



(86) Date de dépôt PCT/PCT Filing Date: 2015/12/23
(87) Date publication PCT/PCT Publication Date: 2016/06/30
(45) Date de délivrance/Issue Date: 2021/08/03
(85) Entrée phase nationale/National Entry: 2017/06/05
(86) N° demande PCT/PCT Application No.: KR 2015/014178
(87) N° publication PCT/PCT Publication No.: 2016/105118
(30) Priorité/Priority: 2014/12/24 (KR10-2014-0188399)

(51) Cl.Int./Int.Cl. *C07D 401/04* (2006.01),
A61K 31/4725 (2006.01), *A61P 3/04* (2006.01),
A61P 3/10 (2006.01)

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(54) Titre : DERIVE DE BIARYLE UTILISABLE EN TANT QU'AGONISTE DU GPR120

(54) Titre: BIARYL DERIVATIVE AS GPR120 AGONIST

(57) Abrégé/Abstract:

The present invention relates to a biaryl derivative expressed by the chemical formula 1, a method for producing the biaryl derivative, a pharmaceutical composition comprising same, and use of same, the biaryl derivative expressed by the chemical formula 1, as a GPR120 agonist, promoting GLP-1 generation in the gastro-intestinal tract, reducing insulin resistance in the liver, muscles and the like from anti-inflammatory activity in the macrophage, pancreatic cells and the like, and allowing effective use in prevention or treatment of inflammation or metabolic diseases such as diabetes, complications from diabetes, obesity, non-alcoholic fatty liver disease, fatty liver disease, and osteoporosis.



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(12) 특허협력조약에 의하여 공개된 국제출원

(19) 세계지식재산권기구
국제사무국(43) 국제공개일
2016 년 6 월 30 일 (30.06.2016)(10) 국제공개번호
WO 2016/105118 A3

(51) 국제특허분류:

C07D 401/04 (2006.01) A61P 3/10 (2006.01)
A61K 31/4725 (2006.01) A61P 3/04 (2006.01)

(21) 국제출원번호: PCT/KR2015/014178

(22) 국제출원일: 2015 년 12 월 23 일 (23.12.2015)

(25) 출원언어: 한국어

(26) 공개언어: 한국어

(30) 우선권정보:

10-2014-0188399 2014 년 12 월 24 일 (24.12.2014) KR

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(81) 지정국 (별도의 표시가 없는 한, 가능한 모든 종류의 국내 권리의 보호를 위하여): 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, IR, IS, JP, KE, KG, KN, KP, KZ, LA, LC, LK, LR, LS, 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, SA, 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) 지정국 (별도의 표시가 없는 한, 가능한 모든 종류의 역내 권리의 보호를 위하여): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), 유라시아 (AM, AZ, BY, KG, KZ, RU, TJ, TM), 유럽 (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).

공개:

- 국제조사보고서와 함께 (조약 제 21 조(3))
- 청구범위 보정 기한 만료 전의 공개이며, 보정서를 접수하는 경우 그에 관하여 별도 공개함 (규칙 48.2(h))

(88) 국제조사보고서 공개일: 2016 년 10 월 13 일

(54) Title: BIARYL DERIVATIVE AS GPR120 AGONIST

(54) 발명의 명칭 : GPR120 효능제로서의 바이아릴 유도체

(57) Abstract: The present invention relates to a biaryl derivative expressed by the chemical formula 1, a method for producing the biaryl derivative, a pharmaceutical composition comprising same, and use of same, the biaryl derivative expressed by the chemical formula 1, as a GPR120 agonist, promoting GLP-1 generation in the gastro-intestinal tract, reducing insulin resistance in the liver, muscles and the like from anti-inflammatory activity in the macrophage, pancreatic cells and the like, and allowing effective use in prevention or treatment of inflammation or metabolic diseases such as diabetes, complications from diabetes, obesity, non-alcoholic fatty liver disease, fatty liver disease, and osteoporosis.

(57) 요약서: 본 발명은 화학식 1 의 바이아릴 유도체, 이의 제조방법, 이를 포함하는 약제학적 조성물 및 이의 용도에 관한 것으로, 본 발명에 따른 화학식 1 의 바이아릴 유도체는 GPR120 효능제로서 위장관에서 GLP-1 생성을 촉진시키고, 대식세포나 췌장세포 등에서의 항염증 작용으로 간이나 근육 등에서 인슐린 저항성을 개선하며, 당뇨병, 당뇨병의 합병증, 비만, 비알콜성 지방간, 지방성 간염, 골다공증 등 대사성 질환이나 염증의 예방 및 치료에 유용하게 사용될 수 있다.

WO 2016/105118 A3

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

DESCRIPTION

TITLE OF INVENTION

BIARYL DERIVATIVE AS GPR120 AGONIST

TECHNICAL FIELD

The present invention relates to novel compound derivatives as GPR120 agonists, a method for preparing the same, a pharmaceutical composition comprising the same as active ingredients and use thereof. Herein a GPR120 agonist means a compound which can be effectively used for preventing or treating metabolic diseases such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis and osteoporosis, or inflammation, by promoting GLP-1 in the gastrointestinal tract and anti-inflammatory action.

BACKGROUND ART

Diabetes is largely divided into two types—i.e., insulin-dependent type 1 diabetes and insulin-independent (insulin-resistant) type 2 diabetes which is found in 90% or more of diabetic patients.

GPR120 agonists, which are noted for possible treatment of type 2 diabetes, are known to have (1) an antidiabetic effect caused by the actions of increasing incretin hormone in intestinal cells, (2) anti-inflammatory action in macrophages, and (3) an action of improvement on insulin resistance in lipocytes. They are also known as a possible treatment of type 1 diabetes due to the improvement on proliferation of pancreas cells by anti-inflammatory action.

G protein-coupled receptor 120 (GPR120) is expressed copiously in the intestines, lungs, adipose tissue, and macrophages which induce inflammation, and is activated by long-chain free fatty acid (FFA). GPR120 stimulates the secretion of glucagon-like peptide-1 (GLP-1) by FFA. GLP-1, an incretin hormone, is known to stimulate the secretion of insulin in the pancreas dependently on blood glucose level, and also to have the effect of improvement of insulin resistance, proliferation of β -cells, appetite loss and increase of satiety. Recently, GPR120 is known to relate with improvement of insulin resistance and anti-inflammatory effect, and therefore, it is regarded as a target for developing a drug to effectively improve insulin resistance, type 2 diabetes and obesity involving low-level chronic inflammation. Furthermore, in animal experiments of type 1 diabetes, GPR120 agonists are reported to improve the

secretion of insulin by the action of proliferation of β -cells.

Since GPR 120 agonists also have anti-inflammatory action, they are reported to be a possible treatment of inflammation-related diseases – for example, steatohepatitis, rheumatoid arthritis, etc.

Considering the above, researches on GPR120 agonists are actively in progress. In the representative compounds presented as GPR120 agonists, two aryl groups are connected with a center bridge structure, and the characteristic feature is that one of two aryl groups is substituted by carboxylic acid. GPR120 agonist compounds are disclosed in WO 2013/185766, WO 2013/139341, WO 2011/159297, WO 2010/080537, WO 2010/104195, WO 2010/048207, WO 2009/147990, WO 2008/066131, WO 2008/103500 and WO 2008/139879.

DISCLOSURE OF INVENTION

TECHNICAL PROBLEM

The object of the present invention is to provide a novel biaryl derivative as a GPR120 agonist.

Another object of the present invention is to provide a method for preparing the biaryl derivative.

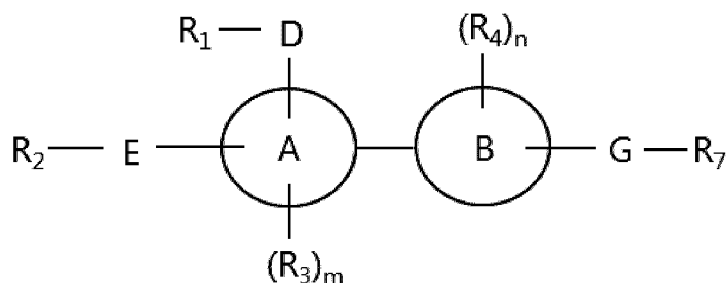
Still another object of the present invention is to provide a pharmaceutical composition for the prevention or treatment of metabolic disease such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis and osteoporosis, or inflammation which comprises the biaryl derivative as an active ingredient, and a method for preparing the composition.

A still further object of the present invention is to provide a method for preventing and treating metabolic disease such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis and osteoporosis, or inflammation which uses the biaryl derivative as an active ingredient.

SOLUTION TO PROBLEM

In one embodiment, there is provided a biaryl derivative of Formula 1, or a pharmaceutically acceptable salt or isomer thereof:

[Formula 1]



wherein,

A and B represent independently aryl or heteroaryl;

D and E may independently not exist, or represent independently C, CH, CH₂, N, NH, O or S;

R₁ and R₂ may independently not exist, or represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, oxo, alkylcycloalkyl, cycloalkylalkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, cycloalkoxy, cycloalkylalkoxy, alkylheterocycloalkyl, aryl, alkylaryl, aralkyl, haloaryl, heteroaryl, alkylheteroaryl or haloalkylaryl;

R₁ and R₂ may be connected to each other, or with D and/or E to form a ring, or may form a fused ring with A; the ring is optionally substituted with alkyl, halogen, alkoxycarbonyl, cycloalkylalkyl, haloaryl or alkylaryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three alkyl, oxo, cycloalkyl, alkoxy, alkylcycloalkyl, aryl or alkylaryl which may be the same or different;

R₃ and R₄ represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkoxy, nitrile, oxo, cycloalkoxy, aryloxy, heteroaryloxy, aminoalkyl, aminocycloalkyl, aminoaryl, alkylamine, cycloalkylamine, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl;

m and n represent independently an integer of 0 to 5;

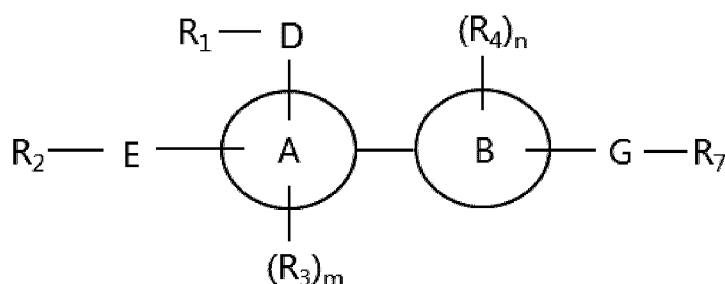
G represents -(CR₅R₆)_p-J-(CR₅R₆)_q, wherein J represents CH₂, O, N, NH, S or a double bond; R₅ and R₆ represent independently hydrogen, halogen, alkyl or cycloalkyl,

hydroxy or amine, or may be connected to each other to form cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form a ring, or may be substituted with alkyl; and p and q represent independently an integer of 0 to 6; and

R₇ represents carboxylic acid or carboxylic acid isostere, provided that the carboxylic acid isostere is not tetrazole.

According to another embodiment, there is provided a biaryl derivative of Formula 1, or a pharmaceutically acceptable salt or isomer thereof:

[Formula 1]



wherein,

A and B represent independently aryl or heteroaryl;

D and E may not exist independently and D and E represent independently C, CH, CH₂, N, NH, O or S;

R₁ and R₂ may not exist independently and R₁ and R₂ represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, oxo, alkylcycloalkyl, cycloalkylalkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, cycloalkoxy, cycloalkylalkoxy, alkylheterocycloalkyl, aryl, alkylaryl, aralkyl, haloaryl, heteroaryl, alkylheteroaryl or haloalkylaryl;

R₁ and R₂ may be connected to each other, or with D and/or E to form a ring, or may form a fused ring with A; the ring is optionally substituted with alkyl, halogen, alkoxycarbonyl, cycloalkylalkyl, haloaryl or alkylaryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three alkyl, oxo, cycloalkyl, alkoxy, alkylcycloalkyl, aryl or alkylaryl which may be the same or different;

R₃ and R₄ represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkoxy, nitrile, oxo, cycloalkoxy, aryloxy, heteroaryloxy, aminoalkyl, aminocycloalkyl, aminoaryl, alkylamine, cycloalkylamine, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl;

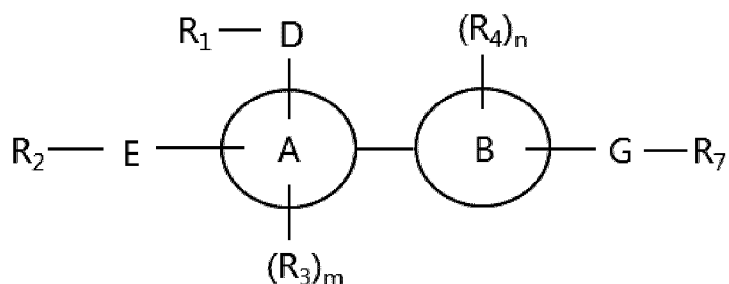
m and n represent independently an integer of 0 to 5;

G represents $-(\text{CR}_5\text{R}_6)_p\text{-J-(CR}_5\text{R}_6)_q$, wherein J represents CH₂, O, N, NH, S or a double bond; R₅ and R₆ represent independently hydrogen, halogen, alkyl or cycloalkyl, hydroxy or amine, or may be connected to each other to form cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form a ring, or may be substituted with alkyl; and p and q represent independently an integer of 0 to 6; and

R₇ represents carboxylic acid or carboxylic acid isostere, provided that the carboxylic acid isostere is not tetrazole.

According to another embodiment, there is provided a biaryl derivative of Formula 1, or a pharmaceutically acceptable salt or isomer thereof:

[Formula 1]



wherein,

A represents pyridinyl, pyrimidinyl, pyrazinyl, indolinyl or indolyl;

B represents naphthalenyl or phenyl;

D and E may independently not exist, or represent independently C, CH, CH₂, N, NH, O or S;

R₁ and R₂ may independently not exist, or represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, oxo, alkylcycloalkyl, cycloalkylalkyl, haloalkyl, alkoxy,

alkoxyalkyl, alkoxyaryl, cycloalkoxy, cycloalkylalkoxy, alkylheterocycloalkyl, aryl, alkylaryl, aralkyl, haloaryl, heteroaryl, alkylheteroaryl or haloalkylaryl;

R₁ and R₂ may be connected to each other, or with D and/or E to form a ring, or may form a fused ring with A; the ring is optionally substituted with alkyl, halogen, alkoxy, carbonyl, cycloalkylalkyl, haloaryl or alkylaryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three alkyl, oxo, cycloalkyl, alkoxy, alkylcycloalkyl, aryl or alkylaryl which may be the same or different;

R₃ and R₄ represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkoxy, nitrile, oxo, cycloalkoxy, aryloxy, heteroaryloxy, aminoalkyl, aminocycloalkyl, aminoaryl, alkylamine, cycloalkylamine, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl;

m and n represent independently an integer of 0 to 5;

G represents $-(CR_5R_6)_p-J-(CR_5R_6)_q$, wherein J represents CH₂, O, N, NH, S or a double bond; R₅ and R₆ represent independently hydrogen, halogen, alkyl or cycloalkyl, hydroxy

or amine, or may be connected to each other to form cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form a ring, or may be substituted with alkyl; and p and q represent independently an integer of 0 to 6; and

R₇ represents carboxylic acid or carboxylic acid isostere,

provided that the carboxylic acid isostere is not tetrazole.

In accordance with preferred embodiments, there is provided a biaryl derivative, which is selected from the group consisting of:

[6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid,

[6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid,

4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid,

4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid,

4-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]butanenitrile,

5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
5-[4-(6-cyclopentylsulfanyl-2-pyridyl)phenyl]pentanoic acid,
5-[4-(2-cyclopentylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
5-[4-(6-cyclopentoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
5-[4-(2-cyclopentoxy-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
{2-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]ethoxy}acetic acid,
5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]hexanoic acid,
5-[4-(6-cyclobutoxy-2-pyridyl)-phenyl]hexanoic acid,
5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
5-[4-(2-ethylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,
5-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]hexanoic acid,
5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,
5-[4-(2-cyclopentoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)-phenyl]hexanoic acid,

5-[4-(6-cyclopentylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]hexanoic acid,
 5-[4-(6-cyclopentoxy-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 4-[4-(2-isopropoxy-3-pyridyl)phenyl]butanoic acid,
 5-[2,6-difluoro-4-(2-hydroxy-3-pyridyl)phenyl]hexanoic acid,
 5-[4-(2-cyclobutoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[4-(2-cyclopropylmethoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 N'-hydroxy-4-[4-(2-propylsulfanyl-3-pyridyl)phenyl]butaneamidine,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4H-1,2,4-oxadiazol-5-one,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4H-1,2,4-oxadiazol-5-thione,
 5-[[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,

5-[(E)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]allyl]thiazolidin-2,4-dione,
 5-[[4-[2-(cyclobutoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclobutylmethoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]anilino]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 4-[[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[(E)-3-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]allyl]-1,1-dioxo-1,2,5-
 thiadiazolidin-3-one,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-anilino]methyl]isoxazol-3-ol,
 5-[3-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]propyl]-1,1-dioxo-1,2,5-thiadiazolidin-
 3-one,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]-N-methyl-anilino]methyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]propyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenoxy]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-anilino]ethyl]isoxazol-3-ol,
 2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
 5-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 5-[4-[2-(cyclopentoxo)-3-pyridyl]-N-ethyl-2,6-difluoro-anilino]pentanoic acid,
 5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)anilino]pentanoic acid,

5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)anilino]pentanoic acid,

5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-anilino]pentanoic acid,

5-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,

2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-N-methyl-anilino]pentanoic acid,

2-[1-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-tetrahydrofuran-3-yloxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-3-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]acetic acid,

6-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-carboxylic acid,

6-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-carboxylic acid,

2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[6-(cyclopentoxo)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrazol-4-yl]acetic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,

3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]propanoic acid,

3-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]propanoic acid,

2-[2-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-anilino]ethyl]cyclopropane carboxylic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetamide,

2-[4-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]piperazin-1-yl]acetic acid,

3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]propanoic acid,

4-[5-(2-cyclopentylsulfanyl-3-pyridyl)indolin-1-yl]butanoic acid,

3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]propanoic acid,

2-[(3R)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,

2-[(3R)-1-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic acid,

2-[(3S)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,

2-[(3S)-1-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic acid,

3h

2-[1-[2-fluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,
 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-phenoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-cyclobutoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-isopropoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-{6-[6-(2-fluoro-phenoxy)-pyridin-2-yl]-naphthalen-2-yl}-propanoic acid,
 5-[4-(2-isopropoxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 4-{1-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,

4-{1-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 {2-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 3-{2-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 3-{2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 3-{2-[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-cyclopropyl}-propanoic acid,
 3-{2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 3-{2-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 3-{2-[4-(2-cyclopentylamino-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 5-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 {4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexyl}-acetic acid,
 3-{2-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 3-{2-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 3-(2-{2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl}-cyclopropyl)-
 propanoic acid,

3-{2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,
 5,5-difluoro-5-[4-(6-isopropylsulfanyl-pyridin-2-yl)-phenyl]-pentanoic acid,
 4-[[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[2,6-difluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(6-cyclopentylsulfanyl-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-ethylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino]-butyric acid,
 2-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenylamino]-methyl]-cyclopropane
 carboxylic acid,
 2-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenylamino]-methyl]-cyclopropane carboxylic
 acid,
 4-[[2-fluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,
 4-[[4-(2-cyclopentylsulfanyl-5-methyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric
 acid,

4-[[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,
 4-[[2,6-difluoro-4-(2-methoxy-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,
 4-({2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl}-methyl-amino)-butyric acid,
 4-[[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-ethyl-amino]-butyric acid,
 4-[[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-ethyl-amino]-butyric acid,
 4-[[2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl]-ethyl-amino]-butyric acid,
 (R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 (E)-(R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hex-2-enoic acid,
 (S)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 5-{2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 5-{2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 5-{2,6-difluoro-4-[2-(oxetan-3-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 4-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 6-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 6-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenylsulfanyl]-butyric acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,

4-[3-(6-cyclopentyloxy-pyridin-2-yl)-phenoxy]-butyric acid,
4-[3-(2-cyclopentyloxy-pyridin-3-yl)-phenoxy]-butyric acid,
5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
4-[4-(2-cyclohexylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenoxy]-butyric acid,
3-[4-(2-cyclopentyloxy-pyridin-3-yl)-benzylsulfanyl]-propionic acid,
2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-cyclobutylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclopentoxo)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2-chloro-4-[6-(cyclopropylmethoxy)-2-pyridyl]-6-fluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-tert-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[5-chloro-6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclopropanecarbonyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutoxymethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-ethoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoro-1-methyl-ethoxy)-2-pyridyl]phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-cyclopentyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-[cyclopropyl(methoxy)methyl]-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-(6-ethoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isopropoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-methoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-propoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(6-isobutoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-butoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclopentoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(4-ethoxypyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-isopropoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-propoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-isobutoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-pyrrolidin-1-ylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-[6-(isopropylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(diethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-[6-(isobutylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclopentylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclopentylamino)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(dimethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-[4-(isobutylamino)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutoxy)-5-methyl-pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-phenylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-cyclopentylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isobutylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(4-isobutylpyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-butylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopentylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[4-(cyclobutoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[4-(cyclopropylmethoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-cyclobutyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(6-cyclobutylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[6-(cyclobutylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclopentylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-(1-{2,6-difluoro-4-[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl}piperidin-4-yl)acetic acid,

2-[1-[4-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-5,6-dimethyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenoxy]butanoic acid,

4-[2,6-dichloro-4-[6-(cyclobutoxy)-2-pyridyl]phenoxy]butanoic acid,

4-[4-[6-(cyclopropylmethoxymethyl)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[6-chloro-4-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenoxy]butanoic acid,

5-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]hexanoic acid,

4-[2-chloro-4-(6-cyclopentyloxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyridin-2-yl)-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclobutylsulfanyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-6-fluoro-4-(6-isopropylsulfanyl-pyridin-2-yl)-phenoxy]-butyric acid,
5-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,
5-([4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-methyl-amino)-methyl)-isoxazol-3-ol,
5-[4-(2-cyclobutoxy-6-methyl-pyrimidin-4-yl)-2,6-difluoro-phenyl]-hexanoic acid,
5-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,
4-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[4-(2-cyclobutoxy-pyrimidin-4-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(4-cyclobutoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(2-cyclobutoxy-pyrimidin-4-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(6-chloro-4-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(6-cyclobutoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(6-cyclopropylmethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
4-[2-chloro-4-(6-cyclopropylmethoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenoxy]-butyric acid,

4-[2-chloro-4-(6-ethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,

{(R)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

2-[1-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

2-[1-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-(6-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

5-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]phenyl]-5,5-difluoro-pentanoic acid,

4-[2,6-difluoro-4-(5-fluoroindol-1-yl)phenoxy]butanoic acid,

4-[2,6-difluoro-N-methyl-4-(6-pyrrolidin-1-yl-2-pyridyl)anilino]butanoic acid,

4-[2,6-difluoro-4-(5-methoxyindol-1-yl)phenoxy]butanoic acid,

4-[4-(5-cyanoindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

4-[2,6-difluoro-4-(4-fluoroindol-1-yl)phenoxy]butanoic acid,

4-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-(7-chloroindol-1-yl)-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[5-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2,6-difluoro-4-(4-methoxyindol-1-yl)phenoxy]butanoic acid,

4-[2,6-difluoro-4-(7-methoxyindol-1-yl)phenoxy]butanoic acid,

2-[1-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

2-{1-[2,6-difluoro-4-(6-propoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-isobutoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-cyclopentoxypyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-butoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(4-propoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(4-isopropoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(4-ethoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(4-isobutoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-isobutylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-cyclopentylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-{1-[2,6-difluoro-4-(6-isopropylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,

2-[1-[2,6-difluoro-4-(6-diethylamino-pyrazin-2-yl)]phenyl]pyrrolidin-3-yl]acetic acid,

2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-pyrrolidin-3-yl]acetic acid,

2-[1-[4-[4-phenoxy-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-pyridin-3-yloxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(4-fluorophenoxy)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-methoxyphenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(p-tolyloxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(3,4-difluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

5-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenyl]-pentanoic acid,

4-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

4-[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

2-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(6-isopropoxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(6-methoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-ethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

(1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-pyrrolidin-3-yl)-acetic acid,

(1-{2,6-difluoro-4-[6-(tetrahydro-thiopyran-4-yloxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-propoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methyl-butoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(2-methoxy-ethoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

{{(S)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

2-[1-[2,6-difluoro-4-[4-[(6-methyl-3-pyridyl)oxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(4-ethylphenoxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(3-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(3,4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(2-pyridyloxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

{1-[4-(6-cyclobutoxy-4-trifluoromethyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-6-trifluoromethyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

{1-[2,6-difluoro-4-(4-propoxy-6-trifluoromethyl-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

(1-{2,6-difluoro-4-[4-(4-fluoro-phenoxy)-6-trifluoromethyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

3-{1-[2,6-difluoro-4-(6-propoxy-pyridin-2-yl)-phenyl]-piperidin-4-yl}-propionic acid,

3-{1-[4-(6-cyclobutyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid, and

3-{1-[4-(6-ethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid, or a pharmaceutically acceptable salt or isomer thereof.

In one embodiment, there is provided the use of the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined herein for the manufacture of a medicament for the prevention or treatment of metabolic disease selected from the group consisting of diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and inflammatory disease.

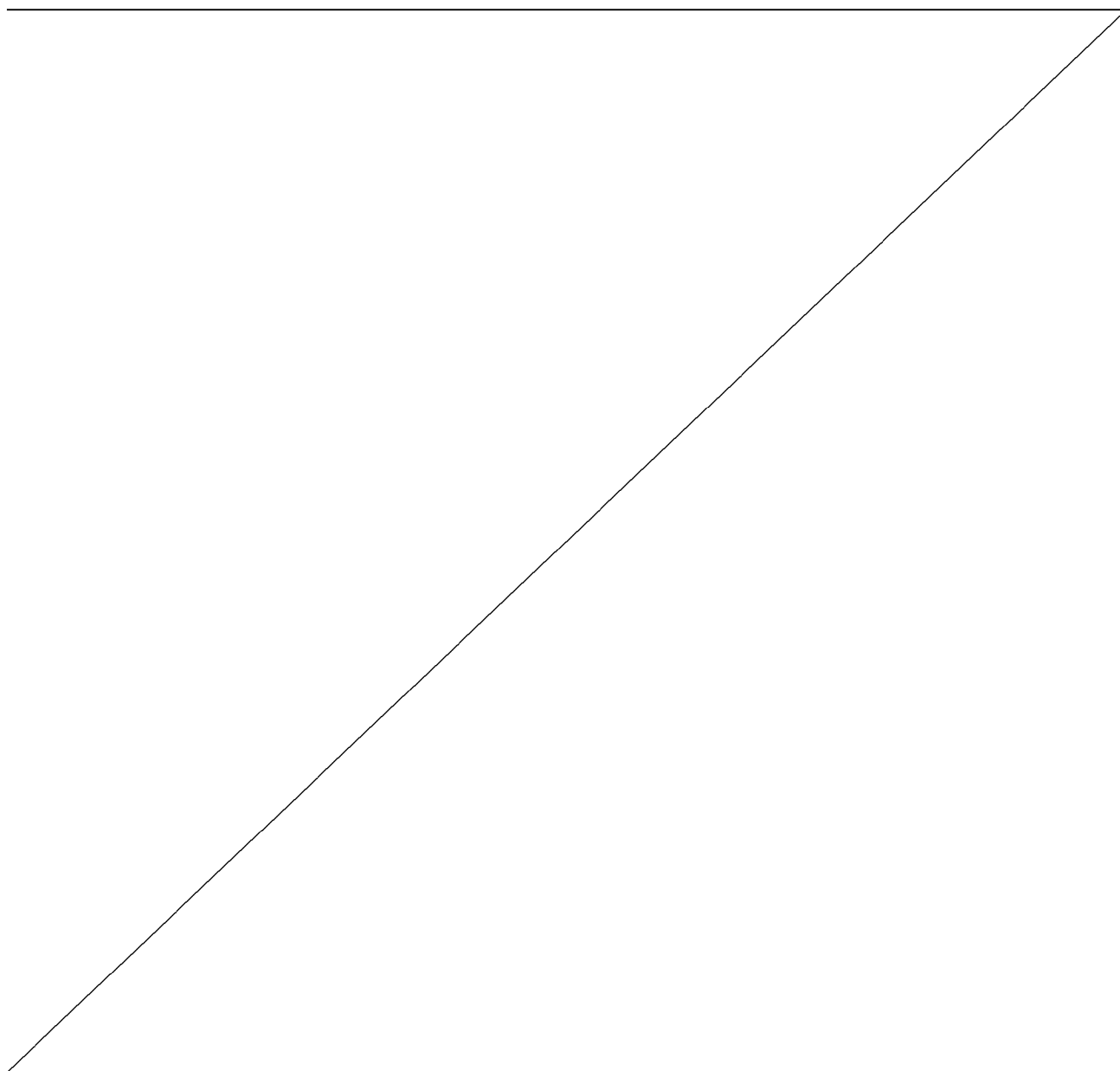
In one embodiment, there is provided the use of the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined herein for the manufacture of a medicament for lowering blood glucose level.

In one embodiment, there is provided a pharmaceutical composition as a GPR120 agonist, comprising the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined herein as a pharmaceutically acceptable carrier.

In one embodiment there is provided the use of the pharmaceutical composition as defined herein for the prevention or treatment of metabolic disease selected from the group consisting of diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and inflammatory disease.

In one embodiment there is provided a pharmaceutical composition for lowering blood glucose level, comprising the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined herein as a pharmaceutically acceptable carrier.

In one embodiment there is provided the use of the pharmaceutical composition as defined herein for lowering blood glucose level.



The compound of Formula 1 according to the present invention may form a pharmaceutically acceptable salt, which includes an acid-addition salt which is formed from an inorganic acid such as hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, hydrobromic acid and hydroiodic acid; an organic acid such as tartaric acid, formic acid, citric acid, acetic acid, trichloroacetic acid, trifluoroacetic acid, gluconic acid, benzoic acid, lactic acid, fumaric acid, maleic acid and salicylic acid; or sulfonic acid such as methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid, which form non-toxic acid-addition salt including pharmaceutically acceptable anion. In addition, a pharmaceutically acceptable carboxylic acid salt includes the salt with alkali metal or alkali earth metal such as lithium, sodium, potassium, calcium and magnesium; salts with amino acid such as lysine, arginine and guanidine; an organic salt such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, diethanolamine, choline and triethylamine. The compound of Formula 1 according to the present invention may be converted into their salts by conventional methods.

Meanwhile, since the compound of Formula 1 according to the present invention can have an asymmetric carbon center and asymmetric axis or plane, they can exist as E- or Z-isomer, R- or S-isomer, racemic mixtures or diastereoisomer mixtures and each diastereoisomer, all of which are within the scope of the present invention.

Herein, unless indicated otherwise, the term “the compound of Formula 1” is used to mean all the compounds of Formula 1, including the pharmaceutically acceptable salts and isomers thereof.

Herein, the following concepts defined to the substituents are used to define the compound of Formula 1.

The term “halogen” or “halo” means fluoride (F), chlorine (Cl), bromine (Br) or iodine (I).

The term “carboxylic acid isostere” includes, but is not limited to, isoxazolol, pyrazolol, isothiazolol, thiazolidinedione, pyrrolidinedione, oxazolidinedione, imidazolidinedione, thiazolidinedione, imidazoledione, pyrroledione, phenol, pyridinol, dioxothiadiazolidineone, tetrazole, triazole, imidazole, sulfonic acid, sulfonamide, acetamide, nitrile, hydroxyacetamidine, oxadiazoleone, oxadiazolethione and the like.

The term “alkyl” means straight or branched hydrocarbons, may include a single bond, a double bond and a triple bond, and is preferably C₁-C₁₀-alkyl. Examples of alkyl include,

but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, *tert*-butyl, acetylene, vinyl, trifluoromethyl and the like.

The term “cycloalkyl” means partially or fully saturated single or fused ring hydrocarbons, and is preferably C₃-C₁₀-cycloalkyl. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl and the like.

Unless otherwise defined, the term “alkoxy” means alkyloxy having 1 to 10 carbon atoms.

Unless otherwise defined, the term “cycloalkoxy” means cycloalkyloxy having 3 to 10 carbon atoms.

Aryl means aromatic hydrocarbons, preferably C₅-C₁₂-aryl, more preferably C₆-C₁₀-aryl, and includes, but is not limited to, phenyl, naphthyl and the like.

Heteroaryl means 3- to 12-membered, more preferably 5- to 10-membered aromatic hydrocarbons which form a single or fused ring—which may be fused with benzo or C₃-C₈ cycloalkyl—including at least one heteroatom selected from N, O and S as a ring member. Examples of heteroaryl include, but are not limited to, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, oxadiazolyl, isoxadiazolyl, tetrazolyl, triazolyl, indolyl, indazolyl, isoxazolyl, oxazolyl, thiazolyl, isothiazolyl, furanyl, benzofuranyl, imidazolyl, thiophenyl, benzthiazole, benzimidazole, quinolinyl, indolinyl, 1,2,3,4-tetrahydroisoquinolyl, 3,4-dihydroisoquinolyl, thiazolopyridyl, 2,3-dihydrobenzofuran, 2,3-dihydrothiophene, 2,3-dihydroindole, benzo[1,3]dioxin, chroman, thiochroman, 1,2,3,4-tetrahydroquinoline, 4H-benzo[1,3]dioxin, 2,3-dihydrobenzo[1,4]-dioxin, 6,7-dihydro-5H-cyclopenta[d]pyrimidine and the like.

Heterocyclyl means partially or fully saturated hydrocarbons which form a single or fused ring including at least one heteroatom selected from N, O and S, and is preferably 3- to 12-membered heterocyclyl. Examples of heterocyclyl include, but are not limited to, pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, piperazinyl, tetrahydrofuran, tetrahydrothiofuran and the like.

Aralkyl, alkylaryl and heteroarylalkyl mean groups which are formed by the combination of the above-mentioned aryl with alkyl or heteroaryl with alkyl. Examples include, but are not limited to, benzyl, thiophene methyl, pyrimidine methyl and the like.

The above-mentioned amine, alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, aralkyl and heteroarylalkyl may be substituted by at least one group selected from the following groups: alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl, heteroarylalkyl, heterocyclylalkyl, oxo,

cyano, halo, nitro, -OR, -OC(O)R, -OC(O)OR, -SR, -S(O)R, -S(O)₂R, -C(O)R, -C(O)OR, -C(S)R, -C(O)NRR, -NR₂, -NRCHO, -NRC(O)R, -NRC(O)NRR, -C(S)NRR, -NRC(S)R and -NRC(S)NRR, wherein R is independently selected from hydrogen, alkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, aralkyl and heteroarylalkyl, and when two Rs are substituted, they may be connected to form cycloalkyl or heterocyclyl.

According to one embodiment of the present invention, in the above Formula 1

A and B represent independently C₅-C₁₂ aryl or 3- to 12-membered heteroaryl having at least one heteroatom selected from N, O and S;

D and E may independently not exist, or represent independently C, CH, CH₂, N, NH, O or S;

R₁ and R₂ may independently not exist, or represent independently hydrogen, halogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, 3- to 12-membered heterocycloalkyl, oxo, C₁-C₁₀ alkyl-C₃-C₁₀ cycloalkyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀ alkyl, halo-C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkoxy-C₁-C₁₀ alkyl, C₁-C₁₀ alkoxy-C₅-C₁₂ aryl, C₃-C₁₀ cycloalkoxy, C₃-C₁₀ cycloalkyl-C₁-C₁₀ alkoxy, C₁-C₁₀ alkyl-3- to 12-membered heterocycloalkyl, C₅-C₁₂ aryl, C₁-C₁₀ alkyl-C₅-C₁₂ aryl, C₅-C₁₂ aryl-C₁-C₁₀ alkyl, halo-C₅-C₁₂ aryl, 3- to 12-membered heteroaryl, C₁-C₁₀ alkyl-3- to 12-membered heteroaryl or halo-C₁-C₁₀ alkyl-C₅-C₁₂ aryl, wherein the heterocycloalkyl and heteroaryl have at least one heteroatom selected from N, O and S;

R₁ and R₂ may be connected each other, or with D and/or E to form C₃-C₁₀ cycloalkyl, C₅-C₁₂ aryl or 3- to 12-membered heterocycloalkyl having at least one heteroatom selected from N, O and S, or may form 3- to 15-membered heterocycle or heteroaryl having at least one heteroatom selected from N, O and S, fused with A; the cycloalkyl, aryl, heterocycloalkyl, heterocycle or heteroaryl is optionally substituted with C₁-C₁₀ alkyl, halogen, C₁-C₁₀ alkoxycarbonyl, C₃-C₁₀ cycloalkyl-C₁-C₁₀ alkyl, halo-C₅-C₁₂ aryl or C₁-C₁₀ alkyl-C₅-C₁₂ aryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three C₁-C₁₀ alkyl, oxo, C₃-C₁₀ cycloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkyl-C₃-C₁₀ cycloalkyl, C₅-C₁₂ aryl or C₁-C₁₀ alkyl-C₅-C₁₂ aryl which may be the same or different;

R₃ and R₄ represent independently hydrogen, halogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₁-C₁₀ alkoxy, nitrile, oxo, C₃-C₁₀ cycloalkoxy, C₅-C₁₂ aryloxy, 3- to 12 membered heteroaryloxy, amino-C₁-C₁₀ alkyl, amino-C₃-C₁₀ cycloalkyl, amino-C₅-C₁₂ aryl, C₁-C₁₀ alkylamine, C₃-C₁₀ cycloalkylamine, amino-3- to 12-membered

heteroaryl, thio-C₁-C₁₀ alkyl, thio-C₅-C₁₂ aryl or thio-3 to 12-membered heteroaryl;

m and n represent independently an integer of 0 to 3;

G represents $-(CR_5R_6)_p-J-(CR_5R_6)_q$, wherein J represents CH₂, O, N, NH, S or double bond; R₅ and R₆ represent independently hydrogen, halogen, C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, hydroxy or amine, or may be connected each other to form C₃-C₁₀ cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form 3- to 12-membered heteroaryl or 3- to 12-membered heterocycloalkyl having 1 or 2 N atoms, or may be substituted with C₁-C₁₀ alkyl; and p and q represent independently an integer of 0 to 6; and

R₇ represents carboxylic acid or carboxylic acid isostere.

According to another embodiment of the present invention, A and B represent independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl having 1 to 3 heteroatoms selected from N, O and S.

According to still another embodiment of the present invention, R₁ and R₂ may independently not exist, or represent independently hydrogen, halogen, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, 3- to 10 membered heterocycloalkyl, oxo, C₁-C₈ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl-C₁-C₈ alkyl, halo-C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy-C₁-C₈ alkyl, C₁-C₈ alkoxy-C₆-C₁₀ aryl, C₃-C₈ cycloalkoxy, C₃-C₈ cycloalkyl-C₁-C₈ alkoxy, C₁-C₈ alkyl-3- to 10-membered heterocycloalkyl, C₆-C₁₀ aryl, C₁-C₈ alkyl-C₆-C₁₀ aryl, C₆-C₁₀ aryl-C₁-C₈ alkyl, halo-C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C₁-C₈ alkyl-5- to 10-membered heteroaryl or halo-C₁-C₈ alkyl-C₆-C₁₀ aryl, wherein the heterocycloalkyl and heteroaryl have 1 to 3 heteroatoms selected from N, O and S;

R₁ and R₂ may be connected each other, or with D and/or E to form C₃-C₈ cycloalkyl, C₆-C₁₀ aryl or 3- to 12-membered heterocycloalkyl having 1 to 3 heteroatoms selected from N, O and S, or may form 3- to 14-membered heterocycle or heteroaryl having 1 to 4 heteroatoms selected from N, O and S, fused with A; the cycloalkyl, aryl, heterocycloalkyl, heterocycle or heteroaryl is optionally substituted with C₁-C₈ alkyl, halogen, C₁-C₈ alkoxycarbonyl, C₃-C₈ cycloalkyl-C₁-C₈ alkyl, halo-C₆-C₁₀ aryl or C₁-C₈ alkyl-C₆-C₁₀ aryl; and

when D and E represent C, CH or N, R₁ and R₂ can represent two or three C₁-C₈ alkyl, oxo, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₁-C₈ alkyl-C₃-C₈ cycloalkyl, C₆-C₁₀ aryl or C₁-C₈ alkyl-C₆-C₁₀ aryl which may be the same or different.

According to still another embodiment of the present invention, R₃ and R₄ represent independently hydrogen, halogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₁-C₁₀ alkoxy, nitrile, oxo or C₃-C₁₀ cycloalkoxy.

According to still another embodiment of the present invention, G represents - (CR₅R₆)_p-J-(CR₅R₆)_q, wherein J represents CH₂, O, N, NH, S or a double bond; R₅ and R₆ represent independently hydrogen, halogen, C₁-C₈ alkyl or C₃-C₈ cycloalkyl, hydroxy or amine, or may be connected each other to form C₃-C₈ cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form 3- to 10-membered heteroaryl or 3- to 12-membered heterocycloalkyl having 1 or 2 N atoms, or may be substituted with C₁-C₈ alkyl; and p and q represent independently an integer of 0 to 5.

