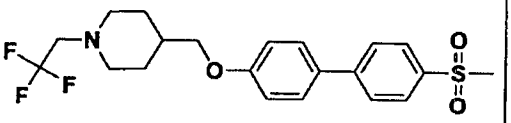
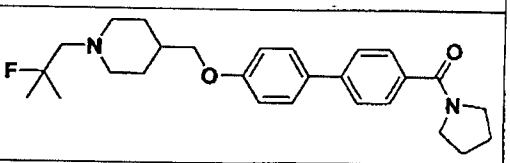
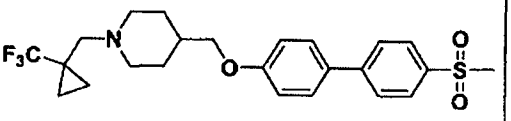
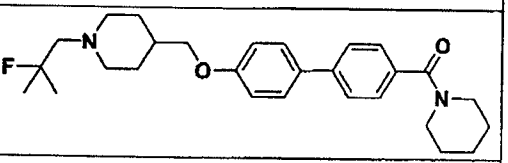
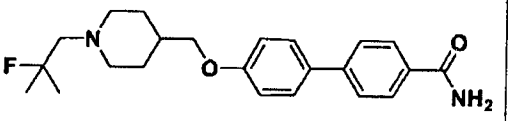
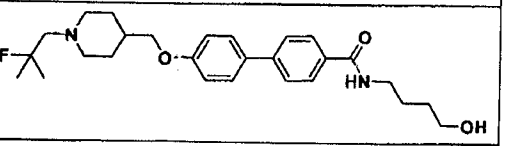
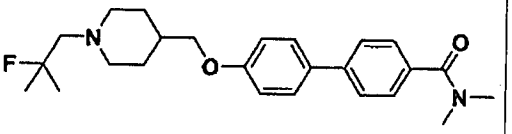
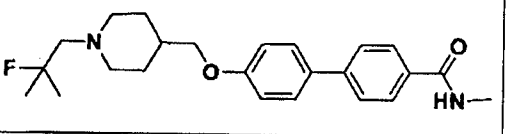
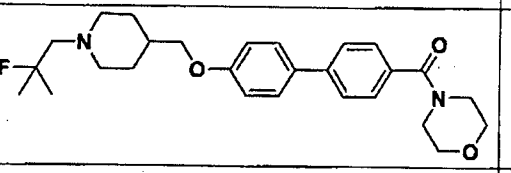
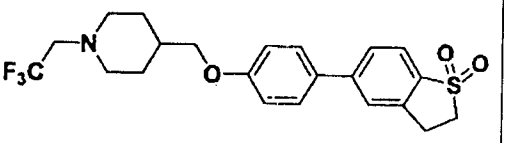
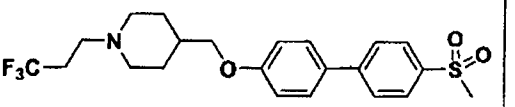
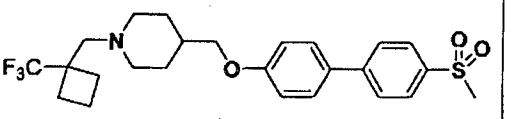
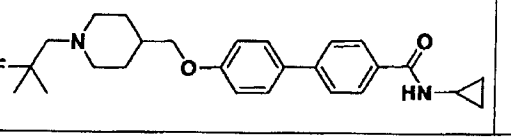
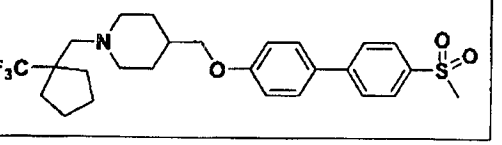
Compound	Structure	Compound	Structure
431		527	
470		528	
498		529	
499		530	
500		531	
515		533	
516		534	
517		540	
524		542	
526		546	

Table 156.

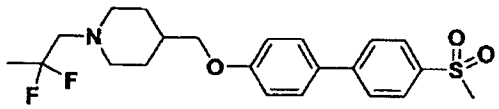
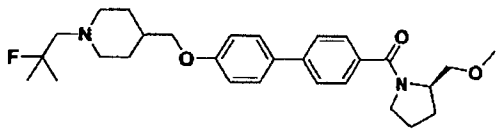
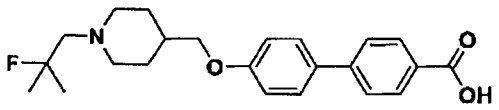
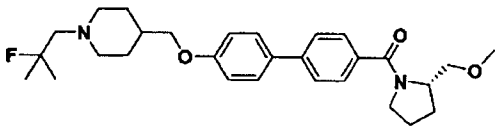
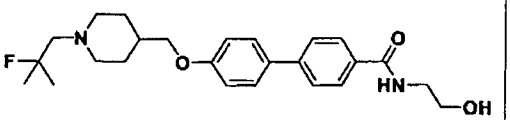
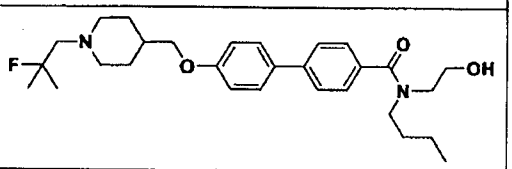
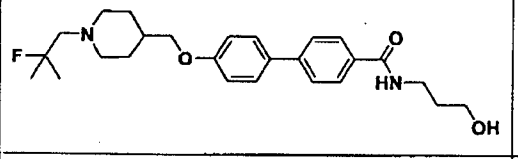
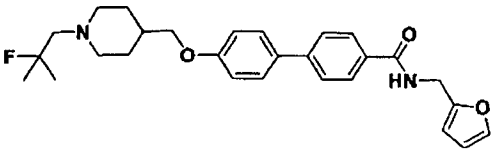
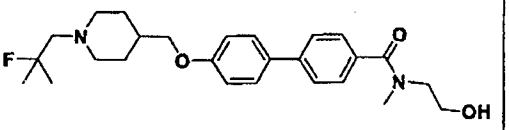
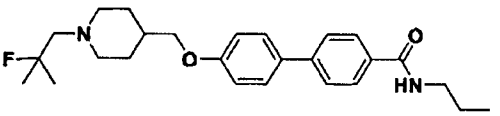
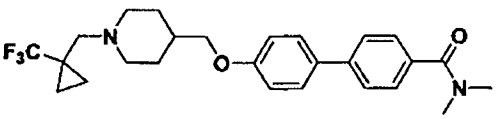
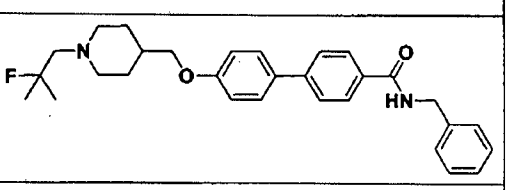
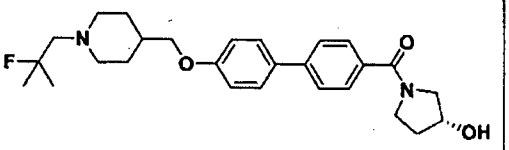
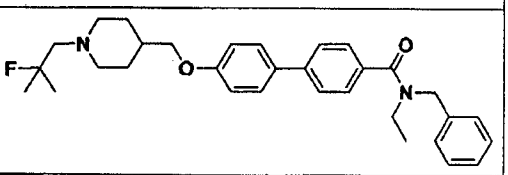
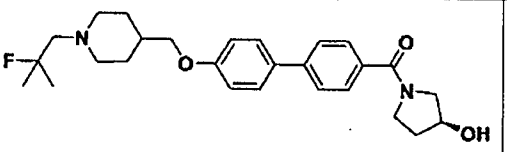
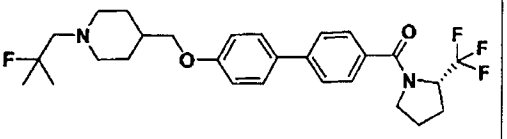
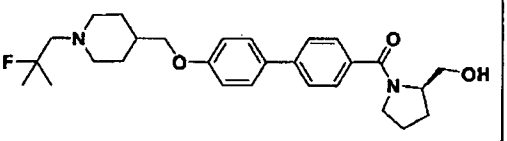
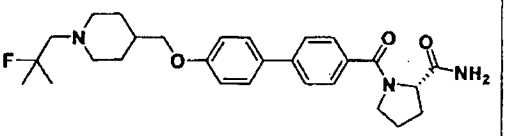
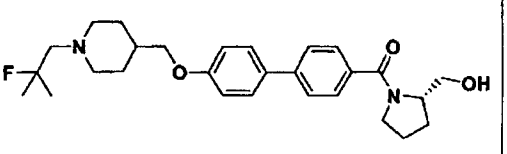
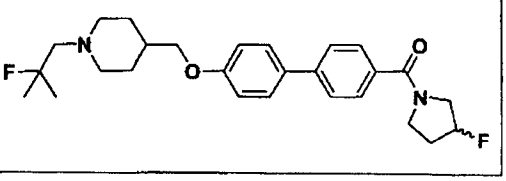
Compound	Structure	Compound	Structure
547		557	
548		558	
549		559	
550		560	
551		561	
552		562	
553		563	
554		564	
555		565	
556		566	

Table 157.

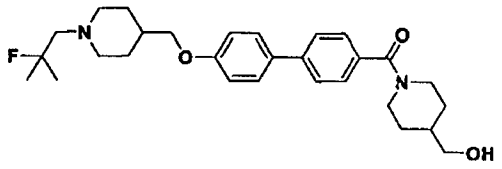
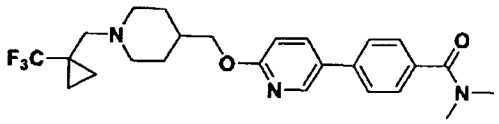
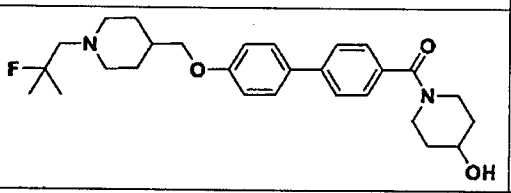
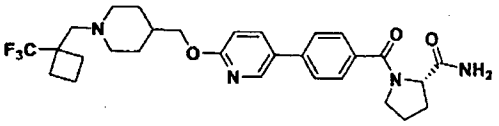
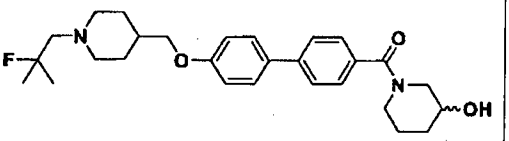
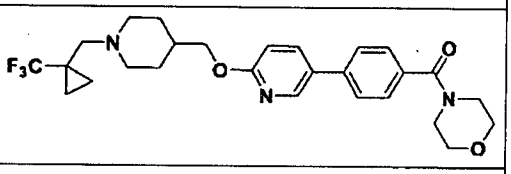
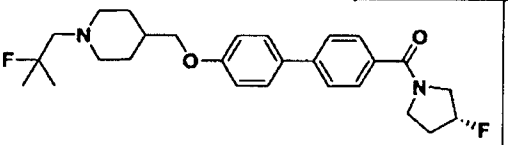
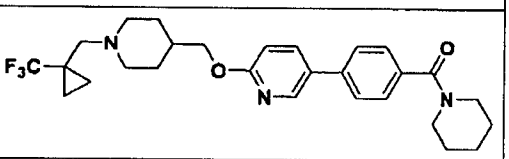
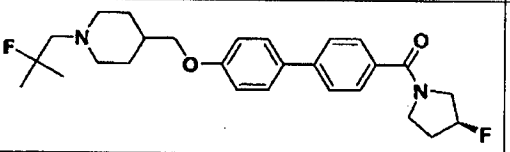
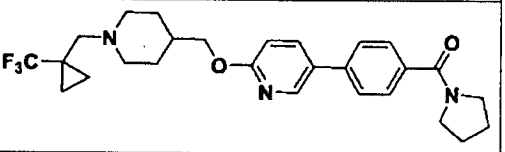
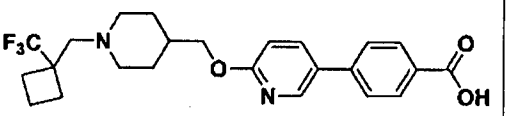
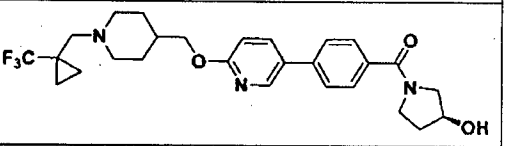
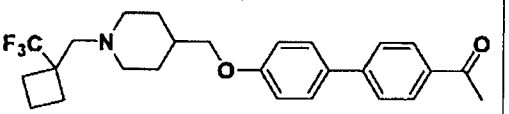
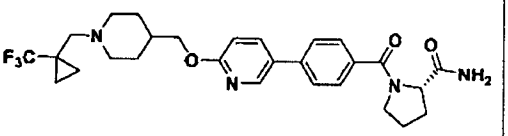
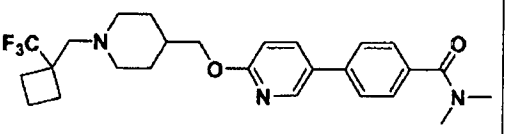
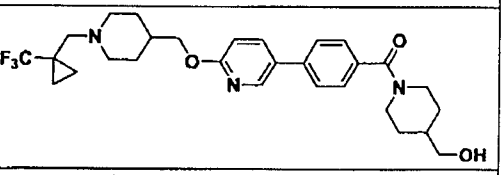
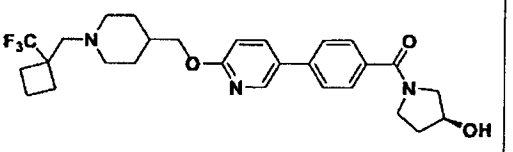
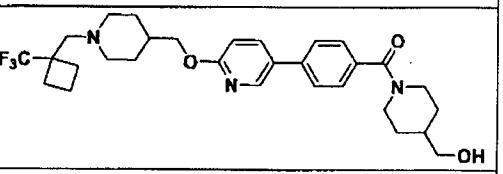
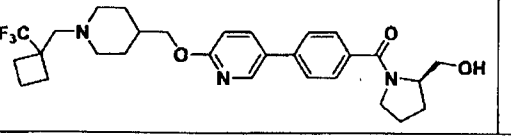
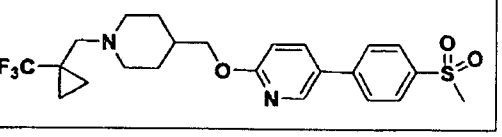
Compound	Structure	Compound	Structure
567		580	
568		581	
569		582	
570		583	
571		584	
574		585	
575		586	
576		587	
578		588	
579		589	

Table 158.

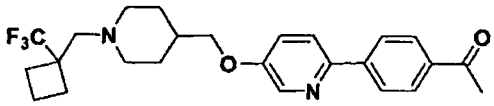
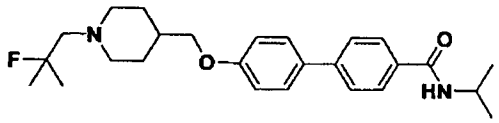
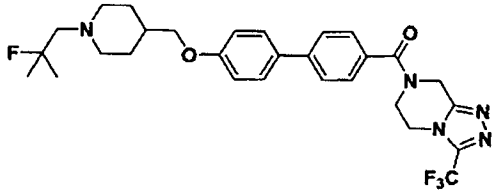
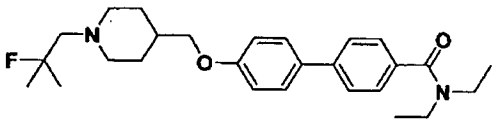
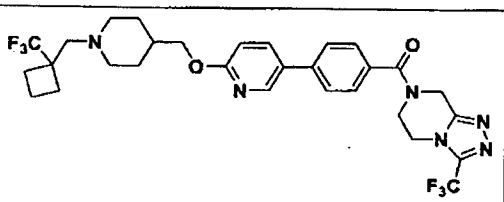
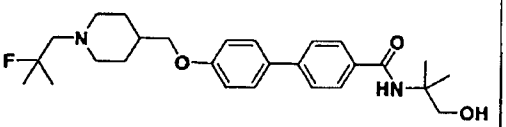
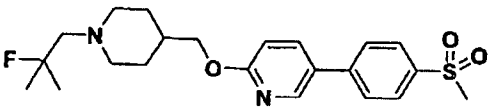
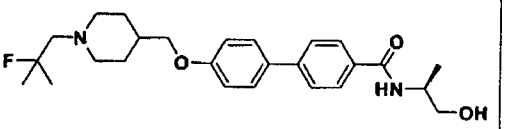
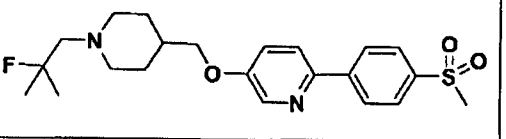
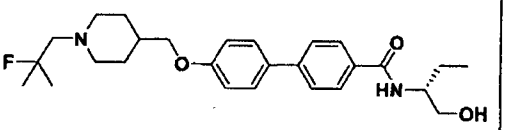
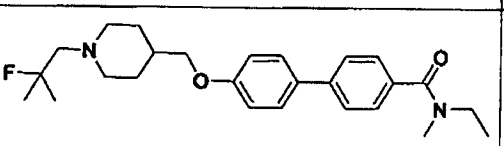
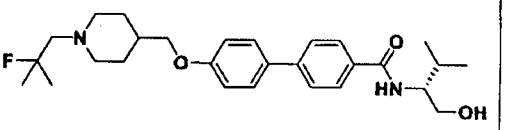
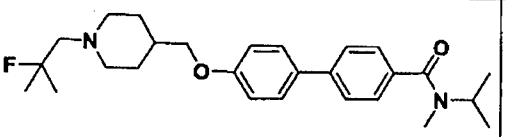
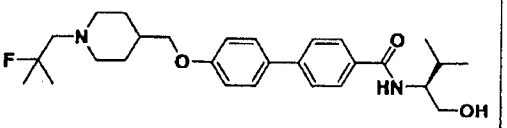
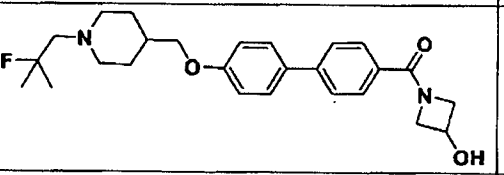
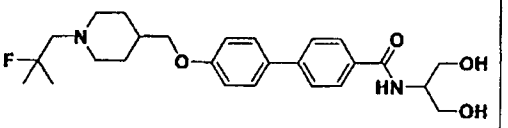
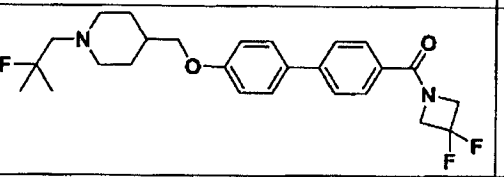
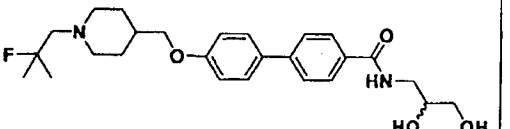
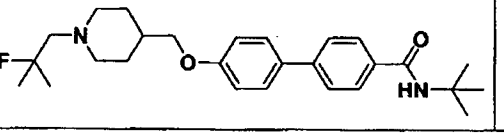
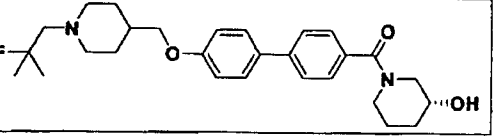
Compound	Structure	Compound	Structure
593		603	
594		604	
595		605	
596		606	
597		607	
598		608	
599		609	
600		610	
601		611	
602		612	

Table 159.