Representative compounds of Formula 1 according to the present invention include, but are not limited to, the following compounds:

3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-quinolin-2-yl]-propionic acid,
 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-quinolin-2-yl]-propionic acid,
 [6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid,
 [6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid,
 4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid,
 4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid,
 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid,
 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-chroman-2-yl]-propionic acid,
 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-chroman-2-yl]-propionic acid,
 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-chroman-2-yl]-propionic acid,
 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid,
 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid,
 [6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid,
 [6-(6-isopropylsulfanyl-pyridin-2-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid,

acid,

3-[6-(2-cyclopentyloxy-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid,

3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid,

4-(3'-benzyloxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

4-(3,5-difluoro-3'-isopropoxy-biphenyl-4-yloxy)-butyric acid,

4-(3,5-difluoro-3'-propoxy-biphenyl-4-yloxy)-butyric acid,

4-(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

4-(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[4-(2,2-dimethyl-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]butanenitrile,

2-cyclobutylsulfanyl-3-{3,5-difluoro-4-[3-(1*H*-tetrazol-5-yl)propoxy]phenyl}pyridine,

2-cyclobutylsulfanyl-3-{4-[3-(1*H*-tetrazol-5-yl)propyl]phenyl}pyridine,

5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid,

5-[4-(6-cyclopentylsulfanyl-2-pyridyl)phenyl]pentanoic acid,

5-[4-(2-cyclopentylsulfanyl-3-pyridyl)phenyl]pentanoic acid,

2-cyclobutylsulfanyl-3-[3,5-difluoro-4-(1*H*-tetrazol-5-ylmethoxy)phenyl]pyridine,

5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]pentanoic acid,

5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,

5-[4-(6-cyclopentoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,

5-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenyl]pentanoic acid,

5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,

5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,

5-[4-(2-cyclopentoxy-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,

{2-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]ethoxy}acetic acid,

5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]hexanoic acid,

5-[4-(6-cyclobutoxy-2-pyridyl)-phenyl]hexanoic acid,

5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,

5-[4-(2-ethylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,

5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,

4-[1-methyl-5-(2-phenoxyphenyl)benzimidazol-2-yl]butanoic acid,
 3-[1-methyl-5-(2-phenoxyphenyl)benzimidazol-2-yl]propanoic acid,
 5-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]hexanoic acid,
 5-(2'-cyclopentylamino-3,5-difluoro-bisphenyl-4-yl)hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,
 5-[4-(2-cyclopentoxo-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-(3'-cyclopentylamino-3,5-difluoro-biphenyl-4-yl)-hexanoic acid,
 5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)-phenyl]hexanoic acid,
 5-[4-(6-cyclopentylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]hexanoic acid,
 5-[4-(6-cyclopentoxo-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 4-[4-(2-isopropoxy-3-pyridyl)phenyl]butanoic acid,
 5-[2,6-difluoro-4-(2-hydroxy-3-pyridyl)phenyl]hexanoic acid,
 5-[4-(2-cyclobutoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[4-(2-cyclopropylmethoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
N-hydroxy-4-[4-(2-propylsulfanyl-3-pyridyl)phenyl]butaneamidine,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4*H*-1,2,4-oxadiazol-5-one,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4*H*-1,2,4-oxadiazol-5-thione,
 5-[[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]allyl]thiazolidin-

2,4-dione,

5-[[4-[2-(cyclobutoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclobutylmethoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]anilino]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 4-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]-1,1-dioxo-1,2,5-

thiadiazolidin-3-one,

5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]methyl]isoxazol-3-ol,
 5-[3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]propyl]-1,1-dioxo-1,2,5-

thiadiazolidin-3-one,

5-[[4-[2-(cyclopentoxy)-3-pyridyl]-*N*-methyl-anilino]methyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]propyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]ethyl]isoxazol-3-ol,
 2-[1-[5-(6-isopropylsulfanyl-2-pyridyl)-2-pyridyl]-3-piperidyl]acetic acid,
 4-[[5-(6-isopropylsulfanyl-2-pyridyl)-2-pyridyl]amino]butanoic acid,
 2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
 5-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 5-[4-[2-(cyclopentoxy)-3-pyridyl]-*N*-ethyl-2,6-difluoro-anilino]pentanoic acid,
 5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)anilino]pentanoic acid,
 5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)anilino]pentanoic acid,
 5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 5-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-*N*-methyl-anilino]pentanoic

acid,

2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-tetrahydrofuran-3-yloxy-3-pyridyl)phenyl]-4-piperidyl]acetic

acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-3-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]acetic acid,
 6-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-

carboxylic acid,

6-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-

carboxylic acid,

2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]azetidin-3-yl]acetic

acid,

2-[1-[4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[6-(cyclopentoxo)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,
 3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]propanoic

acid,

3-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]propanoic

acid,

2-[2-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-anilino]ethyl]cyclopropane
carboxylic acid,

2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetamide,

2-[4-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]piperazin-1-yl]acetic acid,

3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]propanoic
acid,

4-[5-(2-cyclopentylsulfanyl-3-pyridyl)indolin-1-yl]butanoic acid,

3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]propanoic
acid,

2-[(3R)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-
yl]acetic acid,

2-[(3R)-1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic
acid,

2-[(3S)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-
yl]acetic acid,

2-[(3S)-1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic
acid,

2-[1-[2-fluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,

3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(6-phenoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(2-phenoxy-phenyl)-naphthalen-2-yl]-propanoic acid,

3-[6-(6-cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(3-phenoxy-phenyl)-naphthalen-2-yl]-propanoic acid,

3-[6-(3-isopropoxy-phenyl)-naphthalen-2-yl]-propanoic acid,

3-[6-(3-cyclobutoxy-phenyl)-naphthalen-2-yl]-propanoic acid,

3-[6-(6-cyclobutoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(2-isopropoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,

3-[6-(2-cyclopentylloxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,

3-{6-[2-(2-fluoro-phenoxy)-phenyl]-naphthalen-2-yl}-propanoic acid,

3-{6-[6-(2-fluoro-phenoxy)-pyridin-2-yl]-naphthalen-2-yl}-propanoic acid,

4-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenylsulfanyl]-butyric acid,
 4-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2-fluoro-phenylsulfanyl]-butyric acid,
 4-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-phenylsulfanyl]-butyric acid,
 4-(4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-ylphenyl)sulfanylbutanoic acid,
 4-(2-fluoro-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-phenyl)sulfanylbutanoic
 acid,
 5-[4-(2-isopropoxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 4-{1-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric
 acid,
 4-{1-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 butyric acid,
 4-{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 butyric acid,
 4-{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 butyric acid,
 5-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 {2-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 3-{2-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 3-{2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 3-{2-[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-cyclopropyl}-propanoic
 acid,
 3-{2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic
 acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 3-{2-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 3-{2-[4-(2-cyclopentylamino-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 5-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-5,5-difluoro-pentanoic acid,
 {4-[4-(2-cyclopentylloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexyl}-acetic acid,
 3-{2-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic
 acid,
 3-{2-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 3-(2-{2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl}-
 cyclopropyl)-propanoic acid,
 3-{2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-
 propanoic acid,
 5,5-difluoro-5-[4-(6-isopropylsulfanyl-pyridin-2-yl)-phenyl]-pentanoic acid,
 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-phenoxy]-butyric acid,
 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2-fluoro-phenoxy]-butyric acid,
 4-{[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-
 butyric acid,
 4-{[4-(2-cyclopentylloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric
 acid,
 4-{[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-
 butyric acid,
 4-{[2,6-difluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino}-butyric

acid,

4-[(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-[5-(2-cyclopentylsulfanyl-pyridin-3-yl)-indol-1-yl]-butyric acid,

4-[(3,5-difluoro-3'-pyrrolidin-1-yl-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-{[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-
butyric acid,

4-{[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenyl]-methyl-amino}-
butyric acid,

4-{[4-(6-cyclopentyloxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric
acid,

4-{[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino}-butyric
acid,

4-{[4-(2-ethylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino}-butyric
acid,

2-{[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenylamino]-methyl}-
cyclopropane carboxylic acid,

2-{[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenylamino]-methyl}-cyclopropane
carboxylic acid,

4-{[2-fluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino}-butyric
acid,

4-{[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino}-butyric
acid,

4-{[2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl]-methyl-amino}-butyric acid,

4-[(2'-cyclopentylamino-3,5-difluoro-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-[methyl-(3,5,5'-trifluoro-2'-isopropoxy-biphenyl-4-yl)-amino]-butyric acid,

4-{[4-(2-cyclopentyloxy-5-methyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-
amino}-butyric acid,

4-{[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-
butyric acid,

4-{{2,6-difluoro-4-(2-methoxy-pyridin-3-yl)-phenyl}-methyl-amino}-butyric acid,
 4-{{2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl}-methyl-
 amino}-butyric acid,
 4-[(3,5-difluoro-2'-pyrrolidin-1-yl-biphenyl-4-yl)-methyl-amino]-butyric acid,
 4-[(3,5-difluoro-2'-methylamino-biphenyl-4-yl)-methyl-amino]-butyric acid,
 4-{{3,5-difluoro-2'-(isopropyl-methyl-amino)-biphenyl-4-yl}-methyl-amino}-butyric
 acid,
 4-{{4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl}-ethyl-amino}-butyric
 acid,
 4-{{4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl}-ethyl-amino}-butyric
 acid,
 4-{{2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl}-ethyl-amino}-butyric acid,
 (R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 (E)-(R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hex-2-enoic
 acid,
 (S)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 5-{{2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 5-{{2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 5-{{2,6-difluoro-4-[2-(oxetan-3-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 4-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 6-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 6-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenylsulfanyl]-butyric acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[3-(6-cyclopentyloxy-pyridin-2-yl)-phenoxy]-butyric acid,
 4-[3-(2-cyclopentyloxy-pyridin-3-yl)-phenoxy]-butyric acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,

5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 4-[4-(5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-
 butyric acid,
 4-[4-(5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-
 phenylsulfanyl]-butyric acid,
 4-{[4-(5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenyl]-
 methyl-amino}-butyric acid,
 5-[4-(5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenyl]-
 hexanoic acid,
 4-[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-phenoxy]-
 butyric acid,
 4-[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-
 phenylsulfanyl]-butyric acid,
 4-{[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-phenyl]-
 methyl-amino}-butyric acid,
 5-[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-phenyl]-
 hexanoic acid,
 4-(2,6-difluoro-4-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-phenoxy)-butyric acid,
 4-(2,6-difluoro-4-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-phenylsulfanyl)-
 butyric acid,
 4-(2,6-difluoro-N-methyl-4-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-anilino)-
 butyric acid,
 5-(2,6-difluoro-4-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-phenyl)-hexanoic acid,
 7-[4-(3-carboxy-propoxy)-3,5-difluoro-phenyl]-5-fluoro-2,2-dimethyl-2,3-dihydro-
 indol-1-carboxylic acid methyl ester,
 4-[2,6-difluoro-4-(5-fluoro-2,2-dimethyl-2,3-dihydro-1H-indol-7-yl)-phenoxy]-

butyric acid,

4-[4-(3-carboxy-propoxy)-3,5-difluoro-phenyl]-5-fluoro-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester,

4-[2,6-difluoro-4-(5-fluoro-2,2-dimethyl-2,3-dihydro-1H-indol-4-yl)-phenoxy]-butyric acid,

4-[2,6-difluoro-4-(5-fluoro-2,2-dimethyl-2,3-dihydro-1H-indol-7-yl)-phenylsulfanyl]-butyric acid,

3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclopentoxo-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclobutylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid,

3-[6-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-chroman-2-yl]-propionic acid,

3-[6-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclobutylsulfanyl-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclopropylmethoxy-pyridin-3-yl)-chroman-2-yl]-propionic acid,

3-[6-(2-cyclobutoxy-pyridin-3-yl)-chroman-2-yl]-propionic acid,

3-[6-(2-cyclobutoxy-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclopropylmethoxy-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(2-cyclopentylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid,

3-[6-(2-cyclopentylsulfanyl-pyridin-3-yl)-thiochroman-2-yl]-propionic acid,

3-[6-(5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-thiochroman-2-yl]-propionic acid,

3-(6-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-thiochroman-2-yl)-propionic acid,

3-{6-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-thiochroman-2-yl}-propionic acid,

{1-[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-phenyl]-azetidin-3-yl}-acetic acid,

3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-thiochroman-2-yl]-propionic acid,

4-(2,6-difluoro-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-phenoxy)butanoic acid,

4-(4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-ylphenoxy)butanoic acid,

4-(2-fluoro-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-phenoxy)butanoic acid,

4-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-4-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclohexylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenoxy]-butyric acid,
 3-[4-(2-cyclopentylloxy-pyridin-3-yl)-benzylsulfanyl]-propionic acid,
 2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentoxo)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[3-(cyclobutoxy)phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[3-(cyclopropylmethoxy)phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[3-(isopropoxymethyl)phenyl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[3-(ethoxymethyl)phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[3-(cyclobutoxy)-4-fluoro-phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-[3-(cyclobutoxy)-4-methoxy-phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-[3-(cyclobutoxy)-5-fluoro-phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[2-chloro-4-[6-(cyclopropylmethoxy)-2-pyridyl]-6-fluoro-phenyl]-4-
 piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-(6-*tert*-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[3-(cyclobutoxy)-2-methyl-phenyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-[5-chloro-6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-[6-(cyclopropanecarbonyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[4-[6-(cyclobutoxymethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[4-(6-ethoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]phenyl]-4-piperidyl]acetic

acid,

2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoro-1-methyl-ethoxy)-2-pyridyl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-(6-cyclopentyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-[cyclopropyl(methoxy)methyl]-2-pyridyl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic

acid,

2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-(6-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-[2-(cyclobutoxy)thiazol-4-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-

yl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-(6-ethoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-methoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-butoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentoxo)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(4-ethoxypyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isopropoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-propoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-pyrrolidin-1-yl)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[6-(isopropylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(diethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[6-(isobutylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylamino)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(dimethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[4-(isobutylamino)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutoxy)-5-methyl-pyrazin-2-yl]-2,6-difluoro-phenyl]-4-
 piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-phenylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclopentylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutylpyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[5-(cyclobutoxy)-3-methyl-isothiazol-4-yl]-2,6-difluoro-phenyl]-4-
 piperidyl]acetic acid,
 {1-[4-(4-ethoxy-thiazol-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}acetic acid,
 {1-[4-(4-ethoxy-5-methyl-thiazol-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}acetic
 acid,
 2-[1-[4-(6-butylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopentylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-
 piperidyl]acetic acid,
 2-[1-[4-[4-(cyclopropylmethoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-
 piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 {1-[4-(4-cyclopropylmethoxy-thiazol-2-yl)-2,6-difluoro-phenyl]-piperidin-4-
 yl}acetic acid,
 (1-{2,6-difluoro-4-[4-(4-fluoro-phenyl)-thiazol-2-yl]-phenyl}-piperidin-4-yl)-acetic
 acid,
 {1-[4-(4-cyclobutoxy-thiazol-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}acetic acid,
 {1-[4-(4-butoxy-thiazol-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}acetic acid,
 2-(1-{2,6-difluoro-4-[7-(propan-2-yl)-7H-pyrrolo[2,3-*d*]pyrimidin-4-
 yl]phenyl}piperidin-4-yl)acetic acid,

2-[1-[4-(6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-4-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-5,6-dimethyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenoxy]butanoic acid,

4-[2,6-dichloro-4-[6-(cyclobutoxy)-2-pyridyl]phenoxy]butanoic acid,

4-[4-[3-(cyclopropylmethoxymethyl)-2-furyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclopropylmethoxymethyl)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[3-(cyclobutoxy)-5-fluoro-phenyl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[3-(cyclopropylmethoxymethyl)-5-methyl-isoxazol-4-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[6-chloro-4-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[2-(cyclobutoxy)thiazol-4-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[2-(cyclopropylmethoxy)thiazol-4-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenoxy]butanoic acid,

5-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]hexanoic acid,

4-[2-chloro-4-(6-cyclopentyloxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyridin-2-yl)-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclobutylsulfanyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-6-fluoro-4-(6-isopropylsulfanyl-pyridin-2-yl)-phenoxy]-butyric acid,

4-(5-chloro-3'-cyclobutoxy-3-fluoro-biphenyl-4-yloxy)-butyric acid,

4-(5-chloro-3'-cyclopropylmethoxy-3-fluoro-biphenyl-4-yloxy)-butyric acid,

4-(5-chloro-3'-cyclopropylmethoxy-3-fluoro-4'-methoxy-biphenyl-4-yloxy)-butyric acid,

4-(5-chloro-3'-cyclopropylmethoxy-3,4'-difluoro-biphenyl-4-yloxy)-butyric acid,

4-(3'-cyclobutylsulfanyl-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

5-(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yl)-hexanoic acid,

5-(5'-cyclobutoxy-3,5,3'-trifluoro-biphenyl-4-yl)-hexanoic acid,

5-(3'-cyclopropylmethoxy-3,5-difluoro-4'-methoxy-biphenyl-4-yl)-hexanoic acid,

5-(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yl)-hexanoic acid,

5-(5'-cyclobutoxy-3'-fluoro-biphenyl-4-yl)-5,5-difluoro-pentanoic acid,

5-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,

4-(3'-cyclobutanesulfonyl-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

5-([4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-methyl-amino)-methyl-isoxazol-3-ol,

5-[4-(2-cyclobutoxy-6-methyl-pyrimidin-4-yl)-2,6-difluoro-phenyl]-hexanoic acid,

5-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,

4-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[4-(2-cyclobutoxy-pyrimidin-4-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(4-cyclobutoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(2-cyclobutoxy-pyrimidin-4-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-chloro-4-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(2-cyclobutoxy-thiazol-4-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(2-cyclopropylmethoxy-thiazol-4-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclobutoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclopropylmethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclopropylmethoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-ethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 {(R)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(2,2-difluoro-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,
 3-[8-fluoro-6-(2-isopropylsulfanyl-3-pyridyl)thiochroman-2-yl]propanoic acid,
 3-[6-[6-(cyclobutoxy)-2-pyridyl]thiochroman-2-yl]propanoic acid,
 3-[2-[2,6-difluoro-4-(7-methoxy-2,2-dimethyl-3H-benzofuran-4-yl)phenyl]cyclopropyl]propanoic acid,
 3-[2-(2,6-difluoro-4-spiro[3H-benzofuran-2,1'-cyclopentan]-7-yl-phenyl)cyclopropyl]propanoic acid,
 3-[6-[6-(cyclobutoxy)-2-pyridyl]chroman-2-yl]propanoic acid,
 3-[6-[6-(cyclopropylmethoxy)-2-pyridyl]chroman-2-yl]propanoic acid,
 4-[4-(2,3-dimethoxyphenyl)-2,6-difluoro-phenoxy]butanoic acid,
 3-[6-[3-(cyclopropylmethoxy)phenyl]chroman-2-yl]propanoic acid,
 3-[6-[3-(cyclopentoxo)phenyl]chroman-2-yl]propanoic acid,
 4-(2,6-difluoro-N-methyl-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-anilino)butanoic acid,
 5-(2,6-difluoro-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-phenyl)hexanoic acid,
 3-[6-(6-*tert*-butylsulfanyl-2-pyridyl)chroman-2-yl]propanoic acid,
 3-[6-(6-isopropoxy-2-pyridyl)chroman-2-yl]propanoic acid,
 2-[1-(2,6-difluoro-4-spiro[1,3-benzodioxol-2,1'-cyclopentan]-4-yl-phenyl)-4-piperidyl]acetic acid,
 4-[4-(2,3-dipropoxyphenyl)-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(2,3-dipropoxyphenyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic

acid,

4-[4-(2,3-dipropoxyphenyl)-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

2-[1-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-(6-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

5-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]phenyl]-5,5-difluoro-pentanoic acid,

4-[2,6-difluoro-4-(5-fluoroindol-1-yl)phenoxy]butanoic acid,

4-[4-[3-(cyclopropylmethylamino)phenyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[2,6-difluoro-N-methyl-4-(6-pyrrolidin-1-yl-2-pyridyl)anilino]butanoic acid,

4-[2,6-difluoro-4-(5-methoxyindol-1-yl)phenoxy]butanoic acid,

4-[4-(5-cyanoindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[3-(cyclopropylmethoxymethyl)-2-furyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[2,6-difluoro-4-(4-fluoroindol-1-yl)phenoxy]butanoic acid,

4-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[5-(cyclopropylmethoxymethyl)-2-furyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-(7-chloroindol-1-yl)-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[6-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[5-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2,6-difluoro-4-(4-methoxyindol-1-yl)phenoxy]butanoic acid,

4-[2,6-difluoro-4-(7-methoxyindol-1-yl)phenoxy]butanoic acid,

4-[2,6-difluoro-4-[5-(methoxymethyl)indazol-1-yl]phenoxy]butanoic acid,

2-[1-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-[6-(cyclobutoxy)indazol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,

4-[2-chloro-4-[6-(cyclobutoxy)indazol-1-yl]-6-fluoro-phenoxy]butanoic acid,

4-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,

4-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[2-(cyclobutoxy)thiazol-4-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[4-[6-(cyclobutoxy)indazol-1-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclobutoxy)indazol-1-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[4-[6-(cyclobutoxy)indazol-1-yl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic acid,
 2-{1-[2,6-difluoro-4-(6-propoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-isobutoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-cyclopentoxo-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-butoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(4-propoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(4-isopropoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(4-ethoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(4-isobutoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-isobutylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-cyclopentylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-isopropylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 2-{1-[2,6-difluoro-4-(6-diethylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl}acetic acid,
 3-[6-(6-cyclobutoxy-pyrazin-2-yl)-thiochroman-2-yl]-propionic acid,
 2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-pyrrolidin-3-yl]acetic acid,

2-[1-[4-[4-phenoxy-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-pyridin-3-yloxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(4-fluorophenoxy)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(4-methoxyphenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(*p*-tolylloxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(3,4-difluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[4-(5-chloro-2-methyl-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid,

5-[4-(5-chloro-2-methyl-benzofuran-7-yl)-2,6-difluoro-phenyl]-hexanoic acid,

4-[(3'-cyclobutylmethoxy-3,5-difluoro-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-(3'-cyclobutylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

4-{[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-[(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-[(3'-cyclopentylloxy-3,5-difluoro-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-(3'-cyclopropylmethoxy-3,5-difluoro-4'-methoxy-biphenyl-4-yloxy)-butyric acid,

4-(3'-cyclopropylmethoxy-3,5,4'-trifluoro-biphenyl-4-yloxy)-butyric acid,

4-(5'-cyclobutoxy-3,5,3'-trifluoro-biphenyl-4-yloxy)-butyric acid,

4-[(5'-cyclobutylmethoxy-3,5-difluoro-2'-methyl-biphenyl-4-yl)-methyl-amino]-butyric acid,

4-(5'-cyclobutylmethoxy-3,5-difluoro-2'-methyl-biphenyl-4-yloxy)-butyric acid,

4-{[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-

butyric acid,

4-(3'-cyclopropylmethoxy-3,5-difluoro-4'-methyl-biphenyl-4-yloxy)-butyric acid,

4-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,

4-(4'-chloro-3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid,

5-(5'-cyclobutoxy-3,3'-difluoro-biphenyl-4-yl)-pentanoic acid,

4-(5'-cyclobutoxy-3,3'-difluoro-biphenyl-4-yloxy)-butyric acid,

5-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenyl]-pentanoic acid,

4-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

4-[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,

2-(3'-cyclobutoxy-3,5,5'-trifluoro-biphenyl-4-yloxymethyl)-cyclopropane carboxylic acid,

2-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(2-cyclobutoxy-thiazol-4-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxy-methyl]-cyclopropane carboxylic acid,

3-[6-(3-cyclobutoxy-phenyl)-chroman-2-yl]-propionic acid,

3-[6-(6-propoxy-pyridin-2-yl)-chroman-2-yl]-propionic acid,

4-[2,6-difluoro-4-(1H-indol-6-yl)-phenoxy]-butanoic acid,

4-[2,6-difluoro-4-(1-isopropyl-1H-indol-6-yl)-phenoxy]-butanoic acid,

4-[4-(1-cyclopropylmethyl-1H-indol-6-yl)-2,6-difluoro-phenoxy]-butanoic acid

{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

4-[4-(3-chloro-1-isopropyl-1H-indol-6-yl)-2,6-difluoro-phenoxy]-butanoic acid,

{1-[2,6-difluoro-4-(6-isopropoxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

4-[4-(5-cyclopropylmethoxymethyl-thiophen-2-yl)-2,6-difluoro-phenoxy]-butanoic acid,

4-[4-(5-cyclopropylmethoxymethyl-thiophen-3-yl)-2,6-difluoro-phenoxy]-butanoic acid,

{1-[4-(5-cyclopropylmethoxymethyl-thiophen-3-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

4-[4-(4-cyclopropylmethoxymethyl-2-methyl-thiazol-5-yl)-2,6-difluoro-phenoxy]-butanoic acid,

{1-[4-(5-cyclopropylmethoxymethyl-thiophen-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxymethyl-2-methyl-thiazol-5-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

4-[4-(5-cyclobutylmethoxymethyl-thiophen-3-yl)-2,6-difluoro-phenoxy]-butanoic acid,

4-[2,6-difluoro-4-(5-isobutoxymethyl-thiophen-3-yl)-phenoxy]-butanoic acid,
 4-[4-(5-cyclobutoxymethyl-thiophen-3-yl)-2,6-difluoro-phenoxy]-butanoic acid,
 4-[4-(3-cyclopropylmethoxymethyl-thiophen-2-yl)-2,6-difluoro-phenoxy]-butanoic
 acid,
 {1-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-
 yl}-acetic acid,
 {1-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-
 pyrrolidin-3-yl}-acetic acid,
 {1-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic
 acid,
 {1-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[4-(2-cyclobutoxy-thiazol-4-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(2-cyclopropylmethoxy-thiazol-4-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[2,6-difluoro-4-(6-methoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(6-ethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-
 acetic acid,
 {1-[4-(5-cyclobutoxy-3-methyl-isothiazol-4-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-

yl}-acetic acid,

{1-[4-(4-cyclobutoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

(1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-pyrrolidin-3-yl)-acetic acid,

(1-{2,6-difluoro-4-[6-(tetrahydro-thiopyran-4-yloxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl)-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

{1-[2,6-difluoro-4-(5-fluoro-4-propoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methyl-butoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(2-methoxy-ethoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

(1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

{(S)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

2-[1-[2,6-difluoro-4-[4-[(6-methyl-3-pyridyl)oxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(4-ethylphenoxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(3-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[2,6-difluoro-4-[4-(3,4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(2-pyridyloxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

{1-[4-(6-cyclobutoxy-4-trifluoromethyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

(1-{2,6-difluoro-4-[2-(4-fluoro-phenyl)-benzo[b]thiophen-4-yl]-phenyl}-piperidin-4-yl)-acetic acid,

{1-[2,6-difluoro-4-(2-m-tolyl-benzo[b]thiophen-4-yl)-phenyl]-piperidin-4-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-6-trifluoromethyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,

{1-[2,6-difluoro-4-(4-propoxy-6-trifluoromethyl-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,

(1-{2,6-difluoro-4-[4-(4-fluoro-phenoxy)-6-trifluoromethyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,

3-{1-[2,6-difluoro-4-(6-propoxy-pyridin-2-yl)-phenyl]-piperidin-4-yl}-propionic acid,

3-{1-[4-(6-cyclobutyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid, and

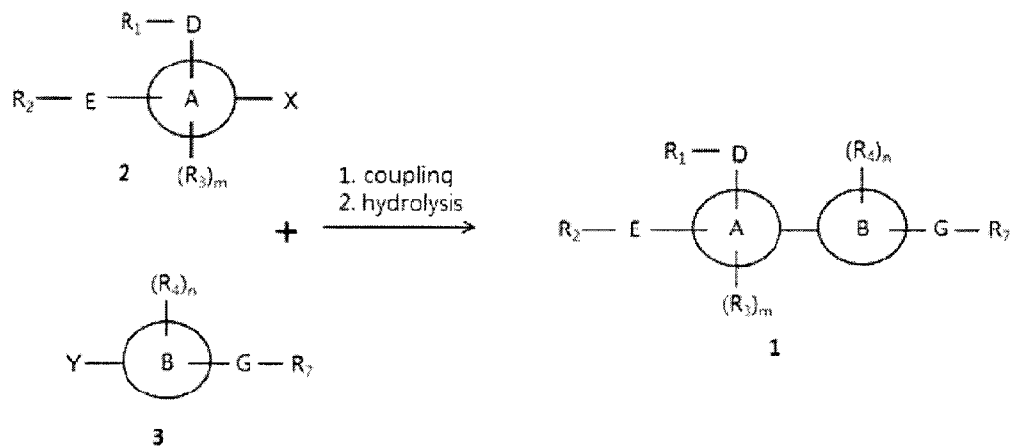
3-{1-[4-(6-ethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid.

The terms and abbreviations used herein retain their original meanings unless indicated otherwise.

The present invention also provides a method for preparing the compound of Formula 1. Hereinafter, the method for preparing the compound of Formula 1 is explained based on exemplary reactions in order to illustrate the present invention. However, a person skilled in the art could prepare the compound of Formula 1 by various methods based on the structure of Formula 1, and such methods should be interpreted as being within the scope of the present invention. That is, the compound of Formula 1 may be prepared by the methods described herein or by combining various methods disclosed in the prior art, which should be interpreted as being within the scope of the present invention. Accordingly, a method for preparing the compound of Formula 1 is not limited to the following methods.

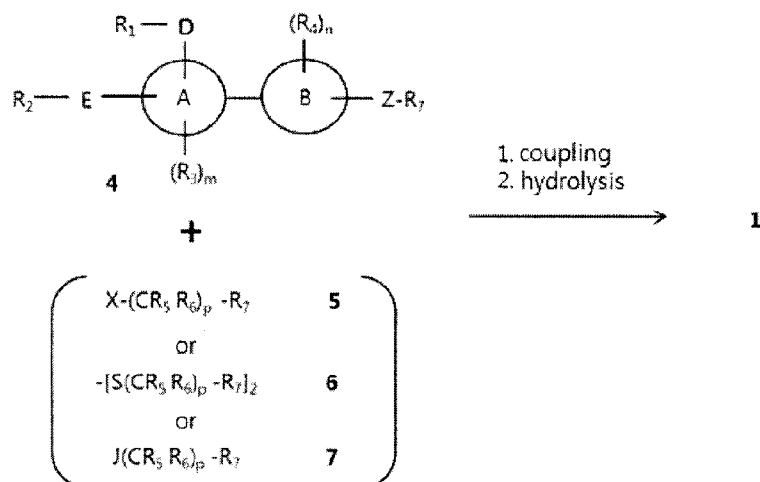
As represented in the following Reaction Scheme 1, the compound of Formula 1 according to the present invention can be prepared by C-C coupling reaction of Compound 2 and Compound 3 in the presence of a conventional metal catalyst, and, if necessary, additional hydrolysis.

[Reaction Scheme 1]



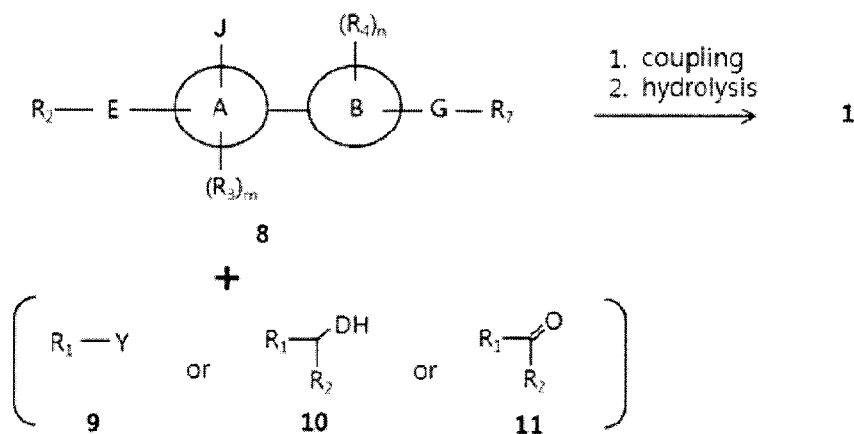
In addition, the compound of Formula 1 according to the present invention can be prepared by coupling reaction of Compound 4 and Compound 5, Compound 6 or Compound 7 in the presence of conventional base or coupling reagents and, if necessary, additional hydrolysis, as represented in the following Reaction Scheme 2. In the Reaction Scheme 2, Z- R_7 and J of Compounds 4 and 7 represent independently halogen, OH, SH or O-alkyl. When Z- R_7 is O-alkyl, it is converted to OH by dealkylation reaction before being subjected to coupling reaction.

[Reaction Scheme 2]



Furthermore, the compound of Formula 1 according to the present invention can be prepared by reacting Compound 8 substituted with J radical with Compound 9 or Compound 10 in the presence of conventional base, metal catalysts or coupling reagents, as represented in the following Reaction Scheme 3. In Reaction Scheme 3, J and Y represent independently halogen, OH, SH or NH₂. When J is amine, “reductive-amination reaction” can be carried out with Compound 11.

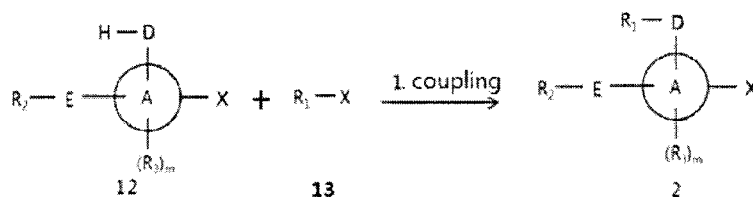
[Reaction Scheme 3]



In Reaction Scheme 1, Compound 2 can be obtained by the coupling reaction of Compound 12 and Compound 13 in the presence of conventional acid, base or coupling reagent,

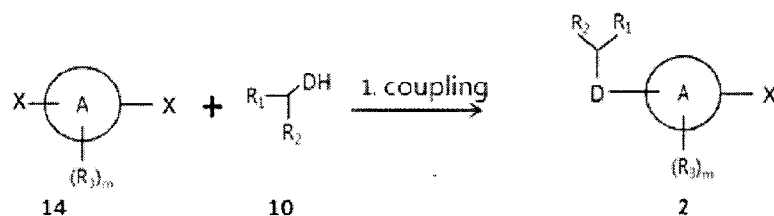
as represented in the following Reaction Scheme 4.

[Reaction Scheme 4]



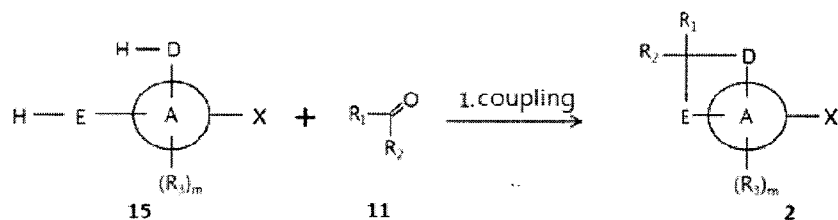
In addition, Compound 2 can be prepared by the coupling reaction of Compound 14 and Compound 10 in the presence of conventional base and metal catalyst, as represented in the following Reaction Scheme 5.

[Reaction Scheme 5]



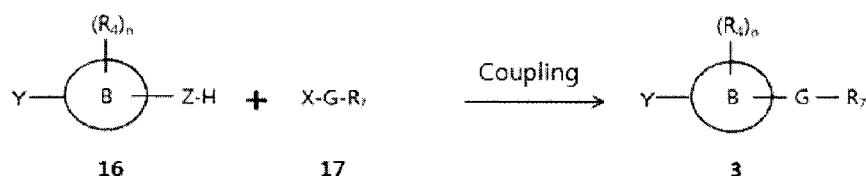
Furthermore, Compound 2 in which R₁ and R₂ form a ring with D and E can be prepared in the presence of conventional acid, as represented in the following Reaction Scheme 6.

[Reaction Scheme 6]



Meanwhile, Compound 3 can be prepared by the coupling reaction of Compound 16 and Compound 17 in the presence of conventional base or coupling reagent, as represented in the following Reaction Scheme 7.

[Reaction Scheme 7]



In the above Reaction Schemes 1 to 7,

X represents halogen or $-\text{OSO}_2\text{CF}_3$,

Y represents boronic acid or boronic acid ester, and

A, B, D, E, G, R₁, R₂, R₃, R₄, R₇, m, n and p are the same as in the above Formula 1.

In the above reaction, transition metal such as palladium (Pd) can be used as a conventional metal catalyst. The above reactions can be carried out in conventional solvents which do not have an adverse effect on the reactions. Preferable solvents include, but are not limited to, one or more selected from dimethylformamide, dimethylacetamide, tetrahydrofuran, acetonitrile, methanol, ethanol, water, 1,2-dichloroethane, dimethylsulfoxide, ethylether, methyl *tert*-butylether, methylene chloride and chloroform.

In the above reactions, unexplained compounds are known compounds or compounds easily obtainable from known compounds by known methods or similar methods.

The compound of Formula 1 obtained by the above methods can be separated or purified from the reaction products by conventional methods such as recrystallization, ionospherisis, silica gel column chromatography or ion-exchange chromatography.

As explained above, the compounds according to the present invention, starting materials or intermediates for the preparation thereof can be prepared by a variety of methods, which should be interpreted as being within the scope of the present invention.

The compound of Formula 1 according to the present invention has the effect of GPR120 agonist. Accordingly, the present invention provides a pharmaceutical composition as a GPR120 agonist comprising the compound of Formula 1, a pharmaceutically acceptable salt or isomer thereof as an active ingredient. Various kinds of prodrugs, which are converted into the compound of Formula I *in vivo*, are also within the scope of the present invention.

Exemplary diseases which can be prevented or treated by the pharmaceutical composition according to the present invention as a GPR120 agonist include, but are not limited

to, metabolic diseases such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and the like, and inflammation. The complications of diabetes include, but are not limited to, neurogenic disease, hyperlipidemia, hypertension, retinosis and renal failure.

In addition, the present invention provides a method for preparing the composition for preventing or treating metabolic diseases such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and the like, and inflammation which comprises the step of mixing the compound of Formula 1, a pharmaceutically acceptable salt or isomer thereof as an active ingredient and a pharmaceutically acceptable carrier.

In the present invention, a “pharmaceutical composition” or a “composition for lowering blood glucose level” may include other components such as carriers, diluents, excipients, etc., in addition to the active ingredient of the present invention. Accordingly, the pharmaceutical composition may include pharmaceutically acceptable carriers, diluents, excipients or combinations thereof, if necessary. The pharmaceutical composition facilitates the administration of compounds into the body. Various methods for administering the compounds include, but are not limited to, oral, injection, aerosol, parenteral and local administration.

Herein, a “carrier” means a compound that facilitates the addition of compounds into the cell or tissue. For example, dimethylsulfoxide (DMSO) is a conventional carrier facilitating the administration of many organic compounds into living cells or tissues.

Herein, a “diluent” means a compound that not only stabilizes a biologically active form but is diluted in solvent dissolving the compounds. A dissolved salt in buffer is used as a diluent in this field. A conventionally used buffer is a phosphate buffer saline mimicking salt form in body fluid. Since a buffer solution can control the pH of the solution at low concentration, a buffer diluent hardly modifies the biological activity of compounds.

Herein, “pharmaceutically acceptable” means such property that does not impair the biological activity and physical property of compounds.

The compounds according to the present invention can be formulated as various pharmaceutically administered dosage forms. In the preparation of the pharmaceutical composition of the present invention, an active component—specifically, the compound of Formula 1 or a pharmaceutically acceptable salt or isomer thereof—is mixed with selected pharmaceutically acceptable carriers considering the dosage form to be prepared. For

example, the pharmaceutical composition of the present invention can be formulated as injections, oral preparations and the like, as needed.

The compound of the present invention can be formulated by conventional methods using known pharmaceutical carriers and excipients, and inserted into a unit or multi-unit containers. The formulations may be solution, suspension or emulsion in oil or aqueous solvent and include conventional dispersing agents, suspending agents or stabilizing agents. In addition, the compound may be, for example, dry powder form which is dissolved in sterilized pyrogen-free water before use. The compound of the present invention can be formulated into suppositories by using a conventional suppository base such as cocoa butter or other glycerides. Solid forms for oral administration include capsules, tablets, pills, powders and granules. Capsules and tablets are preferred. Tablets and pills are preferably enteric-coated. Solid forms are manufactured by mixing the compounds of the present invention with at least one carrier selected from inert diluents such as sucrose, lactose or starch, lubricants such as magnesium stearate, disintegrating agents, binders and the like.

The compound or a pharmaceutical composition comprising the same according to the present invention can be administered in combination with other drugs—for example, other antidiabetics—as required.

The dose of the compound of Formula 1 according to the present invention is determined by a physician's prescription considering the patient's body weight, age and disease condition. A typical dose for adults is in the range of about 0.3 to 500 mg per day according to the frequency and intensity of administration. A typical daily dose of intramuscular or intravenous administration for adults is in the range of about 1 to 300 mg per day which can be administered in divided unit dosages. Some patients need a higher daily dose.

The present invention also provides a method for preventing or treating diseases by using an effective amount of the compound of Formula 1 or a pharmaceutically acceptable salt or isomer thereof as an active ingredient of GPR120 agonist. Representative diseases to be treated by GPR120 agonist include, but are not limited to, metabolic diseases such as the above-mentioned diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis and osteoporosis, and inflammatory diseases. Herein, the term "treatment" is used to mean deterring, delaying or ameliorating the progress of diseases in a subject exhibiting symptoms of diseases. The term "prevention" is used to mean deterring, delaying or ameliorating the

sign of diseases in a subject at risk of exhibiting symptoms of diseases, even if he or she does not exhibit the symptoms.

EFFECTS OF THE INVENTION

The biaryl derivative of Formula 1 according to the present invention as a GPR120 agonist promotes GLP-1 formation in the gastrointestinal tract and improve insulin resistance in the liver or in muscle due to anti-inflammatory action in macrophages, lipocytes, etc., and can accordingly be effectively used for preventing or treating metabolic diseases such as diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and the like, and inflammatory diseases.

MODES FOR THE INVENTION

The present invention is explained in more detail by the following Examples. However, these Examples seek to illustrate the present invention only, and the scope of the present invention is not limited by them.

Hereinafter, M means molar concentration and N means normal concentration. In addition, abbreviations used in the following Preparation Examples and Examples are as follows:

AcCl: acetyl chloride

AcOH: acetic acid

BBr₃: boron tribromide

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

Br₂: bromine

Bu₄NI: tetrabutylammonium iodide

CSA: camphosulfonic acid

CH₃CN: acetonitrile

Cs₂CO₃: cesium carbonate

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCE: 1,2-dichloroethane

DCM: dichloromethane

DIBAL-H: diisobutylaluminum hydride

DIPEA: *N,N*-diisopropylethylamine
DME: 1,2-dimethoxyethane
DMF: *N,N*-dimethylformamide
DMS: dimethyl sulfide
DMSO: dimethyl sulfoxide
DPPF: 1,1'-bis(diphenylphosphino)ferrocene
EtOAc: ethyl acetate
EtOH: ethanol
Et₂O: diethyl ether
Fe(acac)₃: iron(III)acetylacetonate
HCl: hydrochloric acid
Hex: n-hexane
IBX: 2-iodoxybenzoic acid
K₂CO₃: potassium carbonate
KOAc: potassium acetate
LAH: lithium aluminum hydride
LiHMDS: bis(trimethylsilyl)amide lithium
MC: methylene chloride
mCPBA: 3-chloroperbenzoic acid
MeOH: methanol
MgSO₄: magnesium sulfate
MsCl: methanesulfonyl chloride
MTBE: *tert*-butyl methyl ether
NaBH₄: sodium borohydride
NaCl: sodium chloride
Na₂CO₃: sodium carbonate
NaH: sodium hydride
NaOAc: sodium acetate
NaOEt: sodium ethoxide
NaOH: sodium hydroxide
NBS: N-bromosuccinimide
n-BuLi: butyl lithium

NCS: *N*-chlorosuccinimide

NMM: 4-methylmorpholine

NMP: 1-methylpyrrolidin-2-one

Pd/C: palladium/carbon

PdCl₂(dppf)-DCM: 1,1'-bis(diphenylphosphino)ferrocene-palladium(II) dichloride
dichloromethane

PdCl₂(PPh₃)₂: bis(triphenylphosphine)palladium(II) dichloride

Pd₂(dba)₃: tris(dibenzylideneacetone)dipalladium(0)

Pd(OAc)₂: palladium(II) acetate

Pd(PPh₃)₄: tetrakis(triphenylphosphine)palladium(0)

PtO₂: platinum(IV)oxide

SOCl₂: thionyl chloride

SPhos: 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl

TBAB: tetrabutylammonium bromide

TEA: triethylamine

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TMEDA: *N,N,N',N'*-tetramethylethylenediamine

TMSCl: chlorotrimethylsilane

Preparation Example 1: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-propionic acid ethyl ester

Step A: 6-bromo-2-methyl-quinoline

4-Bromo-phenylamine (3.0 g, 17.44 mmol) was dissolved in 30 mL of 6N HCl. Crotonaldehyde (2.44 g, 34.88 mmol) was slowly added thereto, and the reaction mixture was stirred at 100°C for 16 hours. The mixture was cooled to 0°C, neutralized with aqueous ammonia, extracted with EtOAc and purified by column chromatography to obtain the title compound (2 g, 52 %).

¹H-NMR (CDCl₃) δ 8.02~7.92 (2H, m), 7.89 (1H, d), 7.73 (1H, d), 7.32 (1H, d), 1.60 (3H, s)

Step B: 6-bromo-quinolin-2-carbaldehyde

6-Bromo-2-methyl-quinoline (1.0 g, 4.50 mmol) obtained in Step A was dissolved in 1,4-dioxane. Selenium dioxide (0.65 g, 5.85 mmol) was added thereto, and the reaction mixture was stirred at 80°C for 3 hours. The mixture was filtered through Celite and solidified with Et₂O to obtain the title compound (0.93 g, 88 %).

¹H-NMR (CDCl₃) δ 10.20 (1H, s), 8.22 (1H, d), 8.15~8.02 (3H, m), 7.90 (1H, d)

Step C: (E)-3-(6-bromo-quinolin-2-yl)-acrylic acid ethyl ester

6-Bromo-quinolin-2-carbaldehyde (0.93 g, 3.95 mmol) obtained in Step B was dissolved in THF. NaH (60 %)(0.17 g, 4.35 mmol) was slowly added thereto at 0°C, and the reaction mixture was stirred for 30 minutes. Triethyl phosphonoacetate (0.97 g, 4.35 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 16 hours. The reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (0.86 g, 72 %).

¹H-NMR (CDCl₃) δ 8.10 (1H, d), 8.00~7.92 (2H, m), 7.82~7.70 (2H, m), 7.63 (1H, d), 6.97 (1H, d), 4.30 (2H, q), 1.36 (3H, t)

Step D: (E)-3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-acrylic acid ethyl ester

(E)-3-(6-bromo-quinolin-2-yl)-acrylic acid ethyl ester(0.86 g, 2.82 mmol) obtained in Step C, bis(pinacolato)diboron (0.86 g, 3.39 mmol), potassium acetate (0.83 g, 8.47 mmol) and DPPF(0.11 g, 0.2 mmol) were dissolved in 10 mL of 1,4-dioxane and charged with N₂ gas for 5 minutes. PdCl₂(dppf)-DCM (0.16 g, 0.2 mmol) was added thereto, and the reaction mixture was stirred at 80°C for 4 hours. The reaction solution was filtered through Celite and purified by column chromatography to obtain the title compound (0.84 g, 86 %).

¹H-NMR (CDCl₃) δ 8.31 (1H, s), 8.20 (1H, d), 8.10~8.05 (2H, m), 7.89 (1H, d), 7.60 (1H, d), 6.98 (1H, d), 4.30 (2H, q), 1.35 (12H, s), 1.25 (3H, t)

Step E: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-propionic acid ethyl ester

(E)-3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-acrylic acid ethyl ester (0.83 g, 2.35 mmol) obtained in Step D was dissolved in MeOH. 10% Pd/C (0.08 g) was added thereto, and the reaction mixture was stirred at room temperature for 2 hours

under hydrogen atmosphere. After termination of the reaction, the mixture was filtered through Celite and concentrated under reduced pressure to obtain the title compound (0.83 g, 99 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.29 (1H, s), 8.10~7.90 (3H, m), 7.33 (1H, d), 4.17 (2H, q), 3.32 (2H, t), 2.94 (2H, t), 1.39 (12H, s), 1.25 (3H, t)

Preparation Example 2: [6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester

Step A: (6-bromo-naphthalen-2-yloxy)-acetic acid ethyl ester

6-Bromo-naphthalen-2-ol (1.0 g, 4.48 mmol) was dissolved in 20 mL of DMF and cooled to 0°C. Cs_2CO_3 (1.75 g, 5.38 mmol) and bromoacetic acid ethyl ester (0.75 g, 4.48 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Water was added to the reaction solution, and the solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO_4 and purified by column chromatography to obtain the title compound (1.3 g, 94 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.93 (1H, s), 7.70 (1H, d), 7.60 (1H, d), 7.50 (1H, d), 7.24 (1H, d), 7.04 (1H, s), 4.72 (2H, s), 4.29 (2H, q), 1.29 (3H, t)

Step B: [6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester

(6-Bromo-naphthalen-2-yloxy)-acetic acid ethyl ester (0.5 g, 1.62 mmol) obtained in Step A was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.48 g, 83 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.29 (1H, s), 7.80 (2H, d), 7.68 (1H, d), 7.21 (1H, d), 7.06 (1H, s), 4.74 (2H, s), 4.31 (2H, q), 1.38 (12H, s), 1.29 (3H, t)

Preparation Example 3: 4-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester

Step A: 4-(6-bromo-naphthalen-2-yloxy)-butyric acid ethyl ester

6-Bromo-naphthalen-2-ol (1.0 g, 4.48 mmol) and 4-bromo-butyric acid ethyl ester (0.87 g, 4.48 mmol) were reacted in the same manner as in Step A of Preparation Example 2 to obtain the title compound (1.5 g, 94 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.91 (1H, s), 7.65 (1H, d), 7.57 (1H, d), 7.48 (1H, d), 7.15 (1H, d), 7.08 (1H, s), 4.20~4.10 (4H, m), 2.55 (2H, t), 2.18 (2H, t), 1.25 (3H, t)

Step B: 4-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester

4-(6-Bromo-naphthalen-2-yloxy)-butyric acid ethyl ester (1 g, 2.96 mmol) obtained in Step A were reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.8 g, 70 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.27 (1H, s), 7.78~7.75 (2H, m), 7.69 (1H, d), 7.12~7.08 (2H, m), 4.18~4.10 (4H, m), 2.55 (2H, t), 2.18 (2H, t), 1.33 (12H, s), 1.25 (3H, t)

Preparation Example 4: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester

Step A: chroman-2-carboxylic acid

4-Oxo-4*H*-chromene-2-carboxylic acid (4.0 g, 21.03 mmol) was dissolved in 20 mL of acetic acid. 10% Pd/C (0.4 g) was added thereto and stirred at room temperature for 16 hours under 60 psi of hydrogen. The reaction solution was filtered through Celite, diluted with EtOAc, and extracted with sodium bicarbonate aqueous solution. The water layer was again acidified with 6N HCl and extracted with EtOAc. The organic layer was dried with MgSO_4 and concentrated under reduced pressure to obtain the title compound (3.0 g, 80 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.13 (1H, t), 7.05 (1H, d), 6.95~6.85 (2H, m), 4.75 (1H, m), 3.00~2.80 (2H, m), 2.40 (1H, m), 2.20 (1H, m)

Step B: chroman-2-yl-methanol

Chroman-2-carboxylic acid (1.0 g, 5.61 mmol) obtained in Step A was dissolved in 20 mL of THF and cooled to -20°C . Isobutyl chloroformate (0.84 g, 6.17 mmol) and NMM (0.65 g, 6.45 mmol) were added thereto and the mixture was stirred at the same temperature for 1 hour. NaBH_4 (0.42 g, 11.22 mmol) was dissolved in THF at another reactor and cooled to -78°C . The above reaction solution was filtered through Celite, added to another reactor, and the mixture was stirred at room temperature for 2 hours. The reaction solution was extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.8 g, 87 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.15~7.05 (2H, m), 6.90~6.80 (2H, m), 4.15 (1H, m), 3.85~3.70 (2H, m), 2.95~2.75 (2H, m), 2.10~1.80 (3H, m)

Step C: (*E*)-3-chroman-2-yl-acrylic acid ethyl ester

Oxalyl chloride (1.16 g, 9.13 mmol) was added to 30 mL of DCM and cooled to -78°C . DMSO (1.19 g, 15.22 mmol) was slowly added thereto and stirred for 0.5 hour. The solution in which chroman-2-yl-methanol (1.0 g, 6.09 mmol) obtained in Step B was dissolved in 5 mL of DCM and TEA (2.46 g, 24.36 mmol) were sequentially and slowly added. The mixture was stirred at room temperature for 1 hour, and (carbethoxymethylene)triphenylphosphorane (2.54 g, 7.30 mmol) was then added thereto and the reaction of the mixture was carried out at room temperature for 16 hours. Water was added to the reaction solution, and this solution was extracted with DCM to separate an organic layer. The organic layer was dried with MgSO_4 and purified by column chromatography to obtain the title compound (1.47 g, 69 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.20~7.00 (3H, m), 6.90~6.80 (2H, m), 6.18 (1H, m), 4.75 (1H, m), 4.24 (2H, q), 2.95~2.70 (2H, m), 2.15 (1H, m), 1.85 (1H, m), 1.26 (3H, t)

Step D: 3-chroman-2-yl-propionic acid ethyl ester

(*E*)-3-chroman-2-yl-acrylic acid ethyl ester (0.53 g, 2.28 mmol) obtained in Step C was dissolved in MeOH. 10% Pd/C (0.05 g) was added thereto, and the reaction mixture was stirred at room temperature for 16 hours under hydrogen atmosphere. After termination of the reaction, the mixture was filtered through Celite and concentrated under reduced pressure to obtain the title compound (0.51 g, 96 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.12~7.00 (2H, m), 6.84~6.77 (2H, m), 4.16 (2H, q), 4.01 (1H, m), 2.90~2.70 (2H, m), 2.68~2.51 (2H, m), 2.05~1.95 (3H, m), 1.75 (1H, m), 1.22 (3H, t)

Step E: 3-(6-bromo-chroman-2-yl)-propionic acid ethyl ester

3-Chroman-2-yl-propionic acid ethyl ester (0.2 g, 0.85 mmol) obtained in Step D was dissolved in 15 mL of DMF. NBS (0.15 g, 0.85 mmol) was added thereto at 0°C , and the reaction mixture was stirred at room temperature for 24 hours. The reaction solution was concentrated and 50 mL of water was added thereto. The reaction solution was extracted with Et_2O , dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.21 g, 80 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.17~7.10 (2H, m), 6.65 (1H, d), 4.16 (2H, q), 3.97 (1H, m), 2.90~2.70 (2H, m), 2.65~2.50 (2H, m), 2.05~1.95 (3H, m), 1.72 (1H, m), 1.26 (3H, t)

Step F: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester

3-(6-Bromo-chroman-2-yl)-propionic acid ethyl ester (0.21 g, 0.67 mmol) obtained in Step E was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.19 g, 79 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.56~7.52 (2H, m), 6.76 (1H, d), 4.14 (2H, q), 4.04 (1H, m), 2.90~2.75 (2H, m), 2.65~2.50 (2H, m), 2.08~1.97 (3H, m), 1.75 (1H, m), 1.32 (12H, s), 1.26 (3H, t)

Preparation Example 5: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiochroman-2-yl]-propionic acid ethyl ester

Step A: 6-bromo-4-oxo-thiochroman-2-carboxylic acid

4-bromo-benzenethiol (5.0 g, 26.45 mmol) and furan-2,5-dione (2.6 g, 26.45 mmol) were dissolved in 50 mL of toluene and heated to 50°C. TEA (0.1 mL) was slowly added thereto and the reaction mixture was stirred at 50°C for 1 hour. The reaction solution was concentrated under reduced pressure, dissolved in 50 mL of DCM, and cooled to 0°C. AlCl_3 (5.3 g, 39.67 mmol) was added thereto, and the reaction solution was stirred at room temperature for 1 hours, slowly added dropwise to cold concentrated HCl solution, and extracted with DCM. The organic solvent was dried with MgSO_4 , concentrated under reduced pressure and solidified with Et_2O to obtain the title compound (4.3 g, 57 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.98 (1H, d), 7.65 (1H, dd), 7.31 (1H, d), 4.31 (1H, t), 3.09 (2H, m)

Step B: 6-bromo-4-oxo-thiochroman-2-carboxylic acid methyl ester

6-Bromo-4-oxo-thiochroman-2-carboxylic acid (4.3 g, 14.97 mmol) obtained in Step A was dissolved in 50 mL of methanol. Concentrated sulfuric acid (0.8 mL) was added thereto, and the mixture was stirred for 18 hours under reflux. The reaction solution was concentrated under reduced pressure, extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (4.2 g, 93 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.24 (1H, d), 7.51 (1H, dd), 7.13 (1H, d), 4.13 (1H, t), 3.74 (3H, s), 3.17 (2H, d)

Step C: 6-bromo-thiochroman-2-carboxylic acid methyl ester

6-Bromo-4-oxo-thiochroman-2-carboxylic acid methyl ester (2.0 g, 6.64 mmol) obtained in Step B was dissolved in 20 mL of TFA. Triethylsilane (2.1 mL, 13.28 mmol) was added thereto, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (1.5 g, 78 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.22 (2H, m), 7.00 (1H, d), 4.02 (1H, m), 3.76 (3H, s), 2.96~2.72 (2H, m), 2.33~2.18 (2H, m)

Step D: 6-bromo-thiochroman-2-carboxylic acid

6-Bromo-thiochroman-2-carboxylic acid methyl ester (1.5 g, 5.22 mmol) obtained in Step C was dissolved in each 15 mL of THF, MeOH and 1N NaOH aqueous solution, and the mixture was stirred at room temperature for 2 hours. The organic solvent was removed, and adjusted to pH 3 by the use of 1N HCl aqueous solution, and extracted with EtOAc to separate the organic layer. The organic layer was dried with MgSO_4 and concentrated under reduced pressure to obtain the title compound (1.4 g, 98 %).

Step E: (6-bromo-thiochroman-2-yl)-methanol

6-Bromo-thiochroman-2-carboxylic acid (1.4 g, 5.13 mmol) obtained in Step D was dissolved in 50 mL of THF and cooled to -20°C . Isobutyl chloroformate (0.74 mL, 5.64 mmol) and NMM (0.71 mL, 6.48 mmol) were added thereto, and the mixture was stirred at the same temperature for 1.5 hours. NaBH_4 (0.38 g, 10.26 mmol) was dissolved in 20 mL of THF and 5 mL of MeOH at another reactor and cooled to -78°C . The above reaction solution was filtered through Celite and added to another reactor, and the mixture was stirred at room temperature for 2 hours. The reaction solution was extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (1.3 g, 98 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.19 (2H, m), 7.00 (1H, d), 3.78~3.66 (2H, m), 3.49 (1H, m), 2.83~2.71 (2H, m), 2.22 (1H, m), 1.88 ~ 1.78 (2H, m)

Step F: (E)-3-(6-bromo-thiochroman-2-yl)-acrylic acid ethyl ester

Oxalyl chloride (0.64 mL, 7.53 mmol) was added to 30 mL of DCM and cooled to -78°C. DMSO (0.9 mL, 12.55 mmol) was slowly added, and the mixture was stirred for 0.5 hour. The solution in which (6-bromo-thiochroman-2-yl)-methanol (1.3 g, 5.02 mmol) obtained in Step E was dissolved in 5 mL of DCM and TEA (2.8 mL, 20.08 mmol) were sequentially added thereto. The mixture was stirred at room temperature for 1 hour. (Carbethoxymethylene)triphenylphosphorane (2.1 g, 6.02 mmol) was added thereto, and the reaction was carried out at room temperature for 18 hours. Water was added to the reaction solution, and the mixture was extracted with DCM to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.90 g, 55 %).

¹H-NMR (CDCl₃) δ 7.20 (2H, m), 6.97 (1H, m), 6.90 (1H, m), 6.00 (1H, d), 4.20 (2H, q), 4.02 (1H, m), 2.81 (2H, m), 2.28 (1H, m), 1.92 (1H, m), 1.28 (3H, t)

Step G: 3-(6-bromo-thiochroman-2-yl)-propionic acid ethyl ester

(E)-3-(6-bromo-thiochroman-2-yl)-acrylic acid ethyl ester (0.90 g, 2.75 mmol) obtained in Step F was dissolved in 30 mL of DME. *p*-Toluenesulfonyl hydrazide (3.60 g, 19.25 mmol) was added little by little and heated to 90°C. Sodium acetate (2.26 g, 27.50 mmol, 1.4 M aqueous solution) was added thereto, and the mixture was stirred for 18 hours under reflux. Water was added to the reaction solution and the mixture was extracted with DCM. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.80 g, 88 %).

¹H-NMR (CDCl₃) δ 7.16 (2H, m), 6.93 (1H, d), 4.14 (2H, q), 3.29 (1H, m), 2.80 (2H, m), 2.49 (2H, m), 2.20 (1H, m), 2.02 (1H, m), 1.92 (1H, m), 1.77 (1H, m), 1.25 (3H, t)

Step H: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-thiochroman-2-yl]-propionic acid ethyl ester

3-(6-Bromo-thiochroman-2-yl)-propionic acid ethyl ester (0.80 g, 2.43 mmol) obtained in Step G was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.68 g, 74 %).

¹H-NMR (CDCl₃) δ 7.47 (2H, m), 7.08 (1H, d), 4.14 (2H, q), 3.32 (1H, m), 2.84 (2H, m), 2.49 (2H, m), 2.22 (1H, m), 2.00 (2H, m), 1.81 (1H, m), 1.32 (12H, s), 1.25 (3H, t)

Preparation Example 6: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester

Step A: 3-(1,2,3,4-tetrahydro-quinolin-2-yl)-propionic acid ethyl ester

Quinolin-2-carbaldehyde (1 g, 6.36 mmol) was dissolved in THF. NaH (60 %)(0.28 g, 7.00 mmol) was slowly added thereto at 0°C, and the mixture was stirred for 30 minutes. Triethyl phosphonoacetate (1.57 g, 7.00 mmol) was added dropwise, and the mixture was stirred at room temperature for 16 hours. The reaction solution was extracted with EtOAc, purified by column chromatography and dissolved in 30 mL of methanol. 10% PtO₂ (0.1 g) was added thereto, and the mixture was stirred at room temperature for 16 hours under hydrogen atmosphere. After termination of the reaction, the reaction product was filtered through Celite and concentrated under reduced pressure to obtain the title compound (0.7 g, 47 %).

¹H-NMR (CDCl₃) δ 7.00~6.90 (2H, m), 6.62 (1H, t), 6.46 (1H, d), 4.15 (2H, q), 3.85 (1H, brs), 3.32 (1H, m), 2.84~2.70 (2H, m), 2.45 (2H, m), 1.97~1.80 (3H, m), 1.65 (1H, m), 1.24 (3H, t)

Step B: 3-(6-bromo-1,2,3,4-tetrahydro-quinolin-2-yl)-propionic acid ethyl ester

3-(1,2,3,4-Tetrahydro-quinolin-2-yl)-propionic acid ethyl ester (0.7 g, 3.00 mmol) obtained in Step A was dissolved in 15 mL of DMF. NBS (0.53 g, 3.00 mmol) was added thereto at 0°C, and the mixture was stirred at room temperature for 24 hours. The reaction solution was concentrated, and 50 mL of water was added thereto. The mixture was extracted with Et₂O, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.85 g, 91 %).

¹H-NMR (CDCl₃) δ 7.08~7.00 (2H, m), 6.37 (1H, d), 4.12 (2H, q), 3.30 (1H, m), 2.80~2.65 (2H, m), 2.41 (2H, m), 1.95~1.80 (3H, m), 1.50 (1H, m), 1.25 (3H, t)

Step C: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester

3-(6-Bromo-1,2,3,4-tetrahydro-quinolin-2-yl)-propionic acid ethyl ester (0.33 g, 1.07 mmol) obtained in Step B was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.11 g, 29 %).

¹H-NMR (CDCl₃) δ 7.42 (2H, m), 6.44 (1H, d), 4.20~4.05 (3H, m), 3.34 (1H, m),

2.80~2.70 (2H, m), 2.50~2.35 (2H, m), 1.95~1.80 (3H, m), 1.75 (1H, m), 1.31 (12H, s), 1.24 (3H, t)

Preparation Example 7: [1-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester

Step A: 6-bromo-3,4-dihydro-2*H*-isoquinolin-1-one

5-bromo-indan-1-one (2.35 g, 11.13 mmol) was dissolved in 10 mL of DCM and 10 mL of methanesulfonic acid and cooled to 0°C. Sodium azide (1.45 g, 22.27 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was cooled to 0°C, neutralized with NaOH and extracted with EtOAc. The extract was dried with MgSO₄ and purified by column chromatography to obtain the title compound (1.14 g, 45 %).

¹H-NMR (CDCl₃) δ 7.92 (1H, d), 7.48 (1H, d), 7.39 (1H, s), 6.10 (1H, brs), 3.57 (2H, t), 2.99 (2H, t)

Step B: (6-bromo-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl)-acetic acid ethyl ester

6-Bromo-3,4-dihydro-2*H*-isoquinolin-1-one (0.4 g, 1.77 mmol) obtained in Step A was dissolved in 10 mL of THF and cooled to 0°C. NaH (60%)(0.14 g, 3.54 mmol) was added thereto, and the mixture was stirred at room temperature 0.5 hour. Ethyl bromoacetate (0.44 g, 2.65 mmol) was added to the reaction solution, and the mixture was stirred for 2 hours under reflux. The reaction solution was extracted with EtOAc, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.49 g, 89 %).

¹H-NMR (CDCl₃) δ 7.93 (1H, d), 7.47 (1H, d), 7.37 (1H, s), 4.32 (2H, s), 4.23 (2H, q), 3.66 (2H, t), 3.05 (2H, t), 1.29 (3H, t)

Step C: [1-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester

(6-Bromo-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl)-acetic acid ethyl ester (0.79 g, 1.57 mmol) obtained in Step B was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.54 g, 96 %).

¹H-NMR (CDCl₃) δ 8.06 (1H, d), 7.76 (1H, d), 7.64 (1H, s), 4.34 (2H, s), 4.21 (2H, q), 3.65 (2H, t), 3.07 (2H, t), 1.30 (12H, s), 1.26 (3H, t)

Preparation Example 8: 3-[1-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester

Step A: 3-(6-bromo-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl)-propionic acid methyl ester

6-Bromo-3,4-dihydro-2*H*-isoquinolin-1-one (0.3 g, 1.32 mmol) obtained in Step A of Preparation Example 7 was dissolved in 10 mL of THF and cooled to 0°C. NaH (60%)(0.11 g, 2.65 mmol) was added thereto, and the mixture was stirred at room temperature for 0.5 hour. 3-Bromo-propionic acid methyl ester (0.33 g, 2.00 mmol) was added to the reaction solution, and the mixture was stirred for 2 hours under reflux. The reaction solution was extracted with EtOAc, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.38 g, 92 %).

¹H-NMR (CDCl₃) δ 7.90 (1H, d), 7.47 (1H, d), 7.34 (1H, s), 3.80 (2H, t), 3.69 (3H, s), 3.63 (2H, t), 2.94 (2H, t), 2.73 (2H, t)

Step B: 3-[1-oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester

3-(6-Bromo-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl)-propionic acid methyl ester (0.38 g, 1.22 mmol) obtained in Step A was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.36 g, 82 %).

¹H-NMR (CDCl₃) δ 8.03 (1H, d), 7.77 (1H, d), 7.61 (1H, s), 3.82 (2H, t), 3.68 (3H, s), 3.63 (2H, t), 2.98 (2H, t), 2.72 (2H, t), 1.35 (12H, s)

Preparation Example 9: 3-iodo-2-isopropylsulfanyl-pyridine

2-Fluoro-3-iodo-pyridine (0.3 g, 1.34 mmol), Cs₂CO₃ (0.66 g, 1.34 mmol) and propane-2-thiol (0.125 mL, 1.34 mmol) were added to a reactor, and the mixture was stirred at room temperature for 8 hours. Water was added to the reaction solution and the mixture was extracted with EtOAc. An organic layer was separated, and the separated organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.21 g, 56%).

¹H-NMR (CDCl₃) δ 8.40 (1H, m), 7.92 (1H, m), 6.69 (1H, m), 3.95 (1H, m), 1.39 (6H, d)

Preparation Example 10: 2-chloro-6-isopropylsulfanyl-pyridine

2,6-Dichloropyridine (3.0 g, 20.3 mmol) and propane-2-thiol (1.88 mL, 20.3 mmol) were reacted in the same manner as in Preparation Example 9 to obtain the title compound (3.63 g, 95 %).

¹H-NMR (CDCl₃) δ 7.40(1H, t), 7.05(1H, t), 6.98(1H, t), 4.00(1H, m), 1.40(6H, d)

Preparation Example 11: 2-cyclopentyloxy-3-iodo-pyridine

Cyclopentanol (0.038 g, 0.44 mmol) and 2-fluoro-3-iodo-pyridine (0.10 g, 0.44 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.091 g, 70 %).

¹H-NMR (CDCl₃) δ 8.09(1H, m), 7.99(1H, m), 6.59(1H, m), 5.43(1H, m), 2.00(2H, m), 1.94(4H, m), 1.66(2H, m)

Preparation Example 12: 2-chloro-6-cyclopentyloxy-pyridine

6-Chloro-2-pyridinol (1.95 g, 15 mmol) and K₂CO₃ (4.16 g, 30 mmol) were dissolved in 50 mL of DMF. Cyclopentyl bromide (1.94 mL, 18 mmol) was added thereto, and the mixture was stirred at 80°C for 24 hours. Solids were removed, and the filtrate was concentrated to obtain the title compound (2.92 g, 98 %).

¹H NMR (CDCl₃) δ 7.47 (1H, t), 6.84 (1H, d), 6.51 (1H, d), 5.38 (1H, m), 1.97 (2H, m), 1.79 (4H, m), 1.62 (2H, m)

Preparation Example 13: 2-cyclobutylsulfanyl-3-iodo-pyridine**Step A: cyclobutane thiol**

Magnesium (0.99 g, 40.74 mmol) was dissolved in THF (20 mL). Cyclobutyl bromide (5.0 g, 37.03 mmol) was dissolved in THF (5 mL) at 50°C and added thereto, and the mixture was stirred for 2 hours under reflux. Sulfur (1.06 g, 33.33 mmol) was slowly added thereto at 0°C, and the mixture was stirred at 50°C for 2 hours. LAH (0.843 g, 22.22 mmol) was slowly added thereto at 0°C, and the mixture was stirred for 30 minutes under reflux. After termination of the reaction by the use of ammoniumchloride aqueous solution (20 mL) and 1N HCl (20 mL) at 0°C, an organic layer was separated and extracted with Et₂O (30 mL × 3). The organic layer was dried with MgSO₄ and used for the next step.

Step B: 2-cyclobutylsulfanyl-3-iodo-pyridine

Cyclobutane thiol (0.069 g, 0.782 mmol) obtained in Step A and 2-fluoro-3-iodo-pyridine (0.1 g, 0.43 mmol) were dissolved in DMF (3 mL). Cs_2CO_3 (0.26 g, 0.86 mmol) was added thereto, and the mixture was heated to 80°C and stirred. NaCl aqueous solution was added to the reaction solution, and the mixture was extracted with EtOAc. The organic layer was dried with MgSO_4 and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.115 g, 91 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.36(1H, m), 7.90(1H, m), 6.69(1H, m), 4.33(1H, m), 2.54(2H, m), 2.14(2H, m), 2.05(2H, m)

Preparation Example 14: 2-chloro-6-cyclopentylsulfanyl-pyridine

2,6-Dichloropyridine (3.08 g, 20.7 mmol) and Cs_2CO_3 (6.8 g, 20.7 mmol) were dissolved in 40 mL of DMF. Cyclopentylthiol (2.17 mL, 20.7 mmol) was added thereto, and the mixture was stirred at 80°C for 16 hours. Solids were filtered, and the filtrate was concentrated to obtain the title compound (4.24 g, 95 %).

$^1\text{H NMR}$ (CDCl_3) δ 7.40 (1H, t), 7.06 (1H, d), 6.97 (1H, d), 4.01 (1H, m), 2.22 (2H, m), 1.76 (2H, m), 1.64 (4H, m)

Preparation Example 15: 2-cyclopentylsulfanyl-3-iodo-pyridine

2-Fluoro-3-iodo-pyridine (0.065 g, 0.29 mmol), Cs_2CO_3 (0.19 g, 0.58 mmol) and cyclopentylthiol (0.03 g, 0.291 mmol) were dissolved in 2 mL of DMF, and the mixture was stirred at 80°C for 2 hours. NaCl aqueous solution was added to the reaction solution, and the mixture was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO_4 and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.053 g, 65 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.38(1H, m), 7.89(1H, m), 6.68(1H, m), 4.00(1H, m), 2.22(2H, m), 1.80(2H, m), 1.66(4H, m)

Preparation Example 16: 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester**Step A: 4-bromo-2,6-difluoro-phenol**

2,6-Difluorophenol (1.02 g, 7.8 mmol) was dissolved in 15 mL of DMF. NBS (1.40 g, 7.84 mmol) was added thereto at 0°C, and the mixture was stirred at room temperature for 24 hours. The reaction solution was concentrated, and 50 mL of water was added thereto. The reaction solution was extracted with Et₂O and dried with MgSO₄ to obtain the title compound (1.41 g, 86 %).

¹H NMR (CDCl₃) δ 7.08 (2H, m), 5.42 (1H, brs)

Step B: 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

4-Bromo-2,6-difluoro-phenol (1.414 g, 6.76 mmol) obtained in Step A, bis(pinacolato)diboron (1.8 g, 7.09 mmol), potassium acetate (2.66 g, 27 mmol) and DPPF (0.19 g, 0.34 mmol) were dissolved in 23 mL of 1,4-dioxane. The mixture was charged with N₂ gas for 5 minutes, and PdCl₂(dppf)-DCM (0.27 g, 0.34 mmol) was added thereto. The mixture was stirred at 80°C for 3 hours, filtered through Celite and purified by column chromatography to obtain the title compound (1.366 g, 79 %).

¹H NMR (CDCl₃) δ 7.33 (2H, m), 5.25 (1H, s), 1.32 (12H, s)

Step C: 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester

2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (1.87 g, 7.3 mmol) obtained in Step B, Cs₂CO₃ (4.76 g, 14.6 mmol) and 4-bromo-butyric acid ethyl ester (1.42 g, 7.3 mmol) were dissolved in 24 mL of DMF. The mixture was stirred at room temperature for 24 hours. Solids were filtered and purified by column chromatography to obtain the title compound (1.66 g, 61 %).

¹H NMR (CDCl₃) δ 7.29 (2H, m), 4.21 (2H, t), 4.14 (2H, q), 2.56 (2H, t), 2.07 (2H, m), 1.32 (12H, s), 1.25 (3H, t)

Preparation Example 17: 1-benzyloxy-3-iodo-benzene

3-Iodo phenol (0.5 g, 2.27 mmol) was dissolved in acetonitrile (5 mL). Cs₂CO₃ (2.22 g, 6.81 mmol) and bromomethylbenzene (0.27 mL, 2.27 mmol) were sequentially added thereto. The mixture was stirred at 80-85°C for 2 hours. After termination of the reaction, the reaction solution was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title

compound (0.7 g, 99%).

^1H NMR (400 MHz, CDCl_3) δ 7.39-7.23(m, 7H), 6.97-6.87(m, 2H), 4.95(s, 2H)

Preparation Example 18: 1-iodo-3-isopropoxy-benzene

3-Iodo phenol (0.5 g, 2.27 mmol) and 2-bromo-propane (0.21 mL, 2.27 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.59 g, 99%).

^1H NMR (400 MHz, CDCl_3) δ 7.27-7.22(m, 2H), 6.96(t, 1H), 6.86-6.81(m, 1H), 4.54-4.44(m, 1H), 1.31(d, 6H)

Preparation Example 19: 1-iodo-3-propoxy-benzene

3-Iodo phenol (0.5 g, 2.27 mmol) and 1-bromo-propane (0.21 mL, 2.27 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.58 g, 97%).

^1H NMR (400 MHz, CDCl_3) δ 7.28-7.23(m, 2H), 6.97(t, 1H), 6.87-6.82(m, 1H), 3.85(t, 2H), 1.83-1.71(m, 2H), 1.02(t, 3H)

Preparation Example 20: 1-cyclopropylmethoxy-3-iodo-benzene

3-Iodo phenol (0.5 g, 2.27 mmol) and bromomethyl-cyclopropane (0.22 mL, 2.27 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.59 g, 95%).

^1H NMR (400 MHz, CDCl_3) δ 7.26-7.20(m, 2H), 6.93(t, 1H), 6.84-6.80(m, 1H), 3.71(d, 2H), 1.28-1.15(m, 1H), 0.63-0.57(m, 2H), 0.33-0.28(m, 2H)

Preparation Example 21: 1-cyclobutoxy-3-iodo-benzene

3-Iodo phenol (0.5 g, 2.27 mmol) was dissolved in acetonitrile (5 mL). Cs_2CO_3 (2.22 g, 6.81 mmol) and bromocyclobutane (0.21 mL, 2.27 mmol) were sequentially added thereto. The mixture was stirred at 80-85°C for 10 hours, and the reaction solution was cooled and filtered through Celite. The filtrate was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.45 g, 72 %).

^1H NMR (400 MHz, CDCl_3) δ 7.25-7.20(m, 1H), 7.17-7.13(m, 1H), 6.92(t, 1H), 6.77-

6.72(m, 1H), 4.59-4.50(m, 1H), 2.44-2.33(m, 2H), 2.19-2.05(m, 2H), 1.88-1.77(m, 1H), 1.70-1.57(m, 1H)

Preparation Example 22: 7-iodo-2,2-dimethyl-2,3-dihydro-benzofuran

Step A: 1-iodo-2-(2-methyl-allyloxy)-benzene

2-Iodo phenol (0.93 g, 4.23 mmol) was dissolved in DMF (5 mL). K_2CO_3 (0.82 g, 5.92 mmol) and 3-chloro-2-methyl-propene (0.5 mL, 5.08 mmol) were sequentially added thereto. The mixture was stirred at 70-75°C for 12 hours. After termination of the reaction, the reactions solution was cooled. Water was added to the reaction solution, and the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (1.05 g, 91 %).

^1H NMR (500 MHz, $CDCl_3$) δ 7.77(d, 1H), 7.27(t, 1H), 6.79(d, 1H), 6.70(t, 1H), 5.19(s, 1H), 5.02(s, 1H), 4.48(s, 2H), 1.87(s, 3H)

Step B: 2-iodo-6-(2-methyl-allyl)-phenol

1-Iodo-2-(2-methyl-allyloxy)-benzene (1.05 g, 3.83 mmol) obtained in Step A was added to a seal tube, and NMP (5 mL) was then added thereto. The mixture was stirred at 200°C for 12 hours. After termination of the reaction, the reactions solution was cooled. Water was added to the reaction solution, and the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.25 g, 24%).

^1H NMR (500 MHz, $CDCl_3$) δ 7.46-6.54(m, 3H), 3.11(s, 1H), 3.01(s, 1H), 1.50(s, 2H), 1.47(s, 3H)

Step C: 7-iodo-2,2-dimethyl-2,3-dihydro-benzofuran

HCOOH (5 mL) and water (0.5 mL) were added to 2-iodo-6-(2-methyl-allyl)-phenol (0.25 g, 0.91 mmol) obtained in Step B. The mixture was stirred for 12 hours under reflux. After termination of the reaction, the reactions solution was cooled. Water was added to the reaction solution, and the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was concentrated under reduced pressure and purified by column

chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.07 g, 24 %).

^1H NMR (500 MHz, CDCl_3) δ 7.44(d, 1H), 7.06(d, 1H), 6.56(t, 1H), 3.11(s, 2H), 1.50(s, 6H)

Preparation Example 23: 4-iodo-2,2-dimethyl-benzo[1,3]dioxol

Step A: 1-iodo-2,3-dimethoxy-benzene

THF (5 mL) was added to 1,2-dimethoxy-benzene (0.5 g, 3.62 mmol) and cooled to 0-5°C. *n*-BuLi (1.6 mL, 3.98 mmol) was slowly added dropwise thereto, and the mixture was stirred at 0-5°C for 2 hours. The reaction solution was cooled to -78°C, and I_2 (1.01 g, 3.98 mmol)/THF (5 mL) solution was added thereto. The temperature was increased to room temperature, and the reaction solution was stirred for 2 hours. After termination of the reaction, the reaction solution was concentrated under reduced pressure. Saturated NaHCO_3 solution was added to the reaction solution, and extracted with DCM to separate an organic layer. The organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.62 g, 65 %).

^1H NMR (500 MHz, CDCl_3) δ 7.36-7.32(m, 1H), 6.90-6.86(m, 1H), 6.79(t, 1H), 3.85(s, 3H), 3.83(s, 3H)

Step B: 3-iodo-benzene-1,2-diol

1-Iodo-2,3-dimethoxy-benzene (0.62 g, 2.35 mmol) obtained in Step A was dissolved in DCM (23 mL) and cooled to 0-5°C. 1M BBr_3 (0.276 mL, 7.05 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 3 hours. After termination of the reaction, the reaction solution was cooled to -20°C and diluted by slowly adding ethanol. The mixture was stirred at room temperature for 30 minutes, and saturated NaHCO_3 aqueous solution was added thereto. The mixture was extracted with DCM. The organic layer was dried with MgSO_4 , concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.12 g, 22 %).

^1H NMR (500 MHz, CDCl_3) δ 7.18(d, 1H), 6.87(d, 1H), 6.60(t, 1H), 5.64(s, br, 2H)

Step C: 4-iodo-2,2-dimethyl-benzo[1,3]dioxol

Benzene (5 mL) was added to 3-iodo-benzene-1,2-diol (50 mg, 0.21 mmol) obtained in Step B. 2,2-Dimethoxy-propane (0.052 mL, 0.42 mmol) and *p*-TsOH. H_2O (catalytic

amount) were added thereto, and the mixture was stirred for 2 hours under reflux. After termination of the reaction, the reaction solution was cooled, and saturated NaHCO₃ solution was added thereto. The reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (40 mg, 58 %).

¹H NMR (500 MHz, CDCl₃) δ 7.08(d, 1H), 6.68(d, 1H), 6.55(t, 1H), 1.71(s, 6H)

Preparation Example 24: 4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluorophenol

2-Cyclobutylsulfanyl-3-iodo-pyridine (0.193 g, 0.66 mmol) obtained in Preparation Example 13 and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.254 g, 0.992 mmol) obtained in Step B of Preparation Example 16 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.078 g, 40 %).

¹H-NMR (CDCl₃) δ 8.39(1H, m), 7.30(1H, m), 6.98(3H, m), 5.15(1H, s), 4.40(1H, m), 2.49(2H, m), 2.02(4H, m)

Preparation Example 25: 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanenitrile

Step A: 3-(4-bromophenyl)propan-1-ol

3-(4-Bromophenyl)propanoic acid (1.41 g, 6.16 mmol) was dissolved in THF (20 mL). Borane-THF 1.0 M solution (18.5 mL, 18.5 mmol) was slowly added dropwise at 0°C. The mixture was stirred at room temperature for 16 hours. After termination of the reaction, the reaction solution was diluted with water at 0°C and washed with 1N HCl. The reaction solution was extracted with EtOAc, and the organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/5) to obtain the title compound (1.31 g, 99 %).

NMR: ¹H-NMR (CDCl₃) δ 7.39(2H, m), 7.09(2H, m), 3.67(2H, m), 2.67(2H, t), 1.87(2H, m)

Step B: 3-(4-bromophenyl)propyl methanesulfonate

3-(4-Bromophenyl)propan-1-ol (1.07 g, 4.97 mmol) obtained in Step A was dissolved in DCM (12 mL). TEA (1.04 mL, 7.46 mmol) was added thereto, and methanesulfonyl

chloride (0.46 mL, 5.96 mmol) was then slowly added thereto at 0°C. The mixture was stirred for 2 hours. After termination of the reaction, the reaction solution was diluted with water at 0°C, washed with 1N HCl and extracted with DCM. The organic layer was dried with anhydrous magnesiumsulfate to obtain 1.4 g of the title compound, which was used in the next step without purification.

Step C: 4-(4-bromophenyl)butanenitrile

3-(4-Bromophenyl)propyl methanesulfonate (0.557 g, 1.899 mmol) obtained in Step B was dissolved in DMF (9 mL). Sodium cyanide (0.372 g, 7.599 mmol) was added thereto, and the reaction was carried out at 70°C for 16 hours. After termination of the reaction, the reaction solution was diluted with sodium bicarbonate solution and extracted with EtOAc. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.273 g, 64 %).

NMR: ¹H-NMR (CDCl₃) δ 7.43(2H, m), 7.05(2H, m), 2.73(2H, t), 2.31(2H, t), 1.95(2H, m)

Step D: 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanenitrile

4-(4-bromophenyl)butanenitrile (0.273 g, 1.299 mmol) obtained in Step C, bis(pinacolato)diboron (0.346 g, 1.364 mmol), potassium acetate (0.51 g, 5.196 mmol) and DPPF (0.036 g, 0.065 mmol) were dissolved in 1,4-dioxane (10 mL). The mixture was charged with N₂ gas for 5 minutes, and PdCl₂(dppf)-DCM (0.053 g, 0.065 mmol) was added thereto. The reaction solution was stirred at 80°C for 16 hours, filtered through Celite, diluted with water and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.203 g, 57 %).

NMR: ¹H-NMR (CDCl₃) δ 7.74(2H, m), 7.19(2H, m), 2.78(2H, t), 2.29(2H, t), 1.97(2H, m), 1.33(12H, s)

Preparation Example 26: 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester

Step A: 3-(4-bromophenyl)propanal

Oxalyl chloride (0.599 mL, 6.973 mmol) was dissolved in DCM (15 mL), and DMSO

(0.99 mL, 13.94 mmol) dissolved in DCM (10 mL) was slowly added thereto at -78°C. The mixture was stirred for 15 minutes, and 3-(4-bromophenyl)propan-1-ol (1.0 g, 4.64 mmol) dissolved in DCM (10 mL) was slowly added thereto at -78°C. The mixture was stirred for 30 minutes, and TEA (1.96 mL) was slowly added thereto at -78°C. The temperature was slowly increased to room temperature, and the reaction solution was stirred for 3 hours. After termination of the reaction, the reaction solution was diluted with water and extracted with DCM. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/5) to obtain the title compound (0.859 g, 86 %).

NMR: ¹H-NMR (CDCl₃) δ 9.81(1H, s), 7.40 (2H, d), 7.07(2H, d), 2.91(2H, m), 2.77(2H, t)

Step B: (E)-5-(4-bromophenyl)pent-2-enoic acid ethyl ester

3-(4-Bromophenyl)propanal (0.859 g, 4.031 mmol) obtained in Step A and (1-ethoxycarbonyl ethylidene)triphenylphosphorane (1.685 g, 4.837 mmol) were dissolved in benzene (15 mL), and the mixture was stirred at 60°C for 16 hours. After termination of the reaction, the solvent was distilled under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.903 g, 79 %).

NMR: ¹H-NMR (CDCl₃) δ 7.40(2H, m), 7.06(2H, m), 6.94(1H, m), 5.82(1H, m), 4.18(2H, q), 2.72(2H, m), 2.49(2H, m), 1.28(3H, t)

Step C: (E)-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pent-2-enoic acid ethyl ester

(E)-5-(4-bromophenyl)pent-2-enoic acid ethyl ester (0.903 g, 3.18 mmol) obtained in Step B was reacted in the same manner as in Step D of Preparation Example 25 to obtain the title compound (0.429 g, 40 %).

NMR: ¹H-NMR (CDCl₃) δ 7.73(2H, m), 7.18(2H, m), 6.97(1H, m), 5.82(1H, m), 4.16(2H, q), 2.76(2H, m), 2.51(2H, m), 1.33(12H, s), 1.28(3H, t)

Step D: 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester

(E)-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pent-2-enoic acid ethyl ester (0.429 g, 1.29 mmol) and Pd/C (0.05 g) were dissolved in methanol (13 mL). The

mixture was charged with H₂ gas and stirred at room temperature for 8 hours. After termination of the reaction, the reaction product was filtered through Celite to obtain the title compound (0.425 g, 99 %).

NMR: ¹H-NMR (CDCl₃) δ 7.74(2H, m), 7.19(2H, m), 4.10(2H, q), 2.63(2H, m), 2.30(2H, m), 1.64(4H, m), 1.34(12H, s), 1.25(3H, t)

Preparation Example 27: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester

Step A: 3-(4-bromo-2,6-difluoro-phenyl)prop-2-enal

4-bromo-2,6-difluoro-benzaldehyde (1.21 g, 5.47 mmol) and ethyl(triphenylphosphoranylidene)acetaldehyde (1.83 g, 6.022 mmol) were dissolved in benzene (11 mL), and the mixture was stirred at 70°C for 16 hours. After termination of the reaction, the reaction product was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/20) to obtain the title compound (1.27 g, 93 %).

NMR: ¹H-NMR (CDCl₃) δ 9.67(1H, m), 7.51(1H, m), 7.18(2H, m), 6.95(1H, m)

Step B: (E)-5-(4-bromo-2,6-difluoro-phenyl)penta-2,4-dienoic acid ethyl ester

3-(4-Bromo-2,6-difluoro-phenyl)prop-2-enal (1.27 g, 5.14 mmol) obtained in Step A and (1-ethoxycarbonylethylidene)triphenylphosphorane (2.15 g, 6.168 mmol) were dissolved in benzene (11 mL), and the mixture was stirred at 70°C for 16 hours. After termination of the reaction, the reaction product was concentrated under reduced pressure and purified by column chromatography (eluent EtOAc/Hex = 1/20) to obtain the title compound (1.61 g, 98 %).

NMR: ¹H-NMR (CDCl₃) δ 7.40(1H, m), 7.15(3H, m), 6.83(1H, d), 6.03(1H, d), 4.22(2H, q), 1.30(3H, t)

Step C: (E)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]penta-2,4-dienoic acid ethyl ester

(E)-5-(4-bromo-2,6-difluoro-phenyl)penta-2,4-dienoic acid ethyl ester (0.09 g, 0.283 mmol) obtained in Step B was dissolved in DME (4 mL), and bis(pinacolato)diboron (0.086 g, 0.034 mmol), potassium acetate (0.083 g, 0.85 mmol) and PdCl₂(PPh₃)₂ (0.012 g, 0.014 mmol) were added thereto. The mixture was stirred at 80°C for 16 hours, filtered through Celite, diluted with water, and extracted with ethyl acetate. The organic layer was dried with

anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/7) to obtain the title compound (0.068 g, 66 %).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 7.43(1H, m), 7.30~7.20(3H, m), 6.95(1H, d), 6.03(1H, d), 4.23(2H, q), 1.32(15H, m)

Step D: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester

(E)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]penta-2,4-dienoic acid ethyl ester (0.068 g, 0.18 mmol) obtained in Step C and Pd/C (0.01 g) were dissolved in methanol (3 mL). The mixture was charged with H_2 gas and stirred at room temperature for 8 hours. After termination of the reaction, the reaction product was filtered through Celite to obtain the title compound (0.063 g, 92 %).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 7.25(2H, m), 4.10(2H, q), 2.69(2H, m), 2.30(2H, t), 1.70~1.60(4H, m), 1.32(12H, s), 1.23(3H, t)

Preparation Example 28: 3-iodo-2-propylsulfanyl-pyridine

After addition of 31 mL of CH_3CN to 2-fluoro-3-iodo-pyridine (2.08 g, 9.3 mmol) and propane-1-thiol (0.89 mL, 9.8 mmol), Cs_2CO_3 (3.33 g, 10.2 mmol) was added thereto, and the mixture was stirred for 5 hours under reflux. The reaction solution was cooled to room temperature. Solids were filtered, and the filtrate was purified by column chromatography to obtain the title compound (1.58 g, 60%).