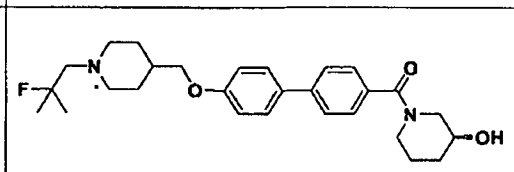
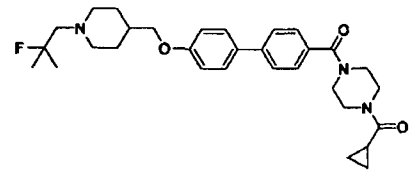
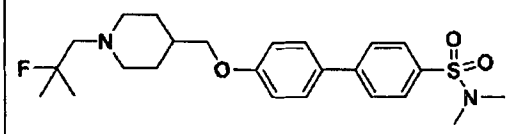
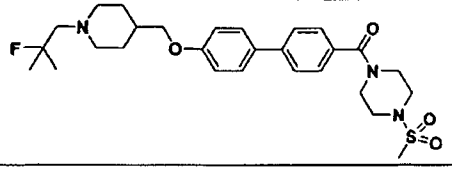
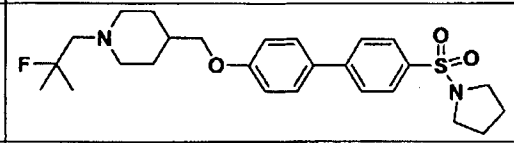
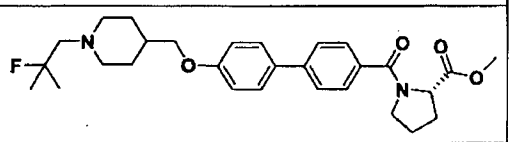
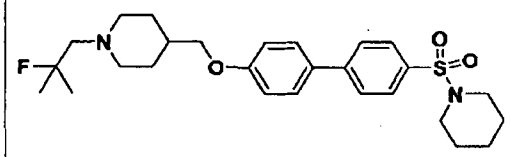
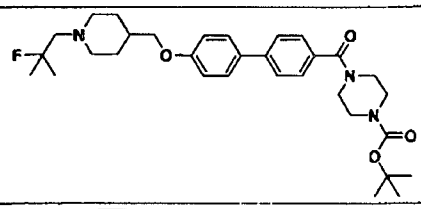
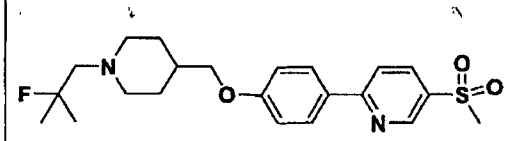
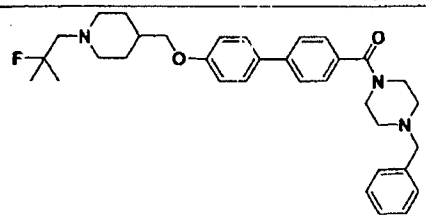
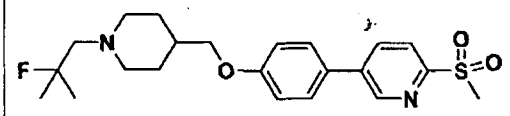
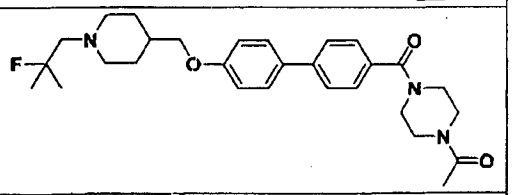
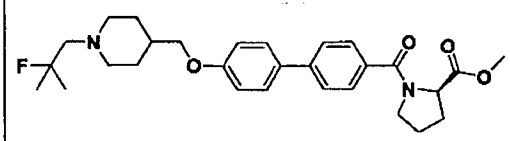
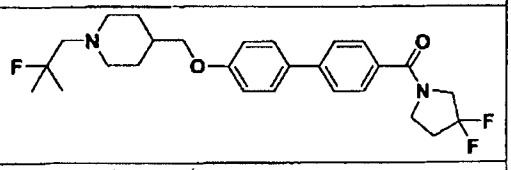
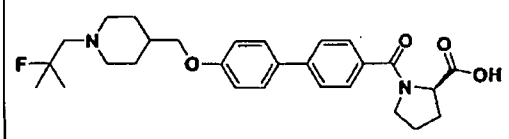
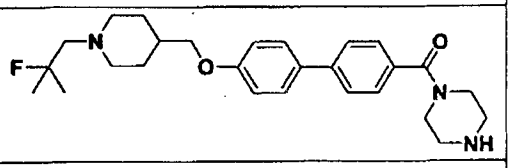
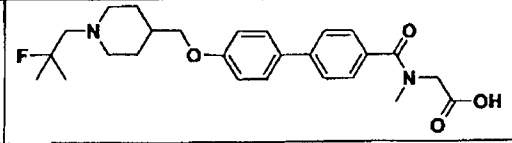
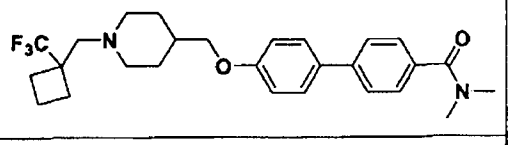
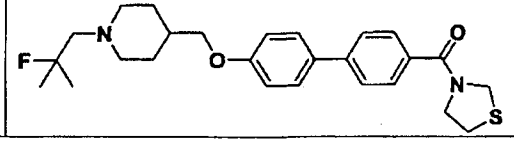
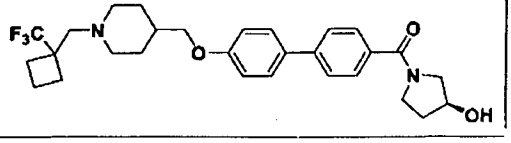
Compound	Structure	Compound	Structure
613		623	
614		624	
615		625	
616		626	
617		627	
618		628	
619		629	
620		630	
621		631	
622		632	

Table 160.

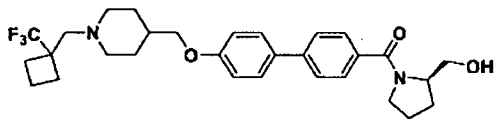
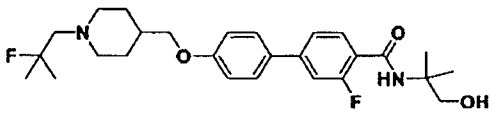
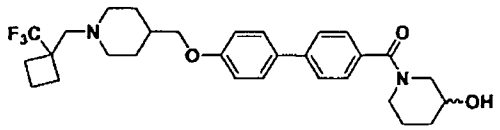
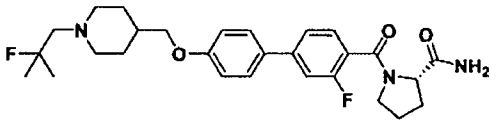
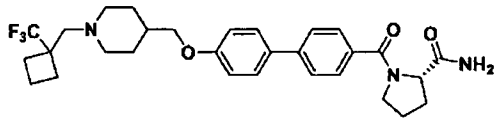
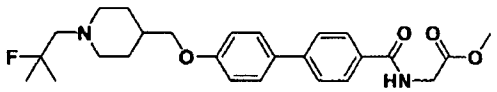
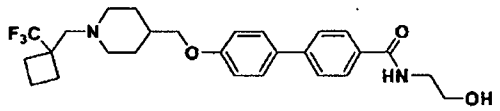
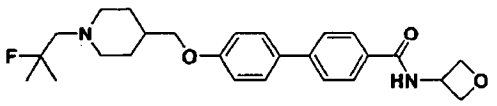
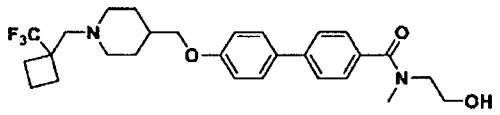
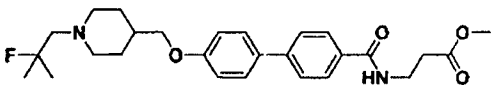
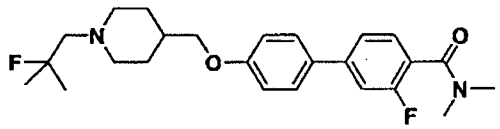
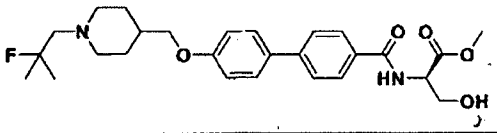
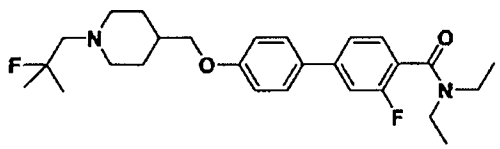
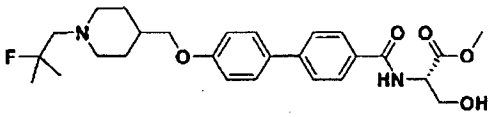
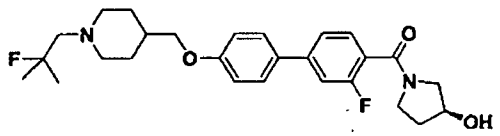
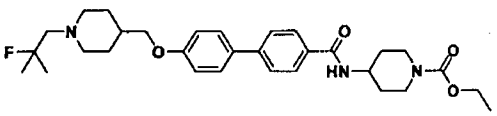
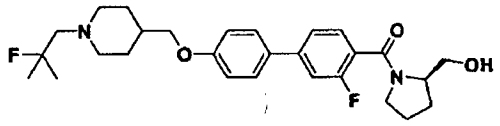
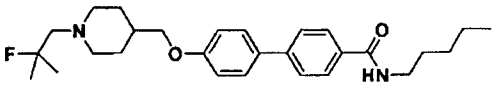
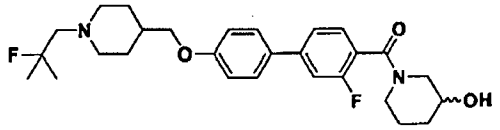
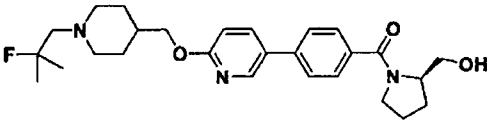
Compound	Structure	Compound	Structure
633		643	
634		644	
635		645	
636		646	
637		647	
638		648	
639		649	
640		650	
641		651	
642		652	

Table 161.

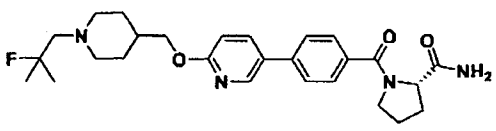
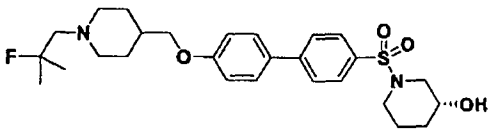
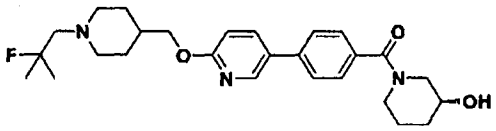
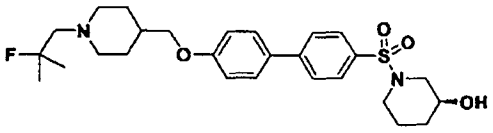
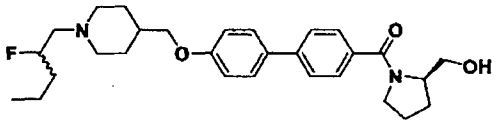
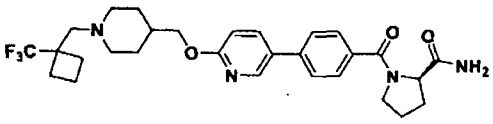
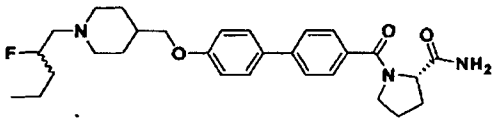
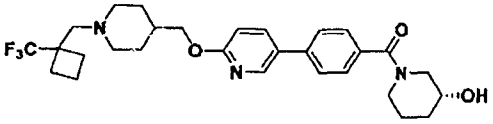
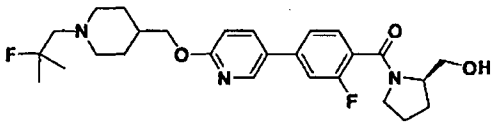
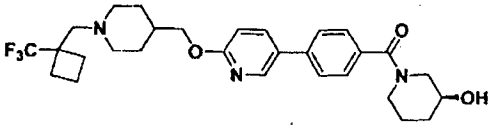
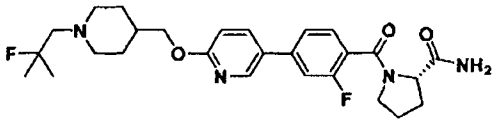
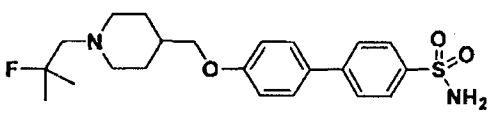
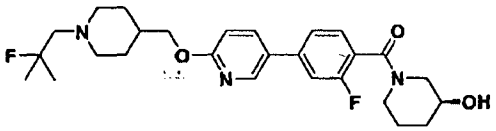
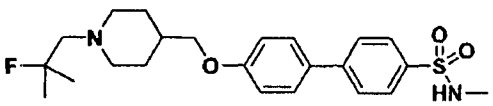
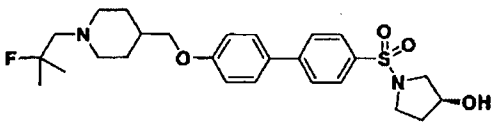
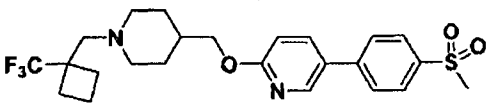
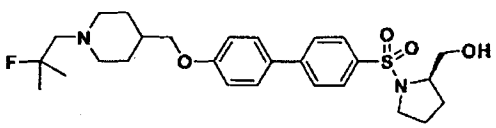
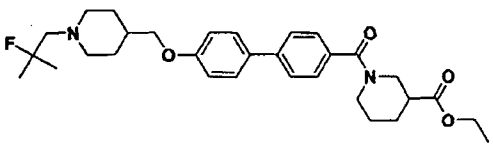
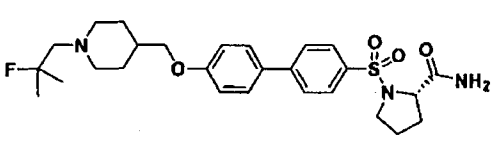
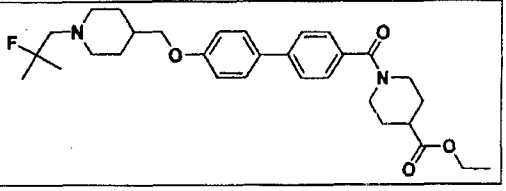
Compound	Structure	Compound	Structure
653		669	
654		670	
655		671	
656		672	
657		673	
658		674	
659		675	
666		676	
667		677	
668		678	

Table 162.

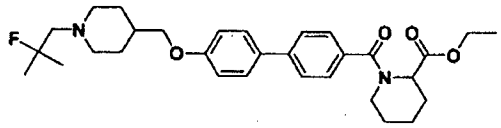
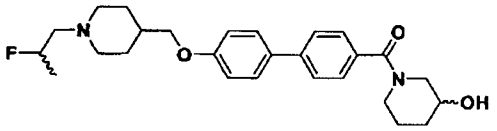
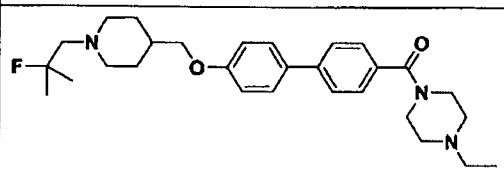
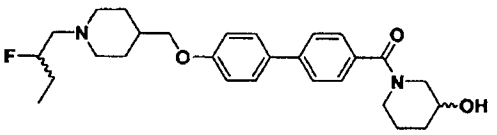
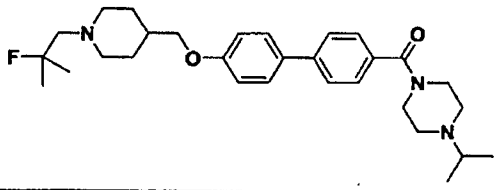
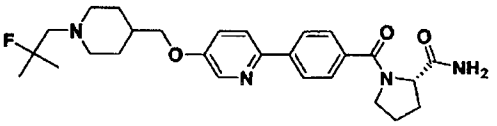
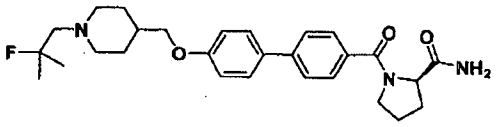
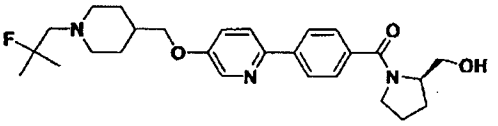
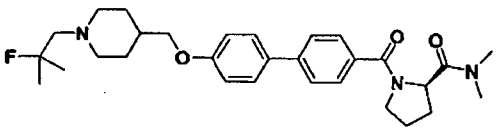
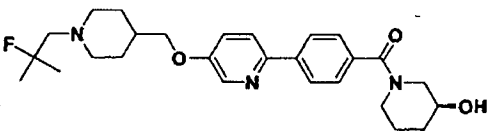
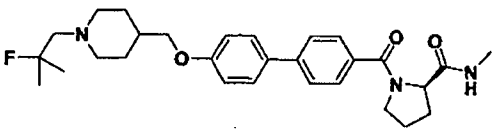
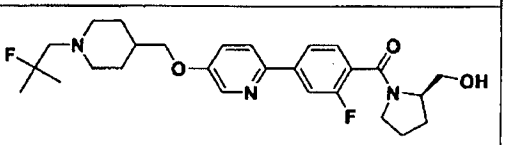
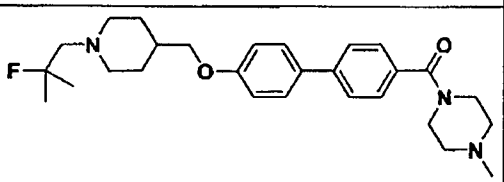
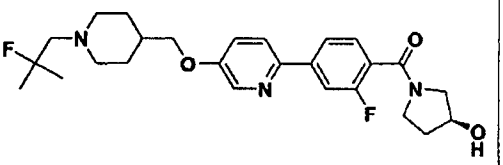
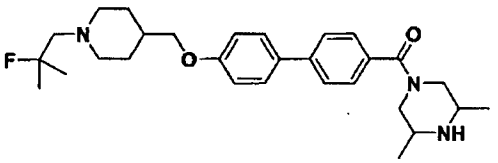
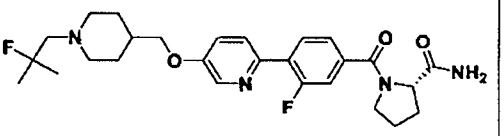
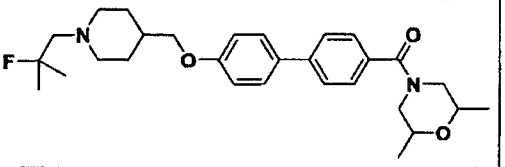
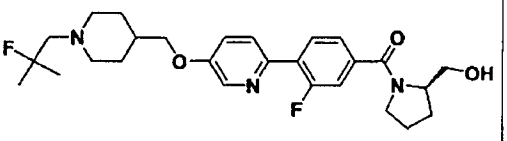
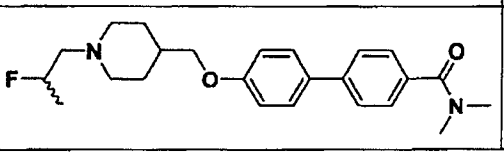
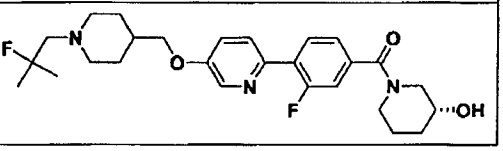
Compound	Structure	Compound	Structure
679		689	
680		690	
681		691	
682		692	
683		693	
684		694	
685		695	
686		696	
687		697	
688		698	

Table 163.

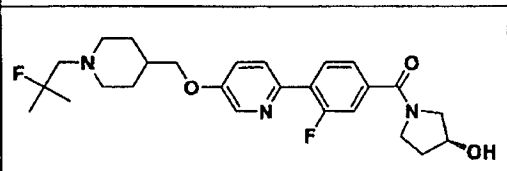
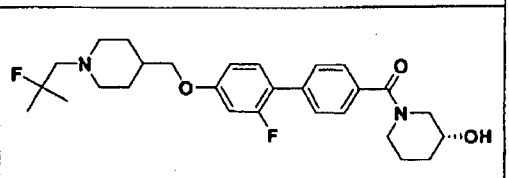
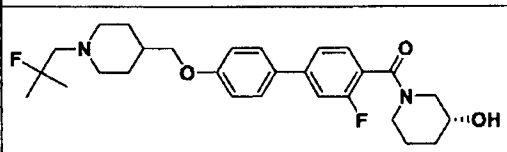
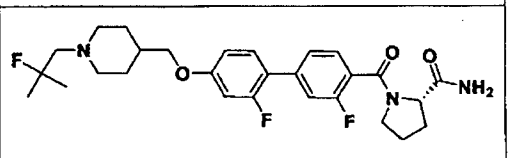
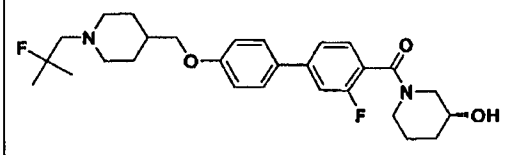
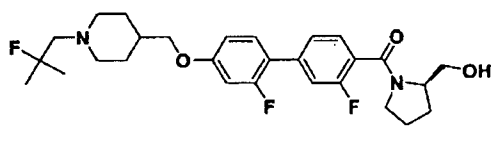
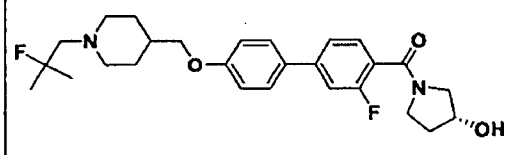
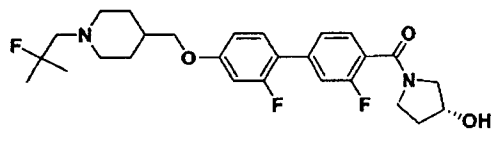
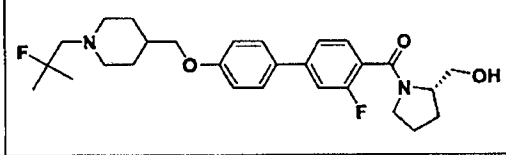
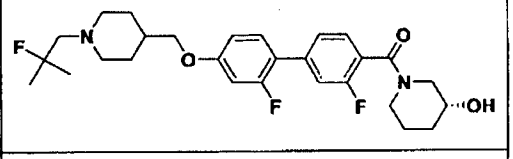
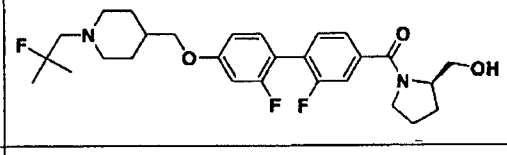
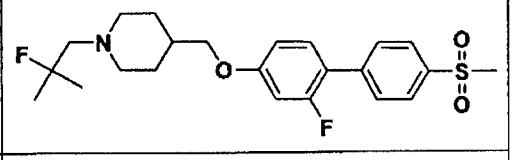
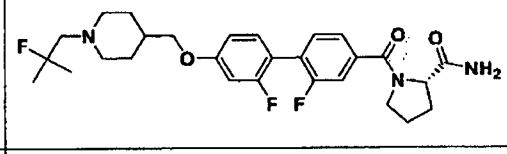
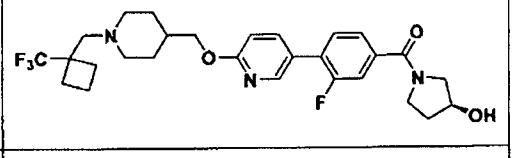
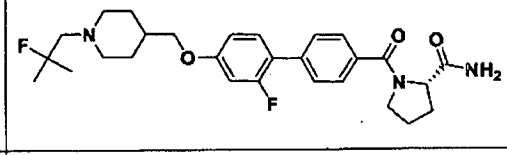
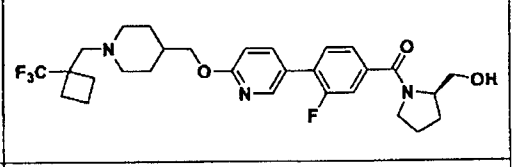
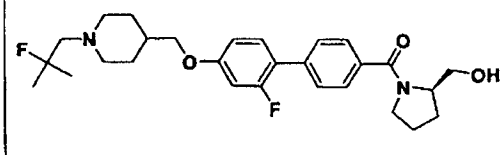
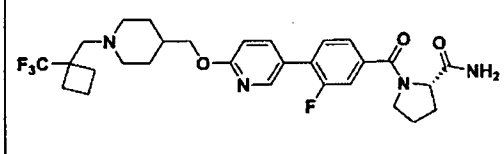
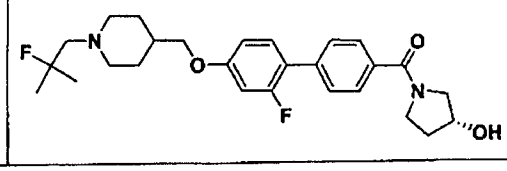
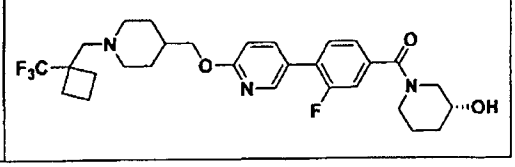
Compound	Structure	Compound	Structure
699		709	
700		710	
701		711	
702		712	
703		713	
704		714	
705		715	
706		716	
707		717	
708		718	

Table 164.

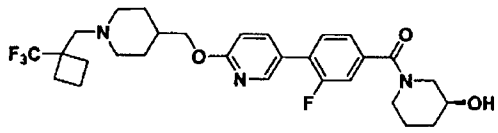
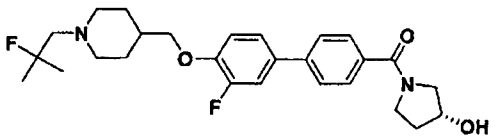
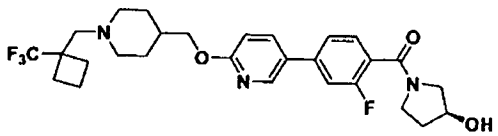
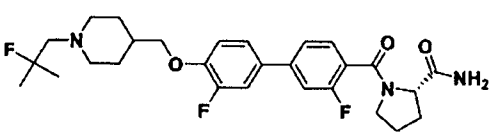
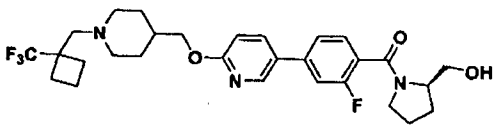
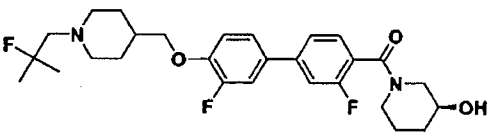
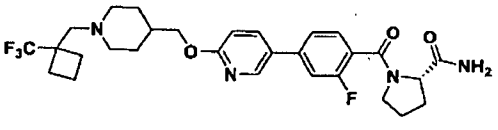
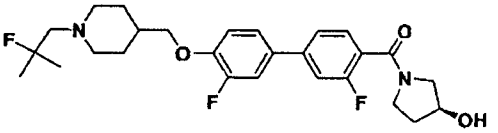
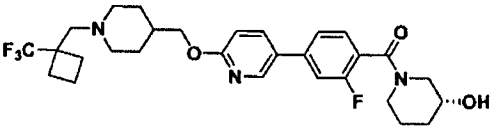
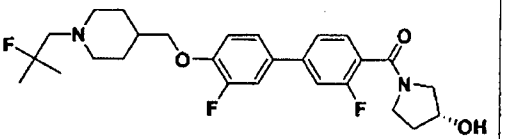
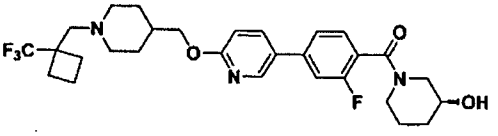
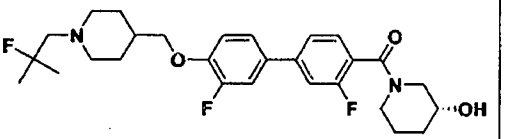
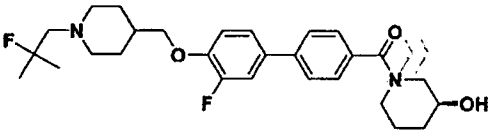
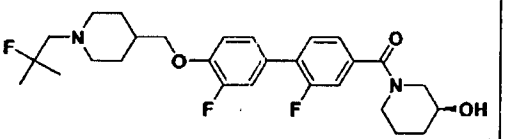
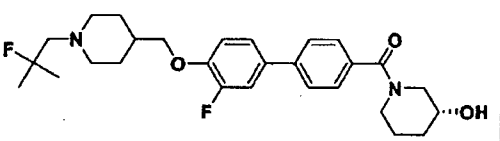
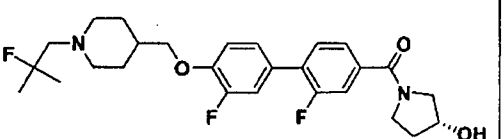
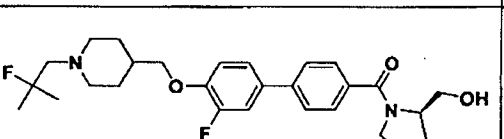
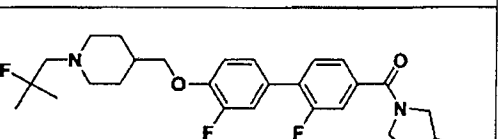
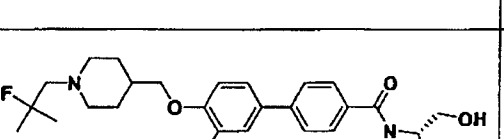
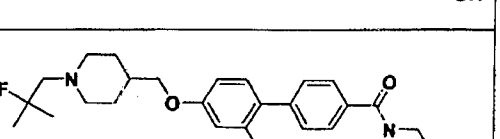
Compound	Structure	Compound	Structure
719		729	
720		730	
721		731	
722		732	
723		733	
724		734	
725		735	
726		736	
727		737	
728		738	

Table 165.

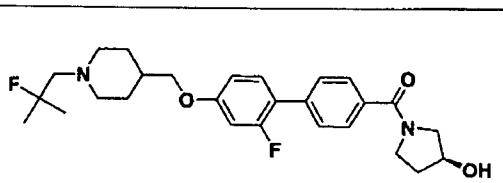
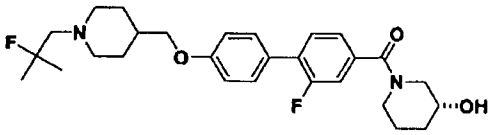
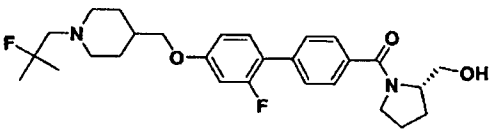
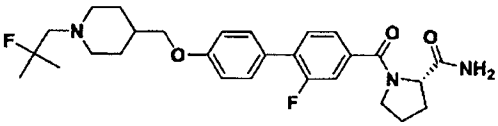
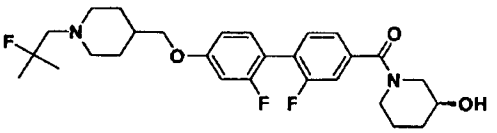
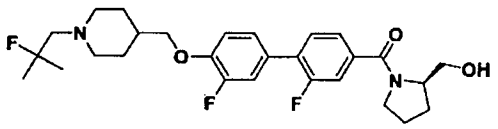
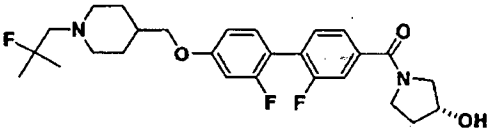
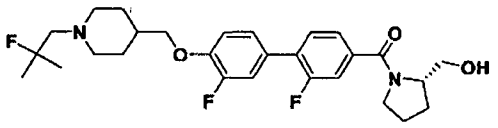
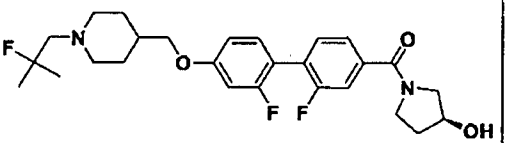
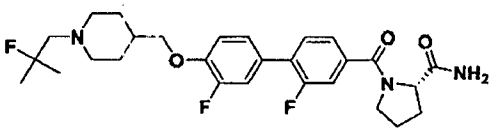
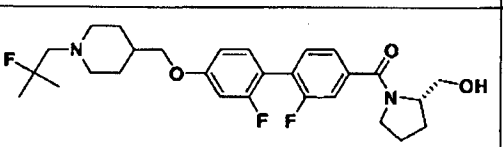
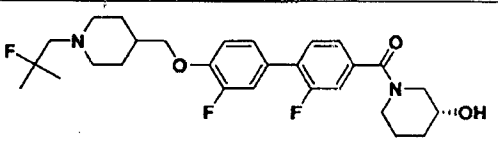
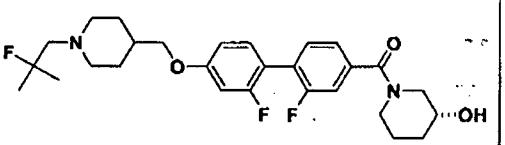
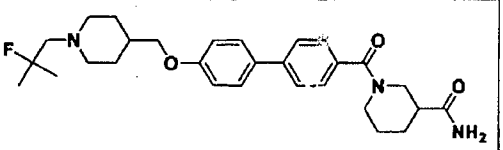
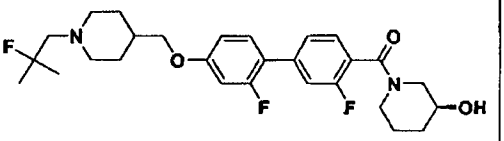
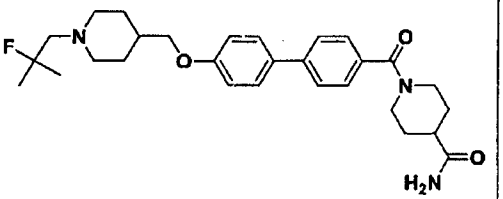
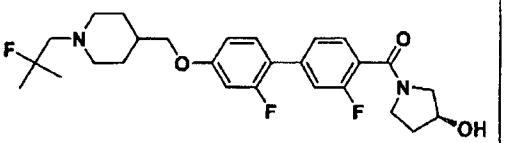
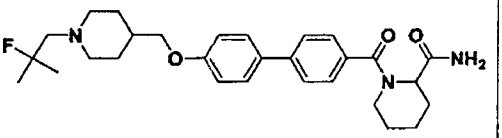
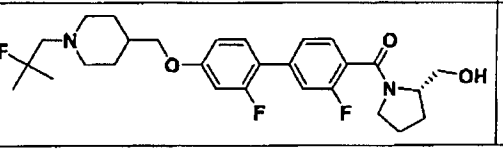
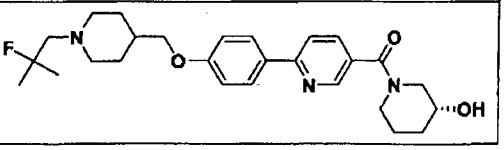
Compound	Structure	Compound	Structure
739		749	
740		750	
741		751	
742		752	
743		753	
744		754	
745		755	
746		756	
747		757	
748		758	

Table 166.

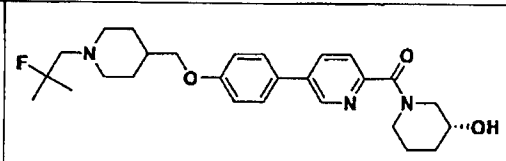
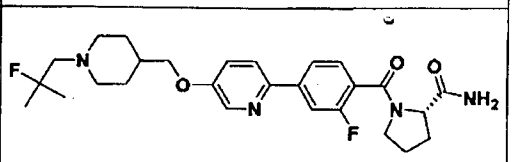
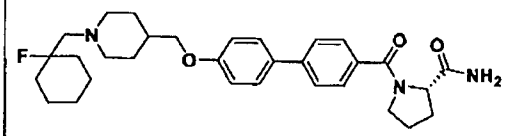
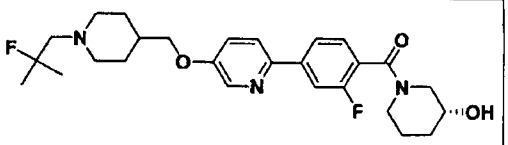
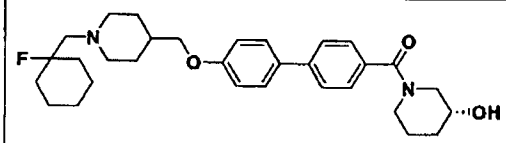
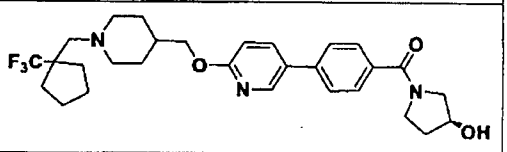
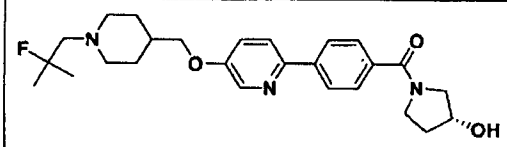
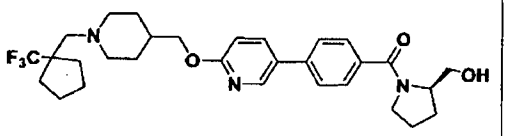
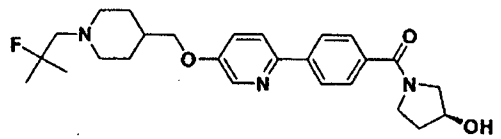
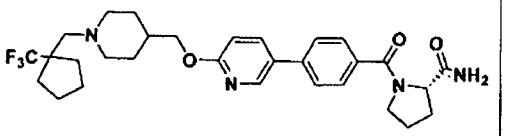
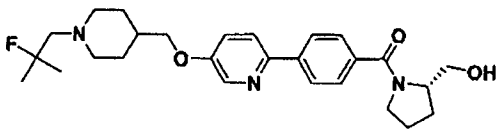
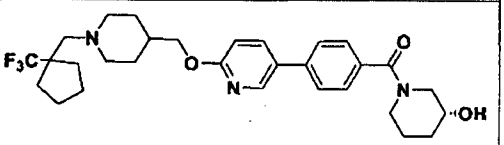
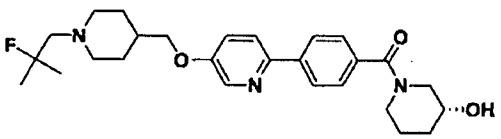
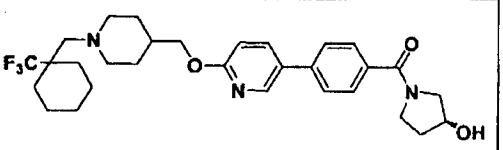
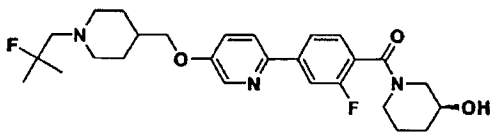
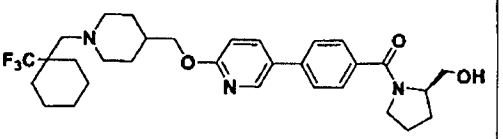
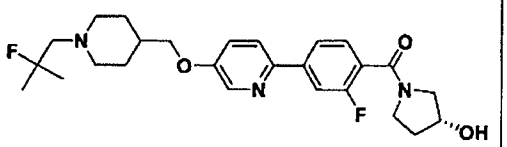
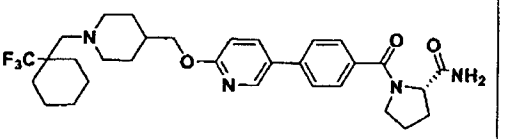
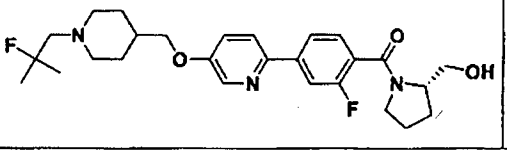
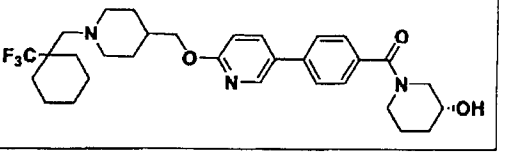
Compound	Structure	Compound	Structure
759		770	
760		771	
761		772	
763		773	
764		774	
765		775	
766		776	
767		777	
768		778	
769		779	

Table 167.