$^1\text{H-NMR}$ (CDCl_3) δ 8.40 (1H, m), 7.92 (1H, m), 6.71 (1H, m), 3.13 (2H, t), 1.75 (2H, m), 1.06 (3H, t)

Preparation Example 29: 2-chloro-6-cyclobutoxy-pyridine

5 mL of DMF was added to 6-chloro-2-pyridone (0.2 g, 1.5 mmol), bromocyclobutane (0.26 g, 1.8 mmol) and K_2CO_3 (0.43 g, 3 mmol), and the mixture was stirred at 80°C for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.28 g, 98 %).

$^1\text{H NMR}$ (CDCl_3) δ 7.49 (1H, t), 6.86 (1H, d), 6.59 (1H, d), 5.16 (1H, m), 2.46 (2H, m), 2.13 (2H, m), 1.83 (1H, m), 1.66 (1H, m)

Preparation Example 30: {2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]ethoxy}acetic acid *tert*-butyl ester

Step A: [2-(4-bromo-2,6-difluoro-phenyl)ethoxy]acetic acid *tert*-butyl ester

2-(4-bromo-2,6-difluoro-phenyl)ethanol (0.116 g, 0.489 mmol), *tert*-butyl bromoacetate (0.57 mL, 3.91 mmol), *tert*-butyl ammonium hydrogen sulfate (0.133 g, 0.391 mmol) were dissolved in toluene (2.5 mL). 6N NaOH (8 mL) was added thereto, and the mixture was stirred for 5 hours. After termination of the reaction, the reaction solution was diluted with water, extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/8) to obtain the title compound (0.15 g, 77 %).

NMR: ¹H-NMR (CDCl₃) δ 7.06(2H, m), 3.95(2H, s), 3.69(2H, t), 2.96(2H, t), 1.46(9H, s)

Step B: {2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]ethoxy}acetic acid *tert*-butyl ester

[2-(4-Bromo-2,6-difluoro-phenyl)ethoxy]acetic acid *tert*-butyl ester (0.15 g, 0.42 mmol) obtained in Step A was reacted in the same manner as in Step C of Preparation Example 27 to obtain the title compound (0.09 g, 53 %).

NMR: ¹H-NMR (CDCl₃) δ 7.26(2H, m), 3.96(2H, s), 3.70(2H, t), 3.03(2H, t), 1.49(9H, s), 1.33(12H, s)

Preparation Example 31: 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexanoic acid ethyl ester

Step A: 3-(4-bromophenyl)but-2-enoic acid ethyl ester

NaH(60 %) was dissolved in THF(20 mL), and 2-diethoxyphosphoryl acetic acid ethyl ester (3.29 mL, 16.57 mmol) was slowly added thereto at 0°C. After 30 minutes, 1-(4-bromophenyl)ethanone (2.0 g, 10.04 mmol) dissolved in THF (10 mL) was slowly added thereto. The mixture was stirred at room temperature for 16 hours. After termination of the reaction, the reaction solution was diluted with water and extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (1.89 g, 70 %).

NMR: ¹H-NMR (CDCl₃) δ 7.51(2H, m), 7.35(2H, m), 6.11(1H, s), 4.22(2H, q),

2.55(3H, s), 1.32(3H, t)

Step B: 3-(4-bromophenyl)butan-1-ol

3-(4-Bromophenyl)but-2-enoic acid ethyl ester (1.89 g, 7.02 mmol) obtained in Step A was dissolved in THF(22 mL), and LAH(0.48 g, 12.86 mmol) was added little by little thereto at 0°C. The mixture was stirred at room temperature for 16 hours. After termination of the reaction, the reaction solution was diluted with 1N HCl at 0°C and extracted with DCM. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, Et₂O/Hex = 1/2) to obtain the title compound (0.437 g, 25 %).

NMR: ¹H-NMR (CDCl₃) δ 7.41(2H, m), 7.08(2H, m), 3.58(2H, m), 2.88(1H, m), 1.85(2H, t), 1.28(3H, d), 0.88(1H, t)

Step C: 3-(4-bromophenyl)butanal

3-(4-Bromophenyl)butan-1-ol (0.437 g, 1.90 mmol) obtained in Step B was reacted in the same manner as in Step A of Preparation Example 26 to obtain the title compound (0.386 g, 89 %).

NMR: ¹H-NMR (CDCl₃) δ 9.70(1H, s), 7.42(2H, m), 7.10(2H, m), 3.33(1H, m), 2.68(2H, m), 1.30(3H, d)

Step D: (E)-5-(4-bromophenyl)hex-2-enoic acid ethyl ester

3-(4-Bromophenyl)butanal (0.386 g, 1.69 mmol) obtained in Step C was reacted in the same manner as in Step B of Preparation Example 26 to obtain the title compound (0.508 g, 99 %).

NMR: ¹H-NMR (CDCl₃) δ 7.41(2H, m), 7.06(2H, m), 6.83(1H, m), 5.76(1H, d), 4.15(2H, q), 2.87(1H, m), 2.45(2H, m), 1.27(6H, m)

Step E: (E)-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hex-2-enoic acid ethyl ester

(E)-5-(4-bromophenyl)hex-2-enoic acid ethyl ester (0.508 g, 1.70 mmol) obtained in Step D were reacted in the same manner as in Step C of Preparation Example 26 to obtain the title compound(0.214 g, 42 %).

NMR: ¹H-NMR (CDCl₃) δ 7.75(2H, m), 7.20(2H, m), 6.85(1H, m), 5.79(1H, d),

4.15(2H, q), 2.89(1H, m), 2.49(2H, m), 1.34(12H, s), 1.27(6H, m)

Step F: 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexanoic acid ethyl ester

(E)-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hex-2-enoic acid ethyl ester (0.314 g, 0.825 mmol) obtained in Step E and Pd/C (0.035 g) were dissolved in methanol (6 mL). The mixture was charged with H₂ gas and stirred at room temperature for 8 hours. After termination of the reaction, the reaction product was filtered through Celite to obtain the title compound (0.314 g, 99 %).

NMR: ¹H-NMR (CDCl₃) δ 7.74(2H, m), 7.19(2H, m), 4.09(2H, q), 2.71(1H, m), 2.24(2H, m), 1.60(3H, m), 1.40(1H), 1.34(12H, s), 1.25(6H, m)

Preparation Example 32: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexanoic acid ethyl ester

Step A: (E)-4-diethoxyphosphorylbut-2-enoic acid ethyl ester(75 %)

(E)-4-bromobut-2-enoic acid ethyl ester (75 %)(10 g, 51.80 mmol) and triethylphosphate (8.88 mL, 51.80mmol) were stirred at 130°C for 16 hours. The reaction product was washed with toluene and distilled under reduced pressure. The obtained title compound was used for the next step without purification.

Step B: (4-bromo-2,6-difluoro-phenyl)-trimethyl-silane

Diisopropylamine (16.11 mL, 113.99 mL) was dissolved in THF (100 mL), and 2.3 M n-BuLi (50 mL) was slowly added thereto at -100°C. The mixture was stirred for 20 minutes, and 1-bromo-3,5-difluoro-benzene (20 g, 103.63 mmol) was dissolved in THF (30 mL) at -100°C and slowly added thereto. The mixture was stirred for 2 hours. TMSCl was dissolved in THF (20 mL) at -100°C and slowly added thereto. The mixture was stirred at room temperature for 16 hours. After termination of the reaction, the reaction solution was diluted with water at 0°C and extracted with Et₂O. The organic layer was dried with anhydrous magnesiumsulfate and distilled under reduced pressure at 30°C or below. The obtained title compound was used for the next step without purification.

NMR: ¹H-NMR (CDCl₃) δ 6.98(2H, m), 0.35(9H, s)

Step C: 1-(4-bromo-2,6-difluoro-phenyl)ethanone

AlCl₃ (16.89 g, 126.7 mmol) was dissolved in DCM (130 mL), and AcCl (9 mL, 126.7 mmol) was added thereto at 0°C. The mixture was stirred for 1 hour. (4-Bromo-2,6-difluoro-phenyl)-trimethyl-silane (27.48 g, 105.59 mmol) obtained in Step B was dissolved in DCM (70 mL) and slowly added thereto at -80°C. The mixture was stirred for 16 hours. After termination of the reaction, the reaction solution was diluted with ammonium chloride aqueous solution at 0°C and extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (19.89 g, 74 %).

NMR: ¹H-NMR (CDCl₃) δ 7.16(2H, m), 2.58(3H, s)

Step D: (2E,4E)-5-(4-bromo-2,6-difluoro-phenyl)hexa-2,4-dienoic acid ethyl ester

(E)-4-diethoxyphosphorylbut-2-enoic acid ethyl ester (75 %) (9.21 g, 36.806 mmol) obtained in Step A was dissolved in THF (70 mL), and LiHMDS (37 mL, 36.80 mmol) was slowly added thereto at -78°C. The mixture was stirred for 30 minutes and cooled to -78°C. 1-(4-Bromo-2,6-difluoro-phenyl)ethanone (7.16 g, 28.31 mmol) obtained in Step C was dissolved in THF (25 mL) and slowly added thereto. The mixture was stirred at room temperature for 16 hours. The reaction solution was diluted with ammonium chloride aqueous solution at 0°C and extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/20) to obtain the title compound (7.95 g, 84 %).

NMR: ¹H-NMR (CDCl₃) δ 7.67(1H, m), 7.12(2H, m), 6.26 (1H, d), 5.96(1H, d), 4.23(2H, q), 2.20(3H, m), 1.31(3H, t)

Step E: (E)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexa-2,4-dienoic acid ethyl ester

(2E,4E)-5-(4-bromo-2,6-difluoro-phenyl)hexa-2,4-dienoic acid ethyl ester (7.95 g, 24.0 mmol) obtained in Step D was dissolved in 1,4-dioxane (80 mL) and was reacted in the same manner as in Step C of Preparation Example 27 to obtain the title compound (7.25 g, 79 %).

NMR: ¹H-NMR (CDCl₃) δ 7.69(1H, m), 7.34(2H, m), 6.29 (1H, d), 5.92(1H, d), 4.22(2H, q), 2.20(3H, m), 1.35(15H, m)

Step F: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexanoic acid ethyl ester

(E)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]hexa-2,4-dienoic acid ethyl ester (7.25 g, 19.16 mmol), Pd/C (0.70 g) obtained in Step E was dissolved in methanol (100 mL), charged with H₂ gas and stirred at room temperature for 8 hours. After termination of the reaction, the reaction solution was filtered through Celite to obtain the title compound (7.16 g, 97 %).

NMR: ¹H-NMR (CDCl₃) δ 7.22(2H, m), 4.08(2H, q), 3.21(1H, m), 2.24(2H, m), 1.80(1H, m), 1.65(1H, m), 1.60(1H, m), 1.45(1H, m), 1.30(15H, m), 1.20(3H, t)

Preparation Example 33: 2-ethylsulfanyl-3-iodo-pyridine

2-Fluoro-3-iodo-pyridine (0.475 g, 2.13 mmol), Cs₂CO₃ (3.47 g, 10.65 mmol), ethanethiol (0.239 mL, 3.19 mmol) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.512 g, 90 %).

¹H-NMR (CDCl₃) δ 8.40(1H, m), 7.92(1H, m), 6.72(1H, m), 3.16(2H, q), 1.39(3H, t)

Preparation Example 34: 3-iodo-2-isopropoxy-pyridine

Isopropyl alcohol (0.043 g, 717 mmol) was dissolved in dry DMF (3 mL). NaH (60 %)(0.03 g, 0.71 mmol) was slowly added dropwise thereto at 0°C, and the mixture was stirred for 30 minutes. The mixture was slowly added to a flask containing 2-fluoro-3-iodo-pyridine (0.10 g, 0.44 mmol) and stirred at room temperature for 1 hour. NH₄Cl aqueous solution was added to the reaction solution, and the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with anhydrous MgSO₄ and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.029 g, 24 %).

¹H-NMR (CDCl₃) δ 8.08(1H, m), 8.00(1H, m), 6.59(1H, m), 5.27(1H, m), 1.38(6H, d)

Preparation Example 35: N-cyclopentyl-2-iodo-aniline

2-Iodoaniline (0.39 g, 1.78 mmol) was dissolved in 6 mL of dichloroethane. Cyclopentanone (0.15 g, 1.78 mmol) and acetic acid (0.11 mL, 1.96 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Sodium triacetoxyborohydride

(0.56 g, 2.67 mmol) added thereto, and the mixture was stirred for 5 hours. The reaction solution was diluted with water and extracted with DCM to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.12 g, 23 %).

¹H-NMR (CDCl₃) δ 7.64 (1H, d), 7.18 (1H, t), 6.60 (1H, d), 6.40 (1H, t), 4.14 (1H, brs), 3.80 (1H, m), 2.02 (2H, m), 1.76 (2H, m), 1.63 (2H, m), 1.53 (2H, m)

Preparation Example 36: 3-bromo-N-cyclopentyl-aniline

3-Bromoaniline (0.306 g, 1.78 mmol) and cyclopentanone (0.15 g, 1.78 mmol) were reacted in the same manner as in Preparation Example 35 to obtain the title compound (0.347 g, 81%).

¹H-NMR (CDCl₃) δ 6.98 (1H, t), 6.77 (1H, d), 6.72 (1H, m), 6.49 (1H, m), 3.77 (2H, m), 2.02 (2H, m), 1.72 (2H, m), 1.62 (2H, m), 1.45 (2H, m)

Preparation Example 37: 2-bromo-6-propylsulfanyl-pyridine

2,6-Dibromopyridine (0.2 g, 0.84 mmol), Cs₂CO₃ (0.412 g, 1.27 mmol) and propanethiol (0.076 mL, 0.84 mmol) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.184 g, 93%).

¹H-NMR (CDCl₃) δ 7.27 (1H, t), 7.11 (2H, m), 3.13 (2H, t), 1.74 (2H, m), 1.04 (3H, t)

Preparation Example 38: 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanoic acid methyl ester

Step A: 4-(4-bromophenyl)butanoic acid methyl ester

4-(4-Aminophenyl)butanoic acid (0.5 g, 2.87 mmol) was dissolved in HBr (2 mL) at 0°C and stirred for 10 minutes. Sodium nitrite (0.192 g, 2.78 mmol) was dissolved in water (1.3 mL) at 0°C and added thereto. CuBr (0.22 g, 1.53 mmol) was dissolved in HBr (2 mL) at 0°C and added thereto. The mixture was stirred at 80°C for 4 hours. After termination of the reaction, the reaction solvent was diluted with methanol at 0°C and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate, and without purification diazomethane (6 mL) was added thereto. The solvent was distilled under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.139 g, 19 %).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 7.42(2H, m), 7.04(2H, m), 3.66(3H, s), 2.59(2H, t), 2.31(2H, m), 1.93(2H, m)

Step B: 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanoic acid methyl ester

4-(4-Bromophenyl)butanoic acid methyl ester (0.165 g, 0.64 mmol) obtained in Step A was reacted in the same manner as in Step C of Preparation Example 27 to obtain the title compound (0.039 g, 57 %).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 7.72(2H, m), 7.19(2H, m), 3.66(3H, s), 2.67(2H, t), 2.32(2H, t), 1.96(2H, m), 1.34(12H, s)

Preparation Example 39: 2-cyclobutoxy-3-iodo-pyridine

Cyclobutanol (0.064 g, 1.34 mmol) and 2-fluoro-3-iodo-pyridine (0.2 g, 0.89 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.16 g, 66%).

$^1\text{H-NMR}$ (CDCl_3) δ 8.07(1H, m), 8.00(1H, m), 6.61(1H, m), 5.18(1H, m), 2.47 (2H, m), 2.20(2H, m), 1.84(1H, m), 1.67(1H, m)

Preparation Example 40: 2-cyclopropylmethoxy-3-iodo-pyridine

Cyclopropyl-methanol (0.089 g, 1.23 mmol) was dissolved in anhydrous DMF (2 mL), and NaH (60 %)(0.054g, 1.35 mmol) was slowly added dropwise thereto at 0°C. The mixture was stirred for 30 minutes. The mixture was slowly added to a flask containing 2-fluoro-3-iodo-pyridine (0.137 g, 0.617 mmol) and stirred at room temperature for 1 hour. NH_4Cl aqueous solution was added to the reaction solution, and the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO_4 and purified by column chromatography (eluent, EtOAc/Hex = 1/5) to obtain the title compound (0.141 g, 83 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.07(1H, m), 8.00(1H, m), 6.61(1H, m), 4.20(2H, d), 1.32(1H, m), 0.60(2H, m), 0.39(2H, m)

Preparation Example 41: 2-cyclobutoxy-3-iodo-pyridine

Cyclobutanol (0.064 g, 1.34 mmol) and 2-fluoro-3-iodo-pyridine (0.2 g, 0.89 mmol)

were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.16 g, 66%).

¹H-NMR (CDCl₃) δ 8.07(1H, m), 8.00(1H, m), 6.61(1H, m), 5.18(1H, m), 2.47 (2H, m), 2.20(2H, m), 1.84(1H, m), 1.67(1H, m)

Preparation Example 42: 2-bromo-6-isopropoxy-pyridine

Propan-2-ol (0.065 mL, 0.84 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.027 g, 14%).

¹H-NMR (CDCl₃) δ 7.37(1H, t), 7.00(1H, d), 6.60(1H, d), 5.27(1H, m), 1.33 (6H, d)

Preparation Example 43: 2-chloro-6-cyclopropylmethoxy-pyridine

6-Chloro-2-pyridone (1.0 g, 7.7 mmol), K₂CO₃ (2.13 g, 15.4 mmol) and (bromomethyl)cyclopropane (1.1 g, 8.1 mmol) were added to 15 mL of DMF, and the mixture was stirred at 80°C for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.65 g, 45 %).

¹H NMR (CDCl₃) δ 7.50 (1H, t), 6.87 (1H, d), 6.67 (1H, d), 4.12 (2H, d), 1.26 (1H, m), 0.62 (2H, m), 0.36 (2H, m)

Preparation Example 44: 2-bromo-6-cyclopropylmethoxy-pyridine

Cyclopropylmethanol (0.068 mL, 0.84 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.1 g, 53%).

¹H-NMR (CDCl₃) δ 7.39(1H, t), 7.03(1H, d), 6.70(1H, d), 4.12(2H, d), 1.24 (1H, m), 0.59 (2H, m), 0.35(2H, m)

Preparation Example 45: 2-bromo-6-propoxy-pyridine

Propanol (0.07 mL, 0.92 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.067 g, 36%).

¹H-NMR (CDCl₃) δ 7.39(1H, t), 7.03(1H, d), 6.65(1H, d), 4.23(2H, t), 1.76 (2H, m), 1.00(3H, t)

Preparation Example 46: 2-chloro-6-isopropoxy-pyridine

Isopropanol (0.97 g, 16.1 mmol) was dissolved in 45 mL of THF and cooled to 0°C. NaH (55 % in mineral oil, 0.7 g, 16 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hour. 2,6-Dichloropyridine (2.0 g, 13.5 mmol) was added thereto, and the mixture was stirred for 16 hours under reflux. The reaction solution was cooled to room temperature, diluted with 20 mL of water and extracted with EtOAc. The separated organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (1.917 g, 82 %).

¹H-NMR (CDCl₃) δ 7.48 (1H, t), 6.83 (1H, d), 6.58 (1H, d), 5.29 (1H, m), 1.34 (6H, d)

Preparation Example 47: 3-iodo-2-propoxy-pyridine

Propanol (0.1 mL, 1.34 mmol) and 2-fluoro-3-iodo-pyridine (0.2 g, 0.89 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.11 g, 46 %).

¹H-NMR (CDCl₃) δ 8.08(1H, m), 8.00(1H, m), 6.61(1H, m), 4.28(2H, t), 1.82(2H, m), 1.04(3H, t)

Preparation Example 48: 2-cyclobutylmethoxy-3-iodo-pyridine

Cyclobutyl-methanol (0.37 g, 4.31 mmol) and 2-fluoro-3-iodo-pyridine (0.60 g, 2.69 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.75 g, 96 %).

¹H-NMR (CDCl₃) δ 8.08 (1H, m), 8.02(1H, m), 6.63(1H, m), 4.29(2H, d), 2.79(1H, m), 2.12(2H, m), 1.96(4H, m)

Preparation Example 49: 3-iodo-2-(tetrahydro-furan-3-yloxy)-pyridine

Tetrahydro-furan-3-ol (0.39 g, 4.44 mmol) and 2-fluoro-3-iodo-pyridine (0.66 g, 2.96 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.68 g, 80 %).

¹H-NMR (CDCl₃) δ 8.08(1H, m), 8.03(1H, m), 6.65(1H, m), 5.53(1H, m), 4.12(1H, m), 4.06(1H, m), 3.94(2H, m), 2.23(2H, m)

Preparation Example 50: 3-iodo-2-(tetrahydro-pyran-4-yloxy)-pyridine

Tetrahydro-pyran-4-ol (0.45 g, 4.44 mmol) and 2-fluoro-3-iodo-pyridine (0.66 g, 2.96 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.80 g, 89 %).

¹H-NMR (CDCl₃) δ 8.07(1H, d), 8.01(1H, d), 6.63(1H, m), 5.30(1H, m), 4.01(2H, m), 3.68(2H, m), 2.04(2H, m), 1.85(2H, m)

Preparation Example 51: N-cyclopentyl-3-iodo-pyridin-2-amine

2-Fluoro-3-iodo-pyridine (0.3 g, 1.34 mmol), cyclopentylamine (0.34 g, 4 mmol) and diisopropylethylamine (0.46 mL, 2.68 mmol) were dissolved in 3.3 mL of CH₃CN and the mixture was stirred at 110°C for 2 hours by the use of microwave. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.155 g, 40%).

¹H-NMR (CDCl₃) δ 8.07 (1H, d), 7.80 (1H, d), 6.28 (1H, m), 4.88 (1H, brs), 4.30 (1H, m), 2.10 (2H, m), 1.75 (2H, m), 1.65 (2H, m), 1.48 (2H, m)

Preparation Example 52: 2-bromo-6-cyclobutylsulfanyl-pyridine

Cyclobutylthiol (0.074 g, 0.84 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.047 g, 22%).

¹H-NMR (CDCl₃) δ 7.27(1H, t), 7.11(1H, d), 7.00(1H, d), 4.28(1H, m), 2.53 (2H, m), 2.08(4H, m)

Preparation Example 53: 1-(3-bromophenyl)pyrrolidine

1,3-Dibromobenzene (1.0 g, 4.24 mmol), pyrrolidine (0.43 mL, 5.0 mmol), sodium *tert*-butoxide (1.14 g, 11.87 mmol) and BINAP (0.2 g, 0.32 mmol) were dissolved in 17 mL of toluene. Pd₂(dba)₃ (0.097 g, 0.1 mmol) was added thereto, and the mixture was stirred 4 hours under reflux. Solids were filtered through Celite and purified by column chromatography to obtain the title compound (0.52 g, 54%).

¹H-NMR (CDCl₃) δ 7.05 (1H, t), 6.75 (1H, d), 6.67 (1H, m), 6.45 (1H, m), 3.26 (4H, m), 2.00 (4H, m)

Preparation Example 54: 2-chloro-6-phenoxy-pyridine

2,6-Dichloropyridine (2.0 g, 13.5 mmol) and phenol (1.4 mL, 14.9 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (3.5 g, 84 %).

¹H-NMR (CDCl₃) δ 7.62(1H, t), 7.41(2H, m), 7.21(1H, t), 7.14(2H, d), 6.74(2H, d)

Preparation Example 55: 2-bromo-4-fluoro-1-isopropoxy-benzene

2-Bromo-4-fluoro-phenol (0.3 g, 1.57 mmol), 2-bromo-propane (0.22 mL) and Cs₂CO₃ (1.53 g) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.33 g, 89%).

¹H-NMR (CDCl₃) δ 7.28 (1H, m), 6.94 (1H, m), 6.88 (1H, m), 4.44 (1H, m), 1.32 (6H, d).

Preparation Example 56: 3-bromo-5-methyl-pyridin-2-ol

5-Methyl-pyridin-2-ol (1 g, 9.16 mmol) was dissolved in 4 mL of CS₂. Br₂ (0.47 mL) was added thereto, and the mixture was stirred at room temperature for 2 hours. Sodium thiosulfate (Na₂S₂O₃) aqueous solution was added thereto, and the reaction solution was extracted with EtOAc. The separated organic layer was dried with MgSO₄ and concentrated under reduced pressure to obtain the title compound (1.7 g, 98%) in a solid form.

¹H-NMR (CDCl₃) δ 7.73 (1H, s), 7.22 (1H, s), 2.10 (3H, s).

Preparation Example 57: 3-bromo-2-cyclopentyloxy-5-methyl-pyridine

3-Bromo-5-methyl-pyridin-2-ol (0.5 g, 2.66 mmol) obtained in Preparation Example 56, bromo-cyclopentan (0.43 mL) and Cs₂CO₃ (2.6 g) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.25 g, 37%).

¹H-NMR (CDCl₃) δ 7.86 (1H, s), 7.60 (1H, s), 5.38 (1H, m), 2.21 (3H, s), 1.93 (2H, m), 1.82 (4H, m), 1.61 (2H, m).

Preparation Example 58: 3-[(4-methoxyphenyl)methoxy]isoxazol-5-carboxylic acid methyl ester

3-Hydroxyisoxazol-5-carboxylic acid methyl ester (4.73 g, 33 mmol) was dissolved in 66 mL of DMF. K₂CO₃ (5.0 g, 36.3 mmol) and 4-methoxybenzyl chloride (4.5 mL, 33 mmol) were added thereto at 0°C, and the mixture was stirred at 60°C for 10 hours. The reaction

solution was concentrated under reduced pressure, diluted with water and extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (4.06 g, 47 %).

¹H-NMR (CDCl₃) δ 7.39 (2H, d), 6.92 (2H, d), 6.54 (1H, s), 5.24 (2H, s), 3.95 (3H, s), 3.81 (3H, s)

Preparation Example 59: [3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]methanol

3-[(4-Methoxyphenyl)methoxy]isoxazol-5-carboxylic acid methyl ester (4.06 g, 15.4 mmol) obtained in Preparation Example 58 was dissolved in 51 mL of MeOH. NaBH₄ (0.87 g, 23 mmol) was added thereto, and the mixture was stirred for 4 hours under reflux. The reaction solution was diluted with water and extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (2.58 g, 71 %).

¹H-NMR (CDCl₃) δ 7.38 (2H, d), 6.92 (2H, d), 5.89 (1H, s), 5.19 (2H, s), 4.66 (2H, d), 3.82 (3H, s), 1.95 (1H, t)

Preparation Example 60: [3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]methyl methanesulfonate

[3-[(4-Methoxyphenyl)methoxy]isoxazol-5-yl]methanol (0.19 g, 0.82 mmol) obtained in Preparation Example 59 was dissolved in 4 mL of DCM. DIPEA (0.29 mL, 1.64 mmol) and methanesulfonyl chloride (0.07 mL, 0.9 mmol) were sequentially added thereto at 0°C, and the mixture was stirred at room temperature for 80 minutes. The reaction solution was diluted with water and extracted with EtOAc. The organic layer was dried with MgSO₄ and used for the next reaction without purification.

¹H-NMR (CDCl₃) δ 7.38 (2H, d), 6.93 (2H, d), 6.08 (1H, s), 5.21 (2H, s), 5.18 (2H, s), 3.82 (3H, s), 3.06 (3H, s)

Preparation Example 61: 3-[(4-methoxyphenyl)methoxy]isoxazol-5-carbaldehyde

[3-[(4-Methoxyphenyl)methoxy]isoxazol-5-yl]methanol (0.4 g, 1.7 mmol) obtained in Preparation Example 59 was dissolved in 8 mL of DCM. Pyridinium chlorochromate (0.74 g, 3.4 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction product was filtered through silica gel to obtain the title compound (0.22 g, 55 %).

¹H-NMR (CDCl₃) δ 9.84 (1H, s), 7.39 (2H, d), 6.93 (2H, d), 6.57 (1H, s), 5.27 (2H, s), 3.83 (3H, s)

Preparation Example 62: 5-[[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]-3-[(4-methoxyphenyl)methoxy]isoxazol

To 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (2.42 g, 9.43 mmol) obtained in Step B of Preparation Example 16, [3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]methanol (2.19 g, 9.31 mmol) obtained in Preparation Example 59 and triphenylphosphine (2.44 g, 9.31 mmol) 93 mL of THF was added and cooled to 0°C. Diisopropyl azodicarboxylate (1.83 mL, 9.31 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (3.07 g, 70 %).

¹H-NMR (CDCl₃) δ 7.37 (2H, d), 7.32 (2H, m), 6.91 (2H, d), 6.00 (1H, s), 5.18 (2H, s), 5.17 (2H, s), 3.82 (3H, s), 1.33 (12H, s)

Preparation Example 63: 3-[(4-methoxyphenyl)methoxy]-5-methyl-isoxazole

5-Methylisoxazol-3-ol (0.64 g, 6.46 mmol) was dissolved in 13 mL of DMF. K₂CO₃ (0.98 g, 7.1 mmol) and 4-methoxybenzyl chloride (0.88 mL, 6.46 mmol) were added thereto, and the mixture was stirred at 60°C for 4 hours. The filtrate obtained by filtering solids was purified by column chromatography to obtain the title compound (0.53 g, 40 %).

¹H-NMR (CDCl₃) δ 7.37 (2H, d), 6.91 (2H, d), 5.62 (1H, s), 5.17 (2H, s), 3.82 (3H, s), 2.33 (3H, s)

Preparation Example 64: 4-[2-(cyclopentoxy)-3-pyridyl]aniline

2-Cyclopentoxy-3-iodo-pyridine (0.3 g, 1 mmol) obtained in Preparation Example 11 and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.22 g, 1 mmol) were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.18 g, 72 %).

¹H-NMR (CDCl₃) δ 8.06 (1H, m), 7.56 (1H, m), 7.39 (2H, d), 6.89 (1H, m), 6.72 (2H, d), 5.50 (1H, m), 3.73 (2H, brs), 1.95 (2H, m), 1.83 (2H, m), 1.75 (2H, m), 1.62 (2H, m)

Preparation Example 65: 4-[2-(cyclopentoxy)-3-pyridyl]benzenethiol

Catalytic amount of copper chloride (I) was added to 12 mL of water. SOCl₂ (0.2 mL, 2.58 mmol) was added thereto at 0°C, and the mixture was stirred at room temperature for 16 hours. 4-[2-(Cyclopentoxo)-3-pyridyl]aniline (0.18 g, 0.71 mmol) obtained in Preparation Example 64 was prepared in another reaction vessel, and 7.1 mL of 3 M HCl aqueous solution was added thereto. Sodium nitrite (0.054 g, 0.78 mmol, 5 M aqueous solution) was slowly added thereto at -5°C, and the mixture was stirred at 0°C for 1 hour, and slowly added to the mixture solution of copper chloride (I) and SOCl₂. The reaction solution was stirred at 0°C for 3 hours and extracted with EtOAc. The organic layer was MgSO₄, and 20 mL of THF was added thereto and cooled to 0°C. Triphenylphosphine (0.27 g, 1 mmol) was added thereto, and the mixture was stirred. After 15 minutes, 20 mL of water was added thereto, and the reaction solution was stirred at room temperature for 16 hours and extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.022 g, 11 %).

¹H-NMR (CDCl₃) δ 8.12 (1H, m), 7.56 (1H, m), 7.44 (2H, d), 7.30 (2H, d), 6.91 (1H, m), 5.50 (1H, m), 1.94 (2H, m), 1.80 (2H, m), 1.72 (2H, m), 1.62 (2H, m)

Preparation Example 66: 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

2,6-Difluoro-4-iodo-aniline (9.35 g, 36.7 mmol) was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (6.46 g, 69 %).

¹H-NMR (CDCl₃) δ 7.24 (2H, m), 3.93 (2H, brs), 1.31 (12H, s)

Preparation Example 67: 4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-aniline

2-Cyclopentoxo-3-iodo-pyridine (1.09 g, 3.8 mmol) obtained in Preparation Example 11 and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.925 g, 3.62 mmol) obtained in Preparation Example 66 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.6 g, 57 %).

¹H-NMR (CDCl₃) δ 8.10 (1H, m), 7.54 (1H, m), 7.11 (2H, m), 6.90 (1H, m), 5.51 (1H, m), 3.78 (2H, brs), 1.95 (2H, m), 1.83 (2H, m), 1.76 (2H, m), 1.65 (2H, m)

Preparation Example 68: 4-[2-(cyclopentoxo)-3-pyridyl]-2,6-difluoro-benzenethiol

4-[2-(Cyclopentoxy)-3-pyridyl]-2,6-difluoro-aniline (0.42 g, 1.47 mmol) obtained in Preparation Example 67 was reacted in the same manner as in Preparation Example 65 to obtain the title compound (0.046 g, 10 %).

¹H-NMR (CDCl₃) δ 8.20 (1H, m), 7.61 (1H, m), 7.22 (2H, m), 7.00 (1H, m), 5.56 (1H, m), 1.99 (2H, m), 1.86 (2H, m), 1.80 (2H, m), 1.70 (2H, m)

Preparation Example 69: 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid methyl ester

Step A: 4-bromo-2,6-difluoro-benzoic acid

70 mL of THF was cooled to -78°C, and diisopropylamine (4 mL, 28.5 mmol) and butyllithium (13 mL, 27.2 mmol, 2.1 M hexane solution) were sequentially added thereto. The mixture was stirred at -78°C for 1 hour, and 1-bromo-3,5-difluorobenzene (5.0 g, 25.9 mmol) dissolved in 15 mL was slowly added thereto. The mixture was stirred at -78°C for 45 minutes, and the reaction solution was transferred to a beaker containing solid carbon dioxide and stirred at room temperature for 16 hours. The reaction solution was adjusted to pH 3 by the addition of 1N HCl aqueous solution and extracted with EtOAc. The organic layer was collected and dried with MgSO₄ to obtain the title compound (5.15 g, 84 %).

¹H-NMR (CDCl₃) δ 7.20 (2H, m)

Step B: 4-bromo-2,6-difluoro-benzoic acid methyl ester

4-Bromo-2,6-difluoro-benzoic acid (5.15 g, 21.7 mmol) obtained in Step A was dissolve in 54 mL of MeOH. SOCl₂ (2.4 mL, 32.6 mmol) was added thereto, and the mixture was stirred for 3 hours under reflux. The reaction solution was concentrated under reduced pressure, diluted with sodium bicarbonate aqueous solution, and extracted with EtOAc. The organic layer was collected and dried with MgSO₄ to obtain the title compound (2.9 g, 53 %).

¹H-NMR (CDCl₃) δ 7.16 (2H, m), 3.95 (3H, s)

Step C: 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid methyl ester

4-Bromo-2,6-difluoro-benzoic acid methyl ester (1.27 g, 5.0 mmol) obtained in Step B was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (1.20 g, 80 %).

¹H-NMR (CDCl₃) δ 7.34 (2H, m), 3.95 (3H, s), 1.34 (12H, s)

Preparation Example 70: 3-[4-(chloromethyl)-3,5-difluoro-phenyl]-2-(cyclopentoxy)pyridine

Step A: 4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-benzoic acid methyl ester

2-Cyclopentoxy-3-iodo-pyridine (0.96 g, 3.3 mmol) obtained in Preparation Example 11 and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid methyl ester (1.04 g, 3.5 mmol) obtained in Preparation Example 69 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.47 g, 42 %).

¹H-NMR (CDCl₃) δ 8.20 (1H, m), 7.61 (1H, m), 7.21 (2H, m), 6.95 (1H, m), 5.53 (1H, m), 3.97 (3H, s), 1.95 (2H, m), 1.81 (2H, m), 1.74 (2H, m), 1.65 (2H, m)

Step B: [4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]methanol

4-[2-(Cyclopentoxy)-3-pyridyl]-2,6-difluoro-benzoic acid methyl ester (0.47 g, 1.41 mmol) obtained in Step A was dissolved in 7 mL of THF. Diisobutylaluminum hydride (1.32 mL, 2.1 mmol, 1.6 M toluene solution) was slowly added thereto at -78°C. The reaction solution was stirred at -78°C for 2 hours and additionally stirred at room temperature for 1 hour. After termination of the reaction, the reaction solution was cooled to -78°C, and MeOH was added thereto. After addition of HCl aqueous solution at 0°C, the reaction solution was stirred for 1 hour. Solids were filtered through Celite, and water was added to the filtrate. The filtrate was extracted with EtOAc. The organic layer was dried with MgSO₄ to obtain the title compound (0.38 g, 90 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, m), 7.58 (1H, m), 7.16 (2H, m), 6.95 (1H, m), 5.53 (1H, m), 4.82 (2H, d), 1.95 (2H, m), 1.89 (1H, t, OH), 1.82 (2H, m), 1.75 (2H, m), 1.64 (2H, m)

Step C: 3-[4-(chloromethyl)-3,5-difluoro-phenyl]-2-(cyclopentoxy)pyridine

[4-[2-(Cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]methanol (0.38 g, 1.27 mmol) obtained in Step B was dissolved in 6.4 mL of CH₃CN, and SOCl₂ (0.19 mL, 2.54 mmol) was slowly added thereto. The mixture was stirred at room temperature for 90 minutes. The reaction solution was concentrated under reduced pressure and water was added thereto. The reaction solution was extracted with EtOAc, and the organic layer was dried with MgSO₄ to obtain the title compound (0.40 g, 99 %).

¹H-NMR (CDCl₃) δ 8.19 (1H, m), 7.59 (1H, m), 7.18 (2H, m), 6.99 (1H, m), 5.53 (1H, m), 4.71 (2H, s), 1.96 (2H, m), 1.82~1.63 (6H, m)

Preparation Example 71: 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butanenitrile

Step A: 3-(4-bromophenyl)propan-1-ol

3-(4-Bromophenyl)propanoic acid (1.67 g, 7.3 mmol) was dissolved in 24 mL of THF and cooled to 0°C. Borane-THF (22 mL, 22 mmol, 1.0 M THF solution) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was cooled to 0°C, and water and 1N HCl aqueous solution were sequentially added thereto. The reaction solution was extracted with EtOAc, and the organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (1.46 g, 93 %).

¹H-NMR (CDCl₃) δ 7.40 (2H, d), 7.08 (2H, d), 3.66 (2H, m), 2.67 (2H, m), 1.86 (2H, m), 1.26 (1H, t, OH)

Step B: 3-(4-bromophenyl)propyl methanesulfonate

3-(4-Bromophenyl)propan-1-ol (1.46 g, 6.79 mmol) obtained in Step A was reacted in the same manner as in Preparation Example 60 to obtain the title compound (1.87 g, 93 %).

¹H-NMR (CDCl₃) δ 7.42 (2H, d), 7.07 (2H, d), 4.22 (2H, t), 3.00 (3H, s), 2.72 (2H, t), 2.05 (2H, m)

Step C: 4-(4-bromophenyl)butanenitrile

3-(4-Bromophenyl)propyl methanesulfonate (1.04 g, 3.55 mmol) obtained in Step B was reacted in the same manner as in Step E of Preparation Example 81 to obtain the title compound (0.73 g, 99 %).

¹H-NMR (CDCl₃) δ 7.44 (2H, d), 7.07 (2H, d), 2.74 (2H, t), 2.32 (2H, t), 1.96 (2H, m)

Step D: 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butanenitrile

4-(4-Bromophenyl)butanenitrile (0.73 g, 3.5 mmol) obtained in Step C was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.7 g, 73 %).

¹H-NMR (CDCl₃) δ 7.70 (2H, d), 7.20 (2H, d), 2.79 (2H, t), 2.30 (2H, t), 1.99 (2H, m),

1.34 (12H, s)

Preparation Example 72: 5-[[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]-2-[(4-methoxyphenyl)methoxy]pyridine

Step A: 6-[(4-methoxyphenyl)methoxy]pyridin-3-carboxylic acid

(4-Methoxyphenyl)methanol (2.6 mL, 21 mmol) was dissolved in 47 mL of DMF. NaH (1.23 g, 28.1 mmol, 55 wt% in mineral oil) was added thereto at 0°C, and the mixture was stirred for 30 minutes. 6-Chloropyridin-3-carboxylic acid (2.22 g, 14 mmol) was added thereto, and the mixture was stirred at 80°C for 7 hours. The reaction solution was concentrated under reduced pressure and water was added thereto. The reaction solution was adjusted to pH 3 by the use of 1 N HCl aqueous solution. The precipitate was filtered and dried to obtain the title compound (1.67 g, 45 %).

¹H-NMR (CDCl₃) δ 8.92 (1H, s), 8.20 (1H, m), 7.41 (2H, d), 6.92 (2H, d), 6.82 (1H, m), 5.40 (2H, s), 3.82 (3H, s)

Step B: 6-[(4-methoxyphenyl)methoxy]pyridin-3-carboxylic acid ethyl ester

6-[(4-Methoxyphenyl)methoxy]pyridin-3-carboxylic acid (1.67 g, 6.4 mmol) obtained in Step A was dissolved in 13 mL of THF. 1,1-Carbonyldiimidazole (1.03 g, 6.4 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hour. 13 mL of anhydrous ethanol was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (1.49 g, 80 %).

¹H-NMR (CDCl₃) δ 8.85 (1H, m), 8.15 (1H, m), 7.40 (2H, d), 6.93 (2H, d), 6.79 (1H, m), 5.37 (2H, s), 4.38 (2H, q), 3.83 (3H, s), 1.39 (3H, t)

Step C: [6-[(4-methoxyphenyl)methoxy]-3-pyridyl]methanol

6-[(4-Methoxyphenyl)methoxy]pyridin-3-carboxylic acid ethyl ester (1.48 g, 5.18 mmol) obtained in Step B was reacted in the same manner as in Step B of Preparation Example 70 to obtain the title compound (0.96 g, 76 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, m), 7.62 (1H, m), 7.39 (2H, d), 6.92 (2H, d), 6.79 (1H, m), 5.31 (2H, s), 4.63 (2H, s), 3.81 (3H, s)

Step D: 5-[[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]-2-[(4-methoxyphenyl)methoxy]pyridine

[6-[(4-Methoxyphenyl)methoxy]-3-pyridyl]methanol (0.144 g, 0.58 mmol) obtained in Step C and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.15 g, 0.58 mmol) obtained in Step B of Preparation Example 16 were reacted in the same manner as in Preparation Example 62 to obtain the title compound (0.155 g, 55 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, m), 7.70 (1H, m), 7.38 (2H, d), 7.28 (2H, m), 6.90 (2H, d), 6.76 (1H, m), 5.29 (2H, s), 5.13 (2H, s), 3.80 (3H, s), 1.32 (12H, s)

Preparation Example 73: 4-[[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]-2-[(4-methoxyphenyl)methoxy]pyridine

Step A: 2-[(4-methoxyphenyl)methoxy]pyridin-4-carboxylic acid

2-Chloropyridin-4-carboxylic acid (2.22 g, 14 mmol) and (4-methoxyphenyl)methanol (2.6 mL, 21 mmol) were reacted in the same manner as in Step A of Preparation Example 72 to obtain the title compound (1.86 g, 51 %).

¹H-NMR (CDCl₃) δ 8.33 (1H, m), 7.45 (1H, m), 7.39 (3H, m), 6.92 (2H, d), 5.35 (2H, s), 3.82 (3H, s)

Step B: 2-[(4-methoxyphenyl)methoxy]pyridin-4-carboxylic acid ethyl ester

2-[(4-Methoxyphenyl)methoxy]pyridin-4-carboxylic acid (0.51 g, 1.97 mmol) obtained in Step A was reacted in the same manner as in Step B of Preparation Example 72 to obtain the title compound (0.39 g, 68 %).

¹H-NMR (CDCl₃) δ 8.28 (1H, m), 7.38 (4H, m), 6.92 (2H, d), 5.36 (2H, s), 4.42 (2H, q), 3.88 (3H, s), 1.38 (3H, t)

Step C: [2-[(4-methoxyphenyl)methoxy]-4-pyridyl]methanol

2-[(4-Methoxyphenyl)methoxy]pyridin-4-carboxylic acid ethyl ester (0.39 g, 1.34 mmol) obtained in Step B was reacted in the same manner as in Step C of Preparation Example 72 to obtain the title compound (0.25 g, 75 %).

¹H-NMR (CDCl₃) δ 8.14 (1H, m), 7.39 (2H, d), 6.90 (4H, m), 5.32 (2H, s), 4.69 (2H, s), 3.81 (3H, s)

Step D: 4-[[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]methyl]-2-[(4-methoxyphenyl)methoxy]pyridine

[2-[(4-Methoxyphenyl)methoxy]-4-pyridyl]methanol (0.25 g, 1 mmol) obtained in Step C and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.26 g, 1 mmol) obtained in Step B of Preparation Example 16 were reacted in the same manner as in Preparation Example 62 to obtain the title compound (0.09 g, 18 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, m), 7.40 (2H, d), 7.28 (2H, m), 6.96 (1H, m), 6.90 (3H, m), 5.30 (2H, s), 5.17 (2H, s), 3.81 (3H, s), 1.32 (12H, s)

Preparation Example 74: 3-[4-(1-chloroethyl)-2,6-difluoro-phenyl]-2-(cyclopentoxy)pyridine

Step A: 1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethaneone

1-(4-Bromo-2,6-difluoro-phenyl)ethaneone (0.97 g, 4.13 mmol) obtained in Step C of Preparation Example 32 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.9 g, 77 %).

¹H-NMR (CDCl₃) δ 7.35 (2H, m), 2.59 (3H, s), 1.34 (12H, s)

Step B: 1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethaneone

1-[2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]ethaneone (0.24 g, 0.89 mmol) obtained in Step A and 2-cyclopentoxy-3-iodo-pyridine (0.024 g, 0.84 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.13 g, 48 %).

¹H-NMR (CDCl₃) δ 8.20 (1H, m), 7.60 (1H, m), 7.21 (2H, m), 6.95 (1H, m), 5.54 (1H, m), 2.64 (3H, s), 1.96 (2H, m), 1.82 (2H, m), 1.75 (2H, m), 1.65 (2H, m)

Step C: 1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethanol

1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethaneone (0.13 g, 0.41 mmol) obtained in Step B was dissolved in 2 mL of MeOH. NaBH₄ (0.031 g, 0.82 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄ to obtain the title compound (0.12 g, 92 %).

¹H-NMR (CDCl₃) δ 8.16 (1H, m), 7.58 (1H, m), 7.12 (2H, m), 6.93 (1H, m), 5.53 (1H, m), 5.28 (1H, m), 2.22 (1H, d, OH), 1.96 (2H, m), 1.80 (4H, m), 1.68 (5H, m)

Step D: 3-[4-(1-chloroethyl)-2,6-difluoro-phenyl]-2-(cyclopentoxy)pyridine

1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethanol (0.12 g, 0.37 mmol) obtained in Step C was dissolved in 3.5 mL of chloroform. SOCl₂ (0.055 mL, 0.75 mmol) was added thereto, and the mixture was stirred at 60°C for 3 hours. The reaction solution was concentrated under reduced pressure to obtain the title compound (0.12 g, 98 %).

¹H-NMR (CDCl₃) δ 8.34 (1H, m), 7.86 (1H, m), 7.18 (1H, m), 7.11 (2H, m), 5.87 (1H, m), 5.48 (1H, m), 2.16 (2H, m), 1.99 (3H, d), 1.89 (2H, m), 1.74 (4H, m)

Preparation Example 75: 2-[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]-sulfamoyl-amino]acetic acid ethyl ester

Step A: (*E*)-3-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]prop-2-enoic acid ethyl ester

(*E*)-3-(4-bromo-2,6-difluoro-phenyl)prop-2-enoic acid ethyl ester (3.8 g, 13 mmol) obtained in Step A of Preparation Example 195 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (2.16 g, 49 %).

¹H-NMR (CDCl₃) δ 7.79 (1H, d), 7.33 (2H, m), 6.78 (1H, d), 4.27 (2H, q), 1.34 (15H, m)

Step B: (*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]prop-2-enoic acid ethyl ester

(*E*)-3-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]prop-2-enoic acid ethyl ester (0.67 g, 1.98 mmol) obtained in Step A and 2-cyclopentoxy-3-iodopyridine (0.55 g, 1.89 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.56 g, 80 %).

¹H-NMR (CDCl₃) δ 8.19 (1H, m), 7.82 (1H, d), 7.61 (1H, m), 7.21 (2H, m), 6.96 (1H, m), 6.76 (1H, d), 5.54 (1H, m), 4.28 (2H, q), 1.96 (2H, m), 1.75 (4H, m), 1.66 (2H, m), 1.35 (3H, t)

Step C: (*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]prop-2-en-1-ol

(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]prop-2-enoic acid ethyl ester (0.4 g, 1.07 mmol) obtained in Step B was reacted in the same manner as in Step B of Preparation Example 70 to obtain the title compound (0.28 g, 78 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, m), 7.60 (1H, m), 7.15 (2H, m), 6.93 (1H, m), 6.72 (2H, m), 5.53 (1H, m), 4.40 (2H, m), 1.95 (2H, m), 1.83 (2H, m), 1.76 (2H, m), 1.65 (2H, m), 1.50 (1H, t, OH)

Step D: [(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]methanesulfonate

(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]prop-2-en-1-ol (0.28 g, 0.84 mmol) obtained in Step C was reacted in the same manner as in Preparation Example 60 to obtain the title compound (0.28 g, 83 %).

¹H-NMR (CDCl₃) δ 8.18 (1H, m), 7.61 (1H, m), 7.17 (2H, m), 6.94 (1H, m), 6.81 (1H, d), 6.67 (1H, m), 5.53 (1H, m), 4.93 (2H, d), 3.07~2.80 (3H, s), 1.95 (2H, m), 1.85 (2H, m), 1.76 (2H, m), 1.66 (2H, m)

Step E: 2-[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]amino]acetic acid ethyl ester

[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl] methanesulfonate (0.28 g, 0.7 mmol) obtained in Step D was dissolved in 3.5 mL of THF. Hydrochloric acid salt of glycine ethyl ester (0.098 g, 0.7 mmol) and TEA (0.58 mL, 4.2 mmol) was added thereto, and the mixture was stirred for 16 hours under reflux. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.076 g, 26 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, m), 7.60 (1H, m), 7.13 (2H, m), 6.92 (1H, m), 6.60 (2H, m), 5.52 (1H, m), 4.20 (2H, q), 3.50 (2H, d), 3.47 (2H, s), 1.95 (2H, m), 1.82 (2H, m), 1.76 (2H, m), 1.65 (2H, m), 1.30 (3H, t)

Step F: 2-[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]-sulfamoyl-amino]acetic acid ethyl ester

Chlorosulfonyl isocyanate (0.024 mL, 0.27 mmol) was dissolved in 1 mL of DCM and cooled to 0°C. *Tert*-butyl alcohol (0.02 g, 0.27 mmol) was added thereto, and the mixture was

stirred at room temperature for 1 hour. 2-[[*(E)*-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]amino]acetic acid ethyl ester (0.076 g, 0.18 mmol, 0.2M DCM solution) obtained in Step E and TEA (0.05 mL, 0.36 mmol) were added thereto, and the mixture was stirred at room temperature for 90 minutes. After addition of water, the reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (0.038 g, 28 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, m), 7.59 (1H, m), 7.15 (2H, m), 6.93 (1H, m), 6.61 (2H, m), 5.53 (1H, m), 4.68 (2H, brs), 4.22 (2H, q), 4.14 (2H, d), 4.11 (2H, s), 1.95 (2H, m), 1.82 (2H, m), 1.75 (2H, m), 1.65 (2H, m), 1.28 (3H, t)

Preparation Example 76: [(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]allyl] methanesulfonate

Step A: (*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]prop-2-enoic acid ethyl ester

(*E*)-3-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]prop-2-enoic acid ethyl ester (0.19 g, 0.57 mmol) obtained in Step A of Preparation Example 75 and 3-iodo-2-cyclobutylsulfanyl-pyridine (0.15 g, 0.51 mmol) obtained in Preparation Example 13 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.15 g, 80 %).

¹H-NMR (CDCl₃) δ 8.44 (1H, m), 7.80 (1H, d), 7.36 (1H, m), 7.05 (3H, m), 6.79 (1H, d), 4.44 (1H, m), 4.29 (2H, q), 2.51 (2H, m), 2.05 (4H, m), 1.36 (3H, t)

Step B: (*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]prop-2-en-1-ol

(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]prop-2-enoic acid ethyl ester (0.15 g, 0.41 mmol) obtained in Step A was reacted in the same manner as in Step B of Preparation Example 70 to obtain the title compound (0.13 g, 99 %).

¹H-NMR (CDCl₃) δ 8.43 (1H, m), 7.35 (1H, m), 7.04 (1H, m), 6.99 (2H, m), 6.73 (2H, m), 4.41 (3H, m), 2.51 (2H, m), 2.04 (4H, m)

Step C: [(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]allyl] methanesulfonate

(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]prop-2-en-1-ol (0.13

g, 0.4 mmol) obtained in Step B was reacted in the same manner as in Preparation Example 60 to obtain the title compound (0.14 g, 87 %).

¹H-NMR (CDCl₃) δ 8.43 (1H, m), 7.36 (1H, m), 7.02 (3H, m), 6.81 (1H, d), 6.68 (1H, m), 4.94 (2H, d), 4.44 (1H, m), 3.08 (3H, s), 2.52 (2H, m), 2.04 (4H, m)

Preparation Example 77: 5-[2-[*tert*-butyl(diphenyl)silyl]oxyethyl]isoxazol-3-ol

Hydroxylamine hydrochloride (0.63 g, 9 mmol) was dissolved in 13 mL of MeOH, and NaOH (0.96 g, 24 mmol, 10 % aqueous solution) was added thereto. 5-[*Tert*-butyl(diphenyl)silyl]oxypent-2-ynoic acid methyl ester (2.77 g, 7.5 mmol, 1.0 M MeOH solution) was added thereto, and the mixture was stirred at room temperature for 48 hours. The reaction solution was adjusted to pH 2 by the use of 6 M HCl aqueous solution, extracted with Et₂O and purified by column chromatography to obtain the title compound (1.0 g, 36 %).

¹H-NMR (CDCl₃) δ 7.62 (4H, m), 7.43 (6H, m), 5.76 (1H, s), 3.91 (2H, t), 2.87 (2H, t), 1.03 (9H, s)

Preparation Example 78: *tert*-butyl-[2-[3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]ethoxy]-diphenyl-silane

5-[2-[*Tert*-butyl(diphenyl)silyl]oxyethyl]isoxazol-3-ol (0.28 g, 0.76 mmol) obtained in Preparation Example 77 was dissolved in 2.5 mL of DMF. K₂CO₃ (0.21 g, 1.52 mmol) and 4-methoxybenzyl chloride (0.1 mL, 0.76 mmol) were added thereto, and the mixture was stirred at 60°C for 10 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.26 g, 70 %).

¹H-NMR (CDCl₃) δ 7.72~7.37 (12H, m), 6.91 (2H, d), 5.71 (1H, s), 5.17 (2H, s), 3.89 (2H, t), 3.81 (3H, s), 2.87 (2H, t), 1.02 (9H, s)

Preparation Example 79: 2-[3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]ethanol

Tert-butyl-[2-[3-[(4-methoxyphenyl)methoxy]isoxazol-5-yl]ethoxy]-diphenyl-silane (0.26 g, 0.53 mmol) obtained in Preparation Example 78 was dissolved in 10 mL of THF. Tetrabutylammonium fluoride (0.53 mL, 0.53 mmol, 1.0 M THF solution) was slowly added thereto at 0°C, and the mixture was stirred for 30 minutes. After addition of ammonium

chloride aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.075 g, 56 %).

¹H-NMR (CDCl₃) δ 7.38 (2H, d), 6.90 (2H, d), 5.75 (1H, s), 5.17 (2H, s), 3.93 (2H, m), 3.82 (3H, s), 2.92 (2H, t), 1.70 (1H, brs)

Preparation Example 80: 2-fluoro-5-(6-isopropylsulfanyl-2-pyridyl)pyridine

Step A: 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine

5-Bromo-2-fluoropyridine (2.0 g, 11.3 mmol), K₂CO₃ (4.46 g, 45 mmol) and bis(pinacolato)diboron (3.17 g, 12.4 mmol) were dissolved in 38 mL of DMF and charged with nitrogen gas for 5 minutes. After addition of catalytic amount of PdCl₂(dppf)-DCM, the mixture was stirred at 80°C for 3 hours. Solids were filtered and purified by column chromatography to obtain the title compound (1.59 g, 60 %).

¹H-NMR (DMSO-d₆) δ 8.45 (1H, d), 8.16 (1H, m), 7.20 (1H, dd), 1.30 (12H, s)

Step B: 2-fluoro-5-(6-isopropylsulfanyl-2-pyridyl)pyridine

2-Chloro-6-isopropylsulfanyl-pyridine (0.14 g, 0.7 mmol) obtained in Preparation Example 10 and 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (0.2 g, 0.9 mmol) obtained in Step A were dissolved in 1.1 mL of 2 M Na₂CO₃ aqueous solution and 5 mL 1,4-dioxane, and charged with nitrogen gas for 5 minutes. After addition of Pd(PPh₃)₄ (43 mg, 0.04 mmol), the mixture was stirred for 4 hours under reflux. The reaction solution was diluted with water and extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.114 g, 62 %).

¹H-NMR (CDCl₃) δ 8.84 (1H, d), 8.43 (1H, m), 7.56 (1H, t), 7.39 (1H, d), 7.13 (1H, d), 7.04 (1H, dd), 4.13 (1H, m), 1.46 (6H, d)

Preparation Example 81: 2-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]acetic acid methyl ester

Step A: 1-(4-bromophenyl)pyrazole

1H-pyrazole (1.0 g, 14.7 mmol) and 4-bromofluorobenzene (5.14 g, 29.4 mmol) were dissolved in 80 mL of DMF. Potassium phosphate (15.6 g, 73.5 mmol) was added thereto,

and the mixture was stirred at 150°C for 27 hours. After addition of 150 mL of water, the reaction solution was extracted with Et₂O to obtain the title compound (3.45 g, 99 %).

¹H-NMR (CDCl₃) δ 7.90 (1H, m), 7.72 (1H, m), 7.58 (4H, m), 6.48 (1H, m)

Step B: 1-(4-bromophenyl)pyrazol-4-carbaldehyde

50 mL of DMF was cooled to 0°C, and POCl₃ was added thereto. The mixture was stirred for 15 minutes. 1-(4-Bromophenyl)pyrazole (3.45 g, 14.7 mmol) obtained in Step A was slowly added thereto, and the mixture was stirred at 110°C for 3 hours. After cooling to room temperature, sodium bicarbonate aqueous solution was added thereto, and the mixture was stirred for 30 minutes. The reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (0.45 g, 12 %).

¹H-NMR (CDCl₃) δ 9.97 (1H, s), 8.42 (1H, s), 8.17 (1H, s), 7.62 (4H, m)

Step C: [1-(4-bromophenyl)pyrazol-4-yl]methanol

1-(4-Bromophenyl)pyrazol-4-carbaldehyde (0.45 g, 1.79 mmol) obtained in Step B was dissolved in 3 mL of THF and 3.6 mL of MeOH. NaBH₄ (0.14 g, 3.76 mmol) was slowly added thereto, and the mixture was stirred for 90 minutes. The adjusted to pH 1 at 0°C. After addition of 1 M NaOH aqueous solution (4 mL, 4 mmol), the reaction solution was extracted with EtOAc to obtain the title compound (0.39 g, 87 %).

¹H-NMR (CDCl₃) δ 7.91 (1H, s), 7.72 (1H, s), 7.57 (4H, m), 4.68 (2H, m), 1.60 (1H, brs)

Step D: 1-(4-bromophenyl)-4-(chloromethyl)pyrazole

[1-(4-Bromophenyl)pyrazol-4-yl]methanol (0.39 g, 1.55 mmol) obtained in Step C was dissolved in 8 mL of DCM. DIPEA (0.4 mL, 2.3 mmol) and methanesulfonyl chloride (0.13 mL, 1.7 mmol) were sequentially added thereto at 0°C, and the mixture was stirred at room temperature for 90 minutes. After addition of water, the organic layer extracted with DCM was purified by column chromatography to obtain the title compound (0.25 g, 58 %).

¹H-NMR (CDCl₃) δ 7.92 (1H, s), 7.73 (1H, s), 7.57 (4H, m), 4.60 (2H, s)

Step E: 2-[1-(4-bromophenyl)pyrazol-4-yl]acetonitrile

1-(4-Bromophenyl)-4-(chloromethyl)pyrazole (0.25 g, 0.9 mmol) obtained in Step D

was dissolved in 4.5 mL of DMSO. Sodium cyanide (0.18 g, 3.6 mmol) was added thereto, and the mixture was stirred at room temperature. After addition of water, the reaction solution was extracted with EtOAc to obtain the title compound (0.19 g, 80 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.93 (1H, s), 7.67 (1H, s), 7.58 (4H, m), 3.68 (2H, s)

Step F: 2-[1-(4-bromophenyl)pyrazol-4-yl]acetic acid

2-[1-(4-Bromophenyl)pyrazol-4-yl]acetonitrile (0.19 g, 0.76 mmol) obtained in Step E was dissolved in 0.45 mL of water and 0.4 mL of concentrated sulfuric acid, and the mixture was stirred for 3 hours under reflux. The precipitate formed by the addition of water was dried to obtain the title compound (0.2 g, 98 %).

$^1\text{H-NMR}$ (DMSO-d_6) δ 8.39 (1H, s), 7.76 (2H, d), 7.67 (3H, m), 3.50 (2H, s)

Step G: 2-[1-(4-bromophenyl)pyrazol-4-yl]acetic acid methyl ester

2-[1-(4-Bromophenyl)pyrazol-4-yl]acetic acid (0.2 g, 0.71 mmol) obtained in Step F was dissolved in 2.4 mL of THF. Diazomethane (3 mL, 0.78 mmol, 0.25 M Et_2O solution) was added thereto, and the mixture was stirred for 20 minutes. The reaction solution was concentrated under reduced pressure to obtain the title compound (0.21 g, 99 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.89 (1H, s), 7.64 (1H, s), 7.55 (4H, m), 3.73 (3H, s), 3.73 (2H, s)

Step H: 2-[1-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]acetic acid methyl ester

2-[1-(4-Bromophenyl)pyrazol-4-yl]acetic acid methyl ester (0.21 g, 0.71 mmol) obtained in Step G, bis(pinacolato)diboron (0.19 g, 0.74 mmol) and DPPF (0.02 g, 0.035 mmol) were dissolved in 3.6 mL of 1,4-dioxane and charged with nitrogen gas. $\text{PdCl}_2(\text{dppf})\text{-DCM}$ (0.03 g, 0.035 mmol) was added thereto, and the mixture was stirred for 1 hour under reflux. Solids were filtered through Celite, and the filtrate was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.096 g, 40 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.97 (1H, s), 7.88 (2H, d), 7.67 (3H, m), 3.73 (3H, s), 3.59 (2H, s), 1.36 (12H, s)

Preparation Example 82: benzyl *N*-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate

Benzyl *N*-(4-bromo-2,6-difluoro-phenyl)carbamate (1.61 g, 4.7 mmol) was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (1.5 g, 82 %).

¹H-NMR (CDCl₃) δ 7.36 (7H, m), 6.20 (1H, brs), 5.21 (2H, s), 1.33 (12H, s)

Preparation Example 83: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]pentanoic acid ethyl ester

Step A: 5-[*N*-benzyloxycarbonyl-2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]pentanoic acid ethyl ester

Benzyl *N*-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.79 g, 2 mmol) obtained in Preparation Example 82 was dissolved in 6.7 mL of DMF. NaH (0.18 g, 55 wt% in mineral oil, 4 mmol) and 5-bromopentanoic acid ethyl ester (0.44 g, 2.1 mmol) were sequentially added thereto at 0°C, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was collected, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.447 g, 45 %).

¹H-NMR (CDCl₃) δ 7.40~7.18 (7H, m), 5.10 (2H, s), 4.08 (2H, q), 3.64 (2H, t), 2.28 (2H, t), 1.62 (2H, m), 1.54 (2H, m), 1.33 (12H, s), 1.21 (3H, t)

Step B: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]pentanoic acid ethyl ester

5-[*N*-benzyloxycarbonyl-2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]pentanoic acid ethyl ester (0.46 g, 0.89 mmol) obtained in Step A was dissolved in 5 mL of MeOH. 10 wt% Pd/C (0.05 g) was added thereto, and the mixture was stirred for 16 hours under hydrogen atmosphere. Solids were filtered through Celite, and the filtrate was concentrated under reduced pressure to obtain the title compound (0.35 g, 99 %).

¹H-NMR (CDCl₃) δ 7.21 (2H, m), 4.12 (2H, q), 3.39 (2H, t), 2.33 (2H, t), 1.71 (2H, m), 1.62 (2H, m), 1.32 (12H, s), 1.25 (3H, t)

Preparation Example 84: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid methyl ester

Step A: 2-[1-(2,6-difluoro-4-nitro-phenyl)-4-piperidyl]acetic acid methyl ester

3,4,5-Trifluoronitrobenzene (1.68 g, 9.43 mmol) was dissolved in 24 mL of DMF. Hydrochloric acid salt of (4-piperidyl)acetic acid methyl ester (2.02 g, 10.4 mmol) and DIPEA (4.1 mL, 23.5 mmol) were sequentially added, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was collected and dried with MgSO₄ to obtain the title compound (3.0 g, 99 %), which was used for the next step without purification.

¹H-NMR (CDCl₃) δ 7.74 (2H, m), 3.69 (3H, s), 3.50 (2H, m), 3.20 (2H, m), 2.31 (2H, d), 2.01 (1H, m), 1.80 (2H, m), 1.42 (2H, m)

Step B: 2-[1-(4-amino-2,6-difluoro-phenyl)-4-piperidyl]acetic acid methyl ester

To 2-[1-(2,6-difluoro-4-nitro-phenyl)-4-piperidyl]acetic acid methyl ester (1.1 g, 3.5 mmol) obtained in Step A, each 12 mL of THF, MeOH and water were added. Ammonium chloride (1.31 g, 24.5 mmol) and iron (1.37 g, 24.5 mmol) were added thereto, and the mixture was stirred for 2 hours under reflux. After termination of the reaction, solids were filtered through Celite. After addition of water, the filtrate was extracted with EtOAc. The organic layer was collected and dried with MgSO₄ to obtain the title compound (0.82 g, 80 %), which was used for the next step without purification.

¹H-NMR (CDCl₃) δ 6.15 (2H, m), 3.68 (3H, s), 3.04 (4H, m), 2.28 (2H, d), 1.90 (1H, m), 1.82 (2H, m), 1.43 (2H, m)

Step C: 2-[1-(4-bromo-2,6-difluoro-phenyl)-4-piperidyl]acetic acid methyl ester

CuBr₂ (0.75 g, 3.36 mmol) was dissolved in 7 mL of CH₃CN. *Tert*-butyl nitrite (0.5 mL, 4.2 mmol) was added thereto, and the mixture was stirred at room temperature for 5 minutes. 2-[1-(4-Amino-2,6-difluoro-phenyl)-4-piperidyl]acetic acid methyl ester (0.8 g, 2.8 mmol) obtained in Step B was dissolved in 1.5 mL of CH₃CN and added thereto. The reaction solution was stirred at room temperature for 1 hour and concentrated under reduced pressure. After addition of water, and reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.61 g, 60 %).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 3.68 (3H, s), 3.19 (2H, m), 3.09 (2H, m), 2.29 (2H, d), 1.93 (1H, m), 1.75 (2H, m), 1.42 (2H, m)

Step D: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid methyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)-4-piperidyl]acetic acid methyl ester (0.61 g, 1.7 mmol) obtained in Step C was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.52 g, 77 %).

¹H-NMR (CDCl₃) δ 7.22 (2H, m), 3.68 (3H, s), 3.31 (2H, m), 3.10 (2H, m), 2.29 (2H, d), 1.95 (1H, m), 1.74 (2H, m), 1.43 (2H, m), 1.32 (12H, s)

Preparation Example 85: 2-[2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]ethyl]cyclopropanecarboxylic acid ethyl ester

Step A: (E)-5-(1,3-dioxoisindolin-2-yl)pent-2-enoic acid ethyl ester

3-(1,3-Dioxoisindolin-2-yl)propanal (2.5 g, 12.3 mmol) was dissolved in 80 mL of DCM. (1-Ethoxycarbonylethylidene)triphenylphosphorane (4.50 g, 12.9 mmol) was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (2.99 g, 89 %).

¹H-NMR (CDCl₃) δ 7.83 (2H, m), 7.72 (2H, m), 6.91 (1H, m), 5.90 (1H, d), 4.16 (2H, q), 3.83 (2H, t), 2.60 (2H, m), 1.26 (3H, t)

Step B: 2-[2-(1,3-dioxoisindolin-2-yl)ethyl]cyclopropanecarboxylic acid ethyl ester

(E)-5-(1,3-dioxoisindolin-2-yl)pent-2-enoic acid ethyl ester (2.0 g, 7.32 mmol) obtained in Step A was dissolved in 10 mL of THF. Diazomethane (88 mL, 22 mmol, 0.25M Et₂O solution) was added thereto, and palladium (II) acetate (0.18 g, 0.8 mmol) was then slowly added thereto. The mixture was stirred at room temperature for 16 hours, and water was added thereto. The reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (1.72 g, 82 %).

¹H-NMR (CDCl₃) δ 7.84 (2H, m), 7.72 (2H, m), 4.10 (2H, q), 3.79 (2H, m), 1.69 (2H, m), 1.38 (2H, m), 1.23 (3H, t), 1.17 (1H, m), 0.72 (1H, m)

Step C: 2-[2-(2,6-difluoro-4-nitro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester

2-[2-(1,3-Dioxoisindolin-2-yl)ethyl]cyclopropanecarboxylic acid ethyl ester (1.72 g, 6 mmol) obtained in Step B was dissolved in 40 mL of EtOH. Hydrazine hydrate (1.4 mL, 30 mmol) was added thereto, and the mixture was stirred at room temperature for 3 hours. To the precipitate formed by the addition of Et₂O 20 mL of DMF, 3,4,5-trifluoronitrobenzene (1.06 g, 6 mmol) and DIPEA (1.57 mL, 9 mmol) were sequentially added, and the mixture was stirred at room temperature for 72 hours. The reaction solution was concentrated under reduced pressure, and water was added thereto. The organic layer extracted with EtOAc was purified by column chromatography to obtain the title compound (1.1 g, 58 %).

¹H-NMR (CDCl₃) δ 7.78 (2H, m), 4.42 (1H, brs), 4.12 (2H, q), 3.62 (2H, m), 1.65 (2H, m), 1.42 (2H, m), 1.27 (3H, t), 1.22 (1H, m), 0.73 (1H, m)

Step D: 2-[2-(4-amino-2,6-difluoro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester

2-[2-(2,6-Difluoro-4-nitro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester (1.1 g, 3.5 mmol) obtained in Step C was reacted in the same manner as in Step B of Preparation Example 84 to obtain the title compound (0.88 g, 88 %).

¹H-NMR (CDCl₃) δ 6.20 (2H, m), 4.12 (2H, q), 3.22 (2H, t), 1.58 (1H, m), 1.49 (1H, m), 1.40 (2H, m), 1.26 (3H, t), 1.18 (1H, m), 0.72 (1H, m)

Step E: 2-[2-(4-bromo-2,6-difluoro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester

2-[2-(4-Amino-2,6-difluoro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester (0.88 g, 3.09 mmol) obtained in Step D was reacted in the same manner as in Step C of Preparation Example 84 to obtain the title compound (0.085 g, 8 %).

¹H-NMR (CDCl₃) δ 6.97 (2H, m), 4.10 (2H, q), 3.66 (1H, brs), 3.41 (2H, m), 1.56 (2H, m), 1.39 (2H, m), 1.27 (3H, t), 1.19 (1H, m), 0.72 (1H, m)

Step F: 2-[2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)anilino]ethyl]cyclopropanecarboxylic acid ethyl ester

2-[2-(4-Bromo-2,6-difluoro-anilino)ethyl]cyclopropanecarboxylic acid ethyl ester (0.085 g, 0.24 mmol) obtained in Step E was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.05 g, 50 %).

¹H-NMR (CDCl₃) δ 7.22 (2H, m), 4.10 (2H, q), 3.92 (1H, brs), 3.48 (2H, t), 1.58 (2H, m), 1.40 (2H, m), 1.31 (12H, s), 1.26 (3H, t), 1.20 (1H, m), 0.71 (1H, m)

Preparation Example 86: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-piperidyl]acetonitrile

Step A: *tert*-butyl 3-(hydroxymethyl)piperidin-1-carboxylate

3-Piperidinemethanol (0.91 g, 7.9 mmol) was dissolved in 13 mL of 1,4-dioxane and 8 mL of water. Di-*tert*-butyl dicarbonate (1.81 g, 8.3 mmol) and 8 mL of 1N NaOH aqueous solution were added thereto. The mixture was stirred at room temperature for 5 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated and dried with MgSO₄ to obtain the title compound (1.5 g, 90 %).

¹H-NMR (DMSO-d₆) δ 4.51 (1H, t), 3.94 (1H, brs), 3.78 (1H, m), 3.36 (1H, m), 3.29 (1H, m), 3.19 (1H, m), 2.69 (1H, m), 1.67 (1H, m), 1.59 (1H, m), 1.46 (1H, m), 1.38 (9H, s), 1.29 (1H, m), 1.09 (1H, m)

Step B: *tert*-butyl 3-(methylsulfonyloxymethyl)piperidin-1-carboxylate

Tert-butyl 3-(hydroxymethyl)piperidin-1-carboxylate (0.31 g, 1.4 mmol) obtained in Step A was dissolved in 7 mL of DCM and cooled to 0°C. DIPEA (0.57 mL, 3.3 mmol) and methanesulfonyl chloride (0.12 mL, 1.54 mmol) were added thereto, and the mixture was stirred for 3 hours. After addition of water, the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO₄ to obtain the title compound (0.41 g, 98 %).

¹H-NMR (CDCl₃) δ 4.10 (2H, m), 3.95 (1H, m), 3.80 (1H, m), 3.02 (3H, s), 2.93 (1H, m), 2.79 (1H, m), 1.96 (1H, m), 1.82 (1H, m), 1.66 (1H, m), 1.49 (1H, m), 1.45 (9H, s), 1.33 (1H, m)

Step C: *tert*-butyl 3-(cyanomethyl)piperidin-1-carboxylate

Tert-butyl 3-(methylsulfonyloxymethyl)piperidin-1-carboxylate (0.41 g, 1.4 mmol) obtained in Step B was dissolved in 7 mL of DMF. Sodium cyanide (0.075 g, 1.54 mmol) was added thereto, and the mixture was stirred at 60°C for 16 hours. The reaction solution was concentrated under reduced pressure, diluted with water, and extracted with EtOAc. The organic layer was separated and dried with MgSO₄ to obtain the title compound (0.29 g, 93 %).

¹H-NMR (CDCl₃) δ 3.90 (1H, m), 3.82 (1H, m), 2.92 (2H, m), 2.30 (2H, m), 1.92 (2H, m), 1.68 (1H, m), 1.49 (1H, m), 1.46 (9H, s), 1.35 (1H, m)

Step D: 2-(3-piperidyl)acetonitrile hydrochloride

Tert-butyl 3-(cyanomethyl)piperidin-1-carboxylate (0.292 g, 1.3 mmol) obtained in Step C was dissolved in 13 mL of DCM and cooled to 0°C. HCl (1.3 mL, 5.6 mmol, 4 M 1,4-dioxane solution) was slowly added thereto. After stirring at 0°C for 1 hour, the reaction solution was concentrated under reduced pressure to obtain the title compound (0.18 g, 86 %).

¹H-NMR (DMSO-d₆) δ 9.16 (2H, brs), 3.21 (2H, t), 2.73 (1H, m), 2.61 (3H, m), 2.11 (1H, m), 1.81 (2H, m), 1.69 (1H, m), 1.27 (1H, m)

Step E: 2-[1-(2,6-difluoro-4-nitro-phenyl)-3-piperidyl]acetonitrile

2-(3-Piperidyl)acetonitrile hydrochloride (1.67 g, 10.4 mmol) obtained in Step D and 3,4,5-trifluoronitrobenzene (1.67 g, 9.45 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (2.53 g, 95 %).

¹H-NMR (CDCl₃) δ 7.76 (2H, m), 3.50 (1H, m), 3.40 (1H, m), 3.17 (1H, m), 3.04 (1H, m), 2.42 (2H, d), 2.16 (1H, m), 2.00 (1H, m), 1.82 (1H, m), 1.74 (1H, m), 1.44 (1H, m)

Step F: 2-[1-(4-bromo-2,6-difluoro-phenyl)-3-piperidyl]acetonitrile

2-[1-(2,6-Difluoro-4-nitro-phenyl)-3-piperidyl]acetonitrile (2.53 g, 9 mmol) obtained in Step E was reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (1.16 g, 41 %).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 3.25 (1H, m), 3.13 (1H, m), 3.02 (1H, m), 2.90 (1H, m), 2.44 (2H, m), 2.13 (1H, m), 1.90 (1H, m), 1.76 (1H, m), 1.70 (1H, m), 1.42 (1H, m)

Step G: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-piperidyl]acetonitrile

2-[1-(4-Bromo-2,6-difluoro-phenyl)-3-piperidyl]acetonitrile (1.16 g, 3.7 mmol) obtained in Step F was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.91 g, 68 %).

¹H-NMR (CDCl₃) δ 7.23 (2H, m), 3.34 (1H, m), 3.22 (1H, m), 3.07 (1H, m), 2.94 (1H, m), 2.44 (2H, m), 2.13 (1H, m), 1.92 (1H, m), 1.76 (1H, m), 1.70 (1H, m), 1.43 (1H, m), 1.32

(12H, s)

Preparation Example 87: 5-[*N*-benzyloxycarbonyl-4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid ethyl ester

Step A: benzyl *N*-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]carbamate

2-Cyclopentoxy-3-iodo-pyridine (0.42 g, 1.47 mmol) obtained in Preparation Example 11 and benzyl *N*-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (0.063 g, 1.61 mmol) obtained in Preparation Example 82 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.5 g, 80 %).

¹H-NMR (CDCl₃) δ 8.16 (1H, m), 7.58 (1H, m), 7.37 (5H, m), 7.19 (2H, m), 6.93 (1H, m), 6.18 (1H, brs), 5.52 (1H, m), 5.24 (2H, s), 1.96 (2H, m), 1.81 (2H, m), 1.76 (2H, m), 1.63 (2H, m)

Step B: 5-[*N*-benzyloxycarbonyl-4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid ethyl ester

Benzyl *N*-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]carbamate (0.23 g, 0.54 mmol) obtained in Step A and 5-bromopentanoic acid ethyl ester (0.12 g, 0.57 mmol) were dissolved in 3.6 mL of DMF. NaH (0.032 g, 0.81 mmol, 55 % in mineral oil) was added thereto, and the mixture was stirred at room temperature for 4 hours. The reaction solution was concentrated under reduced pressure. After addition of water and 1N HCl aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.14 g, 47 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, m), 7.59 (1H, m), 7.40-7.20 (7H, m), 6.95 (1H, m), 5.53 (1H, m), 5.13 (2H, s), 4.09 (2H, q), 3.67 (2H, t), 2.33 (2H, t), 1.97 (2H, m), 1.80-1.60 (10H, m), 1.23 (3H, t)

Preparation Example 88: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-3-yl]acetic acid ethyl ester

Step A: 1-(2,6-difluoro-4-nitro-phenyl)azetidin-3-ol

3,4,5-Trifluoronitrobenzene (5.58 g, 31.5 mmol) and hydrochloric acid salt of 3-hydroxyazetidine (3.8 g, 34.7 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (7.25 g, 99 %).

¹H-NMR (CDCl₃) δ 7.71 (2H, m), 4.80 (1H, m), 4.65 (2H, m), 4.27 (2H, m), 1.85 (1H, brs)

Step B: 2-[1-(2,6-difluoro-4-nitro-phenyl)azetidin-3-ylidene]acetic acid ethyl ester

Oxalyl chloride (1.68 mL, 19.6 mmol) was added to 130 mL of DCM and cooled to -78°C. DMSO (2.77 mL, 39 mmol) was added thereto, and the mixture was stirred for 10 minutes. 1-(2,6-Difluoro-4-nitro-phenyl)azetidin-3-ol (3 g, 13 mmol) obtained in Step A was slowly added thereto, and the mixture was stirred at -78°C for 15 minutes. TEA (8.88 mL, 63.7 mmol) was added thereto, and the mixture was stirred at -78°C for 40 minutes and additionally stirred at room temperature for 30 minutes. (1-ethoxycarbonylethylidene)triphenylphosphorane (4.53 g, 13 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with DCM and purified by column chromatography to obtain the title compound (2.84 g, 73 %).

¹H-NMR (CDCl₃) δ 7.74 (2H, m), 5.81 (1H, m), 5.33 (2H, m), 5.10 (2H, m), 4.21 (2H, q), 1.30 (3H, t)

Step C: 2-[1-(4-amino-2,6-difluoro-phenyl)azetidin-3-yl]acetic acid ethyl ester

2-[1-(2,6-Difluoro-4-nitro-phenyl)azetidin-3-ylidene]acetic acid ethyl ester (2.84 g, 9.52 mmol) obtained in Step B was dissolved in 80 mL of MeOH and 40 mL of THF. After addition of 0.5 g of 10 wt% Pd/C, the mixture was stirred for 16 hours under hydrogen atmosphere. Solids were filtered through Celite to obtain the title compound (2.36 g, 92 %).

¹H-NMR (CDCl₃) δ 6.14 (2H, m), 4.21 (2H, m), 4.13 (2H, q), 3.72 (2H, m), 3.44 (2H, brs), 2.95 (1H, m), 2.66 (2H, d), 1.26 (3H, t)

Step D: 2-[1-(4-bromo-2,6-difluoro-phenyl)azetidin-3-yl]acetic acid ethyl ester

2-[1-(4-Amino-2,6-difluoro-phenyl)azetidin-3-yl]acetic acid ethyl ester (2.36 g, 8.7 mmol) obtained in Step C were reacted in the same manner as in Step C of Preparation Example 84 to obtain the title compound (1.04 g, 36 %).

¹H-NMR (CDCl₃) δ 6.89 (2H, m), 4.34 (2H, m), 4.15 (2H, q), 3.84 (2H, m), 3.01 (1H, m), 2.67 (2H, d), 1.26 (3H, t)

Step E: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-3-yl]acetic acid ethyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)azetidin-3-yl]acetic acid ethyl ester (1.04 g, 3.11 mmol) obtained in Step D was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.62 g, 51 %).

¹H-NMR (CDCl₃) δ 7.15 (2H, m), 4.41 (2H, m), 4.14 (2H, q), 3.91 (2H, m), 3.05 (1H, m), 2.68 (2H, d), 1.31 (12H, s), 1.27 (3H, t)

Preparation Example 89: 6-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester

Step A: 1-(2,6-difluoro-4-nitro-phenyl)piperidin-4-one

3,4,5-Trifluoronitrobenzene (4.0 g, 22.6 mmol) and piperidin-4-one hydrochloride (3.37 g, 24.8 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (5.38 g, 93 %).

¹H-NMR (CDCl₃) δ 7.82 (2H, m), 3.66 (4H, m), 2.62 (4H, m)

Step B: 2-[1-(2,6-difluoro-4-nitro-phenyl)-4-piperidylidene]acetic acid ethyl ester

190 mL of THF was cooled to 0°C, and NaH (1.83 g, 42 mmol, 55 wt% in mineral oil) was added thereto. Triethyl phosphonoacetate (9.7 g, 43.3 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 1-(2,6-Difluoro-4-nitro-phenyl)piperidin-4-one (5.38 g, 21 mmol) obtained in Step A was added thereto, and the mixture was stirred at room temperature for 2 hours. EtOAc was added thereto, and the reaction solution was adjusted to pH 4 by the addition of 1N HCl aqueous solution. The organic layer extracted with EtOAc was purified by column chromatography to obtain the title compound (6.85 g, 99 %).

¹H-NMR (CDCl₃) δ 7.78 (2H, m), 5.75 (1H, s), 4.17 (2H, q), 3.45 (2H, t), 3.42 (2H, t), 3.12 (2H, t), 2.45 (2H, t), 1.31 (3H, t)

Step C: 6-(2,6-difluoro-4-nitro-phenyl)-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester

2-[1-(2,6-Difluoro-4-nitro-phenyl)-4-piperidylidene]acetic acid ethyl ester (0.55 g, 1.68 mmol) obtained in Step B was dissolved in 5.6 mL of THF. After addition of iazomethane

(40 mL, 10 mmol, 0.25 M Et₂O solution), catalytic amount of palladium(II) acetate was added thereto, and the mixture was stirred at room temperature. After termination of the reaction, the reaction solution was concentrated and purified by column chromatography to obtain the title compound (0.4 g, 65 %).

¹H-NMR (CDCl₃) δ 7.77 (2H, m), 4.15 (2H, q), 3.45-3.24 (4H, m), 1.88 (2H, m), 1.59 (3H, m), 1.30 (3H, t), 1.23 (1H, m), 0.97 (1H, m)

Step D: 6-(4-bromo-2,6-difluoro-phenyl)-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester

6-(2,6-Difluoro-4-nitro-phenyl)-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester (0.4 g, 1.1 mmol) obtained in Step C was reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (0.22 g, 52 %).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 4.16 (2H, q), 3.21~3.04 (4H, m), 1.84 (2H, m), 1.56 (3H, m), 1.28 (3H, t), 1.18 (1H, m), 0.94 (1H, m)

Step E: 6-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester

6-(4-Bromo-2,6-difluoro-phenyl)-6-azaspiro[2.5]octan-2-carboxylic acid ethyl ester (0.22 g, 0.58 mmol) obtained in Step D was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.15 g, 60 %).

¹H-NMR (CDCl₃) δ 7.22 (2H, m), 4.14 (2H, q), 3.32~3.10 (4H, m), 1.84 (2H, m), 1.55 (3H, m), 1.30 (12H, s), 1.27 (3H, t), 1.18 (1H, m), 0.94 (1H, m)

Preparation Example 90: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]acetic acid methyl ester

Step A: 1-(2,6-difluoro-4-nitro-phenyl)pyrazol-4-carboxylic acid ethyl ester

3,4,5-Trifluoronitrobenzene (3.17 g, 17.9 mmol) and 4-pyrazolcarboxylic acid ethyl ester (2.50 g, 17.9 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (3.70 g, 70 %).

¹H-NMR (CDCl₃) δ 8.25 (1H, s), 8.23 (1H, s), 8.05 (2H, m), 4.36 (2H, q), 1.38 (3H, t)

Step B: 1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-carboxylic acid ethyl ester

1-(2,6-Difluoro-4-nitro-phenyl)pyrazol-4-carboxylic acid ethyl ester (3.7 g, 12.4 mmol) obtained in Step A was reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (3.0 g, 74 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, s), 8.14 (1H, s), 7.31 (2H, m), 4.34 (2H, q), 1.37 (3H, t)

Step C: [1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-yl]methanol

1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-carboxylic acid ethyl ester (3.0 g, 9.16 mmol) obtained in Step B was dissolved in 46 mL of Et₂O and cooled to -78°C. Diisobutylaluminum hydride (15.2 mL, 23 mmol, 1.5 M toluene solution) was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. Solids, which were formed by the sequential addition of MeOH and potassium sodium tartrate aqueous solution, were filtered through Celite. The filtrate was dried with MgSO₄ to obtain the title compound (2.6 g, 99 %).