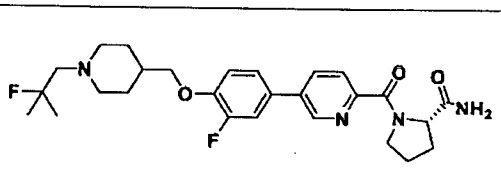
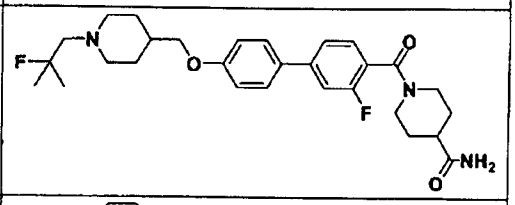
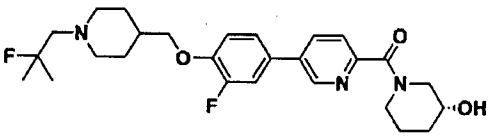
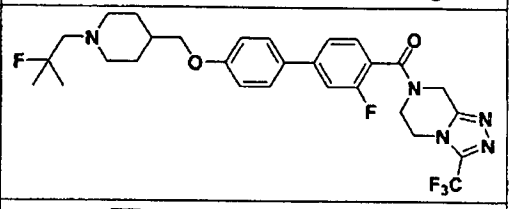
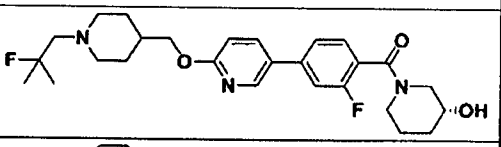
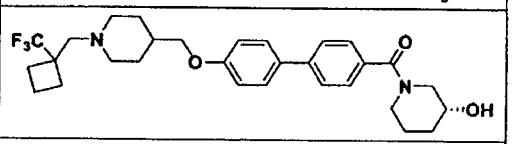
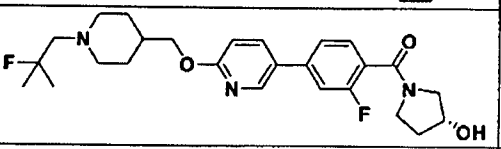
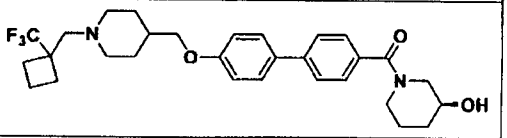
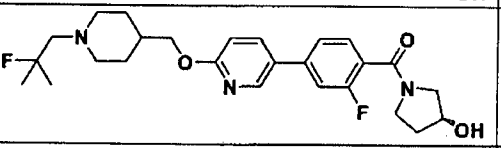
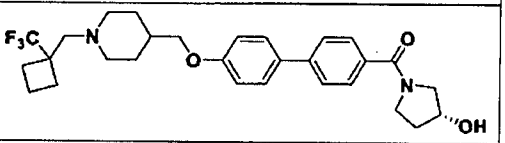
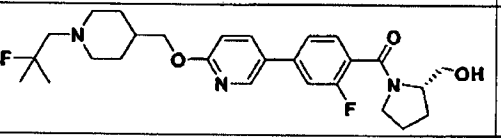
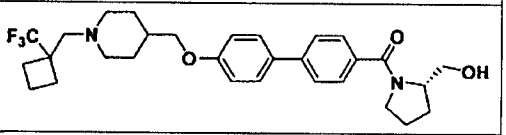
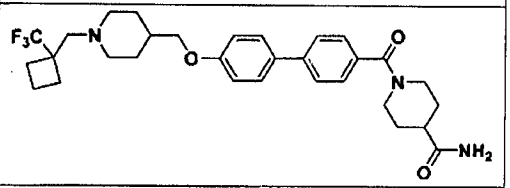
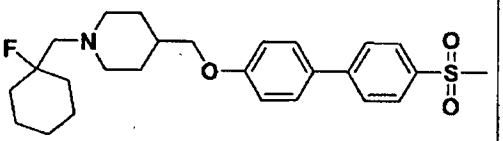
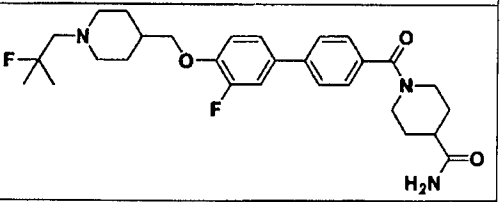
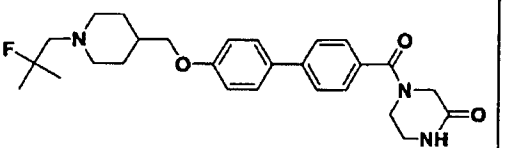
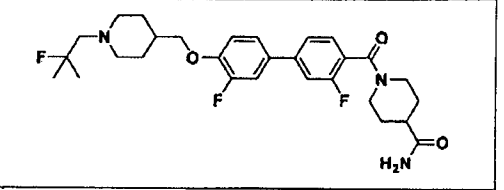
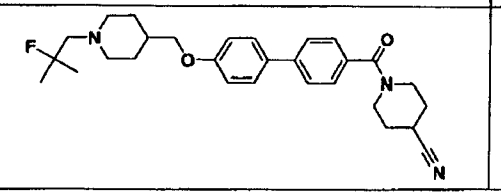
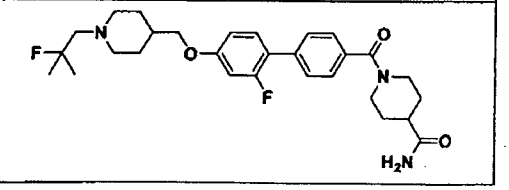
Compound	Structure	Compound	Structure
782		792	
783		793	
784		794	
785		795	
786		796	
787		797	
-	-	798	
789		799	
790		800	
791		801	

Table 168.

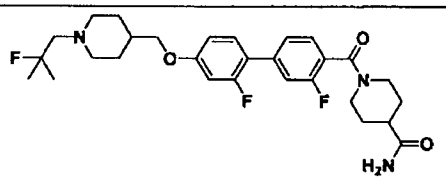
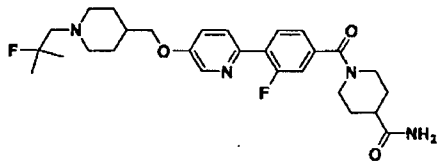
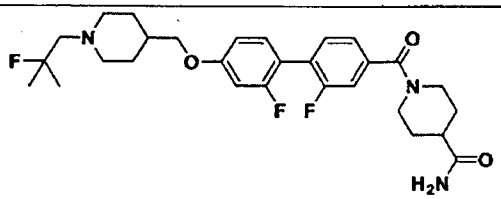
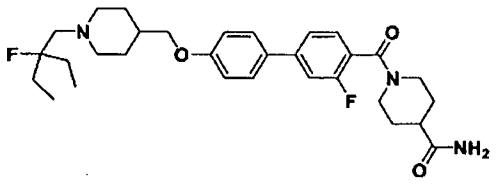
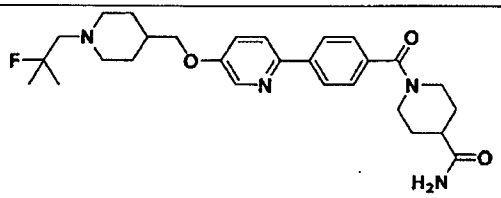
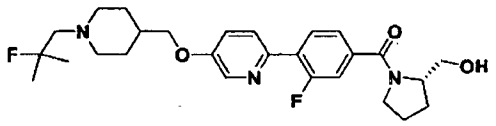
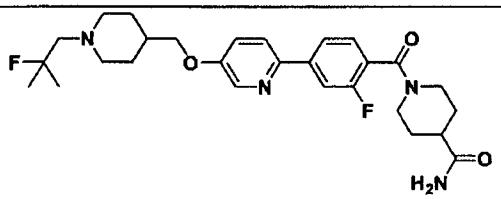
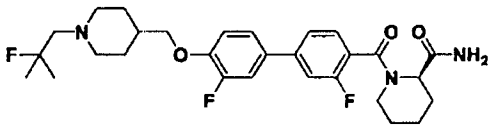
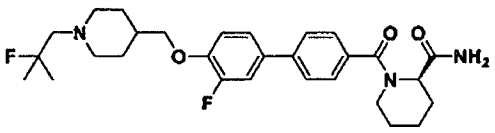
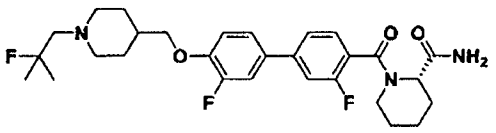
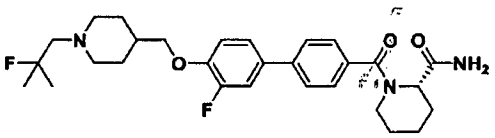
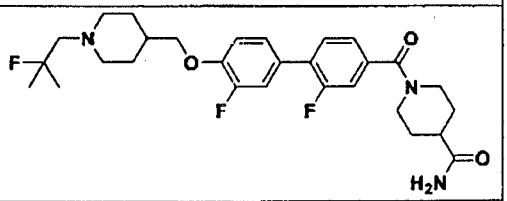
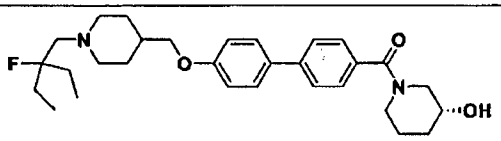
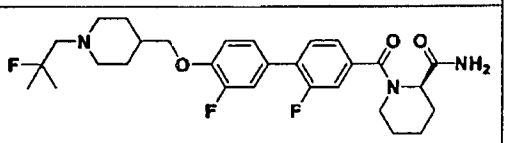
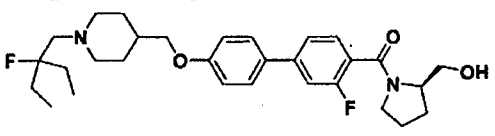
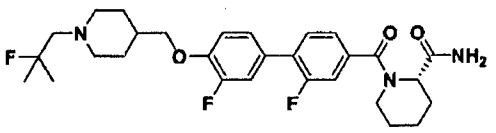
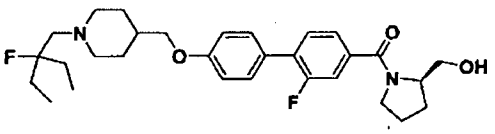
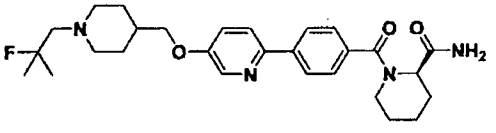
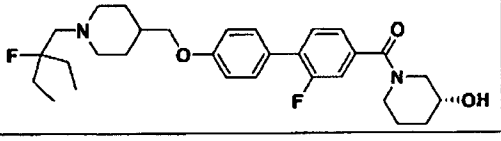
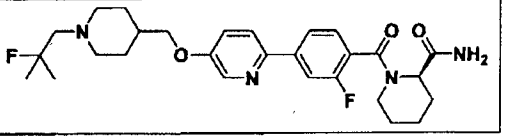
Compound	Structure	Compound	Structure
802		813	
803		814	
804		815	
805		816	
806		817	
807		818	
809		819	
810		820	
811		821	
812		822	

Table 169.

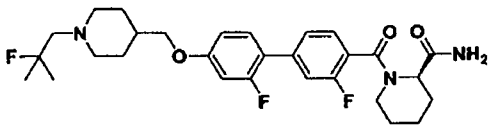
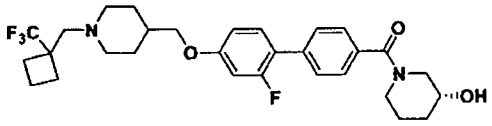
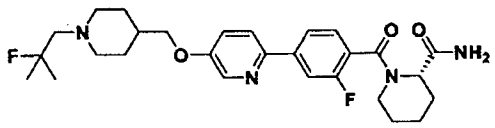
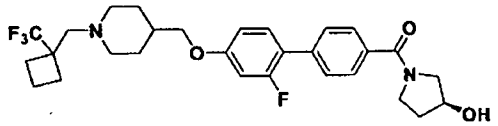
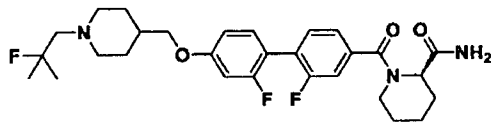
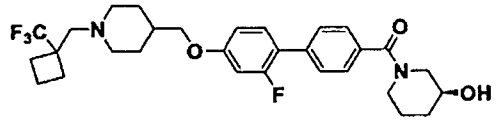
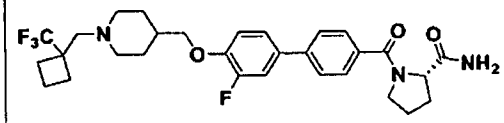
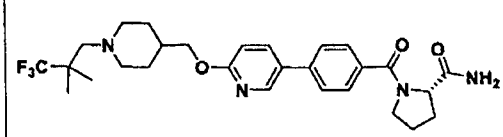
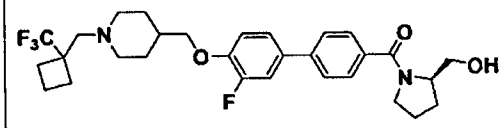
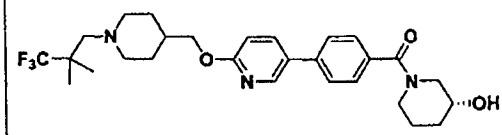
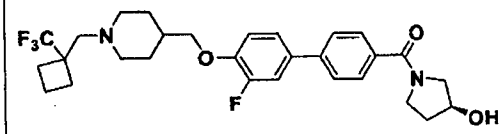
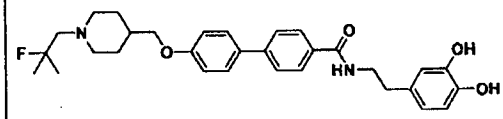
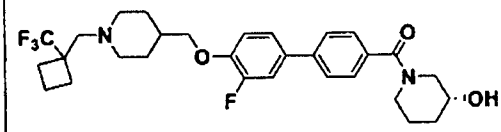
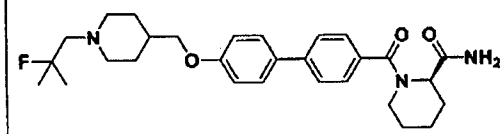
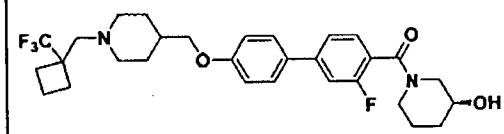
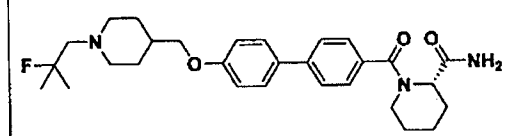
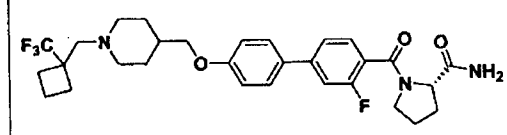
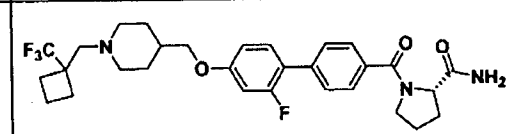
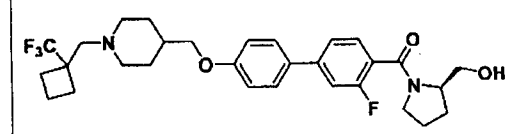
Compound	Structure	Compound	Structure
823		834	
824		835	
825		836	
-	-	837	
828		838	
829		839	
830		840	
831		842	
832		843	
833		844	

Table 170.

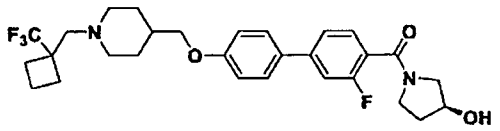
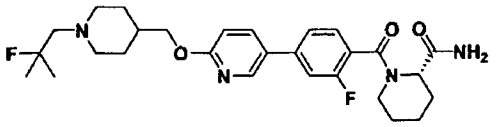
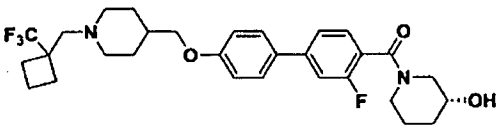
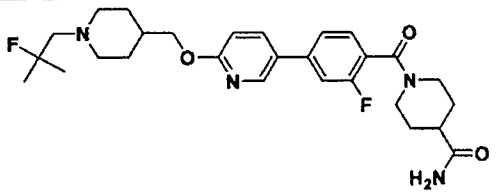
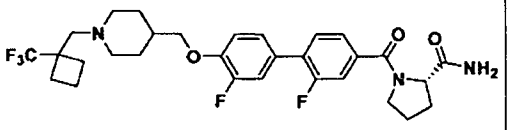
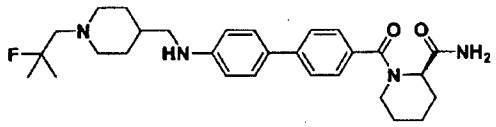
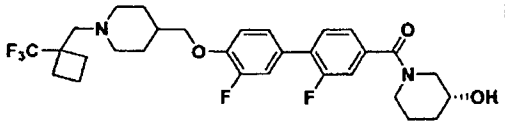
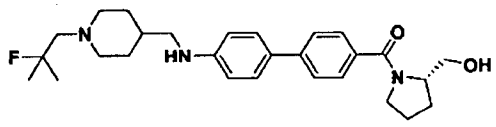
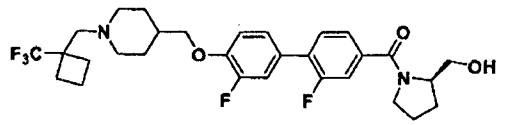
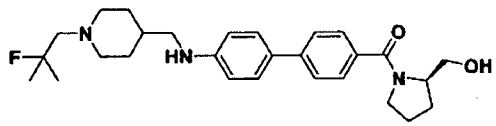
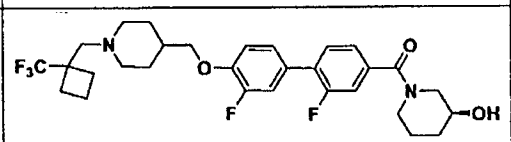
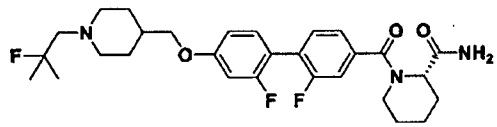
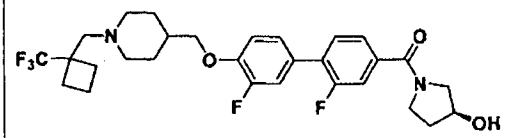
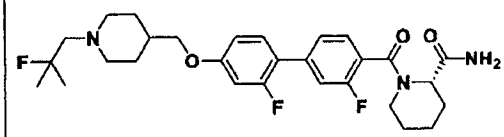
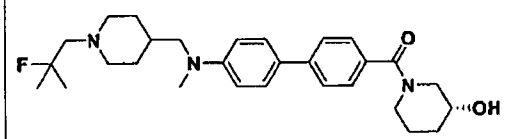
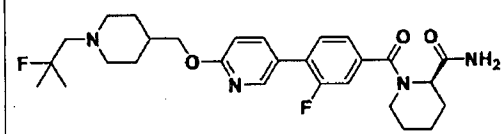
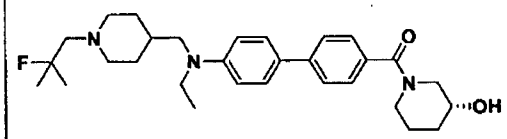
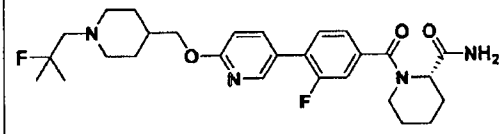
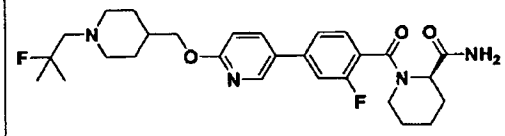
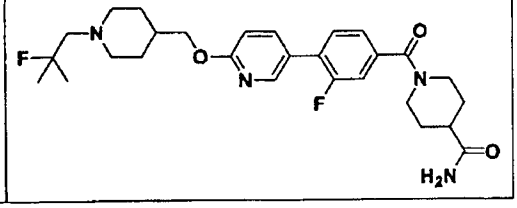
Compound	Structure	Compound	Structure
845		855	
846		856	
847		857	
848		858	
849		859	
850		860	
851		861	
852		862	
853		863	
854		864	

Table 171.