¹H-NMR (CDCl₃) δ 7.81 (1H, s), 7.64 (1H, s), 7.28 (2H, m), 4.70 (2H, d), 1.60 (1H, t)

Step D: 1-(4-bromo-2,6-difluoro-phenyl)-4-(chloromethyl)pyrazol

[1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-yl]methanol (2.6 g, 9.16 mmol) obtained in Step C was reacted in the same manner as in Step D of Preparation Example 81 to obtain the title compound (1.5 g, 53 %).

¹H-NMR (CDCl₃) δ 7.82 (1H, s), 7.67 (1H, s), 7.28 (2H, m), 4.61 (2H, s)

Step E: 2-[1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetonitrile

1-(4-Bromo-2,6-difluoro-phenyl)-4-(chloromethyl)pyrazol (1.5 g, 4.9 mmol) obtained in Step D was reacted in the same manner as in Step E of Preparation Example 81 to obtain the title compound (0.66 g, 45 %).

¹H-NMR (CDCl₃) δ 7.76 (1H, s), 7.67 (1H, s), 7.30 (2H, m), 3.69 (2H, s)

Step F: 2-[1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetic acid

2-[1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetonitrile (0.66 g, 2.21 mmol) obtained in Step E was reacted in the same manner as in Step F of Preparation Example 81 to obtain the title compound (0.58 g, 82 %).

¹H-NMR (CDCl₃) δ 7.76 (1H, s), 7.66 (1H, s), 7.27 (2H, m), 3.65 (2H, s)

Step G: 2-[1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetic acid methyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetic acid (0.58 g, 1.83 mmol) obtained in Step F was dissolved in 6 mL of THF. Diazomethane (13 mL, 3.25 mmol, 0.25 M Et₂O solution) was added thereto, and the mixture was stirred at room temperature for 40 minutes. The reaction solution was concentrated under reduced pressure to obtain the title compound (0.6 g, 99 %).

¹H-NMR (CDCl₃) δ 7.74 (1H, s), 7.65 (1H, s), 7.27 (2H, m), 3.74 (3H, s), 3.60 (2H, s)

Step H: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]acetic acid methyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-yl]acetic acid methyl ester (0.6 g, 1.82 mmol) obtained in Step G was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.52 g, 76 %).

¹H-NMR (CDCl₃) δ 7.75 (1H, s), 7.69 (1H, s), 7.46 (2H, m), 3.74 (3H, s), 3.60 (2H, s), 1.35 (12H, s)

Preparation Example 91: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetic acid ethyl esterStep A: *tert*-butyl 3-hydroxypyrrolidin-1-carboxylate

3-Pyrrolidinol (4.66 g, 53 mmol) was dissolved in 90 mL of DCM. Dimethylaminopyridine (0.65 g, 5.3 mmol) and TEA (8.1 mL, 58.3 mmol) were added thereto. The reaction solution was cooled to 0°C, and di-*tert*-butyl dicarbonate (12.84 g, 58.8 mmol) was added thereto. The mixture was stirred at room temperature for 48 hours. 1 M NaOH aqueous solution (53 mL, 53 mmol) was added thereto, and the mixture was stirred for 10 minutes. After addition of water, the reaction solution was extracted with DCM and dried with MgSO₄. The organic layer was purified by column chromatography to obtain the title compound (8.98 g, 90 %).

¹H-NMR (CDCl₃) δ 4.45 (1H, m), 3.46 (3H, m), 3.33 (1H, m), 1.97 (2H, m), 1.42 (9H, s)

Step B: *tert*-butyl 3-oxopyrrolidin-1-carboxylate

Oxalyl chloride (6.0 mL, 70.5 mmol) was added to 300 mL of DCM and cooled to -78°C. DMSO (9.9 mL, 139 mmol) was added thereto, and the mixture was stirred for 15 minutes. *Tert*-butyl 3-hydroxypyrrolidin-1-carboxylate (8.98 g, 48 mmol) obtained in Step A was added thereto, and the mixture was stirred for 20 minutes. TEA (32 mL, 0.23 mol) was added thereto, and the mixture was stirred at -78°C for 1 hour and additionally stirred at room temperature for 1 hour. After addition of water, the reaction solution was extracted with DCM. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (7.92 g, 89 %).

¹H-NMR (CDCl₃) δ 3.77 (4H, m), 2.59 (2H, t), 1.48 (9H, s)

Step C: *tert*-butyl 3-(2-ethoxy-2-oxo-ethylidene)pyrrolidin-1-carboxylate

Tert-butyl 3-oxopyrrolidin-1-carboxylate (1.82 g, 9.82 mmol) obtained in Step B was dissolved in 49 mL of DCM. (1-Ethoxycarbonyl-ethylidene)triphenylphosphorane (3.59 g, 10.3 mmol) was added thereto, and the mixture was stirred for 72 hours under reflux. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (2.0 g, 80 %).

¹H-NMR (CDCl₃) δ 5.81 (1H, s), 4.42-4.13 (2H, m), 4.18 (2H, q), 3.56 (2H, m), 3.12-2.74 (2H, t), 1.46 (9H, s), 1.28 (3H, t)

Step D: *tert*-butyl 3-(2-ethoxy-2-oxo-ethyl)pyrrolidin-1-carboxylate

Tert-butyl 3-(2-ethoxy-2-oxo-ethylidene)pyrrolidin-1-carboxylate (2.0 g, 7.83 mmol) obtained in Step C was dissolved in 40 mL of EtOH. 0.2 g of 10 wt% Pd/C was added thereto, and the mixture was stirred for 24 hours under hydrogen atmosphere. Solids were filtered and concentrated under reduced pressure to obtain the title compound (1.95 g, 97 %).

¹H-NMR (CDCl₃) δ 4.14 (2H, q), 3.58 (1H, m), 3.45 (1H, m), 3.29 (1H, m), 2.92 (1H, m), 2.56 (1H, m), 2.38 (2H, d), 2.07 (1H, m), 1.51 (1H, m), 1.46 (9H, s), 1.26 (3H, t)

Step E: 2-[1-(2,6-difluoro-4-nitro-phenyl)pyrrolidin-3-yl]acetic acid ethyl ester

Tert-butyl 3-(2-ethoxy-2-oxo-ethyl)pyrrolidin-1-carboxylate (1.95 g, 7.57 mmol) obtained in Step D was dissolved in 7 mL of DCM. HCl (7.8 mL, 30 mmol, 4 M 1,4-dioxane solution) was added thereto, and the mixture was stirred at room temperature for 90 minutes. The reaction solution was concentrated under reduced pressure to obtain hydrochloric acid salt

of 2-pyrrolidin-3-ylacetic acid ethyl ester. The obtained hydrochloric acid salt of 2-pyrrolidin-3-ylacetic acid ethyl ester and 3,4,5-trifluoronitrobenzene (1.34 g, 7.57 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (2.24 g, 94 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.72 (2H, m), 4.17 (2H, q), 3.89 (1H, m), 3.81 (1H, m), 3.76 (1H, m), 3.47 (1H, m), 2.62 (1H, m), 2.46 (2H, d), 2.16 (1H, m), 1.65 (1H, m), 1.27 (3H, t)

Step F: 2-[1-(4-bromo-2,6-difluoro-phenyl)pyrrolidin-3-yl]acetic acid ethyl ester

2-[1-(2,6-Difluoro-4-nitro-phenyl)pyrrolidin-3-yl]acetic acid ethyl ester (2.24 g, 7.12 mmol) obtained in Step E was reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (0.92 g, 37 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.93 (2H, m), 4.15 (2H, q), 3.60 (2H, m), 3.49 (1H, m), 3.24 (1H, m), 2.62 (1H, m), 2.44 (2H, d), 2.13 (1H, m), 1.63 (1H, m), 1.26 (3H, t)

Step G: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetic acid ethyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)pyrrolidin-3-yl]acetic acid ethyl ester (0.92 g, 2.64 mmol) obtained in Step F was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.82 g, 79 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.18 (2H, m), 4.15 (2H, q), 3.70 (2H, m), 3.59 (1H, m), 3.35 (1H, m), 2.60 (1H, m), 2.44 (2H, m), 2.14 (1H, m), 1.61 (1H, m), 1.36 (12H, s), 1.27 (3H, t)

Preparation Example 92: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]propanoic acid ethyl ester

Step A: *tert*-butyl 4-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]piperidin-1-carboxylate

Tert-butyl 4-(hydroxymethyl)piperidin-1-carboxylate (4.0 g, 18.6 mmol) was reacted in the same manner as in Step B of Preparation Example 88 to obtain the title compound (4.36 g, 83 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.89 (1H, dd), 5.78 (1H, d), 4.21 (2H, q), 4.12 (2H, m), 2.76 (2H, m), 2.28 (1H, m), 1.72 (2H, m), 1.45 (9H, s), 1.33 (2H, m), 1.28 (3H, t)

Step B: (*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)-4-piperidyl]prop-2-enoic acid ethyl

ester

Tert-butyl 4-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]piperidin-1-carboxylate (4.33 g, 15.1 mmol) obtained in Step A was dissolved in HCl (15 mL, 60 mmol, 4 M 1,4-dioxane solution) and stirred at 60°C for 90 minutes. After addition of Et₂O, the reaction solution was concentrated under reduced pressure to obtain hydrochloric acid salt of (*E*)-3-(4-piperidyl)prop-2-enoic acid ethyl ester. The obtained hydrochloric acid salt of (*E*)-3-(4-piperidyl)prop-2-enoic acid ethyl ester and 3,4,5-trifluoronitrobenzene (2.67 g, 15.1 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (5.1 g, 99 %).

¹H-NMR (CDCl₃) δ 7.75 (2H, m), 6.94 (1H, dd), 5.86 (1H, d), 4.20 (2H, q), 3.54 (2H, m), 3.22 (2H, m), 2.36 (1H, m), 1.84 (2H, m), 1.64 (2H, m), 1.30 (3H, t)

Step C: (*E*)-3-[1-(4-bromo-2,6-difluoro-phenyl)-4-piperidyl]prop-2-enoic acid ethyl ester

(*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)-4-piperidyl]prop-2-enoic acid ethyl ester (5.1 g, 15 mmol) obtained in Step B were reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (2.45 g, 43 %).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 6.95 (1H, dd), 5.84 (1H, d), 4.20 (2H, q), 3.23 (2H, m), 3.10 (2H, m), 2.29 (1H, m), 1.78 (2H, m), 1.61 (2H, m), 1.30 (3H, t)

Step D: 3-[1-(4-bromo-2,6-difluoro-phenyl)-4-piperidyl]propanoic acid ethyl ester

(*E*)-3-[1-(4-bromo-2,6-difluoro-phenyl)-4-piperidyl]prop-2-enoic acid ethyl ester (2.45 g, 6.54 mmol) obtained in Step C was dissolved in 70 mL of DME. *p*-Toluenesulfonyl hydrazide (8.52 g, 45.6 mmol) was added thereto little by little, and the mixture was heated to 90°C. Sodium acetate (5.36 g, 65.4 mmol, 1.4 M aqueous solution) was added thereto, and the mixture was stirred for 9 hours under reflux. After addition of water, the reaction solution was extracted with DCM. The organic layer was dried with MgSO₄ to obtain the title compound (2.46 g, 99 %).

¹H-NMR (CDCl₃) δ 6.99 (2H, m), 4.13 (2H, q), 3.18 (2H, m), 3.01 (2H, m), 2.34 (2H, m), 1.71 (2H, m), 1.63 (2H, m), 1.37 (3H, m), 1.26 (3H, t)

Step E: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]propanoic acid ethyl ester

3-[1-(4-Bromo-2,6-difluoro-phenyl)-4-piperidyl]propanoic acid ethyl ester (2.46 g, 6.54 mmol) obtained in Step D was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (2.02 g, 73 %).

¹H-NMR (CDCl₃) δ 7.23 (2H, m), 4.14 (2H, q), 3.31 (2H, m), 3.05 (2H, m), 2.34 (2H, m), 1.71 (2H, m), 1.62 (2H, m), 1.36 (3H, m), 1.32 (12H, s), 1.25 (3H, t)

Preparation Example 93: 2-[4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazin-1-yl]acetic acid ethyl ester

Step A: 4-(2-ethoxy-2-oxo-ethyl)piperazin-1-carboxylic acid benzyl ester

1-Piperazincarboxylic acid benzyl ester (3.12 g, 14.2 mmol) was dissolved in 47 mL of THF. Bromoacetic acid ethyl ester (1.73 mL, 15.6 mmol) and TEA (5.92 mL, 42.5 mmol) were sequentially added thereto, and the mixture was stirred for 90 minutes under reflux. The reaction solution was cooled to at room temperature. Solids were filtered, and water was added thereto. The organic layer extracted with EtOAc was dried with MgSO₄ to obtain the title compound (4.3 g, 99 %).

¹H-NMR (CDCl₃) δ 7.35 (5H, m), 5.13 (2H, s), 4.19 (2H, q), 3.56 (4H, m), 3.22 (2H, s), 2.55 (4H, m), 1.27 (3H, t)

Step B: 2-piperazin-1-ylacetic acid ethyl ester

4-(2-Ethoxy-2-oxo-ethyl)piperazin-1-carboxylic acid benzyl ester (4.30 g, 14.0 mmol) obtained in Step A was dissolved in 70 mL of MeOH. 0.43 g of 10 wt% Pd/C was added thereto, and the mixture was stirred for 24 hours under hydrogen atmosphere. Solids were filtered through Celite to obtain the title compound (2.40 g, 99 %).

¹H-NMR (CDCl₃) δ 4.19 (2H, q), 3.20 (2H, s), 2.94 (4H, m), 2.57 (4H, m), 1.28 (3H, t)

Step C: 2-[4-(2,6-difluoro-4-nitro-phenyl)piperazin-1-yl]acetic acid ethyl ester

2-Piperazin-1-ylacetic acid ethyl ester (2.40 g, 13.9 mmol) obtained in Step B, 3,4,5-trifluoronitrobenzene (2.35 g, 13.3 mmol) and DIPEA (3.50 mL, 13.9 mmol) were dissolved in 33 mL of DMF and stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc to obtain the title compound (4.37 g, 99 %).

¹H-NMR (CDCl₃) δ 7.78 (2H, m), 4.22 (2H, q), 3.50 (4H, m), 3.38 (2H, s), 2.85 (4H, m), 1.30 (3H, t)

Step D: 2-[4-(4-bromo-2,6-difluoro-phenyl)piperazin-1-yl]acetic acid ethyl ester

2-[4-(2,6-Difluoro-4-nitro-phenyl)piperazin-1-yl]acetic acid ethyl ester (4.34 g, 13.2 mmol) obtained in Step C was reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (0.27 g, 6 %).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 4.20 (2H, q), 3.26 (2H, s), 3.24 (4H, m), 2.70 (4H, m), 1.27 (3H, t)

Step E: 2-[4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]piperazin-1-yl]acetic acid ethyl ester

2-[4-(4-Bromo-2,6-difluoro-phenyl)piperazin-1-yl]acetic acid ethyl ester (0.27 g, 0.74 mmol) obtained in Step D was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.12 g, 39 %).

¹H-NMR (CDCl₃) δ 7.23 (2H, m), 4.20 (2H, q), 3.30 (4H, m), 3.25 (2H, s), 2.70 (4H, m), 1.33 (12H, s), 1.28 (3H, t)

Preparation Example 94: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]propanoic acid ethyl ester

Step A: *tert*-butyl 4-(hydroxymethyl)pyrazol-1-carboxylate

4-Pyrazolcarboxylic acid ethyl ester (4.45 g, 31.7 mmol) was dissolved in 30 mL of THF. Dimethylaminopyridine (0.19 g, 1.59 mmol), TEA (5.3 mL, 38.1 mmol) and di-*tert*-butyl dicarbonate (8.31 g, 38.1 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 1 hour. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄, and 140 mL of Et₂O was added thereto. After cooling to -78°C, the mixture was reacted in the same manner as in Step C of Preparation Example 90 to obtain the title compound (1.42 g, 22 %).

¹H-NMR (CDCl₃) δ 8.02 (1H, s), 7.68 (1H, s), 4.60 (2H, s), 1.63 (9H, s)

Step B: *tert*-butyl 4-formylpyrazol-1-carboxylate

Tert-butyl 4-(hydroxymethyl)pyrazol-1-carboxylate (1.42 g, 7.1 mmol) obtained in

Step A was dissolved in 40 mL of DCM. MgSO_4 (1.2 g, 9.9 mmol) and manganese dioxide (4.32 g, 50 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Solids were filtered and purified by column chromatography to obtain the title compound (1.03 g, 74%).

$^1\text{H-NMR}$ (CDCl_3) δ 9.96 (1H, s), 8.61 (1H, s), 8.13 (1H, s), 1.67 (9H, s)

Step C: *tert*-butyl 4-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]pyrazol-1-carboxylate

Tert-butyl 4-formylpyrazol-1-carboxylate (1.0 g, 5.28 mmol) obtained in Step B was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (1.05 g, 74 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.21 (1H, s), 7.89 (1H, s), 7.54 (1H, d), 6.29 (1H, d), 4.25 (2H, q), 1.66 (9H, s), 1.31 (3H, t)

Step D: (*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)pyrazol-4-yl]prop-2-enoic acid ethyl ester

Tert-butyl 4-[(*E*)-3-ethoxy-3-oxo-prop-1-enyl]pyrazol-1-carboxylate (0.88 g, 3.3 mmol) obtained in Step C was dissolved in 22 mL of DCM. 11 mL of TFA was added thereto, and the mixture was stirred at room temperature for 6 hours. After addition of Et_2O , the reaction solution was concentrated under reduced pressure to obtain solids. 11 mL of DMSO, 3,4,5-trifluoronitrobenzene (0.58 g, 3.3 mmol) and K_2CO_3 (1.37 g, 9.9 mmol) were sequentially added to the solids, and the mixture was stirred at 90°C for 16 hours. After addition of water, the reaction solution was extracted with EtOAc . The organic layer was dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.73 g, 41 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.04 (3H, m), 7.92 (1H, s), 7.62 (1H, d), 6.32 (1H, d), 4.27 (2H, q), 1.33 (3H, t)

Step E: 3-[1-(4-bromo-2,6-difluoro-phenyl)pyrazol-4-yl]propanoic acid ethyl ester

(*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)pyrazol-4-yl]prop-2-enoic acid ethyl ester (0.71 g, 2.2 mmol) obtained in Step D was reacted in the same manner as in Steps C and D of Preparation Example 88 to obtain the title compound (0.68 g, 86 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.66 (1H, s), 7.47 (1H, s), 7.26 (2H, m), 4.14 (2H, q), 2.88 (2H, t), 2.62 (2H, t), 1.25 (3H, t)

Step F: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrazol-4-yl]propanoic acid ethyl

3-[1-(4-Bromo-2,6-difluoro-phenyl)pyrazol-4-yl]propanoic acid ethyl ester (0.075 g, 0.21 mmol) obtained in Step E was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.03 g, 36 %).

¹H-NMR (CDCl₃) δ 7.66 (1H, s), 7.52 (1H, m), 7.47 (2H, m), 4.15 (2H, q), 2.89 (2H, t), 2.63 (2H, t), 1.35 (12H, s), 1.24 (3H, t)

Preparation Example 95: 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl]butanoic acid ethyl ester

Step A: 5-bromoindoline

10 mL of acetic acid was added to 5-bromoindole (2.5 g, 12.8 mmol) and cooled to 0°C. Sodium triacetoxyborohydride (2.38 g, 37.9 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with Et₂O, and the organic layer washed with sodium bicarbonate aqueous solution. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.95 g, 38 %).

¹H-NMR (CDCl₃) δ 7.19 (1H, d), 7.09 (1H, dd), 6.50 (1H, d), 3.74 (1H, brs), 3.56 (2H, t), 3.02 (2H, t)

Step B: 4-(5-bromoindolin-1-yl)butanoic acid ethyl ester

5-Bromoindoline (0.95 g, 4.8 mmol) obtained in Step A was dissolved in 16 mL of DMF. K₂CO₃ (1.32 g, 9.6 mmol) and 4-bromobutanoic acid ethyl ester (0.94 g, 4.8 mmol) were added thereto, and the mixture was stirred at 70°C for 24 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.59 g, 39 %).

¹H-NMR (CDCl₃) δ 7.12 (2H, m), 6.30 (1H, d), 4.11 (2H, q), 3.35 (2H, t), 3.06 (2H, t), 2.94 (2H, t), 2.39 (2H, t), 1.91 (2H, m), 1.24 (3H, t)

Step C: 4-[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-1-yl]butanoic acid ethyl ester

4-(5-Bromoindolin-1-yl)butanoic acid ethyl ester (0.59 g, 1.88 mmol) obtained in Step B was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.48 g, 70 %).

¹H-NMR (CDCl₃) δ 7.55 (1H, dd), 7.49 (1H, m), 6.41 (1H, d), 4.11 (2H, q), 3.40 (2H, t), 3.15 (2H, t), 2.96 (2H, t), 2.39 (2H, t), 1.92 (2H, m), 1.31 (12H, s), 1.25 (3H, t)

Preparation Example 96: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-3-yl]propanoic acid ethyl ester

Step A: 1-*tert*-butoxycarbonylazetidin-3-carboxylic acid

60 mL of THF and 60 mL of 0.5 M NaOH aqueous solution were added to azetidin-3-carboxylic acid (3 g, 30 mmol). Di-*tert*-butyl dicarbonate (6.8 g, 31.1 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 24 hours. The reaction solution was concentrated under reduced pressure. The reaction solution was adjusted to pH 4 by the addition of water and HCl aqueous solution, and extracted with EtOAc. The organic layer was dried with MgSO₄ to obtain the title compound (4.5 g, 73 %).

¹H-NMR (CDCl₃) δ 4.12 (4H, m), 3.38 (1H, m), 1.44 (9H, s)

Step B: (*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)azetidin-3-yl]prop-2-enoic acid ethyl ester

1-*Tert*-butoxycarbonylazetidin-3-carboxylic acid (3.5 g, 17.4 mmol) obtained in Step A was sequentially reacted in the same manner as in Step A of Preparation Example 71, Step E of Preparation Example 86 and Step B of Preparation Example 88 to obtain the title compound (0.5 g, 9 %).

¹H-NMR (CDCl₃) δ 7.70 (2H, m), 7.14 (1H, m), 5.93 (1H, d), 4.62 (2H, m), 4.28 (2H, m), 4.22 (2H, q), 3.60 (1H, m), 1.30 (3H, t)

Step C: 3-[1-(4-bromo-2,6-difluoro-phenyl)azetidin-3-yl]propanoic acid ethyl ester

(*E*)-3-[1-(2,6-difluoro-4-nitro-phenyl)azetidin-3-yl]prop-2-enoic acid ethyl ester (0.66 g, 2.1 mmol) obtained in Step B was sequentially reacted in the same manner as in Step C of Preparation Example 88 and Step C of Preparation Example 84 to obtain the title compound (0.14 g, 19 %).

¹H-NMR (CDCl₃) δ 6.88 (2H, m), 4.25 (2H, m), 4.14 (2H, q), 3.78 (2H, m), 2.67 (1H,

m), 2.29 (2H, t), 1.96 (2H, m), 1.26 (3H, t)

Step D: 3-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]azetidin-3-yl]propanoic acid ethyl ester

3-[1-(4-Bromo-2,6-difluoro-phenyl)azetidin-3-yl]propanoic acid ethyl ester (0.13 g, 0.38 mmol) obtained in Step C was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.032 g, 21%).

¹H-NMR (CDCl₃) δ 7.15 (2H, m), 4.32 (2H, m), 4.12 (2H, q), 3.85 (2H, m), 2.67 (1H, m), 2.29 (2H, t), 1.97 (2H, m), 1.32 (12H, s), 1.27 (3H, t)

Preparation Example 97: 2-[(3S)-1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetic acid methyl ester

Step A: 2-[(3S)-1-*tert*-butoxycarbonyl]pyrrolidin-3-yl]propanedioic acid ethyl ester

(3S)-3-hydroxypyrrolidin-1-carboxylic acid *tert*-butyl ester (1.5 g, 8 mmol) was dissolved in 16 mL of toluene and cooled to -10°C. TEA (1.7 mL, 12 mmol) and methanesulfonyl chloride (0.8 mL, 10.1 mmol) were slowly added thereto. The mixture was stirred at room temperature for 80 minutes, and solids were filtered. The filtrate was washed with sodium bicarbonate aqueous solution, dried with MgSO₄ and concentrated under reduced pressure to obtain (3S)-3-methylsulfonyloxypyrrolidin-1-carboxylic acid *tert*-butyl ester. 27 mL of EtOH and malonic acid ethyl ester (2.62 g, 16.4 mmol) were prepared in another flask, and sodium (0.37 g, 16 mmol) was added thereto little by little. The mixture was stirred at room temperature for 30 minutes. (3S)-3-methylsulfonyloxypyrrolidin-1-carboxylic acid *tert*-butyl ester was added thereto, and the mixture was stirred for 16 hours under reflux. The reaction solution was cooled to room temperature and adjusted to pH 4 by the addition of water and 1N HCl aqueous solution. The reaction solution was extracted with MTBE to obtain the title compound (2.08 g, 79 %).

¹H-NMR (CDCl₃) δ 4.22 (2H, q), 3.64 (1H, m), 3.50 (1H, m), 3.28 (2H, m), 3.03 (1H, m), 2.81 (1H, m), 2.08 (1H, m), 1.63 (1H, m), 1.45 (9H, s), 1.27 (6H, t)

Step B: 2-[(3S)-1-*tert*-butoxycarbonyl]pyrrolidin-3-yl]propanedioic acid

2-[(3S)-1-*tert*-butoxycarbonyl]pyrrolidin-3-yl]propanedioic acid ethyl ester (2.08 g, 6.3 mmol) obtained in Step A was dissolved in 9 mL of THF. 44 wt% KOH aqueous solution (5

g, 39 mmol) was added thereto, and the mixture was stirred at 45°C for 24 hours. The reaction solution was cooled to room temperature and washed with MTBE. The water layer was adjusted to pH 4 and extracted with EtOAc. The organic layer was dried with MgSO₄ to obtain the title compound (1.42 g, 83 %).

¹H-NMR (CD₃OD) δ 3.63 (1H, m), 3.45 (1H, m), 3.30 (2H, m), 3.05 (1H, m), 2.74 (1H, m), 2.10 (1H, m), 1.71 (1H, m), 1.45 (9H, s)

Step C: 2-[(3S)-1-*tert*-butoxycarbonylpyrrolidin-3-yl]acetic acid

2-[(3S)-1-*tert*-butoxycarbonylpyrrolidin-3-yl]propanedioic acid (1.42 g, 5.22 mmol) obtained in Step B was dissolved in 15 mL of toluene and 0.2 mL of DMSO, and stirred for 16 hours under reflux. The reaction solution was cooled to room temperature. After addition of water, the reaction solution was extracted with MTBE. The organic layer was dried with MgSO₄ to obtain the title compound (1.05 g, 87 %).

¹H-NMR (CD₃OD) δ 3.58 (1H, m), 3.43 (1H, m), 3.27 (1H, m), 2.93 (1H, m), 2.52 (1H, m), 2.40 (2H, d), 2.08 (1H, m), 1.58 (1H, m), 1.45 (9H, s)

Step D: 2-[(3S)-1-(2,6-difluoro-4-nitro-phenyl)pyrrolidin-3-yl]acetic acid methyl ester

2-[(3S)-1-*tert*-butoxycarbonylpyrrolidin-3-yl]acetic acid (1.05 g, 4.58 mmol) obtained in Step C was dissolved in 15 mL of THF. Diazomethane (0.25 M Et₂O solution, 27 mL, 6.87 mmol) was added thereto, and the mixture was stirred at room temperature for 40 minutes. The reaction solution was concentrated under reduced pressure. After addition of 15 mL of DCM and HCl (4 M 1,4-dioxane solution, 4.6 mL), the reaction solution was stirred at room temperature for 90 minutes. The reaction solution was concentrated under reduced pressure and dissolved in 15 mL of DMF. TEA (1.6 mL, 11.5 mmol) and 3,4,5-trifluoronitrobenzene (0.81 g, 4.58 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 48 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc to obtain the title compound (1.33 g, 97 %).

¹H-NMR (CDCl₃) δ 7.72 (2H, m), 3.89 (1H, m), 3.82 (1H, m), 3.76 (1H, m), 3.71 (3H, s), 3.47 (1H, m), 2.63 (1H, m), 2.49 (2H, d), 2.18 (1H, m), 1.64 (1H, m)

Step E: 2-[(3S)-1-(4-bromo-2,6-difluoro-phenyl)pyrrolidin-3-yl]acetic acid methyl

ester

2-[(3S)-1-(2,6-difluoro-4-nitro-phenyl)pyrrolidin-3-yl]acetic acid methyl ester (1.33 g, 4.43 mmol) obtained in Step D was sequentially reacted in the same manner as in Steps B and C of Preparation Example 84 to obtain the title compound (0.38 g, 25 %).

¹H-NMR (CDCl₃) δ 6.93 (2H, m), 3.69 (3H, s), 3.60 (2H, m), 3.48 (1H, m), 3.24 (1H, m), 2.63 (1H, m), 2.45 (2H, d), 2.13 (1H, m), 1.62 (1H, m)

Step F: 2-[(3S)-1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetic acid methyl ester

2-[(3S)-1-(4-bromo-2,6-difluoro-phenyl)pyrrolidin-3-yl]acetic acid methyl ester (0.37 g, 1.1 mmol) obtained in Step E was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.18 g, 43 %).

¹H-NMR (CDCl₃) δ 7.17 (2H, m), 3.70 (5H, m), 3.59 (1H, m), 3.35 (1H, m), 2.61 (1H, m), 2.46 (2H, m), 2.12 (1H, m), 1.62 (1H, m), 1.31 (12H, s)

Preparation Example 98: 2-[(3R)-1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]pyrrolidin-3-yl]acetic acid methyl ester

(3R)-3-hydroxypyrrolidin-1-carboxylic acid *tert*-butyl ester (1.0 g, 5.34 mmol) was reacted in the same manner as in Steps A, B, C, D, E and F of Preparation Example 97 to obtain the title compound (0.14 g, 7 %).

¹H-NMR (CDCl₃) δ 7.17 (2H, m), 3.70 (5H, m), 3.59 (1H, m), 3.35 (1H, m), 2.61 (1H, m), 2.46 (2H, m), 2.12 (1H, m), 1.62 (1H, m), 1.31 (12H, s)

Preparation Example 99: 2-[1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester

Step A: 1-(2-fluoro-4-nitro-phenyl)piperidin-4-one

1,2-Difluoro-4-nitro-benzene (1.50 g, 9.42 mmol) was dissolved in 31 mL of DMF. TEA (3.3 mL, 23.5 mmol) and hydrate of 4-piperidone hydrochloride (1.52 g, 9.9 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 48 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with MgSO₄ to obtain the title compound (2.03 g, 91 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.02 (1H, m), 7.96 (1H, m), 6.98 (1H, t), 3.65 (4H, t), 2.65 (4H, t)

Step B: 2-[1-(2-fluoro-4-nitro-phenyl)-4-piperidylidene]acetic acid ethyl ester

1-(2-Fluoro-4-nitro-phenyl)piperidin-4-one (2.03 g, 8.55 mmol) obtained in Step A was reacted in the same manner as in Step B of Preparation Example 89 to obtain the title compound (2.65 g, 99 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.95 (1H, m), 7.92 (1H, m), 6.91 (1H, m), 5.76 (1H, s), 4.17 (2H, q), 3.43 (2H, m), 3.38 (2H, m), 3.16 (2H, m), 2.50 (2H, m), 1.30 (3H, t)

Step C: 2-[1-(4-bromo-2-fluoro-phenyl)-4-piperidyl]acetic acid ethyl ester

2-[1-(2-Fluoro-4-nitro-phenyl)-4-piperidylidene]acetic acid ethyl ester (2.65 g, 8.6 mmol) obtained in Step B was sequentially reacted in the same manner as in Step C of Preparation Example 88 and Step C of Preparation Example 84 to obtain the title compound (0.72 g, 24 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.15 (2H, m), 6.81 (1H, t), 4.14 (2H, q), 3.38 (2H, m), 2.67 (2H, m), 2.29 (2H, d), 1.92 (1H, m), 1.82 (2H, m), 1.48 (2H, m), 1.26 (3H, t)

Step D: 2-[1-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester

2-[1-(4-Bromo-2-fluoro-phenyl)-4-piperidyl]acetic acid ethyl ester (0.22 g, 0.64 mmol) obtained in Step C was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.20 g, 80 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.48 (1H, m), 7.41 (1H, m), 6.92 (1H, t), 4.14 (2H, q), 3.52 (2H, m), 2.72 (2H, m), 2.29 (2H, d), 1.94 (1H, m), 1.83 (2H, m), 1.50 (2H, m), 1.32 (12H, s), 1.27 (3H, t)

Preparation Example 100: 1-(6-bromo-naphthalen-2-yl)-ethaneone

2-Bromo-naphthalene (0.5 g, 2.41 mmol), AlCl_3 (0.338 g, 2.53 mmol) and AcCl (0.172 mL, 2.41 mmol) were dissolved in 3.4 mL of nitrobenzene, and stirred at 100°C for 4 hours under reflux. After addition of water, the reaction solution extracted with EtOAc. The organic layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.3 g, 49%).

¹H-NMR (CDCl₃) δ 8.43 (1H, s), 8.06 (2H, m), 7.82 (2H, t), 7.63 (1H, m), 2.72 (3H, s).

Preparation Example 101: 6-bromo-naphthalen-2-carboxylic acid

1-(6-Bromo-naphthalen-2-yl)-ethaneone (0.22 g, 0.88 mmol) obtained in Preparation Example 100 was dissolved in 3 mL of 1,4-dioxane. NaOH (0.353 g, 8.8 mmol) dissolved in 3 mL of water and 9-11% NaOCl solution (1.67 mL, 2.64 mmol) were added thereto, and the mixture was heated to 70°C and stirred for 4 hours. After addition of NaHSO₃ aqueous solution and water, the reaction solution was extracted with ether. 1N HCl was added thereto, and the organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.156 g, 70%).

¹H-NMR (CDCl₃) δ 8.56 (1H, s), 8.05 (2H, m), 7.79 (2H, m), 7.58 (1H, m).

Preparation Example 102: (6-bromo-naphthalen-2-yl)-methanol

6-Bromo-naphthalen-2-carboxylic acid (0.42 g, 1.67 mmol) obtained in Preparation Example 101 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.307 g, 77%).

¹H-NMR (CDCl₃) δ 8.00 (1H, s), 7.83-7.69 (3H, m), 7.57-7.52 (2H, m), 4.85 (2H, m), 1.75 (1H, t).

Preparation Example 103: 2-bromo-6-chloromethyl-naphthalene

(6-Bromo-naphthalen-2-yl)-methanol (0.307 g, 1.29 mmol) obtained in Preparation Example 102 was dissolved in 5 mL of acetonitrile. Thionyl-chloride (0.188 mL, 2.59 mmol) was added thereto at 0°C, and the mixture was stirred at room temperature for 1 hour. The reaction solution was distilled under reduced pressure and purified by column chromatography to obtain the title compound (0.248 g, 75%).

¹H-NMR (CDCl₃) δ 8.00 (1H, s), 7.83-7.68 (3H, m), 7.58-7.53 (2H, m), 4.73 (2H, s).

Preparation Example 104: 2-(6-bromo-naphthalen-2-ylmethyl)-malonic acid dimethyl ester

NaH (60% in mineral oil, 0.058 g, 1.45 mmol) was dissolved in 3 mL of DMF. Dimethyl malonate (0.166 mL, 1.45 mmol) was added thereto, and the mixture was stirred for

15 minutes. 2-Bromo-6-chloromethyl-naphthalene (0.248 g, 0.97 mmol) obtained in Preparation Example 103 was added thereto, and the mixture was heated to 60°C and stirred for 4 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.26 g, 76%).

¹H-NMR (CDCl₃) δ 7.96 (1H, s), 7.71-7.62 (3H, m), 7.52 (1H, m), 7.36 (1H, m), 3.75 (1H, m), 3.69 (6H, s), 3.87 (2H, d).

Preparation Example 105: 3-(6-bromo-naphthalen-2-yl)-propionic acid

2-(6-Bromo-naphthalen-2-ylmethyl)-malonic acid dimethyl ester (0.26 g, 0.74 mmol) obtained in Preparation Example 104 was dissolved in 12 mL of ethanol and 12 mL of THF. 6 mL of 4N KOH was added thereto, and the mixture was heated to 60°C and stirred for 1 hour. The reaction solution was distilled under reduced pressure. Solids obtained by the addition of 2N HCl were dissolved in 6 mL of pyridine, heated to 60°C and stirred for 1 hour. The reaction solution was distilled under reduced pressure. After addition of 2N HCl and water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.055 g, 26%).

¹H-NMR (CDCl₃) δ 7.96 (1H, s), 7.70-7.62 (3H, m), 7.53 (1H, m), 7.36 (1H, m), 3.11 (2H, t), 2.77 (2H, t).

Preparation Example 106: 3-(6-bromo-naphthalen-2-yl)-propionic acid methyl ester

3-(6-Bromo-naphthalen-2-yl)-propionic acid (0.055 g, 0.2 mmol) obtained in Preparation Example 105 was reacted in the same manner as in Step G of Preparation Example 81 to obtain the title compound (0.052 g, 91%).

¹H-NMR (CDCl₃) δ 7.96 (1H, s), 7.70-7.61 (3H, m), 7.53 (1H, m), 7.36 (1H, m), 3.67 (3H, s), 3.10 (2H, t), 2.72 (2H, t).

Preparation Example 107: 3-[6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yl]-propionic acid methyl ester

3-(6-Bromo-naphthalen-2-yl)-propionic acid methyl ester (0.085 g, 0.29 mmol)

obtained in Preparation Example 106 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.083 g, 84%).

¹H-NMR (CDCl₃) δ 8.32 (1H, s), 7.80 (2H, d), 7.75 (1H, d), 7.62 (1H, s), 7.32 (1H, d), 3.67 (3H, s), 3.12 (2H, t), 2.73 (2H, t), 1.39 (12H, s).

Preparation Example 108: 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester

6-Bromo-naphthalen-2-carboxylic acid methyl ester (1 g, 3.77 mmol) was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.824 g, 70%).

¹H-NMR (CDCl₃) δ 8.59 (1H, s), 8.39 (1H, s), 8.05 (1H, d), 7.92 (3H, m), 3.98 (3H, s), 1.40 (12H, s).

Preparation Example 109: 6-(6-phenoxy-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.2 g, 0.64 mmol) obtained in Preparation Example 108 and 2-chloro-6-phenoxy-pyridine (0.132 g, 0.64 mmol) obtained in Preparation Example 54 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.17 g, 74%).

¹H-NMR (CDCl₃) δ 8.58 (1H, s), 8.45 (1H, s), 8.06 (2H, m), 7.93 (2H, m), 7.78 (1H, t), 7.63 (1H, d), 7.44 (2H, m), 7.24 (3H, m), 6.82 (1H, d), 3.98 (3H, s).

Preparation Example 110: 2-[6-(6-phenoxy-pyridin-2-yl)-naphthalen-2-ylmethyl]-malonic acid dimethyl ester

6-(6-Phenoxy-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.17 g, 0.48 mmol) obtained in Preparation Example 109 was sequentially reacted in the same manner as in Preparation Examples 102, 103 and 104 to obtain the title compound (0.125 g, 59%).

¹H-NMR (CDCl₃) δ 8.39 (1H, s), 8.02 (1H, m), 7.82-7.74 (3H, m), 7.61 (2H, m), 7.43 (2H, m), 7.32 (1H, m), 7.23 (3H, m), 6.78 (1H, d), 3.78 (1H, t), 3.69 (6H, s), 3.38 (2H, d).

Preparation Example 111: 6-(2-phenoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.62 g, 2.34 mmol) obtained in Preparation Example 108 and 2-phenoxyphenylboronic acid (0.5 g, 2.34 mmol) were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.8 g, 96%).

¹H-NMR (CDCl₃) δ 8.57 (1H, s), 8.03 (2H, m), 7.92 (1H, d), 7.86 (1H, d), 7.77 (1H, m), 7.56 (1H, m), 7.35 (1H, m), 7.24 (3H, m), 7.05 (2H, m), 6.94 (2H, m), 3.98 (3H, s).

Preparation Example 112: 2-[6-(2-phenoxy-phenyl)-naphthalen-2-ylmethyl]-malonic acid dimethyl ester

6-(2-Phenoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester (0.8 g, 2.26 mmol) obtained in Preparation Example 111 was sequentially reacted in the same manner as in Preparation Examples 102, 103 and 104 to obtain the title compound (0.64 g, 64%).

¹H-NMR (CDCl₃) δ 7.95 (1H, s), 7.74 (2H, m), 7.68 (1H, m), 7.61 (1H, m), 7.55 (1H, m), 7.32 (2H, m), 7.25 (3H, m), 7.04 (2H, m), 6.94 (2H, m), 3.79 (1H, m), 3.68 (6H, s), 3.38 (2H, d).

Preparation Example 113: 6-(6-cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.2 g, 0.64 mmol) obtained in Preparation Example 108 and 2-chloro-6-cyclopentylsulfanyl-pyridine (0.136 g, 0.64 mmol) obtained in Preparation Example 14 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.03 g, 13%).

¹H-NMR (CDCl₃) δ 8.62 (1H, s), 8.52 (1H, s), 8.25 (1H, m), 8.08 (1H, m), 8.03 (1H, d), 7.97 (1H, d), 7.58 (2H, m), 7.15 (1H, m), 4.25 (1H, m), 4.00 (3H, s), 2.30 (2H, m), 1.84-1.73 (6H, m).

Preparation Example 114: 2-[6-(6-cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-ylmethyl]-malonic acid dimethyl ester

6-(6-Cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.03 g, 0.08 mmol) obtained in Preparation Example 113 was sequentially reacted in the same manner as in Preparation Examples 102, 103 and 104 to obtain the title compound (0.019 g,

51%).

¹H-NMR (CDCl₃) δ 8.45 (1H, s), 8.16 (1H, m), 7.86 (2H, m), 7.68 (1H, s), 7.55 (2H, m), 7.35 (1H, m), 7.13 (1H, m), 4.25 (1H, m), 3.80 (1H, t), 3.70 (6H, s), 3.41 (2H, d), 2.31 (2H, m), 1.73-1.60 (6H, m).

Preparation Example 115: 6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-carboxylic acid methyl ester

Step A: 3-chloro-2-phenoxy-pyridine

2,3-Dichloro-pyridine (0.3 g, 2.03 mmol), phenol (0.286 g, 3.04 mmol), Cu (0.257 g, 4.05 mmol) and Cs₂CO₃ (1.98 g, 6.08 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.193 g, 77%).

Step B: 6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.242 g, 0.78 mmol) obtained in Preparation Example 108 and 3-chloro-2-phenoxy-pyridine (0.16 g, 0.78 mmol) obtained in Step A were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.06 g, 22%).

¹H-NMR (CDCl₃) δ 8.63 (1H, s), 8.20 (1H, m), 8.12 (1H, s), 8.08 (1H, m), 7.92 (1H, m), 7.86 (2H, m), 7.39 (2H, m), 7.20-7.13 (4H, m), 6.80 (1H, m), 4.00 (3H, s).

Preparation Example 116: [6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-yl]-methanol

6-(2-Phenoxy-pyridin-3-yl)-naphthalen-2-carboxylic acid methyl ester (0.06 g, 0.17 mmol) obtained in Preparation Example 115 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.024 g, 43%).

¹H-NMR (CDCl₃) δ 8.18 (1H, m), 8.08 (1H, s), 7.88 (3H, m), 7.82 (2H, m), 7.51 (1H, d), 7.38 (2H, t), 7.19-7.12 (4H, m), 4.87 (2H, d), 1.78 (1H, t).

Preparation Example 117: 6-(3-phenoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.125 g, 0.40 mmol) obtained in Preparation Example 108 and 1-bromo-3-

phenoxy-benzene (0.1 g, 0.40 mmol) were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.032 g, 22%).

¹H-NMR (CDCl₃) δ 8.62 (1H, s), 8.09-8.00 (3H, m), 7.92 (1H, d), 7.76 (1H, m), 7.46 (2H, m), 7.37 (3H, m), 7.10 (4H, m), 3.99 (3H, s).

Preparation Example 118: [6-(3-phenoxy-phenyl)-naphthalen-2-yl]-methanol

6-(3-Phenoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester (0.032 g, 0.09 mmol) obtained in Preparation Example 117 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.029 g, 98%).

¹H-NMR (CDCl₃) δ 8.01 (1H, s), 7.88 (3H, m), 7.71 (1H, m), 7.52-7.34 (6H, m), 7.14-7.03 (4H, m), 4.88 (2H, d), 1.75 (1H, t).

Preparation Example 119: 6-(3-isopropoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

Step A: 1-bromo-3-isopropoxy-benzene

3-Bromo phenol (0.2 g, 1.16 mmol) and 2-bromo-propanol (0.163 mL, 1.73 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.193 g, 77%).

Step B: 6-(3-isopropoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.280 g, 0.89 mmol) obtained in Preparation Example 108 and 1-bromo-3-isopropoxy-benzene (0.193 g, 1.39 mmol) obtained in Step A were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.078 g, 27%).

¹H-NMR (CDCl₃) δ 8.63 (1H, s), 8.10-8.00 (3H, m), 7.92 (1H, m), 7.80 (1H, m), 7.39 (1H, m), 7.26 (2H, m), 6.93 (1H, m), 4.66 (1H, m), 3.99 (3H, s), 1.39 (6H, d).

Preparation Example 120: [6-(3-isopropoxy-phenyl)-naphthalen-2-yl]-methanol

6-(3-Isopropoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester (0.305 g, 0.9 mmol) obtained in Preparation Example 119 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.196 g, 70%).

¹H-NMR (CDCl₃) δ 8.03 (1H, s), 7.88 (3H, m), 7.73 (1H, m), 7.50 (1H, m), 7.36 (1H,

m), 7.26 (2H, m), 6.91 (1H, m), 4.88 (2H, d), 4.66 (1H, m), 1.77 (1H, t), 1.39 (6H, d).

Preparation Example 121: 6-(3-cyclobutoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

Step A: 1-bromo-3-cyclobutoxy-benzene

3-Bromo phenol (0.2 g, 1.16 mmol) and bromocyclobutane (0.163 mL, 1.73 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (0.262 g, 100%).

Step B: 6-(3-cyclobutoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.435 g, 1.39 mmol) obtained in Preparation Example 108 and 1-bromo-3-cyclobutoxy-benzene (0.317 g, 1.39 mmol) obtained in Step A were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.305 g, 65%).

¹H-NMR (CDCl₃) δ 8.63 (1H, s), 8.10-8.00 (3H, m), 7.92 (1H, m), 7.79 (1H, m), 7.38 (1H, m), 7.26 (1H, m), 7.17 (1H, s), 6.86 (1H, m), 4.74 (1H, m), 3.99 (3H, s), 2.50 (2H, m), 2.24 (2H, m), 1.90 (1H, m), 1.72 (1H, m).

Preparation Example 122: [6-(3-cyclobutoxy-phenyl)-naphthalen-2-yl]-methanol

6-(3-Cyclobutoxy-phenyl)-naphthalen-2-carboxylic acid methyl ester (0.305 g, 0.9 mmol) obtained in Preparation Example 121 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.196 g, 70%).

¹H-NMR (CDCl₃) δ 8.02 (1H, s), 7.88 (3H, m), 7.74 (1H, m), 7.50 (1H, m), 7.36 (1H, m), 7.26 (1H, m), 7.17 (1H, s), 6.83 (1H, m), 4.88 (2H, d), 4.74 (1H, m), 2.50 (2H, m), 2.23 (2H, m), 1.90 (1H, m), 1.73 (2H, m).

Preparation Example 123: 6-(6-cyclobutoxy-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.39 g, 1.25 mmol) obtained in Preparation Example 108 and 2-chloro-6-cyclobutoxy-pyridine (0.23 g, 1.25 mmol) obtained in Preparation Example 29 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.21 g, 50%).

¹H-NMR (CDCl₃) δ 8.62 (1H, s), 8.51 (1H, s), 8.22 (1H, m), 8.10-7.91 (3H, m), 7.68 (1H, t), 7.48 (1H, m), 6.70 (1H, d), 5.35 (1H, m), 3.98 (3H, s), 2.60 (2H, m), 2.24 (2H, m), 1.89 (1H, m), 1.76 (1H, m).

Preparation Example 124: [6-(6-cyclobutoxy-pyridin-2-yl)-naphthalen-2-yl]-methanol

6-(6-Cyclobutoxy-pyridin-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.21 g, 0.6 mmol) obtained in Preparation Example 123 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.155 g, 80%).

¹H-NMR (CDCl₃) δ 8.47 (1H, s), 8.17 (1H, m), 7.93 (2H, m), 7.84 (1H, s), 7.66 (1H, t), 7.48 (2H, m), 6.67 (1H, d), 5.35 (1H, m), 4.89 (2H, d), 2.57 (2H, m), 2.24 (2H, m), 1.89 (1H, m), 1.78 (2H, m).

Preparation Example 125: 6-(2-isopropoxy-pyridin-3-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.144 g, 0.46 mmol) obtained in Preparation Example 108 and 3-iodo-2-isopropoxy-pyridine (0.124 g, 0.46 mmol) obtained in Preparation Example 34 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.092 g, 62%).

¹H-NMR (CDCl₃) δ 8.62 (1H, s), 8.18 (1H, m), 8.06 (2H, m), 7.97 (1H, d), 7.89 (1H, d), 7.80 (1H, m), 7.72 (1H, m), 6.97 (1H, m), 5.45 (1H, m), 3.99 (3H, s), 1.36 (6H, d).

Preparation Example 126: 6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-carboxylic acid methyl ester

6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-carboxylic acid methyl ester (0.223 g, 0.7 mmol) obtained in Preparation Example 108 and 2-cyclopentyloxy-3-iodo-pyridine (0.207 g, 0.7 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.123 g, 49%).

¹H-NMR (CDCl₃) δ 8.62 (1H, s), 8.19 (1H, m), 8.08 (1H, m), 8.03 (1H, s), 7.96 (1H, d), 7.89 (1H, d), 7.77 (1H, m), 7.73 (1H, m), 6.97 (1H, m), 5.57 (1H, m), 4.00 (3H, s), 1.95 (2H, m), 1.85 (2H, m), 1.73 (2H, m), 1.63 (2H, m).

Preparation Example 127: 2-chloro-6-(2-fluoro-phenoxy)-pyridine

2,6-Dichloropyridine (0.2 g, 1.35 mmol) and 2-fluoro-phenol (0.151 g, 1.35 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (0.045 g, 15 %).

¹H-NMR (CDCl₃) δ 7.64 (1H, m), 7.27 (2H, m), 7.20 (2H, m), 7.05 (1H, d), 6.85 (1H, d).

Preparation Example 128: 3-[6-(2-bromo-phenyl)-naphthalen-2-yl]-propionic acid methyl ester

3-(6-Bromo-naphthalen-2-yl)-propionic acid methyl ester (0.1 g, 0.34 mmol) obtained in Preparation Example 106 and 2-bromophenylboronic acid (0.068 g, 0.34 mmol) were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.012 g, 9%).

¹H-NMR (CDCl₃) δ 7.81-7.23 (9H, m), 7.10 (1H, m), 3.70 (3H, s), 3.07 (2H, t), 2.72 (2H, t).

Preparation Example 129: 3-{6-[2-(2-fluoro-phenoxy)-phenyl]-naphthalen-2-yl}-propionic acid methyl ester

3-[6-(2-Bromo-phenyl)-naphthalen-2-yl]-propionic acid methyl ester (0.012 g, 0.03 mmol) obtained in Preparation Example 128 was dissolved in 1 mL of 1,4-dioxane. CuI (0.001 g, 0.006 mmol), Cs₂CO₃ (0.021 g, 0.06 mmol) and 2-fluoro-phenol (0.006 mL, 0.06 mmol) were added thereto, and the mixture was stirred for 18 hours under reflux. The reaction solution was filtered through Celite and purified by column chromatography to obtain the title compound (0.012 g, 92 %).

¹H-NMR (CDCl₃) δ 7.82-7.35 (4H, m), 7.20-7.04 (8H, m), 6.80 (2H, m), 3.67 (3H, s), 3.06 (2H, t), 2.70 (2H, t).

Preparation Example 130: 2-(4-bromo-phenyl)-2-methyl-propionic acid ethyl ester

(4-Bromo-phenyl)-acetic acid ethyl ester (0.1 g, 0.41 mmol) was dissolved in 1 mL of THF. t-BuOK (0.092 g, 0.82 mmol) was added thereto, and iodomethane (0.051 mL, 0.82 mmol) was added thereto at 0°C. The mixture was stirred at room temperature for 18 hours. After addition of 1N HCl and water, the reaction solution was extracted with EtOAc. The

organic layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.047 g, 42%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.42 (2H, d), 7.21 (2H, d), 4.11 (2H, q), 1.54 (6H, s), 1.18 (3H, t).

Preparation Example 131: 2-(4-bromo-phenyl)-2-methyl-propan-1-ol

2-(4-Bromo-phenyl)-2-methyl-propionic acid ethyl ester (0.236 g, 0.87 mmol) obtained in Preparation Example 130 was reacted in the same manner as in Step B of Preparation Example 31 to obtain the title compound (0.17 g, 85%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.45 (2H, d), 7.26 (2H, d), 3.61 (2H, d), 1.55 (1H, m), 1.31 (6H, s).

Preparation Example 132: 2-(4-bromo-phenyl)-2-methyl-propionaldehyde

2-(4-Bromo-phenyl)-2-methyl-propan-1-ol (0.17 g, 0.74 mmol) obtained in Preparation Example 131 was dissolved in 2.5 mL of MC and 0.5 mL of DMSO. IBX (0.249 g, 0.89 mmol) was added thereto at 0°C , and the mixture was stirred at room temperature for 4 hours. After addition of water, the reaction solution was extracted with MC. The organic layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.052 g, 30%).

$^1\text{H-NMR}$ (CDCl_3) δ 9.46 (1H, s), 7.50 (2H, d), 7.13 (2H, d), 1.44 (6H, s)

Preparation Example 133: 3-(4-bromo-phenyl)-3-methyl-butyraldehyde

2-(4-Bromo-phenyl)-2-methyl-propionaldehyde (0.33 g, 1.45 mmol) obtained in Preparation Example 132 was reacted in the same manner as in Preparation Example 152 to obtain the title compound (0.275 g, 78%).

$^1\text{H-NMR}$ (CDCl_3) δ 9.52 (1H, m), 7.45 (2H, d), 7.24 (2H, d), 2.66 (2H, m), 1.44 (6H, s).

Preparation Example 134: (E)-5-(4-bromo-phenyl)-5-methyl-hex-2-enoic acid ethyl ester

3-(4-Bromo-phenyl)-3-methyl-butyraldehyde (0.275 g, 1.14 mmol) obtained in Preparation Example 133 was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (0.348 g, 98%).

¹H-NMR (CDCl₃) δ 7.42 (2H, d), 7.19 (2H, d), 6.69 (1H, m), 5.74 (1H, d), 4.15 (2H, q), 2.48 (2H, d), 1.32 (6H, s), 1.25 (3H, t).

Preparation Example 135: (E)-5-methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hex-2-enoic acid ethyl ester

(E)-5-(4-bromo-phenyl)-5-methyl-hex-2-enoic acid ethyl ester (0.348 g, 1.12 mmol) obtained in Preparation Example 134 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.291 g, 72%).

¹H-NMR (CDCl₃) δ 7.75 (2H, d), 7.34 (2H, d), 6.70 (1H, m), 5.76 (1H, d), 4.12 (2H, q), 2.50 (2H, d), 1.33 (18H, s), 1.24 (3H, t).

Preparation Example 136: 5-methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hexanoic acid ethyl ester

(E)-5-methyl-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hex-2-enoic acid ethyl ester (0.291 g, 0.81 mmol) obtained in Preparation Example 135 was reacted in the same manner as in Step E of Preparation Example 1 to obtain the title compound (0.248 g, 84%).

¹H-NMR (CDCl₃) δ 7.75 (2H, d), 7.33 (2H, d), 4.08 (2H, q), 2.17 (2H, t), 1.65 (2H, m), 1.35 (20H, m), 1.22 (3H, t).

Preparation Example 137: 2-(4-bromo-2-fluoro-phenyl)-2-methyl-propionitrile

Step A: (4-bromo-2-fluoro-phenyl)-acetonitrile

4-Bromo-1-bromomethyl-2-fluoro-benzene (0.5 g, 1.87 mmol) was reacted in the same manner as in Preparation Example 149 to obtain the title compound (0.386 g, 96%).

Step B: 2-(4-bromo-2-fluoro-phenyl)-2-methyl-propionitrile

(4-Bromo-2-fluoro-phenyl)-acetonitrile (0.24 g, 1.12 mmol) obtained in Step A was reacted in the same manner as in Preparation Example 143 to obtain the title compound (0.235 g, 86%).

¹H-NMR (CDCl₃) δ 7.40-7.26 (3H, m), 1.78 (6H, s).

Preparation Example 138: 2-(4-bromo-2-fluoro-phenyl)-2-methyl-

propionaldehyde

2-(4-Bromo-2-fluoro-phenyl)-2-methyl-propionitrile (0.235 g, 0.97 mmol) obtained in Preparation Example 137 was reacted in the same manner as in Preparation Example 151 to obtain the title compound (0.2 g, 84%).

¹H-NMR (CDCl₃) δ 9.61 (1H, m), 7.34 (1H, m), 7.26 (1H, m), 7.16 (1H, t), 1.44 (6H, s).

Preparation Example 139: 3-(4-bromo-2-fluoro-phenyl)-3-methyl-butyraldehyde

2-(4-Bromo-2-fluoro-phenyl)-2-methyl-propionaldehyde (0.2 g, 0.82 mmol) obtained in Preparation Example 138 was reacted in the same manner as in Preparation Example 152 to obtain the title compound (0.067 g, 31%).

¹H-NMR (CDCl₃) δ 9.51 (1H, t), 7.25-7.16 (3H, m), 2.81 (2H, s), 1.43 (6H, s).

Preparation Example 140: (E)-5-(4-bromo-2-fluoro-phenyl)-5-methyl-hex-2-enoic acid ethyl ester

3-(4-Bromo-2-fluoro-phenyl)-3-methyl-butyraldehyde (0.067 g, 0.26 mmol) obtained in Preparation Example 139 was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (0.072 g, 84%).

¹H-NMR (CDCl₃) δ 7.20 (2H, m), 7.08 (1H, t), 6.66 (1H, m), 5.79 (1H, d), 4.14 (2H, q), 2.62 (2H, d), 1.37 (6H, s), 1.25 (3H, t).

Preparation Example 141: (E)-5-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-hex-2-enoic acid ethyl ester

(E)-5-(4-bromo-2-fluoro-phenyl)-5-methyl-hex-2-enoic acid ethyl ester (0.072 g, 0.22 mmol) obtained in Preparation Example 140 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.045 g, 54%).

¹H-NMR (CDCl₃) δ 7.47 (1H, d), 7.42 (1H, d), 7.23 (1H, t), 6.66 (1H, m), 5.75 (1H, d), 4.11 (2H, q), 2.65 (2H, d), 1.32 (18H, s), 1.23 (3H, t).

Preparation Example 142: 5-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-hexanoic acid ethyl ester

(E)-5-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-

hex-2-enoic acid ethyl ester (0.045 g, 0.12 mmol) obtained in Preparation Example 141 was reacted in the same manner as in Step E of Preparation Example 1 to obtain the title compound (0.02 g, 44%).

¹H-NMR (CDCl₃) δ 7.47 (1H, d), 7.38 (1H, d), 7.23 (1H, t), 4.06 (2H, q), 2.19 (2H, t), 1.75 (2H, m), 1.35 (20H, m), 1.21 (3H, t).

Preparation Example 143: 2-(4-bromo-2,6-difluoro-phenyl)-2-methyl-propionitrile

(4-Bromo-2,6-difluoro-phenyl)-acetonitrile (0.4 g, 1.72 mmol) obtained in Preparation Example 149 was dissolved in 2 mL of DMF and 2 mL of THF. NaH (60% in mineral oil, 0.152 g, 3.79 mmol) and iodomethane (0.236 mL, 3.79 mmol) were added thereto at 0°C, and the mixture was stirred at room temperature for 3 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.372 g, 83%).

¹H-NMR (CDCl₃) δ 7.12 (2H, m), 1.86 (6H, s).

Preparation Example 144: 2-(4-bromo-2,6-difluoro-phenyl)-2-methyl-propionaldehyde

2-(4-Bromo-2,6-difluoro-phenyl)-2-methyl-propionitrile (0.372 g, 1.43 mmol) obtained in Preparation Example 143 was reacted in the same manner as in Preparation Example 151 to obtain the title compound (0.328 g, 87%).

¹H-NMR (CDCl₃) δ 9.60 (1H, m), 7.08 (2H, m), 1.50 (6H, s).

Preparation Example 145: 3-(4-bromo-2,6-difluoro-phenyl)-3-methyl-butyraldehyde

2-(4-Bromo-2,6-difluoro-phenyl)-2-methyl-propionaldehyde (0.328 g, 1.25 mmol) obtained in Preparation Example 144 was reacted in the same manner as in Preparation Example 152 to obtain the title compound (0.16 g, 46%).

¹H-NMR (CDCl₃) δ 9.61 (1H, s), 7.01 (2H, m), 2.86 (2H, s), 1.54 (6H, s).

Preparation Example 146: (E)-5-(4-bromo-2,6-difluoro-phenyl)-5-methyl-hex-2-enoic acid ethyl ester

3-(4-Bromo-2,6-difluoro-phenyl)-3-methyl-butyraldehyde (0.16 g, 0.58 mmol) obtained in Preparation Example 145 was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (0.17 g, 85%).

¹H-NMR (CDCl₃) δ 6.98 (2H, m), 6.74 (1H, m), 5.78 (1H, d), 4.14 (2H, q), 2.64 (2H, d), 1.46 (6H, s), 1.25 (3H, t).

Preparation Example 147: 5-(4-bromo-2,6-difluoro-phenyl)-5-methyl-hexanoic acid ethyl ester

(E)-5-(4-bromo-2,6-difluoro-phenyl)-5-methyl-hex-2-enoic acid ethyl ester (0.17 g, 0.49 mmol) obtained in Preparation Example 146 was reacted in the same manner as in Preparation Example 174 to obtain the title compound (0.15 g, 87%).

¹H-NMR (CDCl₃) δ 6.96 (2H, m), 4.08 (2H, q), 2.23 (2H, t), 1.72 (2H, m), 1.43 (8H, m), 1.22 (3H, t).

Preparation Example 148: 5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-5-methyl-hexanoic acid ethyl ester

5-(4-Bromo-2,6-difluoro-phenyl)-5-methyl-hexanoic acid ethyl ester (0.15 g, 0.43 mmol) obtained in Preparation Example 147 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.07 g, 41%).

¹H-NMR (CDCl₃) δ 7.20 (2H, m), 4.08 (2H, q), 2.21 (2H, t), 1.75 (2H, m), 1.46 (8H, m), 1.32 (12H, s), 1.21 (3H, t).

Preparation Example 149: (4-bromo-2,6-difluoro-phenyl)-acetonitrile

5-Bromo-2-bromomethyl-1,3-difluoro-benzene (1.1 g, 3.85 mmol) was dissolved in 6 mL of ethanol and 2 mL of water. KCN (0.268 g, 4.12 mmol) was added thereto and heated to 60°C, and the mixture was stirred for 2 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.8 g, 89%).

¹H-NMR (CDCl₃) δ 7.17 (2H, m), 3.69 (2H, s).

Preparation Example 150: 1-(4-bromo-2,6-difluoro-phenyl)-cyclopropanecarbonitrile

(4-Bromo-2,6-difluoro-phenyl)-acetonitrile (0.4 g, 1.72 mmol) obtained in Preparation Example 149 was dissolved in 1 mL of toluene and 1.7 mL of 50% NaOH aqueous solution. 1-Bromo-2-chloroethane (0.287 mL, 3.44 mmol) and benzyltriethylammonium chloride (0.098 g, 0.43 mmol) were added thereto at 0°C, the mixture was heated to 40°C and stirred for 18 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.27 g, 60%).

¹H-NMR (CDCl₃) δ 7.12 (2H, m), 1.76 (2H, m), 1.36 (2H, m).

Preparation Example 151: 1-(4-bromo-2,6-difluoro-phenyl)-cyclopropanecarbaldehyde

1-(4-Bromo-2,6-difluoro-phenyl)-cyclopropanecarbonitrile (0.270 g, 1.05 mmol) obtained in Preparation Example 150 was dissolved in 5 mL of MC. DIBAL-H (0.77 mL, 1.15 mmol) was added thereto at -78°C, and the mixture was stirred for 2 hours and additionally stirred at room temperature for 1 hour. After addition of 1N HCl and KNa tartrate aqueous solution, the reaction solution was extracted with MC. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.216 g, 79%).

¹H-NMR (CDCl₃) δ 8.83 (1H, s), 7.10 (2H, m), 1.70 (2H, m), 1.46 (2H, m).

Preparation Example 152: [1-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-acetaldehyde

(Methoxymethyl)triphenylphosphonium chloride (0.425 g, 1.24 mmol) was dissolved in 3 mL of THF. LiHMDS (1.24 mL, 1.24 mmol) were added thereto at 0°C, and the mixture was stirred for 15 minutes. 1-(4-Bromo-2,6-difluoro-phenyl)-cyclopropanecarbaldehyde (0.216 g, 0.83 mmol) obtained in Preparation Example 151 was added thereto 0 °C, and the mixture was stirred at room temperature for 18 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography. The purified organic layer was dissolved in 2N HCl (0.2 M) and THF (0.1 M), and heated to 70°C, the mixture was stirred for 18 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title

compound (0.375 g, 84%).

¹H-NMR (CDCl₃) δ 9.77 (1H, s), 7.02 (2H, m), 2.49 (2H, d), 0.99 (4H, m).

Preparation Example 153: (E)-4-[1-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-but-2-enoic acid ethyl ester

[1-(4-Bromo-2,6-difluoro-phenyl)-cyclopropyl]-acetaldehyde (0.375 g, 1.36 mmol) obtained in Preparation Example 152 was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (0.443 g, 94%).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 6.90 (1H, m), 5.72 (1H, d), 4.15 (2H, q), 2.37 (2H, d), 1.27 (3H, t), 0.87 (4H, m).

Preparation Example 154: 4-[1-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-butyric acid ethyl ester

(E)-4-[1-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-but-2-enoic acid ethyl ester (0.443 g, 1.28 mmol) obtained in Preparation Example 153 was reacted in the same manner as in Preparation Example 174 to obtain the title compound (0.414 g, 93%).

¹H-NMR (CDCl₃) δ 7.02 (2H, m), 4.10 (2H, q), 2.26 (2H, t), 1.63 (2H, m), 1.50 (2H, m), 1.24 (3H, t), 0.79 (4H, s).

Preparation Example 155: 4-{1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropyl}-butyric acid ethyl ester

4-[1-(4-Bromo-2,6-difluoro-phenyl)-cyclopropyl]-butyric acid ethyl ester (0.414 g, 1.19 mmol) obtained in Preparation Example 154 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.322 g, 70%).

¹H-NMR (CDCl₃) δ 7.20 (2H, m), 4.08 (2H, q), 2.24 (2H, t), 1.62 (2H, m), 1.54 (2H, m), 1.32 (12H, s), 1.20 (3H, t), 0.80 (4H, m).

Preparation Example 156: 1-bromo-4-(2-bromo-1,1-difluoro-ethyl)-benzene

2-Bromo-1-(4-bromo-phenyl)-ethaneone (0.5 g, 1.8 mmol) was dissolved in 4 mL of MC. DAST (diethylaminosulfur trifluoride, 0.58 g, 3.6 mmol) was added thereto at 0°C, and the mixture was stirred at 0°C for 1 hour, at room temperature for 2 hours, and at 40°C for 4 hours. After addition of water, the reaction solution was extracted with MC. The organic

layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.345 g, 64%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.60 (2H, d), 7.38 (2H, d), 3.72 (2H, t).

Preparation Example 157: acetic acid 2-(4-bromo-phenyl)-2,2-difluoro-ethyl ester

1-Bromo-4-(2-bromo-1,1-difluoro-ethyl)-benzene (0.324 g, 1.08 mmol) obtained in Preparation Example 156 was dissolved in 4 mL of DMF. KOAc (0.424 g, 4.32 mmol) and 18-crown-6 (0.028 g, 0.11 mmol) were added thereto and heated to 80°C , and the mixture was stirred for 18 hours. After addition of water, the reaction solution was extracted with ether. The organic layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.216 g, 71%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.59 (2H, d), 7.38 (2H, d), 4.44 (2H, t), 2.06 (3H, s).

Preparation Example 158: 2-(4-bromo-phenyl)-2,2-difluoro-ethanol

Acetic acid 2-(4-bromo-phenyl)-2,2-difluoro-ethyl ester (0.21 g, 0.77 mmol) obtained in Preparation Example 157 was dissolved in 4 mL of ethanol and 1 mL of water. NaOH (0.062 g, 1.55 mmol) was added thereto, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.176 g, 96%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.59 (2H, d), 7.40 (2H, d), 3.96 (2H, m), 1.87 (1H, m).

Preparation Example 159: [2-(4-bromo-phenyl)-2,2-difluoro-ethoxy]-acetic acid ethyl ester

2-(4-Bromo-phenyl)-2,2-difluoro-ethanol (0.24 g, 1.01 mmol) obtained in Preparation Example 158 was reacted in the same manner as in Preparation Example 164 to obtain the title compound (0.24 g, 70%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.57 (2H, d), 7.42 (2H, d), 4.20 (2H, q), 4.18 (2H, s), 3.99 (2H, t), 1.26 (3H, t).

Preparation Example 160: {2,2-difluoro-2-[4-(4,4,5,5-tetramethyl-

[1,3,2]dioxaborolan-2-yl)-phenyl]-ethoxy}-acetic acid ethyl ester

[2-(4-Bromo-phenyl)-2,2-difluoro-ethoxy]-acetic acid ethyl ester (0.24 g, 0.74 mmol) obtained in Preparation Example 159 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.22 g, 80%).

¹H-NMR (CDCl₃) δ 7.86 (2H, d), 7.51 (2H, d), 4.20 (2H, q), 4.14 (2H, s), 4.00 (2H, t), 1.34 (12H, s), 1.25 (3H, t).

Preparation Example 161: (E)-4-(4-bromo-phenyl)-4,4-difluoro-but-2-enoic acid ethyl ester

2-(4-Bromo-phenyl)-2,2-difluoro-ethanol (0.5 g, 2.11 mmol) obtained in Preparation Example 158 was reacted in the same manner as in Step C of Preparation Example 4 to obtain the title compound (0.42 g, 65%).

¹H-NMR (CDCl₃) δ 7.59 (2H, d), 7.35 (2H, d), 6.95 (1H, m), 6.26 (1H, d), 4.23 (2H, q), 1.28 (3H, t).

Preparation Example 162: 4-(4-bromo-phenyl)-4,4-difluoro-butyric acid ethyl ester

(E)-4-(4-bromo-phenyl)-4,4-difluoro-but-2-enoic acid ethyl ester (0.42 g, 1.38 mmol) obtained in Preparation Example 161 was reacted in the same manner as in Preparation Example 174 to obtain the title compound (0.24 g, 57%).

¹H-NMR (CDCl₃) δ 7.56 (2H, d), 7.34 (2H, d), 4.11 (2H, q), 2.47 (4H, m), 1.22 (3H, t).

Preparation Example 163: 4-(4-bromo-phenyl)-4,4-difluoro-butan-1-ol

4-(4-Bromo-phenyl)-4,4-difluoro-butyric acid ethyl ester (0.244 g, 0.79 mmol) obtained in Preparation Example 162 was reacted in the same manner as in Step C of Preparation Example 90 to obtain the title compound (0.2 g, 95%).

¹H-NMR (CDCl₃) δ 7.56 (2H, d), 7.34 (2H, d), 3.66 (2H, m), 2.20 (2H, m), 1.70 (2H, m), 1.26 (1H, m).

Preparation Example 164: 4-(4-bromo-phenylsulfanyl)-butyric acid ethyl ester

4-Bromo-benzenethiol (0.5 g, 2.64 mmol) was dissolved in 5 mL of THF and cooled

to 0°C. NaH (60% in mineral oil, 0.11 g, 2.64 mmol) was added thereto, and the mixture was stirred for 30 minutes. 4-Bromo-butyric acid ethyl ester (0.42 mL, 2.91 mmol) was added thereto, and the mixture was stirred at room temperature for 4 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.80 g, 99 %).

¹H-NMR (CDCl₃) δ 7.38 (2H, d), 7.19 (2H, d), 4.13 (2H, q), 2.93 (2H, t), 2.43 (2H, t), 1.93 (2H, m), 1.24 (3H, t).

Preparation Example 165: methanesulfonic acid 4-(4-bromo-phenyl)-4,4-difluoro-butyl ester

4-(4-Bromo-phenyl)-4,4-difluoro-butan-1-ol (0.263 g, 0.99 mmol) obtained in Preparation Example 163 was reacted in the same manner as in Step B of Preparation Example 25 to obtain the title compound (0.28 g, 82%).

¹H-NMR (CDCl₃) δ 7.56 (2H, d), 7.32 (2H, d), 4.26 (2H, t), 3.00 (3H, s), 2.23 (2H, m), 1.94 (2H, m).

Preparation Example 166: 5-(4-bromo-phenyl)-5,5-difluoro-pentanenitrile

Methanesulfonic acid 4-(4-bromo-phenyl)-4,4-difluoro-butyl ester (0.28 g, 0.82 mmol) obtained in Preparation Example 165 was reacted in the same manner as in Step C of Preparation Example 25 to obtain the title compound (0.21 g, 94%).

¹H-NMR (CDCl₃) δ 7.58 (2H, d), 7.34 (2H, d), 2.42 (2H, t), 2.24 (2H, m), 1.87 (2H, m).

Preparation Example 167: 5-(4-bromo-phenyl)-5,5-difluoro-pentanoic acid

5-(4-Bromo-phenyl)-5,5-difluoro-pentanenitrile (0.21 g, 0.77 mmol) obtained in Preparation Example 166 was dissolved in 2 mL of ethanol and 2 mL of water. NaOH (0.107 g, 2.68 mmol) was added thereto, and the mixture was stirred for 3 hours under reflux. After addition of 1N HCl, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.26 g, 48 %).

¹H-NMR (CDCl₃) δ 7.56 (2H, d), 7.34 (2H, d), 2.41 (2H, t), 2.15 (2H, m), 1.78 (2H,

m).

Preparation Example 168: 5-(4-bromo-phenyl)-5,5-difluoro-pentanoic acid methyl ester

5-(4-Bromo-phenyl)-5,5-difluoro-pentanoic acid (0.212 g, 0.72 mmol) obtained in Preparation Example 167 was reacted in the same manner as in Step G of Preparation Example 81 to obtain the title compound (0.19 g, 85%).

¹H-NMR (CDCl₃) δ 7.57 (2H, d), 7.34 (2H, d), 3.66 (3H, s), 2.35 (2H, t), 2.15 (2H, m), 1.76 (2H, m).

Preparation Example 169: 5,5-difluoro-5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pentanoic acid methyl ester

5-(4-Bromo-phenyl)-5,5-difluoro-pentanoic acid methyl ester (0.190 g, 0.62 mmol) obtained in Preparation Example 168 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.13 g, 59%).

¹H-NMR (CDCl₃) δ 7.85 (2H, d), 7.46 (2H, d), 3.65 (3H, s), 2.34 (2H, t), 2.16 (2H, m), 1.76 (2H, m), 1.35 (12H, s).

Preparation Example 170: (E)-3-(4-bromo-2,6-difluoro-phenyl)-acrylic acid ethyl ester

4-Bromo-2,6-difluoro-benzaldehyde (1.52 g, 6.88 mmol) was reacted in the same manner as in Step A of Preparation Example 85 to obtain the title compound (1.3 g, 65%).

¹H-NMR (CDCl₃) δ 7.66 (1H, d), 7.13 (2H, m), 6.70 (1H, d), 4.27 (2H, q), 1.32 (3H, t).

Preparation Example 171: 2-(4-bromo-2,6-difluoro-phenyl)-cyclopropanecarboxylic acid ethyl ester

Trimethylsulfoxonium iodide (0.462 g, 2.10 mmol) was dissolved in 5 mL of DMSO. NaH (60% in mineral oil, 0.084 g, 2.10 mmol) was added thereto, and the mixture was stirred for 30 minutes. After cooling to 0°C, (E)-3-(4-bromo-2,6-difluoro-phenyl)-acrylic acid ethyl ester (0.51 g, 1.75 mmol) obtained in Preparation Example 170 was added thereto, and the mixture was stirred at room temperature for 4 hours. After addition of water, the reaction

solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.26 g, 48 %).

¹H-NMR (CDCl₃) δ 7.02 (2H, m), 4.19 (2H, q), 2.42 (1H, m), 2.14 (1H, m), 1.54 (2H, m), 1.28 (3H, t).

Preparation Example 172: [2-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-methanol

2-(4-Bromo-2,6-difluoro-phenyl)-cyclopropanecarboxylic acid ethyl ester (0.26 g, 0.85 mmol) obtained in Preparation Example 171 was reacted in the same manner as in Step C of Preparation Example 90 to obtain the title compound (0.17 g, 76%).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 3.70 (1H, m), 3.57 (1H, m), 1.66 (2H, m), 1.45 (1H, t), 1.19 (1H, m), 0.93 (1H, m).

Preparation Example 173: (E)-3-[2-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-acrylic acid ethyl ester

[2-(4-Bromo-2,6-difluoro-phenyl)-cyclopropyl]-methanol (0.314 g, 1.19 mmol) obtained in Preparation Example 172 was reacted in the same manner as in Step C of Preparation Example 4 to obtain the title compound (0.36 g, 91%).

¹H-NMR (CDCl₃) δ 7.00 (2H, m), 6.56 (1H, m), 5.93 (1H, d), 4.19 (2H, q), 2.04 (2H, m), 1.63 (1H, m), 1.28 (4H, m).

Preparation Example 174: 3-[2-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-propionic acid ethyl ester

(E)-3-[2-(4-bromo-2,6-difluoro-phenyl)-cyclopropyl]-acrylic acid ethyl ester (0.228 g, 0.69 mmol) obtained in Preparation Example 173 was dissolved in 5 mL of DME. p-Toluenesulfonylhydrazide (0.897 g, 4.82 mmol) were added thereto, and the mixture was stirred for 5 minutes under reflux. 4.9 mL of 1.4 M NaOAc solution was added thereto, and the mixture was stirred for 18 hours under reflux. The reaction solution was diluted with water and extracted with DCM to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.19 g, 82%).

¹H-NMR (CDCl₃) δ 6.99 (2H, m), 4.12 (2H, q), 2.48 (2H, t), 1.77 (1H, m), 1.67 (1H, m), 1.53 (1H, m), 1.32 (1H, m), 1.26 (3H, t), 1.12 (1H, m), 0.80 (1H, m).

Preparation Example 175: 3-{2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-cyclopropyl}-propionic acid ethyl ester

3-[2-(4-Bromo-2,6-difluoro-phenyl)-cyclopropyl]-propionic acid ethyl ester (0.190 g, 0.57 mmol) obtained in Preparation Example 174 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.183 g, 84%).

¹H-NMR (CDCl₃) δ 7.18 (2H, m), 4.14 (2H, q), 2.49 (2H, t), 1.77 (1H, m), 1.68 (2H, m), 1.38 (1H, m), 1.32 (12H, s), 1.24 (4H, m), 0.81 (1H, m).

Preparation Example 176: 8-(4-bromo-2-fluoro-phenyl)-1,4-dioxa-spiro[4.5]dec-7-ene

4-Bromo-2-fluoro-1-iodo-benzene (0.68 g, 2.25 mmol) and 8-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,4-dioxa-spiro[4.5]dec-7-ene (0.5 g, 1.88 mmol) were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.4 g, 68%).

¹H-NMR (CDCl₃) δ 7.20 (2H, m), 7.12 (1H, t), 5.84 (1H, m), 4.01 (4H, s), 2.58 (2H, m), 2.44 (2H, m), 1.88 (2H, t).

Preparation Example 177: 8-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1,4-dioxa-spiro[4.5]dec-7-ene

8-(4-Bromo-2-fluoro-phenyl)-1,4-dioxa-spiro[4.5]dec-7-ene (0.27 g, 0.86 mmol) obtained in Preparation Example 176 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.2 g, 64%).

¹H-NMR (CDCl₃) δ 7.50 (1H, m), 7.43 (1H, m), 7.27 (1H, m), 5.89 (1H, m), 4.02 (4H, s), 2.64 (2H, m), 2.48 (2H, m), 1.90 (2H, t), 1.34 (12H, s).

Preparation Example 178: 8-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1,4-dioxa-spiro[4.5]decane

8-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1,4-dioxa-spiro[4.5]dec-7-ene (0.2 g, 0.55 mmol) obtained in Preparation Example 177 was reacted in the same manner as in Step E of Preparation Example 1 to obtain the title compound (0.17 g, 84%).

¹H-NMR (CDCl₃) δ 7.52 (1H, m), 7.43 (1H, m), 7.28 (1H, m), 3.98 (4H, s), 2.94 (1H, m), 1.87-1.68 (8H, m), 1.33 (12H, s).

Preparation Example 179: 2-cyclopentyloxy-3-[4-(1,4-dioxaspiro[4.5]dec-8-yl)-3-fluoro-phenyl]-pyridine

8-[2-Fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-1,4-dioxaspiro[4.5]decane (0.17 g, 0.47 mmol) obtained in Preparation Example 178 and 2-cyclopentyloxy-3-iodo-pyridine (0.2 g, 0.7 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.113 g, 60%).

¹H-NMR (CDCl₃) δ 8.12 (1H, m), 7.58 (1H, m), 7.28 (3H, m), 6.90 (1H, m), 3.99 (4H, s), 2.94 (1H, m), 1.89-1.72 (14H, m), 1.54 (2H, m).

Preparation Example 180: 4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexanone

2-Cyclopentyloxy-3-[4-(1,4-dioxaspiro[4.5]dec-8-yl)-3-fluoro-phenyl]-pyridine (0.113 g, 0.28 mmol) obtained in Preparation Example 179 was added to 1N HCl (0.15 mL) dissolved in 3 mL of THF and stirred at room temperature for 16 hours. The reaction solution was diluted with sodium bicarbonate solution and extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.048 g, 48 %).

¹H-NMR (CDCl₃) δ 8.14 (1H, m), 7.58 (1H, m), 7.30 (2H, m), 7.25 (1H, m), 6.92 (1H, m), 5.51 (1H, m), 3.37 (1H, m), 2.53 (4H, m), 2.25 (2H, m), 1.97 (4H, m), 1.75 (4H, m), 1.62 (2H, m).

Preparation Example 181: {4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexylidene}-acetic acid ethyl ester

4-[4-(2-Cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexanone (0.045 g, 0.13 mmol) obtained in Preparation Example 180 was reacted in the same manner as in Step C of Preparation Example 1 to obtain the title compound (0.045 g, 83%).

¹H-NMR (CDCl₃) δ 8.13 (1H, m), 7.59 (1H, m), 7.29 (2H, m), 7.20 (1H, m), 6.91 (1H, m), 5.70 (1H, s), 5.52 (1H, m), 4.16 (2H, q), 4.00 (1H, m), 3.17 (1H, m), 2.42 (2H, m), 2.10 (3H, m), 1.95 (2H, m), 1.84-1.62 (8H, m), 1.30 (3H, t).

Preparation Example 182: {4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexyl}-acetic acid ethyl ester

{4-[4-(2-Cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexylidene}-acetic acid ethyl ester (0.045 g, 0.11 mmol) obtained in Preparation Example 181 was reacted in the same manner as in Step E of Preparation Example 1 to obtain the title compound (0.045 g, 99%).

¹H-NMR (CDCl₃) δ 8.13 (1H, m), 7.60 (1H, m), 7.27 (3H, m), 6.91 (1H, m), 5.51 (1H, m), 4.15 (2H, q), 2.85 (1H, m), 2.49-2.25 (2H, m), 1.95-1.59 (16H, m), 1.26 (3H, t), 1.22 (1H, m).

Preparation Example 183: 4-{{2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl}-methyl-amino}-butyric acid methyl ester

3,4,5-Trifluoronitrobenzene (9.4 g, 53 mmol) and hydrochloric acid salt of 4-methylamino-butyric acid methyl ester (8.9 g, 53 mmol) were reacted in the same manner as in Preparation Example 84 to obtain the title compound (10 g, 51 %).

¹H-NMR (CDCl₃) δ 7.24 (2H, d), 3.64 (3H, s), 3.16 (2H, t), 2.88 (3H, m), 2.36 (2H, t), 1.85 (2H, m), 1.31(12H, s)

Preparation Example 184: 4-[5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indol-1-yl]-butyric acid ethyl ester

5-Bromo-1H-indole (0.10 g, 0.51 mmol) and 4-bromo-butyric acid ethyl ester (0.10 g, 0.51 mmol) were reacted in the same manner as in Preparation Example 3 to obtain the title compound (0.060 g, 33 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, s), 7.65 (1H, d), 7.34 (1H, d), 7.07 (1H, d), 6.51 (1H, d), 4.21 (2H, t), 4.11 (2H, m), 2.25 (2H, t), 2.14 (2H, m), 1.36 (12H, s), 1.24 (3H, t)

Preparation Example 185: 2-bromo-6-cyclopentyloxy-pyridine

Cyclopentanol (0.077 mL, 0.84 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.09 g, 44%).

¹H-NMR (CDCl₃) δ 7.36(1H, t), 7.00(1H, d), 6.60(1H, d), 5.36 (1H, m), 1.98(2H, m), 1.77 (4H, m), 1.61(2H, m)

Preparation Example 186: 2-bromo-6-cyclobutoxy-pyridine

Cyclobutanol (0.06 mL, 0.84 mmol) and 2,6-dibromopyridine (0.2 g, 0.84 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (0.06 g, 31%).

¹H-NMR (CDCl₃) δ 7.39(1H, t), 7.01(1H, d), 6.61(1H, d), 5.14(1H, m), 2.45 (2H, m), 2.11 (2H, m), 1.82 (1H, m), 1.65(1H, m)

Preparation Example 187: 4-{{2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl}-methyl-amino}-butyric acid methyl ester

3,4-Difluoronitrobenzene (1.30 g, 8.17 mmol) and hydrochloric acid salt of 4-methylamino-butyric acid methyl ester (1.64 g, 9.81 mmol) were reacted in the same manner as in Preparation Example 84 to obtain the title compound (0.25 g, 8.7 %).

¹H-NMR (CDCl₃) δ 7.45 (1H, m), 7.40 (1H, m), 6.83 (1H, m), 3.65 (3H, s), 3.25 (2H, t), 2.86 (3H, s), 2.36 (2H, t), 1.91 (2H, m), 1.31 (12H, s)

Preparation Example 188: 4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluorophenylamine

2-Cyclopentylsulfanyl-3-iodo-pyridine (0.70 g, 2.29 mmol) obtained in Preparation Example 15 and 2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.59 g, 2.29 mmol) obtained in Preparation Example 66 were reacted in the same manner as in Preparation Example 67 to obtain the title compound (0.40 g, 57 %).

¹H-NMR (CDCl₃) δ 8.40 (1H, m), 7.31 (1H, m), 6.99 (1H, m), 6.93 (2H, m), 4.07 (1H, m), 3.82 (2H, s), 2.19 (2H, m), 1.71 (2H, m), 1.61 (4H, m)

Preparation Example 189: 4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenylamine

2-Cyclopentylsulfanyl-3-iodo-pyridine (1.2 g, 3.9 mmol) obtained in Preparation Example 15 and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.86 g, 3.9 mmol) were reacted in the same manner as in Preparation Example 67 to obtain the title compound (1.0 g, 94 %).

¹H-NMR (CDCl₃) δ 8.37 (1H, m), 7.33 (1H, m), 7.23 (2H, d), 7.00 (1H, m), 6.74 (2H, d), 4.08 (1H, m), 3.76 (2H, s), 2.19 (2H, m), 1.70 (2H, m), 1.59 (4H, m)

Preparation Example 190: 4-{[2,6-difluoro-4-(2-fluoro-pyridin-3-yl)-phenyl]-methyl-amino}-butyric acid methyl ester

2-Fluoro-3-iodo-pyridine (0.20 g, 0.90 mmol) and 4-{[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-methyl-amino}-butyric acid methyl ester (0.33 g, 0.90 mmol) obtained in Preparation Example 183 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.25 g, 82 %).