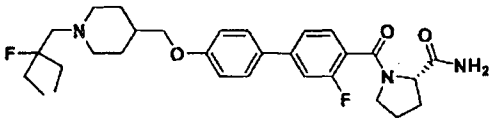
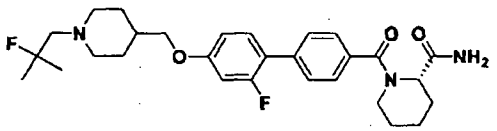
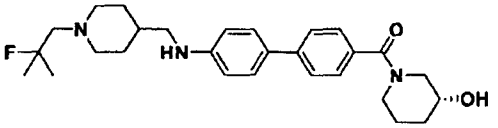
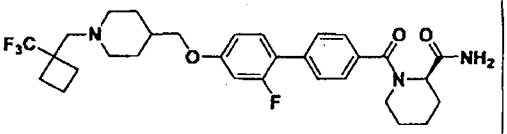
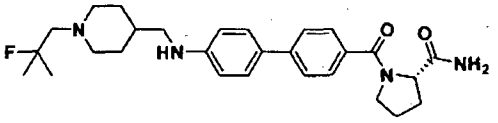
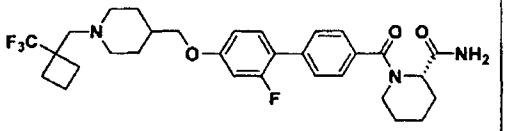
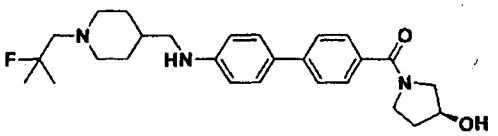
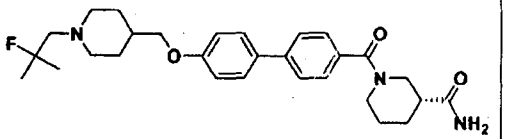
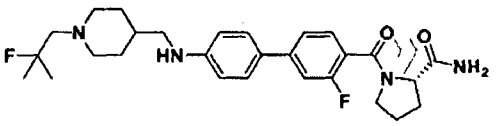
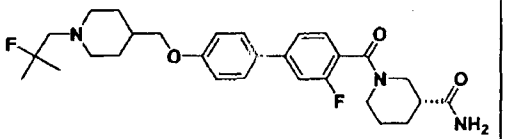
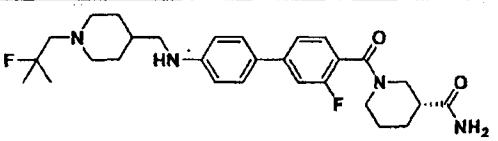
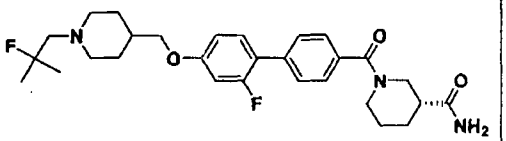
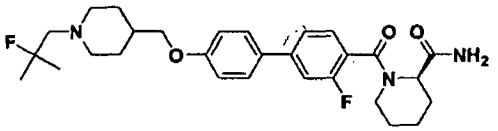
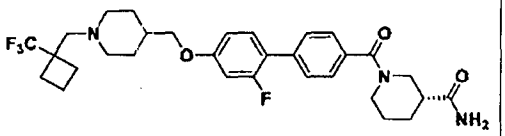
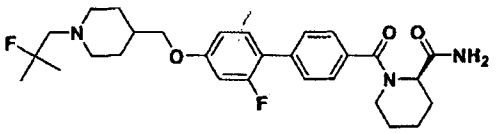
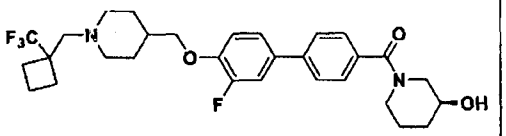
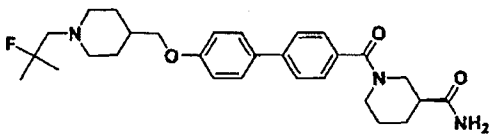
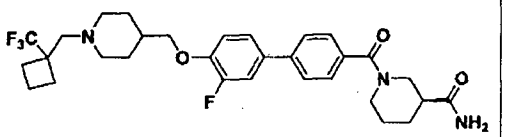
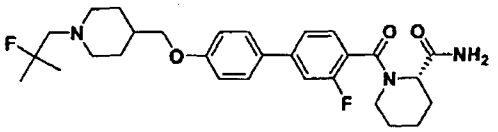
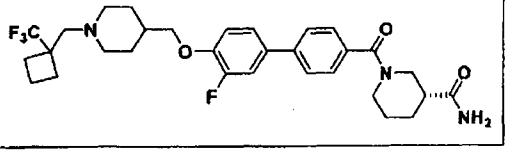
Compound	Structure	Compound	Structure
866		876	
867		877	
868		878	
869		879	
870		880	
871		881	
872		882	
873		883	
874		884	
875		885	

Table 172.

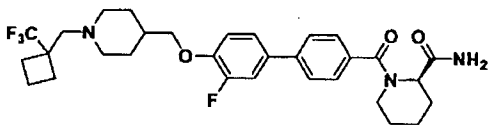
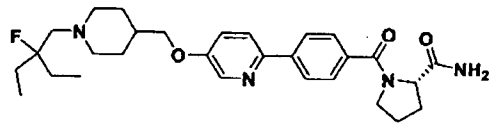
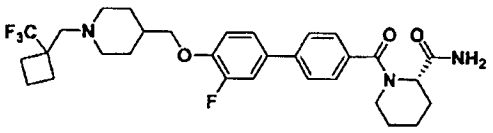
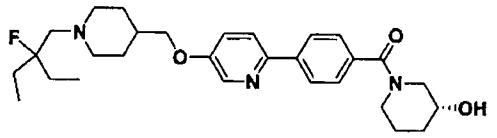
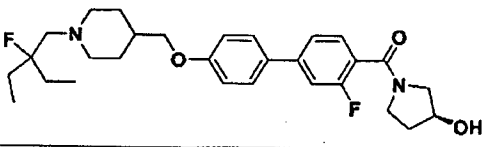
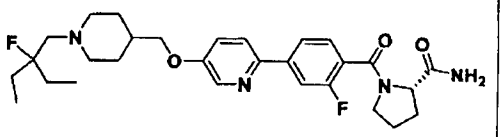
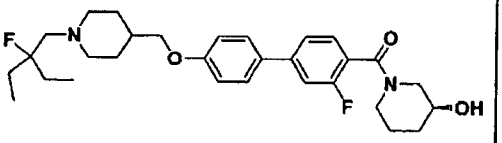
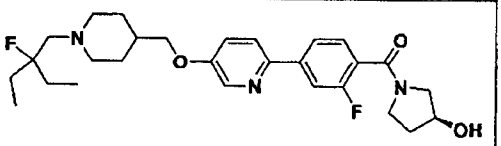
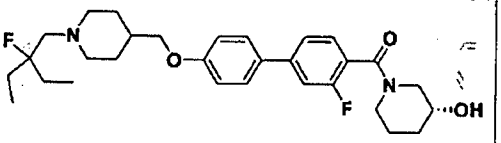
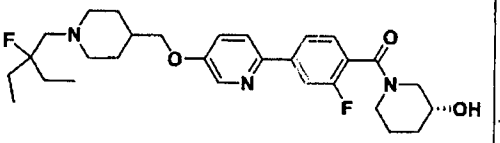
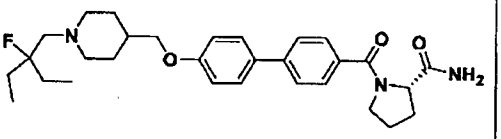
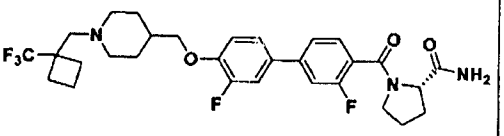
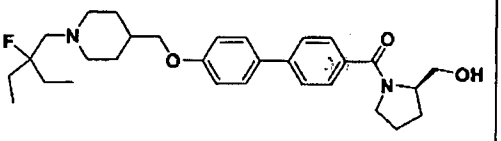
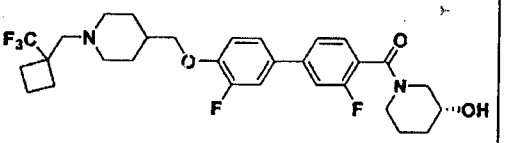
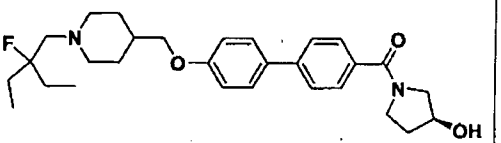
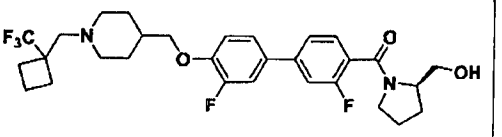
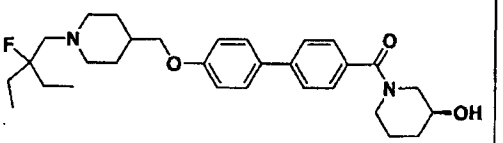
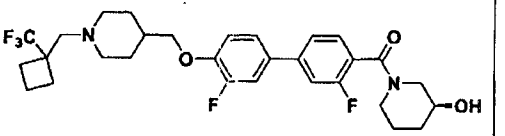
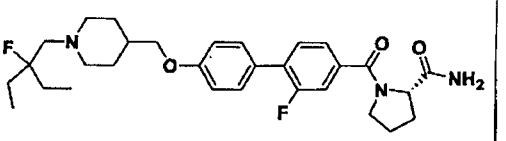
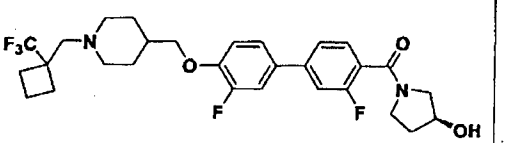
Compound	Structure	Compound	Structure
886		896	
887		897	
888		898	
889		899	
890		900	
891		901	
892		902	
893		903	
894		904	
895		905	

Table 173.

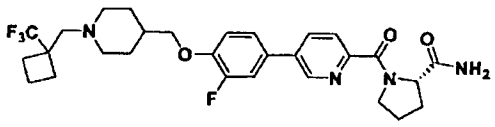
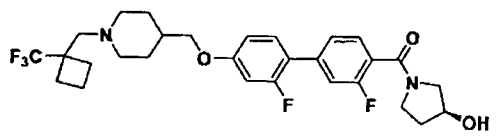
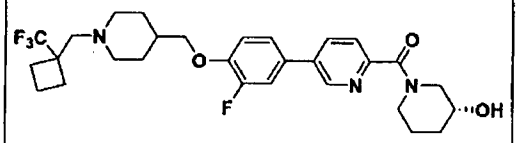
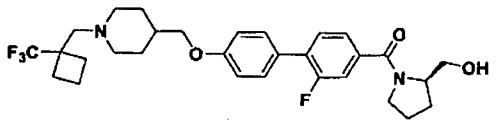
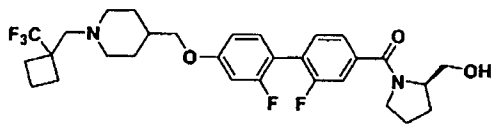
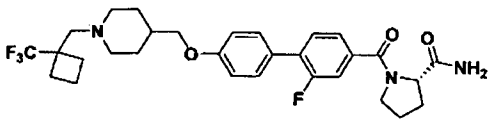
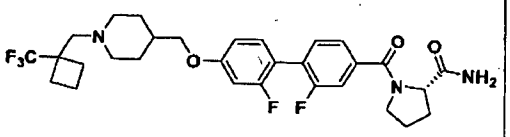
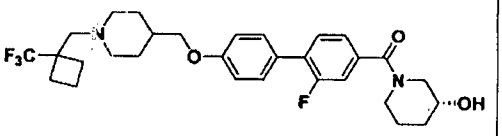
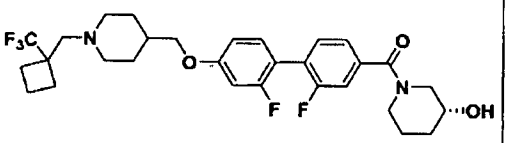
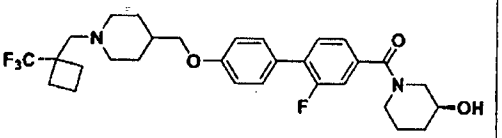
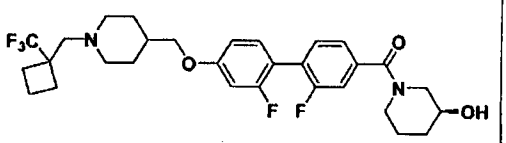
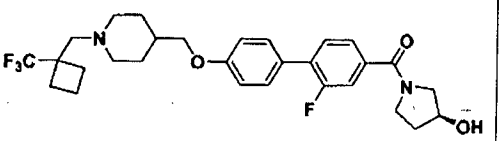
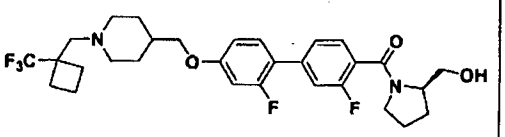
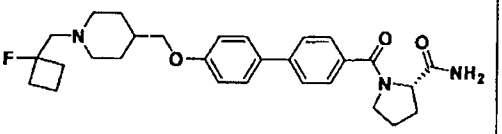
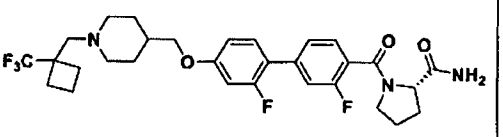
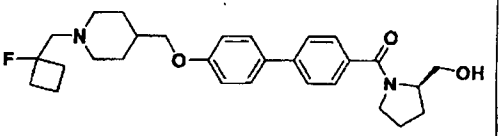
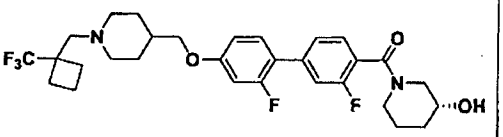
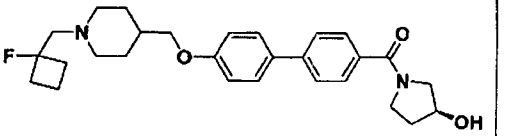
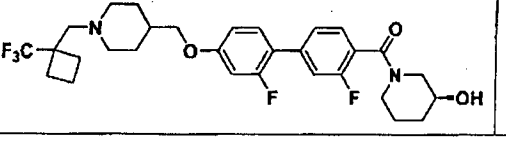
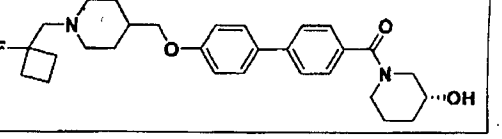
Compound	Structure	Compound	Structure
906		916	
907		917	
908		918	
909		919	
910		920	
911		921	
912		922	
913		923	
914		924	
915		925	

Table 174.

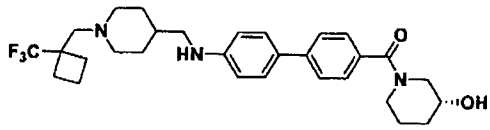
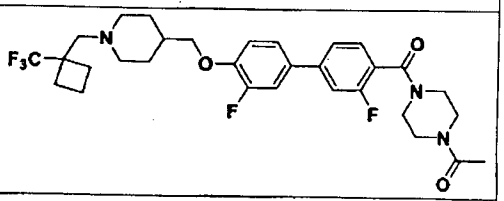
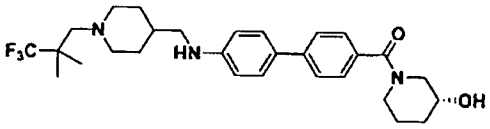
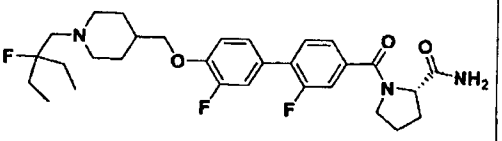
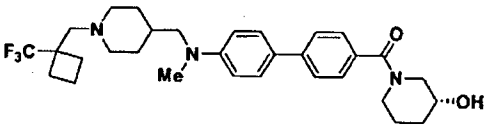
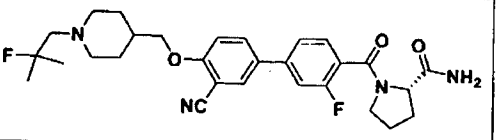
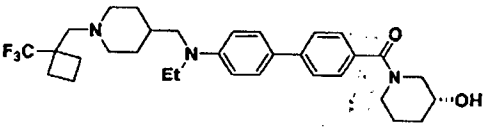
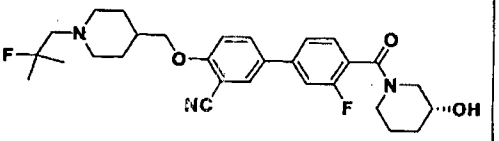
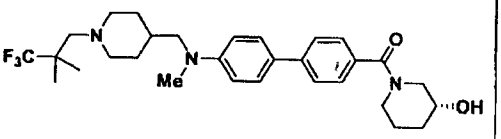
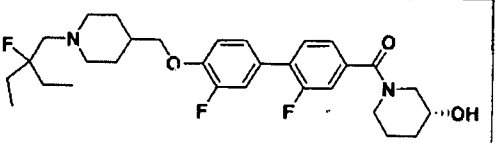
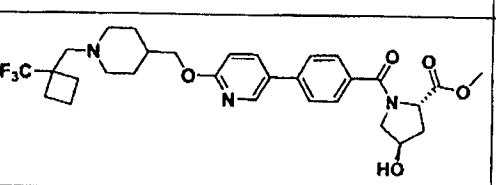
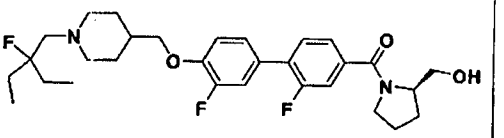
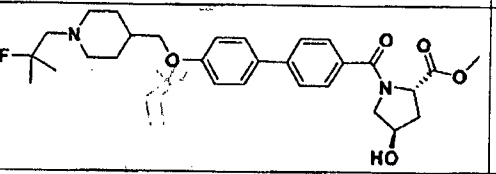
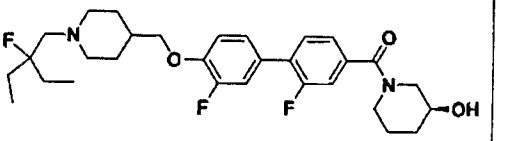
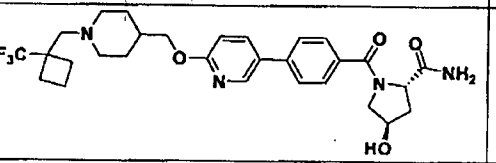
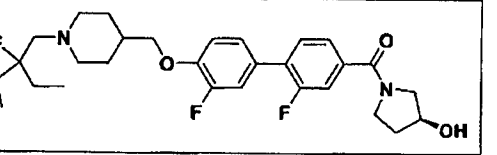
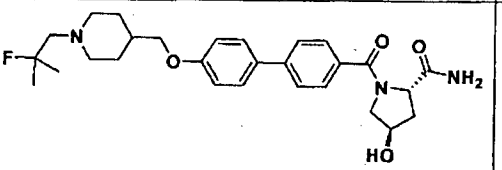
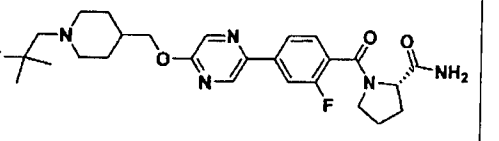
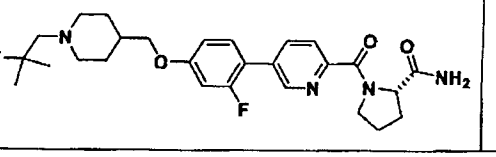
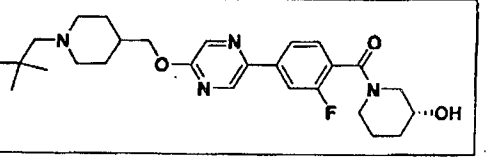
Compound	Structure	Compound	Structure
926		936	
927		937	
928		938	
929		939	
930		940	
931		941	
932		942	
933		943	
934		944	
935		945	

Table 175.

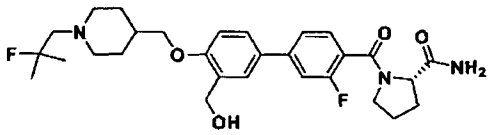
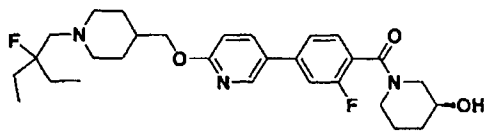
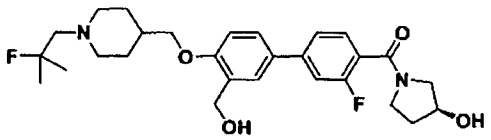
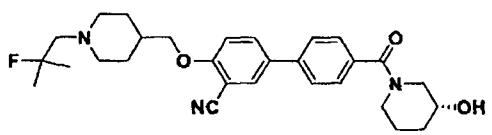
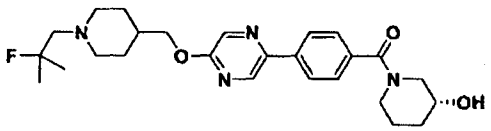
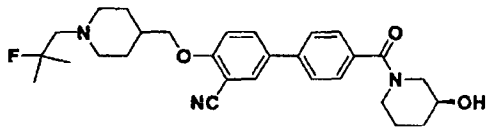
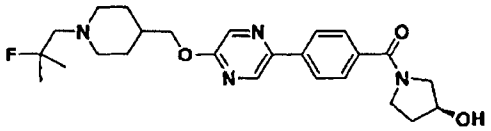
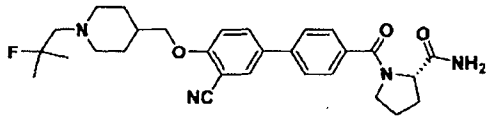
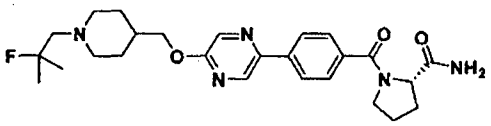
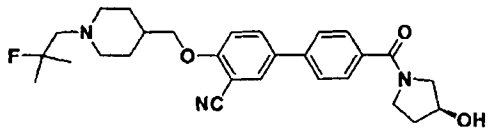
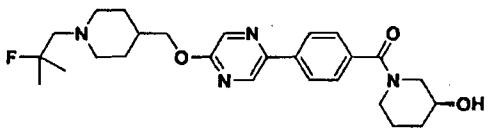
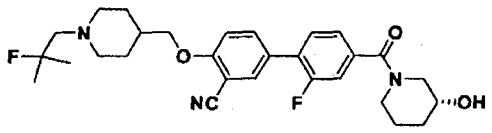
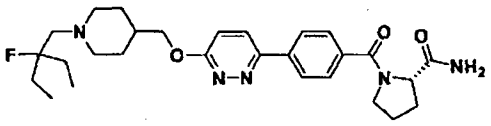
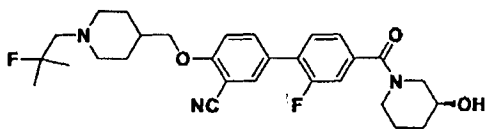
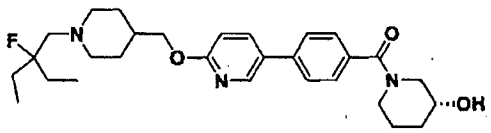
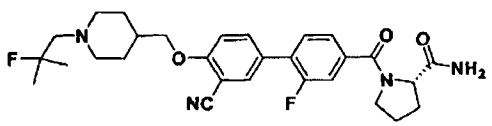
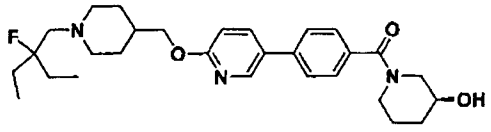
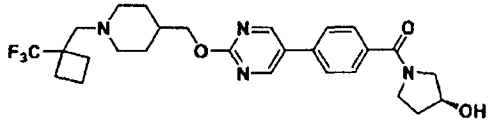
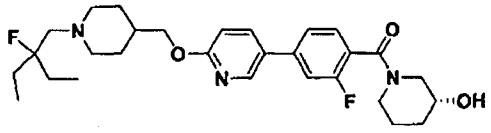
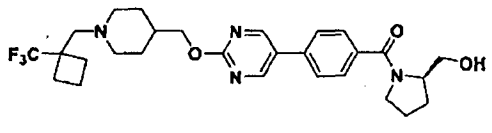
Compound	Structure	Compound	Structure
946		957	
947		963	
948		964	
949		965	
950		966	
951		967	
953		968	
954		969	
955		970	
956		971	

Table 176.

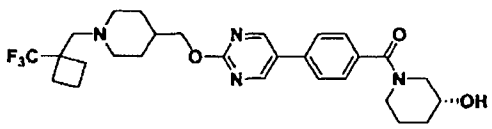
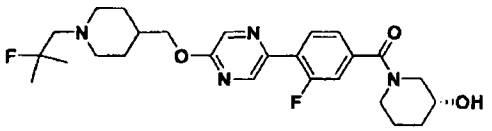
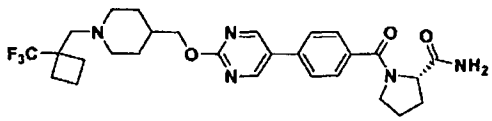
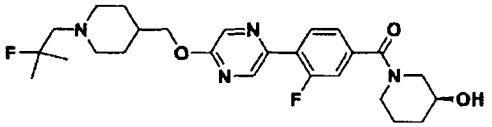
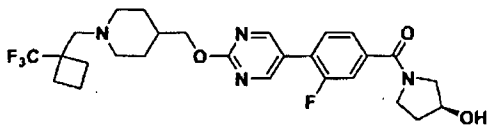
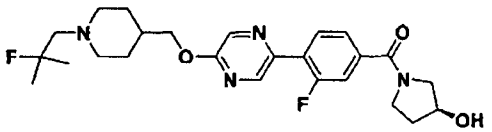
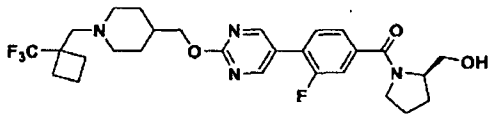
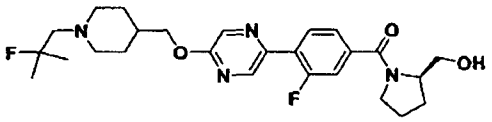
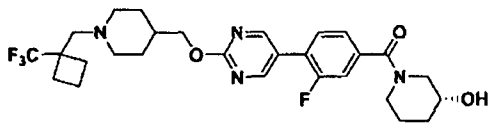
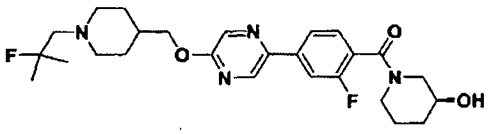
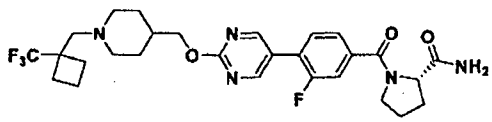
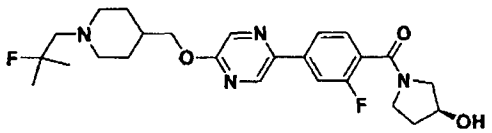
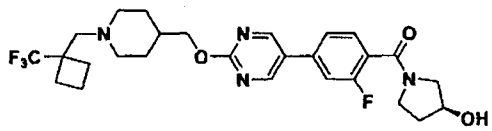
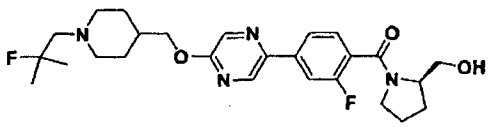
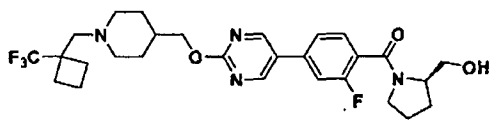
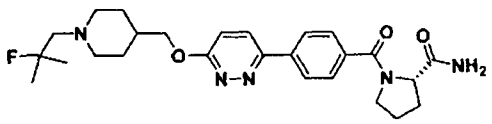
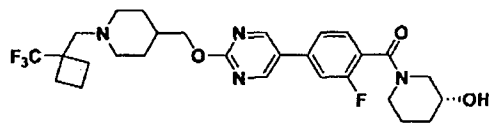
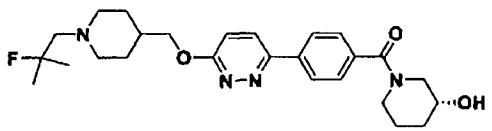
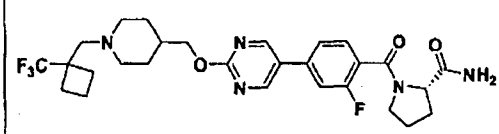
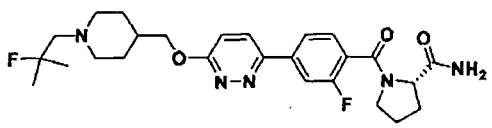
Compound	Structure	Compound	Structure
972		982	
973		983	
974		984	
975		985	
976		986	
977		987	
978		988	
979		989	
980		990	
981		991	

Table 177.

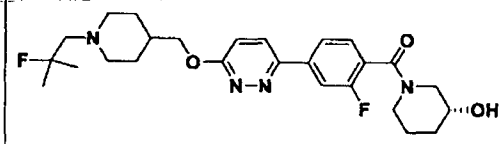
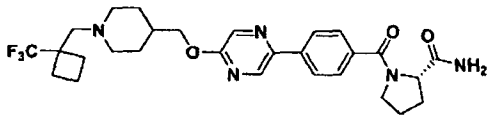
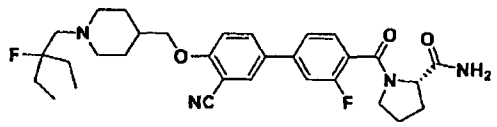
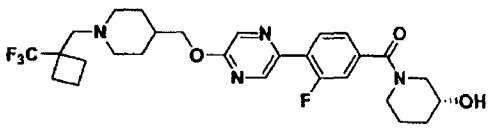
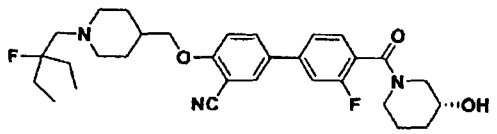
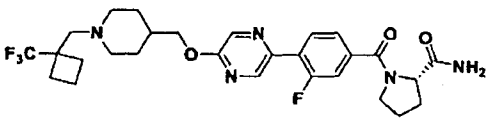
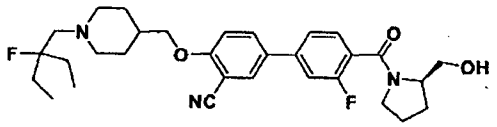
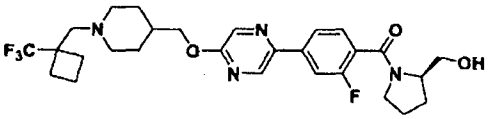
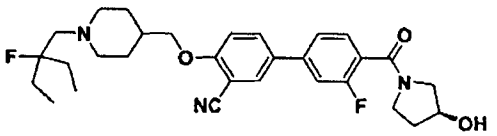
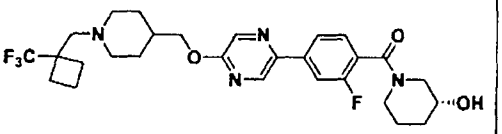
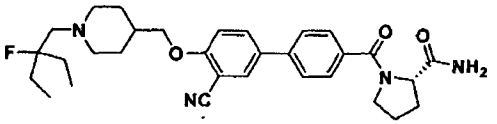
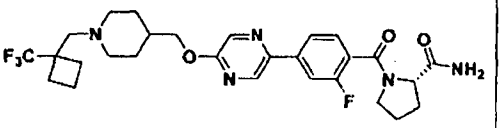
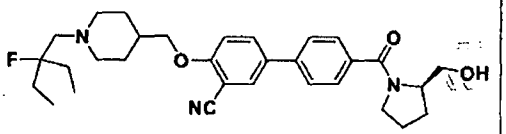
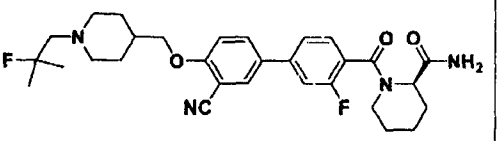
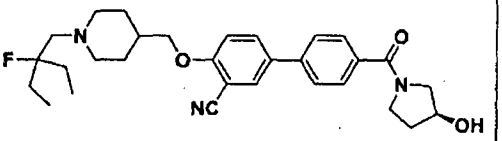
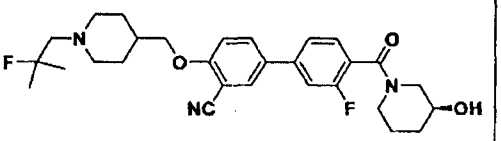
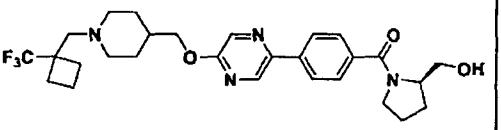
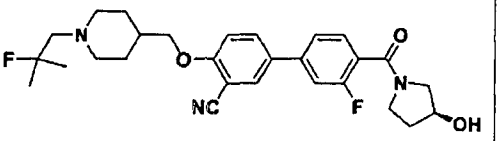
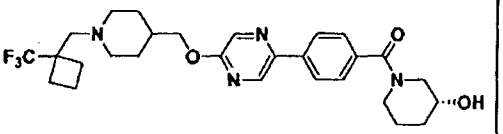
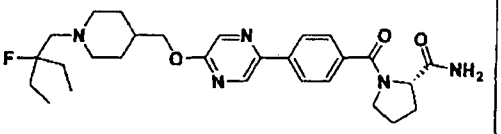
Compound	Structure	Compound	Structure
992		1009	
1000		1010	
1001		1011	
1002		1012	
1003		1013	
1004		1014	
1005		1015	
1006		1016	
1007		1017	
1008		1018	

Table 178.

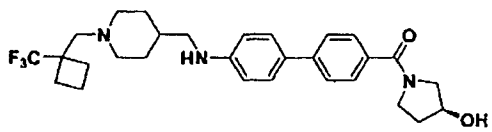
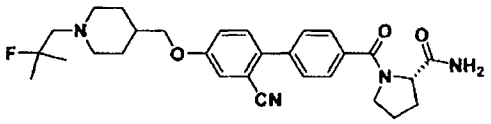
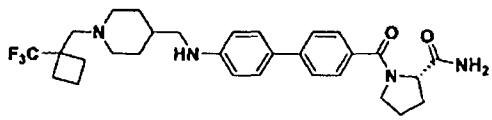
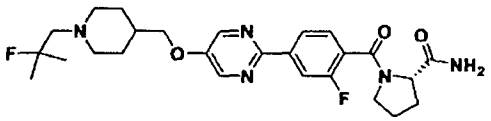
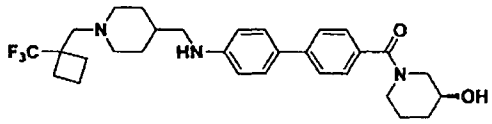
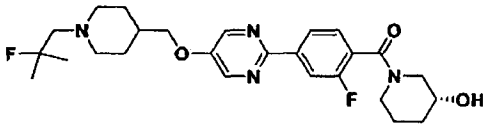
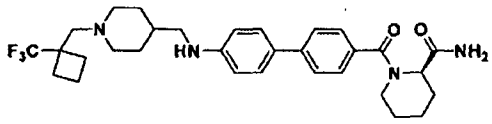
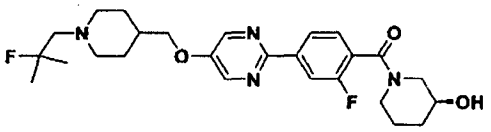
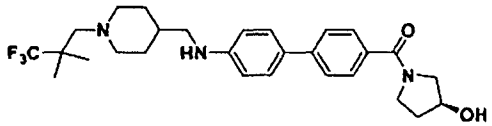
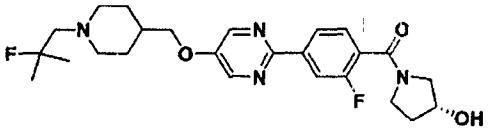
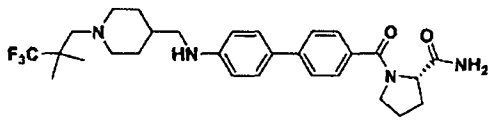
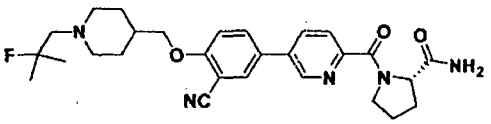
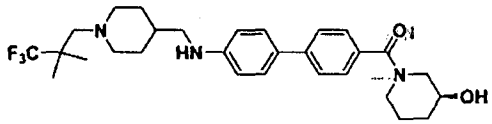
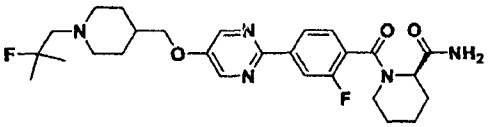
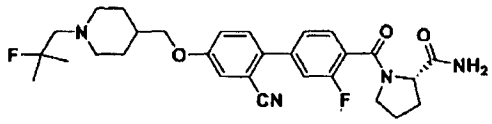
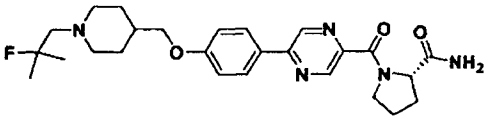
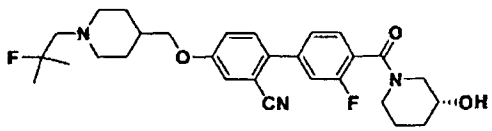
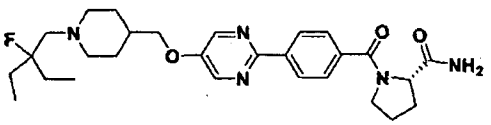
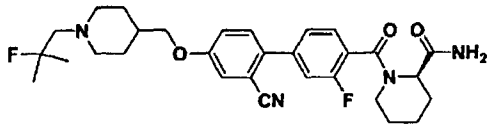
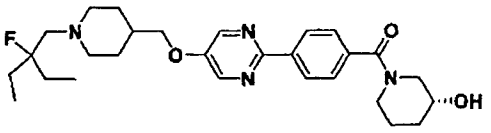
Compound	Structure	Compound	Structure
1020		1031	
1021		1032	
1022		1033	
1023		1034	
1024		1035	
1025		1036	
1026		1037	
1028		1038	
1029		1051	
1030		1052	

Table 179.

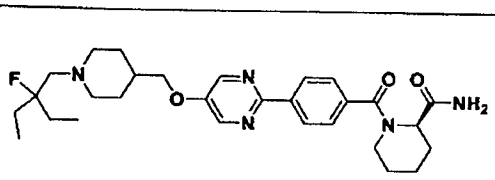
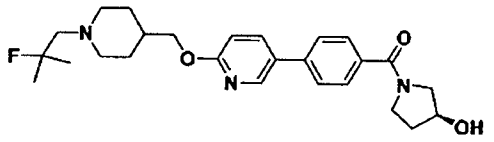
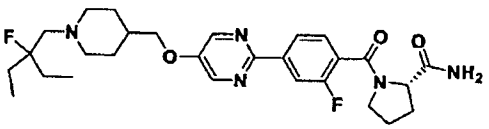
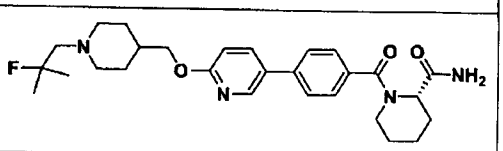
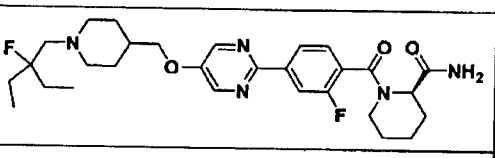
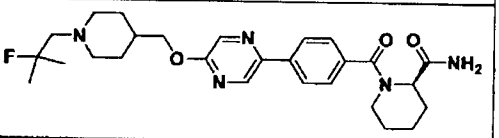
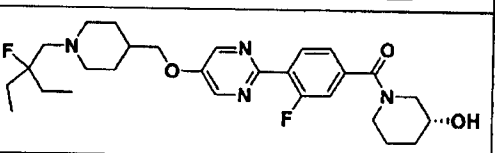
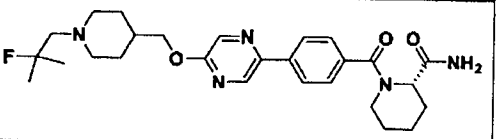
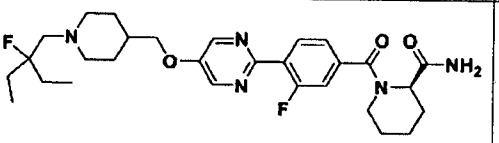
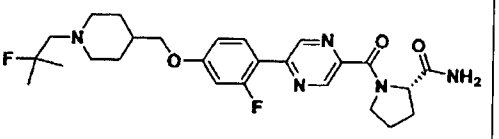
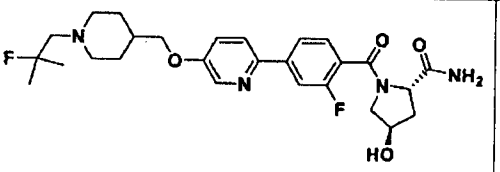
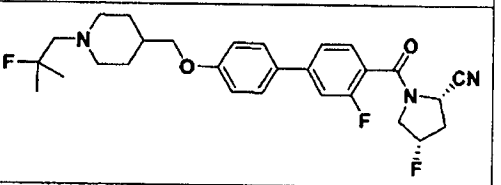
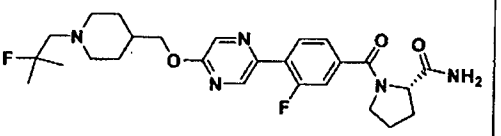
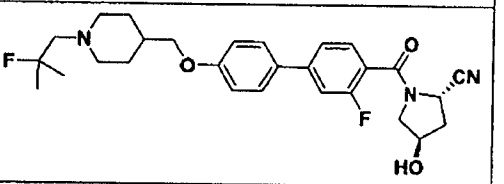
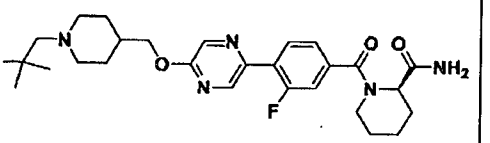
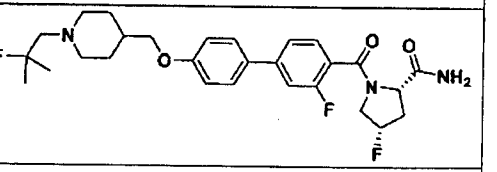
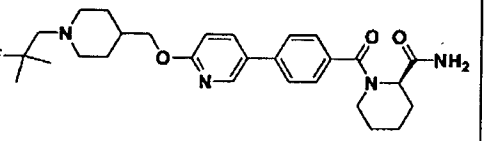
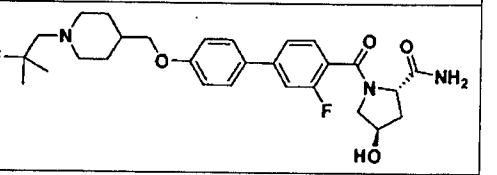
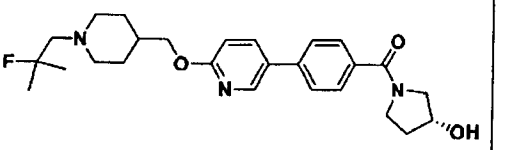
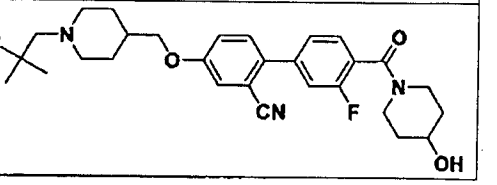
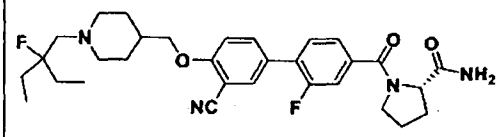
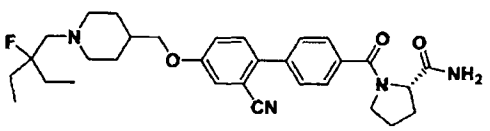
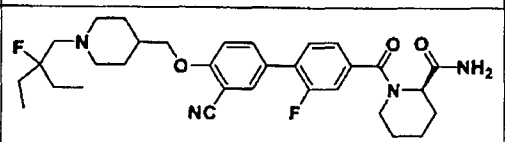
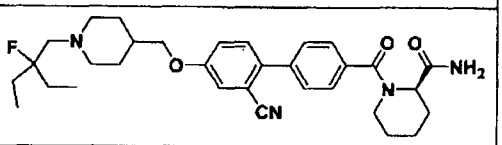
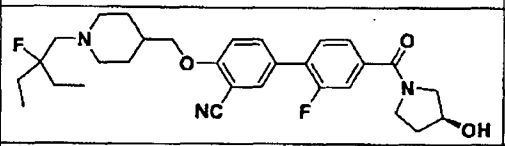
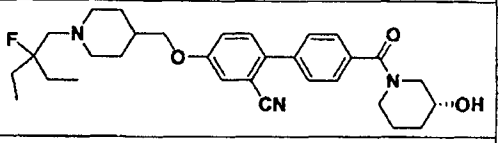
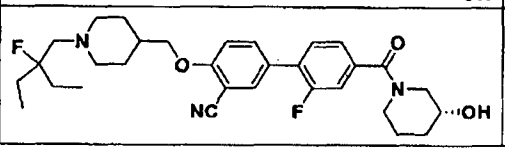
Compound	Structure	Compound	Structure
1053		1078	
1054		1079	
1055		1080	
1056		1081	
1057		1082	
1067		1097	
1072		1098	
1073		1099	
1076		1100	
1077		1115	

Table 180.

Compound	Structure	Compound	Structure
1119		1124	
1120		1125	
1121		1126	
1123		-	-

Protocol of Experiment: Activity test of the compound of the present invention

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

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

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

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

Table 181. Result of activity test for human GPR119

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
	10	289
517	0.1	192
	1	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
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
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

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

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:

A. a vehicle group (10 % EtOH, 20 % HPBCD in saline),

B. a positive control group administered with MBX-2982 (10 mg/kg), and

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

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

	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
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

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:

A. a vehicle group (10 % EtOH, 20 % HPBCD in D.W.),

B. a positive control group administered with Sitagliptin (30 mg/kg), and

C. test groups administered with compound 770 and Compound 1028 (10, 30 mg/kg and combination administration with sitagliptin 30 mg/kg).

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

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)

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.

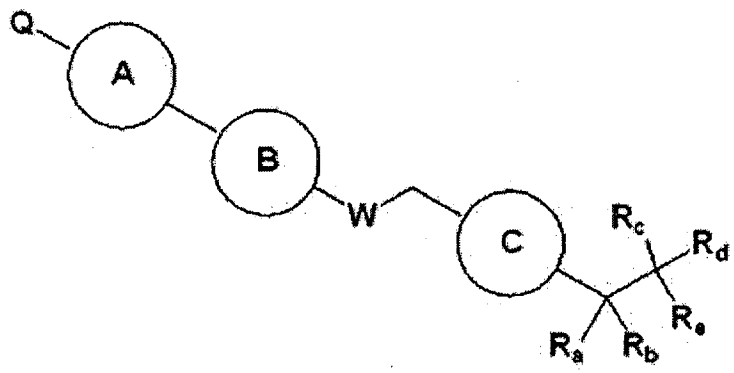
Table 183.

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

CLAIMS

1. A piperidine derivative of the following formula 1, stereoisomers thereof or pharmaceutically acceptable salts thereof:

[Formula 1]



wherein

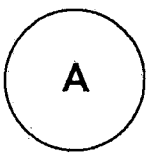
W is O or N-R_h;

R_a, R_b and R_h are each independently H or C_{1-3} alkyl;

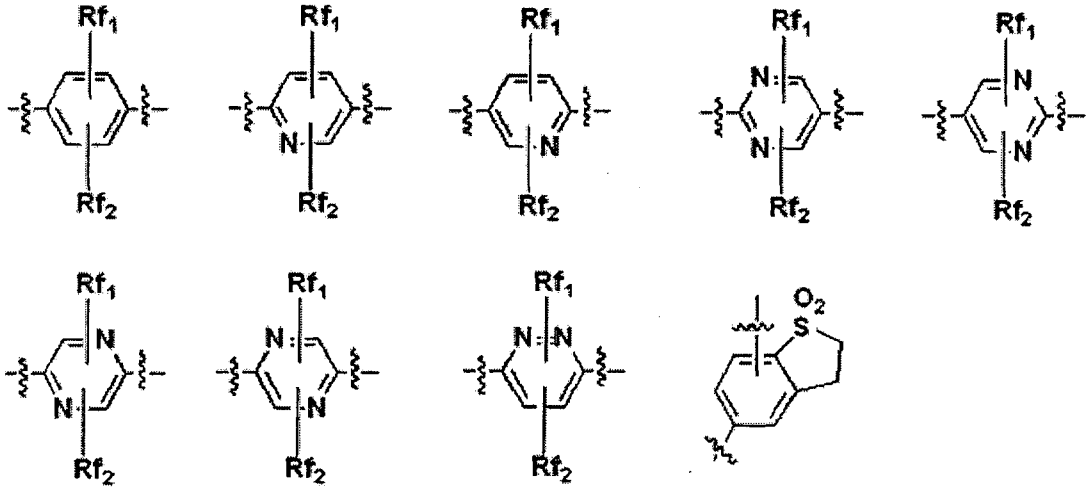
R_c is -F or -C_{1-3} hyperfluoride alkyl;

R_d and R_e are each independently selected from the group consisting of H, halogen, -C_{1-5} alkyl and -C_{3-7} cycloalkyl, wherein -C_{1-5} alkyl and -C_{3-7} cycloalkyl are each independently unsubstituted or substituted with halogen, -CN, -OC_{1-5} alkyl or -C_{1-5} alkyl;

or R_d and R_e are combined to form a -C_{3-7} cycloalkyl, wherein the -C_{3-7} cycloalkyl is unsubstituted or substituted with halogen, -OC_{1-5} alkyl or -C_{1-5} alkyl;

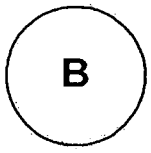


is selected from the group consisting of:

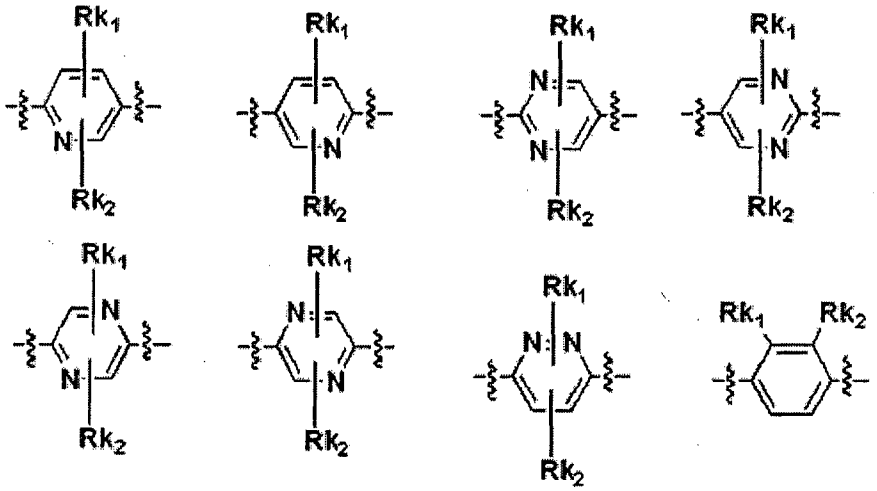


, wherein

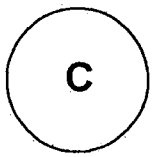
Rf_1 and Rf_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or -CN ;

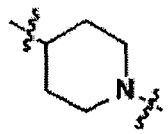


is selected from the group consisting of:

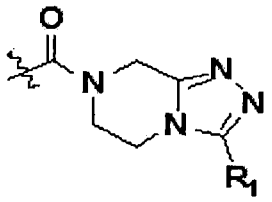


, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or -CN ;



is  ;

Q is H, -S(O)R_1, -S(O)$_2R_1$, -C(O)R_1, -C(O)OR_1, -C(O)NHR_1, -C(O)NR_2R_3, -S(O)$_2$NHR_1,



-S(O)$_2$NR_2R_3 or ,

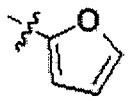
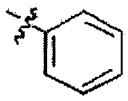
wherein

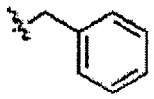
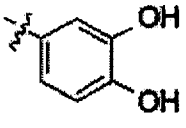
R_1 is H, -CF_3, -C_{1-5} alkyl, 3 to 7-membered heterocyclic ring, C_{3-7} cycloalkyl, or Ar,

R_2 and R_3 are each independently C_{1-5} alkyl, C_{3-7} cycloalkyl, 3 to 7-membered heterocyclic ring or Ar (in R_1, R_2 and R_3, -C_{1-5} alkyl, 3 to 7-membered heterocyclic ring, C_{3-7} cycloalkyl and Ar may be each independently substituted with Rx_1 and Rx_2.),

or R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C(O), wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Ar is C6 monocyclic aromatic compound; or 5- or 6-membered heteroaryl group comprising 1 to 3 members selected from the group consisting of N, O and S,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, -CF_3, 3- to 7- membered heterocyclic ring, -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{1-5} alkyl(OH), -C_{1-5} alkyl(OR_4), -C_{1-5} alkyl(halogen), -C(O)NR_4R_5, -C(O)R_4, -C(O)OR_4, -S(O)$_2R_4$, -OR_4,  ,  ,

 or  [wherein R_4 and R_5 are each independently H, -C_{1-5} alkyl or -C_{3-7} cycloalkyl.].

2. The piperidine derivative, stereoisomers thereof or pharmaceutically acceptable salts thereof according to claim 1, wherein

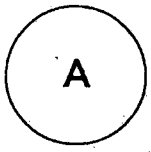
W is O;

R_a and R_b are each independently H;

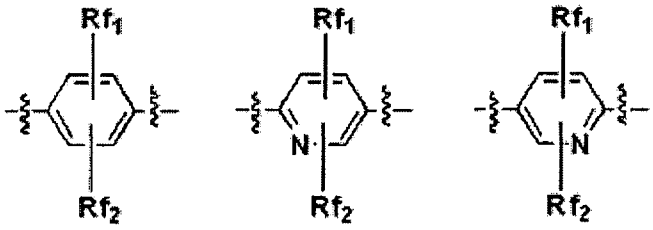
R_c is -F or -CF_3;

R_d and R_e are each independently -C_{1-5} alkyl,

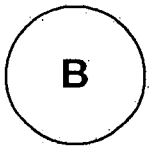
or R_d and R_e are combined to form a -C_{3-7} cycloalkyl, wherein the -C_{3-7} cycloalkyl is unsubstituted or substituted with halogen, -OC_{1-5} alkyl or -C_{1-5} alkyl;



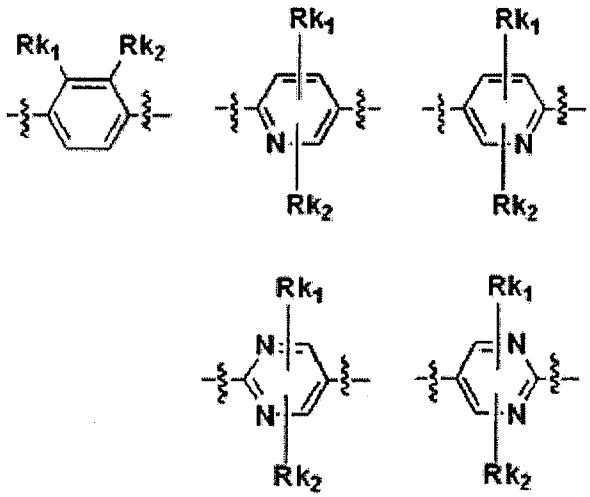
is selected from the group consisting of:



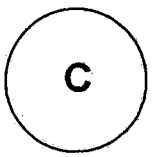
,wherein Rf_1 and Rf_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;

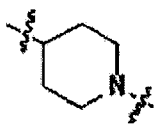


is selected from the group consisting of:



, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;



is  ;

Q is -$S(O)_2R_1$, -$C(O)NR_2R_3$ or -$S(O)_2NR_2R_3$,

wherein R_1, R_2 and R_3 are each independently C_{1-5} alkyl substituted with Rx_1 and Rx_2,

or R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C(O),

wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, $-CF_3$, 3- to 7-membered heterocyclic ring, $-C_{1-5}$ alkyl, $-C_{3-7}$ cycloalkyl, $-C_{1-5}$ alkyl(OH), $-C_{1-5}$ alkyl(OR_4), $-C_{1-5}$ alkyl(halogen), $-C(O)NR_4R_5$, $-C(O)R_4$, $-C(O)OR_4$, $-S(O)_2R_4$ or $-OR_4$ [wherein R_4 and R_5 are each independently H, $-C_{1-5}$ alkyl or $-C_{3-7}$ cycloalkyl.].

3. The piperidine derivative, stereoisomers thereof or pharmaceutically acceptable salts thereof according to claim 1, wherein

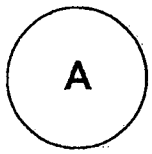
W is O;

R_a and R_b are each independently H;

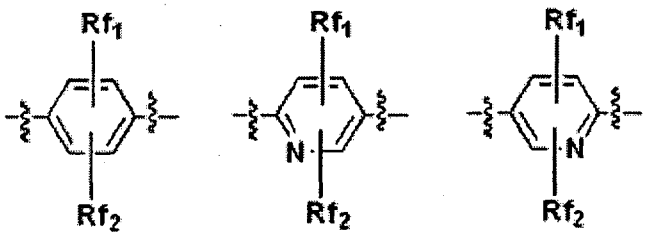
R_c is -F or $-CF_3$;

R_d and R_e are each independently $-C_{1-5}$ alkyl,

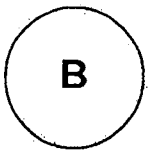
or R_d and R_e are combined to form $-C_{3-7}$ cycloalkyl, wherein the $-C_{3-7}$ cycloalkyl is unsubstituted or substituted with halogen, $-OC_{1-5}$ alkyl or $-C_{1-5}$ alkyl;



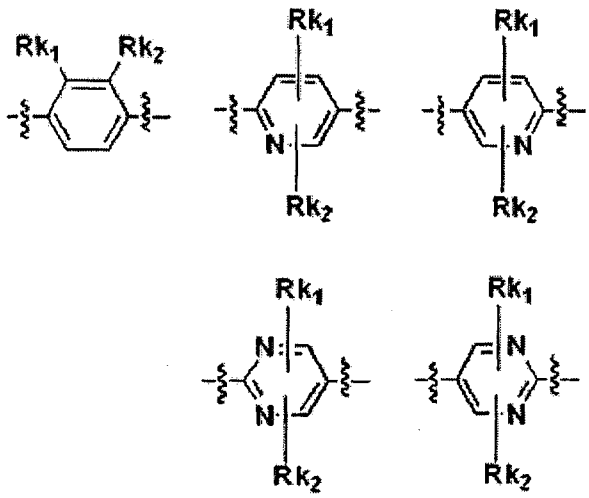
is selected from the group consisting of:



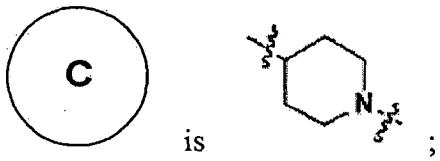
, wherein Rf_1 and Rf_2 are each independently H, halogen, $-C_{1-5}$ alkyl, $-C_{1-5}$ alkyl(OH), $-OC_{1-5}$ alkyl or –CN;



is selected from the group consisting of:



, wherein Rk_1 and Rk_2 are each independently H, halogen, -C_{1-5} alkyl, -C_{1-5} alkyl(OH), -OC_{1-5} alkyl or –CN;



;

Q is -$C(O)NR_2R_3$,

wherein R_2 and R_3 together with the N atoms to which they are bonded may form a 5- or 6-membered heterocyclic aromatic or non-aromatic ring compound further having 0 to 3 members selected independently from the group consisting of N, O, S and C(O),

wherein the heterocyclic aromatic or non-aromatic ring compound may be substituted with Rx_1 and Rx_2,

wherein Rx_1 and Rx_2 are each independently H, -OH, halogen, -CN, -CF_3, 3- to 7-membered heterocyclic ring, -C_{1-5} alkyl, -C_{3-7} cycloalkyl, -C_{1-5} alkyl(OH), -C_{1-5} alkyl(OR_4), -C_{1-5} alkyl(halogen), -$C(O)NR_4R_5$, -$C(O)R_4$, -$C(O)OR_4$, -$S(O)_2R_4$ or -OR_4 [wherein R_4 and R_5 are each independently H, -C_{1-5} alkyl or -C_{3-7} cycloalkyl.].

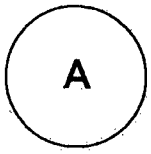
4. The piperidine derivative, stereoisomers thereof or pharmaceutically acceptable salts thereof according to claim 1, wherein

W is O;

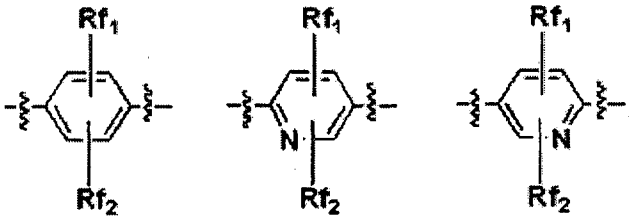
R_a and R_b are each independently H;

R_c is –F or -CF_3;

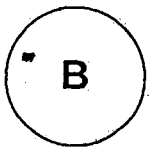
R_d and R_e are each independently selected from the group consisting of -CH_3 and -CH_2CH_3.



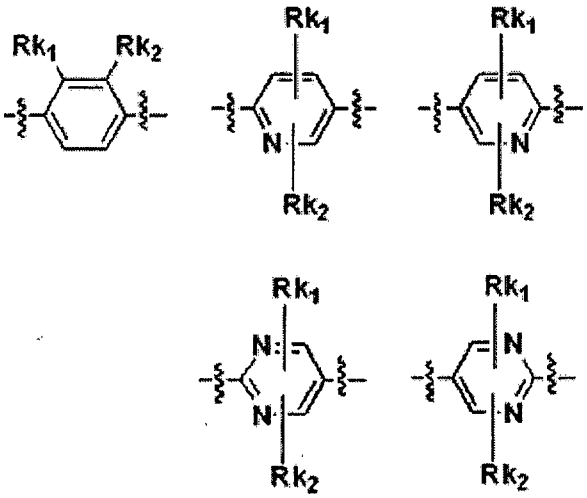
is selected from the group consisting of:



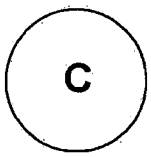
, wherein Rf_1 and Rf_2 are each independently H, -F or –CN;

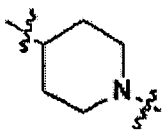


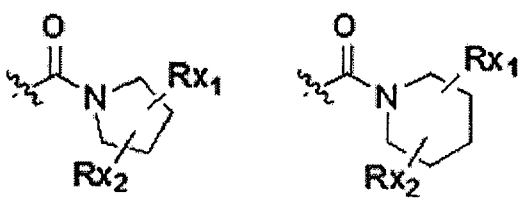
is selected from the group consisting of:



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



is  ;

Q is selected from the group consisting of:  , wherein

Rx_1 and Rx_2 are each independently H, OH, -F, -CN, $-CF_3$, $-CH_2OH$ or $-C(O)NH_2$.

5. The piperidine derivative, stereoisomers thereof, pharmaceutically acceptable salts thereof according to claim 1, wherein the piperidine derivative is selected from the group consisting of:

1-(2-fluoro-2-methylpropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide;

methyl 4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylate;

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(2,2,2-trifluoroethyl)piperidine;

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidine;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(morpholino)methanone;

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-(3,3,3-trifluoropropyl)piperidine;

N-cyclopropyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

N-cyclobutyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

N-cyclopentyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

N-cyclohexyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(pyrrolidin-1-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperidin-1-yl)methanone;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(4-hydroxybutyl)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide;

5-(4-((1-(2,2,2-trifluoroethyl)piperidin-4-yl)methoxy)phenyl)-2,3-dihydrobenzo[b]thiophene 1,1-dioxide;

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidine;

4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)-1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidine;

1-(2,2-difluoropropyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxylic acid;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(3-hydroxypropyl)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)-N-methylbiphenyl-4-carboxamide;

N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone;

N-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(2-hydroxyethyl)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(furan-2-ylmethyl)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-propylbiphenyl-4-carboxamide;

N-benzyl-N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(trifluoromethyl)pyrrolidin-1-yl)methanone;

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

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(hydroxymethyl)piperidin-1-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-hydroxypiperidin-1-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-fluoropyrrolidin-1-yl)methanone;

4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoic acid;

1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)ethanone;

N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzamide;

(S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

N,N-dimethyl-4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzamide;

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

morpholino(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

piperidin-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

pyrrolidin-1-yl(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

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

(4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(4-(hydroxymethyl)piperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclopropyl)methyl)piperidin-4-yl)methoxy)pyridine;

1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)ethanone;

(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]pyrazin-7(8H)-yl)methanone;

(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

2-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5-(4-(methylsulfonyl)phenyl)pyridine;

5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-2-(4-(methylsulfonyl)phenyl)pyridine;

N-ethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropyl-N-methylbiphenyl-4-carboxamide;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxyazetidin-1-yl)methanone;

(3,3-difluoroazetidin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

N-tert-butyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-isopropylbiphenyl-4-carboxamide;

N,N-diethyl-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide;

(S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxypropan-2-yl)biphenyl-4-carboxamide;

(R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxybutan-2-yl)biphenyl-4-carboxamide;

(R)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide;

(S)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-3-methylbutan-2-yl)biphenyl-4-carboxamide;

N-(1,3-dihydroxypropan-2-yl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

N-(2,3-dihydroxypropyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-sulfonamide;

1-(2-fluoro-2-methylpropyl)-4-((4'-(pyrrolidin-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

1-(2-fluoro-2-methylpropyl)-4-((4'-(piperidin-1-ylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

2-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-5-(methylsulfonyl)pyridine;

5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)-2-(methylsulfonyl)pyridine;

(R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate;

(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylic acid;

2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-ylcarboxamido)acetic acid;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(thiazolidin-3-yl)methanone;

(4-(cyclopropanecarbonyl)piperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-(methylsulfonyl)piperazin-1-yl)methanone;

(S)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxylate;

tert-butyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazine-1-carboxylate;

(4-benzylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

1-(4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone;

(3,3-difluoropyrrolidin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(piperazin-1-yl)methanone;

N,N-dimethyl-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

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

N-(2-hydroxyethyl)-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

N-(2-hydroxyethyl)-N-methyl-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide;

N,N-diethyl-3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(1-hydroxy-2-methylpropan-2-yl)biphenyl-4-carboxamide;

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

methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)acetate;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-(oxetan-3-yl)biphenyl-4-carboxamide;

methyl 3-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)propanoate;

(R)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydroxypropanoate;

(S)-methyl 2-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)-3-hydroxypropanoate;

ethyl 4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylcarboxamido)piperidine-1-carboxylate;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-pentylbiphenyl-4-carboxamide;

(R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-1-(4'-((1-(2-fluoropentyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidin-3-ol;

(R)-(1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidin-2-yl)methanol;

(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)pyrrolidine-2-carboxamide;

(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol;

(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-ylsulfonyl)piperidin-3-ol;

(R)-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(S)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-sulfonamide;

4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-N-methylbiphenyl-4-sulfonamide;

5-(4-(methylsulfonyl)phenyl)-2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridine;

ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-3-carboxylate;

ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxylate;

ethyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxylate;

(4-ethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-isopropylpiperazin-1-yl)methanone;

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

(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N,N-dimethylpyrrolidine-2-carboxamide;

(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-N-methylpyrrolidine-2-carboxamide;

(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(4-methylpiperazin-1-yl)methanone;

(3,5-dimethylpiperazin-1-yl)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(2,6-dimethylmorpholino)(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)-N,N-dimethylbiphenyl-4-carboxamide;

(4'-((1-(2-fluoropropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(4'-((1-(2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

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

(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

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

(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

1-(2-fluoro-2-methylpropyl)-4-((2-fluoro-4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

(S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(3'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

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

(S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypyrrolidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypyrrolidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone;

(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2',3-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(2,3'-difluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide;

1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide;

(R)-(6-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-3-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(5-(4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(4'-((1-((1-fluorocyclohexyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

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

(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclopentyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(S)-(3-hydroxypyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

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

(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-((1-(trifluoromethyl)cyclohexyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

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

(R)-(5-(3-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

1-((1-fluorocyclohexyl)methyl)-4-((4'-(methylsulfonyl)biphenyl-4-yloxy)methyl)piperidine;

4-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-2-one;

1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carbonitrile;

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

(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]pyrazin-7(8H)-yl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(R)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

(S)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)methanone;

1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide;

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

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

1-(2'-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-4-carboxamide;

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

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

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

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

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

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

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

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

(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

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

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

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

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

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

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

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

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

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

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

(R)-(3-hydroxypiperidin-1-yl)(4-(6-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)methanone;

N-(3,4-dihydroxyphenethyl)-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenyl-4-carboxamide;

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

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

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

(R)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(2'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(4'-(((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)(methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-(ethyl((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

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

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

(R)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-2-carboxamide;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

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

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

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

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

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

(R)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(S)-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-3-carboxamide;

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

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

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

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

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

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

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

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

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

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

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

(S)-(3'-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

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

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

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

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3-fluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

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

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

(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

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

(S)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorophenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-2-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

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

(R)-(5-(3-fluoro-4-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)phenyl)pyridin-2-yl)(3-hydroxypiperidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((R)-3-hydroxypiperidin-1-yl)methanone;

(2,2'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)((S)-3-hydroxypiperidin-1-yl)methanone;

(R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2',3-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

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

(R)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

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

(R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(4'-((1-((1-fluorocyclobutyl)methyl)piperidin-4-yl)methoxy)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone;

(R)-(4'-(ethyl((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4'-(methyl((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methyl)amino)biphenyl-4-yl)methanone;

(2S,4R)-methyl 4-hydroxy-1-(4-(6-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyridin-3-yl)benzoyl)pyrrolidine-2-carboxylate;

(2S,4R)-methyl 1-(4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carboxylate;

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

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

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

1-(4-(3,3'-difluoro-4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperazin-1-yl)ethanone;

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

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

(R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2,3'-difluorobiphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-1-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-3'-(hydroxymethyl)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(S)-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-5'-(hydroxymethyl)biphenyl-4-yl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(S)-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(4-(6-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyridin-3-yl)-2-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

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

(S)-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(R)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-2'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

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

(S)-(3-hydroxypyrrolidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)methanone;

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

(S)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

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

(S)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4-(2-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrimidin-5-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(S)-1-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(2-fluoro-4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridazin-3-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

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

(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-3'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

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

(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(2-(hydroxymethyl)pyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(R)-(2-(hydroxymethyl)pyrrolidin-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)methanone;

(R)-(3-hydroxypiperidin-1-yl)(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)methanone;

(S)-1-(4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(3-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(2-(hydroxymethyl)pyrrolidin-1-yl)methanone;

(R)-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-1-(2-fluoro-4-(5-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

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

(S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(S)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

(S)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(S)-(3-hydroxypiperidin-1-yl)(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

(R)-1-(4'-((1-((1-(trifluoromethyl)cyclobutyl)methyl)piperidin-4-yl)methylamino)biphenylcarbonyl)piperidine-2-carboxamide;

(S)-(3-hydroxypyrrolidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

(S)-1-(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenylcarbonyl)pyrrolidine-2-carboxamide;

(S)-(3-hydroxypiperidin-1-yl)(4'-((1-(3,3,3-trifluoro-2,2-dimethylpropyl)piperidin-4-yl)methylamino)biphenyl-4-yl)methanone;

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

(R)-3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile;

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

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

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

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(S)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-(2-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

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

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

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

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

(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)phenyl)(3-hydroxypiperidin-1-yl)methanone;

(R)-1-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)benzoyl)piperidine-2-carboxamide;

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

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

(R)-(4-(5-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)pyrimidin-2-yl)-3-fluorophenyl)(3-hydroxypiperidin-1-yl)methanone;

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

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

(S)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)pyrrolidine-2-carboxamide;

(R)-1-(3-fluoro-4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)piperidine-2-carboxamide;

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

(R)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

(S)-(4-(6-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyridin-3-yl)phenyl)(3-hydroxypyrrolidin-1-yl)methanone;

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

(R)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)piperidine-2-carboxamide;

(S)-1-(4-(5-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)pyrazin-2-yl)benzoyl)piperidine-2-carboxamide;

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

(2S,4S)-4-fluoro-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)pyrrolidine-2-carbonitrile;

(2S,4R)-1-(3-fluoro-4'-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)biphenylcarbonyl)-4-hydroxypyrrolidine-2-carbonitrile;

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

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

3'-fluoro-4-((1-(2-fluoro-2-methylpropyl)piperidin-4-yl)methoxy)-4'-(4-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile;

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

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

(S)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypyrrolidine-1-carbonyl)biphenyl-3-carbonitrile;

(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-2'-fluoro-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-3-carbonitrile;

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

(R)-1-(2'-cyano-4'-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)biphenylcarbonyl)piperidine-2-carboxamide; and

(R)-4-((1-(2-ethyl-2-fluorobutyl)piperidin-4-yl)methoxy)-4'-(3-hydroxypiperidine-1-carbonyl)biphenyl-2-carbonitrile.

6. The piperidine derivative, stereoisomers thereof or pharmaceutically acceptable salts thereof according to claim 5, wherein the piperidine derivative is selected from the group consisting of:

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

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

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

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

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

7. A pharmaceutical composition comprising the piperidine derivative, stereoisomers thereof or pharmaceutically acceptable salts thereof according to any one of claims 1 to 6; and pharmaceutically acceptable carriers.

8. The pharmaceutical composition according to claim 7, wherein the composition is used for treatment of a disease associated with GPR119 agonist.

9. The pharmaceutical composition according to claim 7, wherein said disease associated with GPR119 agonist is diabetes mellitus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/005096

A. CLASSIFICATION OF SUBJECT MATTER

C07D 401/12(2006.01)i, C07D 401/14(2006.01)i, A61K 31/444(2006.01)i, A61P 3/10(2006.01)i

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 401/12; C07D 211/30; C07C 43/225; C09K 19/30; C09K 19/34; C07C 45/56; C07D 401/04; C07D 321/10; C07C 45/41; C07D 401/14; A61K 31/444; A61P 3/10

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: piperidine, GPR119 agonist

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010-006191 A1 (IRM LLC et al.) 14 January 2010 See abstract, claims and the entire document.	3-9
A	DE 102004037515 A1 (MERCK PATENT GMBH, Germany) 17 March 2005 See abstract, claims and the entire document.	3-9
A	WO 02-34739 A1 (MERCK PATENT GMBH) 02 May 2002 See abstract, claims and the entire document.	3-9
A	WO 02-06196 A1 (MERCK PATENT GMBH) 24 January 2002 See abstract, claims and the entire document.	3-9

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2013 (23.10.2013)	**24 October 2013 (24.10.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
LEE, Jae Jeong
Telephone No. +82-42-481-3488

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/005096

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

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

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

2. ☒ Claims Nos.: 1-2
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claims 1-2 are too broad to make meaningful search.

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

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/005096

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010-006191 A1	14/01/2010	AU 2009-268527 A1	14/01/2010
		AU 2009-268527 B2	01/11/2012
		CA 2730511 A1	14/01/2010
		CA 2730511 C	11/06/2013
		CN102137844 A	27/07/2011
		CN102137844 B	22/05/2013
		EA017260 B1	30/11/2012
		EA201100138 A1	30/08/2011
		EP 2331503 A1	15/06/2011
		EP 2331503 B1	21/08/2013
		JP 2011-527701 A	04/11/2011
		KR 10-2011-0031377 A	25/03/2011
		KR 20110031377 A	25/03/2011
		MX 2011000392 A	01/03/2011
		US 2011-0190298 A1	04/08/2011
		US 8334288 B2	18/12/2012
DE102004037515 A1	17/03/2005	None	
WO 02-34739 A1	02/05/2002	AT269856 T	15/07/2004
		AU 1228202 A	06/05/2002
		AU 2002-12282 A1	06/05/2002
		AU 2002-12297 A1	24/06/2002
		AU 2002-13983 A1	06/05/2002
		AU 2002-20728 A1	24/06/2002
		CN 1479703 A	03/03/2004
		CN 1479703 C0	05/11/2008
		DE 60104014 D1	29/07/2004
		DE 60104014 T2	11/08/2005
		EP 1326854 A1	16/07/2003
		EP 1326854 B1	23/06/2004
		EP 1326855 A1	16/07/2003
		EP 1326855 B1	23/01/2008
		EP 1341742 A1	10/09/2003
		EP 1341742 B1	25/05/2005
		EP 1341746 A1	10/09/2003
		EP 1341746 B1	15/09/2004
		JP 04-156367 B2	24/09/2008
		JP 04-246491 B2	02/04/2009
		JP 04-262477 B2	13/05/2009
		JP 04-964377 B2	27/06/2012
		JP 04-970340 B2	04/07/2012
		JP 2002-212144 A	31/07/2002
		JP 2004-515535 A	27/05/2004
		JP 2004-525090 A	19/08/2004
		JP 2004-538244 A	24/12/2004
		JP 2008-303214 A	18/12/2008
		KR 10-0765554 B1	09/10/2007
		US 2003-0230737 A1	18/12/2003

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2013/005096

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
		US 2004-0046150 A1	11/03/2004
		US 2004-0059137 A1	25/03/2004
		US 2006-0224023 A1	05/10/2006
		US 6706338 B2	16/03/2004
		US 6780477 B2	24/08/2004
		US 6916940 B2	12/07/2005
		US 7105708 B2	12/09/2006
		US 7385067 B2	10/06/2008
		WO 02-34739 A1	02/05/2002
		WO 02-34740 A1	02/05/2002
		WO 02-48073 A1	20/06/2002
		WO 02-48081 A1	20/06/2002
WO 02-06196 A1	24/01/2002	AT 384036 T	15/02/2008
		AU 2001-66092 A1	30/01/2002
		AU 6609201 A	30/01/2002
		DE 60132456 D1	06/03/2008
		DE 60132456 T2	08/01/2009
		EP 1299334 A1	09/04/2003
		EP 1299334 B1	16/01/2008
		JP 05-265838 B2	14/08/2013
		JP 2004-504286 A	12/02/2004
		JP 2004-504286 T	12/02/2004
		KR 10-0849981 B1	01/08/2008
		TW 538118 A	21/06/2003
		TW 538118 B	21/06/2003
		US 2003-175445 A1	18/09/2003
		US 7060331 B2	13/06/2006
		WO 02-06196 A1	24/01/2002