¹H-NMR (CDCl₃) δ 8.20 (1H, m), 7.82 (1H, m), 7.28 (1H, m), 7.09 (2H, m), 3.66 (3H, s), 3.18 (2H, t), 2.90 (3H, s), 2.40 (2H, t), 1.88 (2H, m), 1.59 (4H, m)

Preparation Example 191: 1-(2-iodo-phenyl)-pyrrolidine

Step A: 2-pyrrolidin-1-yl-phenylamine

Fluoro-2-nitro-benzene (0.70 g, 4.96 mmol) and pyrrolidine (0.42 g, 5.95 mmol) were sequentially reacted in the same manner as in Steps A and B of Preparation Example 84 to obtain the title compound (0.70 g, 87 %).

Step B: 1-(2-iodo-phenyl)-pyrrolidine

2-Pyrrolidin-1-yl-phenylamine (0.70 g, 4.31 mmol) obtained in Step A⁰¹ was added to 19 mL of water and cooled to 0°C. 5 mL of sulfuric acid 5 mL was added, and sodium nitrite (0.30 g, 4.31 mmol) dissolved in water was then slowly added thereto. While maintaining the temperature, the mixture was stirred for 30 minutes. Potassium iodide (0.93 g, 5.60 mmol) dissolved in 10 mL of water was added thereto. The temperature was increased to 60°C, and the mixture was stirred for 3 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.18 g, 12 %).

¹H-NMR (CDCl₃) δ 7.83 (1H, m), 7.25 (1H, m), 6.95 (1H, m), 6.67 (1H, m), 3.29 (4H, m), 1.94 (4H, m)

Preparation Example 192: (2-iodo-phenyl)-methyl-amine

Fluoro-2-nitro-benzene (1.00 g, 7.09 mmol) and methylamine hydrochloride (0.57 g, 8.50 mmol) were reacted in the same manner as in Preparation Example 191 to obtain the title compound (0.35 g, 21 %).

¹H-NMR (CDCl₃) δ 7.65 (1H, m), 7.25 (1H, m), 6.57 (1H, m), 6.46 (1H, m), 4.20 (1H,

s), 2.89 (3H, d)

Preparation Example 193: (2-iodo-phenyl)-isopropyl-methyl-amine

Fluoro-2-nitro-benzene (1.30 g, 9.21 mmol) and isopropyl-methyl-amine (0.81 g, 11.1 mmol) were reacted in the same manner as in Preparation Example 191 to obtain the title compound (0.35 g, 14 %).

¹H-NMR (CDCl₃) δ 7.85 (1H, m), 7.28 (1H, m), 7.06 (1H, m), 6.77 (1H, m), 3.48 (1H, m), 2.62 (3H, s), 1.12 (6H, d)

Preparation Example 194: 4-{{[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-ethyl-amino}-butyric acid methyl ester

3,4,5-Trifluoronitrobenzene (0.68 g, 3.84 mmol) and hydrochloric acid salt of 4-ethylamino-butyric acid methyl ester (0.58 g, 3.20 mmol) were reacted in the same manner as in Preparation Example 84 to obtain the title compound (0.38 g, 31 %).

¹H-NMR (CDCl₃) δ 7.25 (2H, m), 3.63 (3H, s), 3.18 (4H, m), 2.35 (2H, t), 1.74 (2H, m), 1.32 (12H, s), 1.02 (3H, t)

Preparation Example 195: (R)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hexanoic acid ethyl ester

Step A: (E)-3-(4-bromo-2,6-difluoro-phenyl)prop-2-enoic acid ethyl ester

4-Bromo-2,6-difluoro-benzaldehyde (2.0 g, 13.6 mmol) and (1-ethoxycarbonyl-ethylidene)triphenylphosphorane (5.7 g, 16.3 mmol) were reacted in the same manner as in Step B of Preparation Example 27 to obtain the title compound (3.9 g, 99 %).

Step B: (E)-3-(4-bromo-2,6-difluoro-phenyl)-acrylic acid

(E)-3-(4-bromo-2,6-difluoro-phenyl)prop-2-enoic acid ethyl ester (1.13 g, 3.88 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (1.0 g, 98 %).

Step C: (R)-3-[(E)-3-(4-bromo-2,6-difluoro-phenyl)-acryloyl]-4-phenyl-oxazolidin-2-one

(E)-3-(4-bromo-2,6-difluoro-phenyl)-acrylic acid (0.50 g, 1.9 mmol) obtained in Step

B was dissolved in 10 mL of THF and cooled to -78°C. Trimethylacetyl chloride (0.29 g, 2.4 mmol) was added thereto, and the mixture was stirred for 15 minutes. (R)-4-phenyl-oxazolidin-2-one (0.42 g, 2.6 mmol) was dissolved in 10 mL of THF and cooled to -78°C, and n-butyllithium (1.16 mL, 2.7 mmol) was then added thereto. This solution was added to the first solution by the use of a cannula. While maintaining the temperature, the mixture was stirred for 1.5 hours. The temperature was increased to room temperature, and the mixture was stirred for 16 hours. After termination of the reaction by the use of saturated ammonium chloride solution, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.50 g, 64 %).

Step D: (R)-3-[(R)-3-(4-bromo-2,6-difluoro-phenyl)-butyryl]-4-phenyl-oxazolidin-2-one

CuBr-DMS (1.18 g, 5.7 mmol) was added to 10 mL of THF and stirred at -40 °C for 30 minutes. DMS (3.38 g, 54.4 mmol) and methylmagnesium bromide (1.74 mL, 5.2 mmol) was added thereto, and the mixture was stirred for 30 minutes. The temperature was increased to -20°C, and (R)-3-[(E)-3-(4-bromo-2,6-difluoro-phenyl)-acryloyl]-4-phenyl-oxazolidin-2-one (0.52 g, 1.3mmol) obtained in Step C was dissolved in 3 mL of THF and slowly added thereto. While maintaining the temperature, the mixture was stirred for 2.5 hours. The temperature was slowly increased to room temperature, and the mixture was stirred at room temperature for 72 hours. After termination of the reaction by the use of saturated ammonium chloride solution, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.33 g, 61 %).

Step E: (E)-(R)-5-(4-bromo-2,6-difluoro-phenyl)-hex-2-enoic acid ethyl ester

(R)-3-[(R)-3-(4-bromo-2,6-difluoro-phenyl)-butyryl]-4-phenyl-oxazolidin-2-one (0.33 g, 0.78 mmol) obtained in Step D was sequentially reacted in the same manner as in Preparation Example 151 and Step A of Preparation Example 85 to obtain the title compound (0.11 g, 42 %).

Step F: (R)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-

hexanoic acid ethyl ester

(E)-(R)-5-(4-bromo-2,6-difluoro-phenyl)-hex-2-enoic acid ethyl ester (0.15 g, 0.45 mmol) obtained in Step E was sequentially reacted in the same manner as in Steps G and H of Preparation Example 5 to obtain the title compound (0.070 g, 40 %).

¹H-NMR (CDCl₃) δ 7.22(2H, m), 4.08(2H, q), 3.21(1H, m), 2.24(2H, m), 1.80(1H, m), 1.65(1H, m), 1.60(1H, m), 1.45(1H, m), 1.30(15H, m), 1.20(3H, t)

Preparation Example 196: (E)-(R)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hex-2-enoic acid ethyl ester

(E)-(R)-5-(4-bromo-2,6-difluoro-phenyl)-hex-2-enoic acid ethyl ester (0.11 g, 0.33 mmol) obtained in Step E of Preparation Example 195 was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.10 g, 80 %).

¹H-NMR (CDCl₃) δ 7.24 (2H, m), 6.84 (1H, m), 5.80 (1H, m), 4.15 (2H, m), 3.40 (1H, m), 2.66 (2H, m), 1.30 (18H, m)

Preparation Example 197: (S)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-hexanoic acid ethyl ester

Step A: (S)-3-[(E)-3-(4-bromo-2,6-difluoro-phenyl)-acryloyl]-4-phenyl-oxazolidin-2-one

(E)-3-(4-bromo-2,6-difluoro-phenyl)-acrylic acid (1.03 g, 3.9 mmol) obtained in Step B of Preparation Example 195 and (S)-4-phenyl-oxazolidin-2-one (0.86 g, 5.3 mmol) were reacted in the same manner as in Step C of Preparation Example 195 to obtain the title compound (1.30 g, 81 %).

Step B: (S)-3-[(S)-3-(4-bromo-2,6-difluoro-phenyl)-butyryl]-4-phenyl-oxazolidin-2-one

(S)-3-[(E)-3-(4-bromo-2,6-difluoro-phenyl)-acryloyl]-4-phenyl-oxazolidin-2-one (1.30 g, 3.2 mmol) obtained in Step A of Preparation Example 197 was reacted in the same manner as in Step D of Preparation Example 195 to obtain the title compound (1.0 g, 74 %).

Step C: (E)-(S)-5-(4-bromo-2,6-difluoro-phenyl)-hex-2-enoic acid ethyl ester

(S)-3-[(S)-3-(4-bromo-2,6-difluoro-phenyl)-butyryl]-4-phenyl-oxazolidin-2-one (0.70

g, 1.6 mmol) obtained in Step B Preparation Example 197 was reacted in the same manner as in Step E of Preparation Example 195 to obtain the title compound (0.50 g, 91 %).

Step D: (S)-5-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenyl]-hexanoic acid ethyl ester

((E)-(S)-5-(4-bromo-2,6-difluoro-phenyl)-hex-2-enoic acid ethyl ester (0.37 g, 1.12 mmol) obtained in Step C of Preparation Example 197 was reacted in the same manner as in Step F of Preparation Example 195 to obtain the title compound (0.16 g, 37 %).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 7.22(2H, m), 4.08(2H, q), 3.21(1H, m), 2.24(2H, m), 1.80(1H, m), 1.65(1H, m), 1.60(1H, m), 1.45(1H, m), 1.30(15H, m), 1.20(3H, t)

Preparation Example 198: 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester

Step A: 2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol

4-Bromo-2-fluorophenol (1.9 g, 9.9 mmol), bis(pinacolato)diboron (2.9 g, 11.4 mmol), potassium acetate (3.90 g, 39.7 mmol) and DPPF (0.27 g, 0.49 mmol) were dissolved in 32 mL of 1,4-dioxane, and charged with N_2 gas for 5 minutes. $\text{PdCl}_2(\text{dppf})\text{-DCM}$ (0.4 g, 0.49 mmol) was added thereto, and the mixture was stirred for 4 hours under reflux stirred. The reaction solution was filtered through Celite and purified by column chromatography to obtain the title compound (2.2 g, 93 %).

$^1\text{H NMR}$ (CDCl_3) δ 7.49 (2H, m), 6.98 (1H, t), 5.31 (1H, brs), 1.33 (12H, s)

Step B: 4-[2-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester

2-Fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.56 g, 2.3 mmol) obtained in Step A, 4-bromo-butyric acid ethyl ester (0.34 mL, 2.3 mmol) and Cs_2CO_3 (0.92 g, 2.8 mmol) were dissolved in 8 mL of DMF, and stirred at room temperature for 16 hours. The reaction solution was concentrated and purified by column chromatography to obtain the title compound (0.52 g, 63 %).

$^1\text{H NMR}$ (CDCl_3) δ 7.49 (2H, m), 6.93 (1H, t), 4.15 (2H, t), 4.10 (2H, q), 2.53 (2H, t), 2.15 (2H, m), 1.33 (12H, s), 1.25 (3H, t)

Preparation Example 199: 6-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-heptanoic acid ethyl ester

1-(4-Bromo-2,6-difluoro-phenyl)ethaneone (2.50 g, 10.6 mmol) obtained in Step C of Preparation Example 32 and (methoxymethyl)triphenylphosphonium chloride (4.38 g, 12.8 mmol) were sequentially reacted in the same manner as in Preparation Example 152, Step A of Preparation Example 85, Step B of Preparation Example 70, Step C of Preparation Example 4, Step C of Preparation Example 26 and Step D of Preparation Example 26 to obtain the title compound (0.50 g, 13 %).

¹H-NMR (CDCl₃) δ 7.23 (2H, m), 4.09 (2H, m), 3.22 (1H, m), 2.22 (2H, t), 1.77 (1H, m), 1.61 (5H, m), 1.33 (18H, s)

Preparation Example 200: 4-[3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy]-butyric acid ethyl ester

3-Bromo-phenol (0.75 g, 4.34 mmol) and 4-bromo-butyric acid ethyl ester (1.01 g, 5.20 mmol) were reacted in the same manner as in Preparation Example 3 to obtain the title compound (1.1 g, 76 %).

¹H-NMR (CDCl₃) δ 7.37 (1H, d), 7.31 (2H, m), 6.99 (1H, m), 4.14 (2H, m), 4.03 (2H, t), 2.52 (2H, t), 2.11 (2H, m), 1.33 (12H, s), 1.27 (3H, t)

Preparation Example 201: 5-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pentanoic acid ethyl ester

4-Bromo-2-fluoro-benzaldehyde (0.40 g, 1.97 mmol) and ethyl(triphenylphosphoranylidene)acetaldehyde (0.66 g, 2.17 mmol) were reacted in the same manner as in Preparation Example 27 to obtain the title compound (0.35 g, 51 %).

¹H-NMR (CDCl₃) δ 7.48 (1H, d), 7.42 (1H, d), 7.17 (1H, t), 4.12 (2H, m), 2.68 (2H, t), 2.33 (2H, t), 1.67 (4H, m), 1.34 (12H, s), 1.25 (3H, t)

Preparation Example 202: 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylsulfanyl]-butyric acid ethyl ester

4-(4-Bromo-phenylsulfanyl)-butyric acid ethyl ester (0.83 g, 2.7 mmol) obtained in Preparation Example 164 and bis(pinacolato)diboron (0.76 g, 3.0 mmol) were reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.73 g, 75%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.70 (2H, d), 7.27 (2H, d), 4.11 (2H, q), 2.99 (2H, t), 2.44 (2H, t), 1.96 (2H, m), 1.32 (12H, s), 1.24 (3H, t).

Preparation Example 203: 4-bromo-2-fluoro-benzenethiol

Step A: 4-bromo-2-fluoro-benzenesulfonyl chloride

4-Bromo-2-fluoroaniline (1 g, 5.26 mmol) was reacted in the same manner as in Step A of Preparation Example 206 to obtain the title compound (0.49 g, 34%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.85 (1H, m), 7.55 (2H, m).

Step B: 4-bromo-2-fluoro-benzenethiol

4-Bromo-2-fluoro-benzenesulfonyl chloride (0.49 g, 1.79 mmol) obtained in Step A was reacted in the same manner as in Step B of Preparation Example 206 to obtain the title compound (0.37 g, 99%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.23 (1H, m), 7.16 (2H, m), 3.57 (1H, s).

Preparation Example 204: 4-(4-bromo-2-fluoro-phenylsulfanyl)-butyric acid ethyl ester

4-Bromo-2-fluoro-benzenethiol (0.37 g, 1.81 mmol) obtained in Preparation Example 203, NaH (60% in mineral oil, 0.07 g, 1.81 mmol) and 4-bromo-butyric acid ethyl ester (0.28 mL, 1.99 mmol) were reacted in the same manner as in Preparation Example 164 to obtain the title compound (0.43 g, 75 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.23 (3H, m), 4.12 (2H, q), 2.92 (2H, t), 2.44 (2H, t), 1.90 (2H, m), 1.25 (3H, t).

Preparation Example 205: 4-[2-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylsulfanyl]-butyric acid ethyl ester

4-(4-Bromo-2-fluoro-phenylsulfanyl)-butyric acid ethyl ester (0.43 g, 1.36 mmol) obtained in Preparation Example 204 and bis(pinacolato)diboron (0.34 g, 1.50 mmol) were reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.27 g, 53%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.50 (1H, d), 7.43 (1H, d), 7.32 (1H, t), 4.11 (2H, q), 2.98 (2H, t), 2.45 (2H, t), 1.93 (2H, m), 1.33 (12H, s), 1.24 (3H, t).

Preparation Example 206: 4-bromo-2,6-difluoro-benzenethiol**Step A: 4-bromo-2,6-difluoro-benzenesulfonyl chloride**

CuCl₂ (0.77 g, 5.77 mmol) was dissolved in 200 mL of water. SOCl₂ (29 mL, 0.40 mol) was added thereto at 0°C, and the mixture was stirred at room temperature for 18 hours. 4-Bromo-2,6-difluoroaniline (20 g, 0.096 mol) was dissolved in 240 mL of HCl and 900 mL of water, and the solution in which NaNO₂ (7 g, 0.10 mol) was dissolved in 200 mL of water was added thereto at 0°C. The above thionyl chloride solution was added thereto, and the reaction was carried out at room temperature for 1 hour to obtain the title compound (24 g, 85 %) in a solid form.

Step B: 4-bromo-2,6-difluoro-benzenethiol

4-Bromo-2,6-difluoro-benzenesulfonyl chloride (24 g, 0.08 mol) obtained in Step A was dissolved in 270 mL of THF. PPh₃ (75 g, 0.28 mol) was added thereto, and the mixture was stirred at room temperature for 15 minutes. After addition of water, the mixture was stirred at room temperature for 18 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (15 g, 83 %).

¹H-NMR (CDCl₃) δ 7.10 (2H, d), 3.58 (1H, s).

Preparation Example 207: 4-(4-bromo-2,6-difluoro-phenylsulfanyl)-butyric acid ethyl ester

4-Bromo-2,6-difluoro-benzenethiol (15 g, 0.066 mol) obtained in Preparation Example 206, NaH (60% in mineral oil, 2.6 g, 0.066 mol) and 4-bromo-butyric acid ethyl ester (10 mL, 0.073 mol) were reacted in the same manner as in Preparation Example 164 to obtain the title compound (18.56 g, 82 %).

¹H-NMR (CDCl₃) δ 7.11 (2H, d), 4.11 (2H, q), 2.90 (2H, t), 2.43 (2H, t), 1.82 (2H, m), 1.24 (3H, t).

Preparation Example 208: 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylsulfanyl]-butyric acid ethyl ester

4-(4-Bromo-2,6-difluoro-phenylsulfanyl)-butyric acid ethyl ester (11.6 g, 0.034 mol)

obtained in Preparation Example 207 and bis(pinacolato)diboron (9.5 g, 0.038 mol) were reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (10.6 g, 80%).

$^1\text{H-NMR}$ (CDCl_3) δ 7.30 (2H, d), 4.09 (2H, q), 2.94 (2H, t), 2.43 (2H, t), 1.83 (2H, m), 1.33 (12H, s), 1.22 (3H, t).

Preparation Example 209: 3-iodo-2-(oxetan-3-yloxy)-pyridine

Oxetan-3-ol (0.93 g, 12.6 mmol) and 2-fluoro-3-iodo-pyridine (1.40 g, 6.30 mmol) were reacted in the same manner as in Preparation Example 34 to obtain the title compound (1.60 g, 92 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.05 (2H, m), 6.67 (1H, m), 5.61 (1H, m), 5.01 (2H, t), 4.79 (2H, m)

Preparation Example 210: 7-bromo-5-chloro-2,2-dimethyl-2,3-dihydro-benzofuran

The title compound was obtained by the method disclosed in WO 2009/119088 A1.

$^1\text{H NMR}$ (CDCl_3) δ 7.25 (2H, s), 7.02 (1H, m), 3.06 (2H, s), 1.50 (6H, s)

Preparation Example 211: 4-bromo-7-methoxy-2,2-dimethyl-2,3-dihydro-benzofuran

The title compound was obtained by the method disclosed in WO 2005/075456 A1.

$^1\text{H NMR}$ (CDCl_3) δ 6.94 (1H, d), 6.67 (1H, d), 3.88 (3H, s), 3.08 (2H, s), 1.57 (6H, s)

Preparation Example 212: 7-bromospiro[3H-benzofuran-2,1'-cyclopentan]

The title compound was obtained by the method disclosed in WO 2011/159297 A1.

$^1\text{H NMR}$ (CDCl_3) δ 7.23 (1H, d), 7.04 (1H, d), 6.67 (1H, t), 3.23 (2H, s), 2.14 (2H, m), 1.93 (2H, m), 1.72 (4H, m)

Preparation Example 213: 5-fluoro-7-iodo-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester

Step A: 5-fluoro-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester

The title compound was obtained by the method disclosed in US 2013/0109734 A1.

¹H-NMR (CDCl₃) δ 7.71 (1H, brs), 6.83 (2H, m), 3.84 (3H, s), 2.99 (2H, s), 1.55 (6H, s)

Step B: 5-fluoro-7-iodo-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester

5-fluoro-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester (0.1 g, 0.45 mmol) obtained in Step A was dissolved in 3 mL of THF and cooled to -78°C. 1.7M *tert*-butyllithium pentane solution (0.7 mL, 1.16 mmol) was added dropwise thereto, and the mixture was stirred at -78°C for 1 hour. 1,2-Diiodo-ethane (0.38 g, 1.35 mmol) was dissolved in 1 mL of THF and slowly added dropwise thereto, and the mixture was stirred at -78°C for 30 minutes. The temperature was increased to room temperature, and the mixture was additionally stirred for 1 hour. After termination of the reaction by the addition of sodium thiosulfate aqueous solution and sodium bicarbonate aqueous solution, the reaction solution was extracted with ethyl acetate to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.074 g, 47 %).

¹H-NMR (CDCl₃) δ 7.78 (1H, brs), 6.89 (1H, t), 3.88 (3H, s), 3.00 (2H, s), 1.61 (6H, s)

Preparation Example 214: 5-fluoro-4-iodo-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester

5-Fluoro-2,2-dimethyl-2,3-dihydro-indol-1-carboxylic acid methyl ester (0.26 g, 1.16 mmol) obtained in Step A of Preparation Example 213 was dissolved in 10 mL of THF. TMEDA (0.8 mL, 5.22 mmol) was added dropwise thereto and cooled to -78°C. 1.4M *sec*-BuLi hexane solution (2.5 mL, 3.49 mmol) was added dropwise thereto, and the mixture was stirred at -78°C for 1 hour. 1,2-Diiodo-ethane (0.38 g, 1.35 mmol) was dissolved in 5 mL of THF and slowly added dropwise thereto. The mixture was stirred at -78°C for 30 minutes. The temperature was increased to room temperature, and the mixture was additionally stirred for 1.5 hours. After termination of the reaction by the addition of sodium thiosulfate aqueous solution and sodium bicarbonate aqueous solution, the reaction solution was extracted with ethyl acetate to separate an organic layer. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.170 g, 42 %).

¹H-NMR (CDCl₃) δ 7.35 (1H, dd), 6.86 (1H, dd), 3.81 (3H, s), 2.96 (2H, s), 1.48 (6H, s)

Preparation Example 215: 4-iodospiro[1,3-benzodioxol-2,1'-cyclopentan]**Step A: 1-iodo-2,3-dimethoxy-benzene**

1,2-Dimethoxybenzene (500 mg, 3.62 mmol) was dissolved in THF (5 mL) and cooled to 0-5°C. n-BuLi (2.5 M in Hexane, 1.6 mL, 3.98 mmol) was slowly added dropwise thereto, and the mixture was stirred at 0-5°C for 2 hours and cooled to -78°C. I₂ (1.01 g, 3.98 mmol)/THF (5 mL) solution was slowly added thereto, and the mixture was stirred at room temperature for 2 hours and concentrated under reduced pressure. The concentrated solution was diluted with saturated NaHCO₃ solution, extracted with DCM and separated. The extract solution was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (620 mg, 65 % yield).

¹H NMR (500 MHz, CDCl₃) δ 7.36-7.32(m, 1H), 6.90-6.86(m, 1H), 6.79(dd, 1H), 3.85(s, 3H), 3.83(s, 3H)

Step B: 3-iodo-benzene-1,2-diol

1-Iodo-2,3-dimethoxy-benzene (0.62 g, 2.35 mmol) obtained in Step A was dissolved in DCM (3 mL) and cooled to 0-5°C. 1M BBr₃ (7.04 mL, 7.05 mmol) was added thereto, and the mixture was stirred at room temperature for 3 hours stirred. After termination of the reaction, the reaction solution was cooled to -20°C and diluted by slowly adding ethanol. The mixture was stirred at room temperature for 30 minutes. Saturated NaHCO₃ aqueous solution was added thereto, and the reaction solution was extracted with DCM. The organic layer was dried with anhydrous magnesiumsulfate, concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (0.12 g, 22 % yield).

¹H NMR (500 MHz, CDCl₃) δ 7.18(d, 1H), 6.87(d, 1H), 6.60(dd, 1H), 5.64(s, br, 2H)

Step C: 4-iodospiro[1,3-benzodioxol-2,1'-cyclopentane]

Toluene (5 mL) was added to 3-iodo-benzene-1,2-diol (60 mg, 0.254 mmol) obtained in Step B. Cyclopentanone (0.025 mL, 0.28 mmol) and p-TsOH.H₂O (catalytic amount) were added thereto, and the mixutre was stirred at 130-140°C for 12 hours by the use of a Dean-Stark appratus. After termination of the reaction, the reaction solution was cooled. After addition of saturated NaHCO₃ solution, the reaction solution was extracted with EtOAc to separate an

organic layer. The organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/4) to obtain the title compound (25 mg, 33 %).

^1H NMR (500 MHz, CDCl_3) δ 7.08(d, 1H), 6.68(d, 1H), 6.55(dd, 1H), 2.20-2.06(m, 4H), 1.90-1.79(m, 4H)

Preparation Example 216: 2-bromo-3-iodophenol

Step A: 2-bromo-3-methoxy-phenylamine

2-Bromo-1-methoxy-3-nitrobenzene (1 g, 4.31 mmol), Fe (1.68 g, 30.17 mmol) and NH_4Cl (1.61 g, 30.17 mmol) were dissolved in THF (4 mL)/MeOH (4 mL)/ H_2O (2 mL) solution and stirred for 1 hour under reflux. After termination of the reaction, the reaction solution was cooled to room temperature, diluted with saturated NaHCO_3 solution and extracted with EtOAc. The extract solution was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/5) to obtain the title compound (0.83 g, 95 % yield).

^1H NMR (500 MHz, CDCl_3) δ 7.05(dd, 1H), 6.42(d, 1H), 6.31(d, 1H), 3.86(s, 3H)

Step B: 2-bromo-1-iodo-3-methoxybenzene

35% HCl (3 mL) and ice (3 g) were added to 2-bromo-3-methoxy-phenylamine (0.83 g, 4.11 mmol) obtained in Step A, and cooled to 0-5°C. NaNO_2 (0.31 g, 4.52 mmol)/ H_2O (2 mL) solution was slowly added thereto, and the mixture was stirred at 0-5°C for 20 minutes. Pre-prepared KI (6.82 g, 41.1 mmol)/ H_2O (10 mL) solution was slowly added dropwise to the reaction solution, and the reaction was carried out at room temperature for 12 hours. After termination of the reaction, NaOH solution was added thereto, and the reaction solution was extracted with DCM. The organic layer was washed with saturated NaHCO_3 aqueous solution and water. The extracted organic layer was concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (0.88 g, 68 %).

^1H NMR (500 MHz, CDCl_3) δ 7.48(d, 1H), 7.00(dd, 1H), 6.85(d, 1H), 3.87(s, 3H)

Step C: 2-bromo-3-iodophenol

2-Bromo-1-iodo-3-methoxybenzene (0.88 g, 2.81 mmol) obtained in Step B was dissolved in DCM (4 mL) and cooled to 0-5°C. 1M BBr_3 (8.4 mL, 8.43 mmol) was slowly added dropwise thereto, and the mixture was stirred at 0-5°C for 1 hour and additionally stirred

at room temperature for 1 hour. After termination of the reaction, the reaction solution was cooled to -20°C and diluted by slowly adding methanol. The mixture was stirred at room temperature for 30 minutes. After addition of saturated NaHCO₃ aqueous solution, the reaction solution was extracted with DCM. The organic layer was dried with anhydrous magnesium sulfate, concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/5) to obtain the title compound (0.723 g, 86%).

¹H NMR (500 MHz, CDCl₃) δ 7.43-7.39(m, 1H), 7.02-6.92 (m, 2H), 5.61 (s, 1H)

Preparation Example 217: 4-bromo-2,6-difluoro-benzenethiol

Step A: 4-bromo-2,6-difluoro-benzenesulfonyl chloride

CuCl₂ (0.77 g, 5.77 mmol) was dissolved in 200 mL of water. SOCl₂ (29 mL, 0.40 mol) was added thereto at 0°C, and the mixture was stirred at room temperature for 18 hours. 4-Bromo-2,6-difluoroaniline (20 g, 0.096 mol) was dissolved in 240 mL of HCl and 900 mL of water, and the solution in which NaNO₂ (7 g, 0.10 mol) was dissolved in 200 mL of water was added thereto at 0°C. The above thionyl chloride solution was added thereto, and the reaction was carried out at room temperature for 1 hour to obtain the title compound (24 g, 85 %) in a solid form.

Step B: 4-bromo-2,6-difluoro-benzenethiol

4-Bromo-2,6-difluoro-benzenesulfonyl chloride (24 g, 0.08 mol) obtained in Step A was dissolved in 270 mL of THF. PPh₃ (75 g, 0.28 mol) was added thereto, and the mixture was stirred at room temperature for 15 minutes. After addition of water, the mixture was stirred at room temperature for 18 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was separated, dried with MgSO₄ and purified by column chromatography to obtain the title compound (15 g, 83 %).

¹H-NMR (CDCl₃) δ 7.10 (2H, d), 3.58 (1H, s).

Preparation Example 218: 4-(4-bromo-2,6-difluoro-phenylsulfanyl)-butyric acid ethyl ester

4-Bromo-2,6-difluoro-benzenethiol (15 g, 0.066 mol) obtained in Preparation Example 217, NaH (60% in mineral oil, 2.6 g, 0.066 mol) and 4-bromo-butyric acid ethyl ester (10 mL, 0.073 mol) were reacted in the same manner as in Preparation Example 34 to obtain the title

compound (18.56 g, 82 %).

¹H-NMR (CDCl₃) δ 7.11 (2H, d), 4.11 (2H, q), 2.90 (2H, t), 2.43 (2H, t), 1.82 (2H, m), 1.24 (3H, t).

Preparation Example 219: 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-phenylsulfanyl]-butyric acid ethyl ester

4-(4-Bromo-2,6-difluoro-phenylsulfanyl)-butyric acid ethyl ester (11.6 g, 0.034 mol) obtained in Preparation Example 218, bis(pinacolato)diboron (9.5 g, 0.038 mol), potassium acetate (8.4 g, 0.085 mol) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium(II) (2.5 g, 0.003 mol) were reacted in the same manner as in Step D of Example 1 to obtain the title compound (10.6 g, 80%).

¹H-NMR (CDCl₃) δ 7.30 (2H, d), 4.09 (2H, q), 2.94 (2H, t), 2.43 (2H, t), 1.83 (2H, m), 1.33 (12H, s), 1.22 (3H, t).

Preparation Example 220: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester

Step A: 2-[1-(4-bromo-2,6-difluoro-phenyl)-4-piperidyl]acetic acid ethyl ester

2-[1-(2,6-Difluoro-4-nitro-phenyl)-4-piperidylidene]acetic acid ethyl ester (11.44 g, 35 mmol) obtained in Step B of Preparation Example 89 was dissolved in 100 mL of MeOH and 50 mL of DCM. 0.7 g of 10 wt% Pd/C was added thereto, and the mixture was stirred for 20 minutes under 40 psi of hydrogen atmosphere. Solids were filtered through Celite and concentrated under reduced pressure to obtain 2-[1-(4-amino-2,6-difluoro-phenyl)-4-piperidyl]acetic acid ethyl ester. This compound was reacted in the same manner as in Step C of Preparation Example 84 to obtain the title compound (6.53 g, 52 %).

¹H-NMR (CDCl₃) δ 6.99 (2H, m), 4.14 (2H, q), 3.18 (2H, m), 3.08 (2H, m), 2.28 (2H, d), 1.93 (1H, m), 1.75 (2H, m), 1.46 (2H, m), 1.27 (3H, m)

Step B: 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester

2-[1-(4-Bromo-2,6-difluoro-phenyl)-4-piperidyl]acetic acid ethyl ester (6.53 g, 18 mmol) obtained in Step A was reacted in the same manner as in Step D of Preparation Example 84 to obtain the title compound (4.68 g, 63 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.22 (2H, m), 4.14 (2H, q), 3.31 (2H, m), 3.10 (2H, m), 2.28 (2H, d), 1.96 (1H, m), 1.74 (2H, m), 1.42 (2H, m), 1.32 (12H, s), 1.26 (3H, t)

Preparation Example 221: 4-[2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butanoic acid ethyl ester

Step A: 4-(4-bromo-2-chloro-6-fluoro-phenoxy)butanoic acid ethyl ester

After addition of 15 mL of DMF, 4-bromo-2-chloro-6-fluoro-phenol (2.25 g, 10.0 mmol), K_2CO_3 (2.07 g, 15.0 mmol) and 4-bromobutanoic acid ethyl ester (1.95 g, 10.0 mmol) were stirred at 80°C for 5 hours. The reaction solution was cooled to room temperature. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (3.29 g, 97 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.32 (1H, m), 7.18 (1H, m), 4.12 (4H, m), 2.60 (2H, t), 2.10 (2H, m), 1.27 (3H, t)

Step B: 4-[2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butanoic acid ethyl ester

4-(4-Bromo-2-chloro-6-fluoro-phenoxy)butanoic acid ethyl ester (1.45 g, 4.27 mmol) Step A obtained in Step A was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (1.42 g, 86 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.58 (1H, m), 7.41 (1H, m), 4.16 (4H, m), 2.60 (2H, t), 2.10 (2H, m), 1.32 (12H, s), 1.26 (3H, t)

Preparation Example 222: 4-[2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butanoic acid ethyl ester

Step A: 4-(4-bromo-2,6-dichloro-phenoxy)butanoic acid ethyl ester

After addition of 15 mL of DMF 4-bromo-2,6-dichloro-phenol (2.42 g, 10.0 mmol), K_2CO_3 (2.07 g, 15.0 mmol) and 4-bromobutanoic acid ethyl ester (1.95 g, 10.0 mmol) were stirred at 80°C for 5 hours. The reaction solution was cooled to room temperature. After addition of water, the reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (3.10 g, 87 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.44 (2H, s), 4.16 (2H, q), 4.04 (2H, t), 2.63 (2H, t), 2.16 (2H, m),

1.27 (3H, t)

Step B: 4-[2,6-dichloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butanoic acid ethyl ester

4-(4-Bromo-2,6-dichloro-phenoxy)butanoic acid ethyl ester (1.20 g, 3.37 mmol) obtained in Step A was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.825 g, 61 %).

¹H-NMR (CDCl₃) δ 7.70 (2H, s), 4.16 (2H, q), 4.07 (2H, t), 2.65 (2H, t), 2.16 (2H, m), 1.33 (12H, s), 1.27 (3H, t)

Preparation Example 223: 2-[1-[2,6-difluoro-4-(3-hydroxyphenyl)phenyl]-4-piperidyl]acetic acid ethyl ester

3-Iodophenol (0.17 g, 0.77 mmol) and 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester (0.35 g, 0.85 mmol) obtained in Preparation Example 220 was reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.21 g, 75 %).

¹H-NMR (CDCl₃) δ 7.30 (1H, m), 7.06 (3H, m), 6.97 (1H, m), 6.81 (1H, m), 4.88 (1H, brs), 4.15 (2H, q), 3.27 (2H, m), 3.13 (2H, m), 2.29 (2H, d), 1.96 (1H, m), 1.77 (2H, m), 1.47 (2H, m), 1.27 (3H, t)

Preparation Example 224: [1-(2,6-difluoro-4-thiocarbamoyl-phenyl)-piperidin-4-yl]-acetic acid ethyl ester

Step A: [1-(4-cyano-2,6-difluoro-phenyl)-piperidin-4-yl]-acetic acid ethyl ester

3,4,5-Trifluorobenzonitrile (3.14 g, 20 mmol) and hydrochloric acid salt of 2-(4-piperidin)acetic acid ethyl ester (4.15 g, 20 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (4.80 g, 78 %).

¹H-NMR (CDCl₃) δ 7.16 (2H, m), 4.19 (2H, q), 3.45 (2H, m), 3.19 (2H, m), 2.32 (2H, d), 2.03 (1H, m), 1.82 (2H, m), 1.43 (2H, m), 1.31 (3H, t)

Step B: [1-(2,6-difluoro-4-thiocarbamoyl-phenyl)-piperidin-4-yl]-acetic acid ethyl ester

[1-(4-Cyano-2,6-difluoro-phenyl)-piperidin-4-yl]-acetic acid ethyl ester (1.54 g, 5.0

mmol) obtained in Step A, magnesium dichloride hexahydrate (4.07 g, 40.0 mmol) and sodium thiolate hydrate (3.70 g, 50.0 mmol) were dissolved in DMF (20 mL) and stirred for 3 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was washed with sodium chloride aqueous solution, dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.41 g, 82 %).

¹H-NMR (CDCl₃) δ 7.64 (1H, s), 7.45 (2H, m), 7.16 (1H, s), 4.19 (2H, q), 3.42 (2H, m), 3.17 (2H, m), 2.32 (2H, d), 2.00 (1H, m), 1.80 (2H, m), 1.46 (2H, m), 1.31 (3H, t)

Preparation Example 225: 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

Step A: 4-bromo-2-chloro-6-fluoro-aniline

4-Bromo-2-fluoro-aniline (5.0 g, 26 mmol) was dissolved in 52 mL of CH₃CN. *N*-chlorosuccinimide (4.37 g, 33 mmol) was added thereto, and the mixture was stirred for 3 hours under reflux. The reaction solution was cooled to room temperature. After addition of NaHCO₃ aqueous solution, the reaction solution was extracted with DCM. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (4.41 g, 75 %).

¹H-NMR (CDCl₃) δ 7.21 (1H, m), 7.09 (1H, m), 4.08 (2H, brs)

Step B: 2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline

4-Bromo-2-chloro-6-fluoro-aniline (4.4 g, 20 mmol) obtained in Step A was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (3.68 g, 67 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, m), 7.32 (1H, m), 4.28 (2H, brs), 1.33 (12H, s)

Preparation Example 226: 4-chloro-2-(cyclopropylmethoxy)-6-methyl-pyrimidine

20 mL of THF was added to cyclopropylmethanol (0.36 g, 5.0 mmol) and cooled to 0°C. NaH (60 wt% in mineral oil, 0.24 g, 6.0 mmol) was added thereto, and the mixture was stirred for 30 minutes. 2,6-Dichloro-4-methyl-pyrimidine (0.815 g, 5.0 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was purified by column

chromatography to obtain the title compound (0.37 g, 37 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.83 (1H, s), 4.19 (2H, d), 2.43 (3H, s), 1.31 (1H, m), 0.61 (2H, m), 0.37 (2H, m)

Preparation Example 227: 2-chloro-4-(cyclopropylmethoxy)-6-methyl-pyrimidine

20 mL of THF was added to cyclopropylmethanol (0.36 g, 5.0 mmol) and cooled to 0°C. NaH (60 wt% in mineral oil, 0.24 g, 6.0 mmol) was added thereto, and the mixture was stirred for 30 minutes. After addition of 2,6-dichloro-4-methyl-pyrimidine (0.815 g, 5.0 mmol), the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.41 g, 41 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.54 (1H, s), 4.23 (2H, d), 2.46 (3H, s), 1.30 (1H, m), 0.56 (2H, m), 0.40 (2H, m)

Preparation Example 228: 2-chloro-4-(cyclobutoxy)-6-methyl-pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (0.815 g, 5.0 mmol) and cyclobutanol (0.36 g, 5.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.455 g, 46 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.44 (1H, s), 5.21 (1H, m), 2.45 (2H, m), 2.41 (3H, s), 2.14 (2H, m), 1.85 (1H, m), 1.67 (1H, m)

Preparation Example 229: 4-chloro-2-(cyclobutoxy)-6-methyl-pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (0.815 g, 5.0 mmol) and cyclobutanol (0.36 g, 5.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.455 g, 46 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.81 (1H, s), 5.21 (1H, m), 2.45 (2H, m), 2.41 (3H, s), 2.14 (2H, m), 1.85 (1H, m), 1.67 (1H, m)

Preparation Example 230: 2-chloro-4-(cyclobutoxy)pyrimidine

Cyclobutanol (0.58 g, 8.05 mmol) and 2,4-dichloropyrimidine (1 g, 6.71 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.4 g,

32 %) and the by-product, 4-chloro-2-cyclobutoxy-pyrimidine (0.4 g, 32 %).

¹H-NMR (CDCl₃) δ 8.27 (1H, d), 6.61 (1H, d), 5.26 (1H, m), 2.48 (2H, m), 2.16 (2H, m), 1.88 (1H, m), 1.70 (1H, m).

Preparation Example 231: 2-chloro-4-(cyclopropylmethoxy)pyrimidine

Cyclopropylmethanol (0.72 g, 10.0 mmol) and 2,4-dichloropyrimidine (1.49 g, 10.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.78 g, 42 %).

¹H-NMR (CDCl₃) δ 8.32 (1H, m), 6.71 (1H, m), 4.26 (2H, d), 1.30 (1H, m), 0.68 (2H, m), 0.42 (2H, m)

Preparation Example 232: 2-chloro-6-(cyclobutoxy)pyrazine

Cyclobutanol (0.36 g, 5.0 mmol) and 2,6-dichloropyrazine (0.745 g, 5.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.53 g, 57 %).

¹H-NMR (CDCl₃) δ 8.15 (1H, s), 8.11 (1H, s), 5.22 (1H, m), 2.53 (2H, m), 2.20 (2H, m), 1.91 (1H, m), 1.73 (1H, m)

Preparation Example 233: 2-chloro-6-(cyclopropylmethoxy)pyrazine

Cyclopropylmethanol (0.72 g, 10.0 mmol) and 2,6-dichloropyrazine (1.49 g, 10.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.49 g, 81 %).

¹H-NMR (CDCl₃) δ 8.18 (1H, s), 8.16 (1H, s), 4.21 (2H, d), 1.33 (1H, m), 0.68 (2H, m), 0.42 (2H, m)

Preparation Example 234: 2-chloro-6-methoxy-pyrazine

MeOH (0.27 mL, 6.7 mmol) was dissolve in 15 mL of THF. NaH (60 wt% in mineral oil, 0.32 g, 8.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,6-Dichloropyrazine (1.0 g, 6.7 mmol) dissolved in 20 mL of THF was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column

chromatography to obtain the title compound (0.71 g, 73 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.14 (1H, s), 8.13 (1H, s), 3.99 (3H, s)

Preparation Example 235: 2-chloro-6-propoxy-pyrazine

Propan-1-ol (0.4 g, 6.7 mmol) was dissolved in 15 mL of THF. NaH (60 wt% in mineral oil, 0.32 g, 8.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,6-Dichloropyrazine (1.0 g, 6.7 mmol) dissolved in 20 mL of THF was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.77 g, 66 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.12 (1H, s), 8.11 (1H, s), 4.29 (2H, t), 1.82 (2H, m), 1.03 (3H, t)

Preparation Example 236: 2-butoxy-6-chloro-pyrazine

Butan-1-ol (0.5 g, 6.7 mmol) was dissolved in 15 mL of THF. NaH (60 wt% in mineral oil, 0.32 g, 8.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,6-Dichloropyrazine (1.0 g, 6.7 mmol) dissolved in 20 mL of THF was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.15 g, 92 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.11 (1H, s), 8.10 (1H, s), 4.33 (2H, t), 1.78 (2H, m), 1.48 (2H, m), 0.98 (3H, t)

Preparation Example 237: 2-chloro-6-isobutoxy-pyrazine

2-Methylpropan-1-ol (0.5 g, 6.7 mmol) was dissolved in 15 mL of THF. NaH (60 wt% in mineral oil, 0.32 g, 8.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,6-Dichloropyrazine (1.0 g, 6.7 mmol) dissolved in 20 mL of THF was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.04 g, 83 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.12 (2H, s), 4.10 (2H, d), 2.11 (1H, m), 1.03 (6H, d)

Preparation Example 238: 2-chloro-6-(cyclopentoxy)pyrazine

Cyclopentanol (0.58 g, 6.7 mmol) was dissolved in 15 mL of THF. NaH (60 wt% in mineral oil, 0.32 g, 8.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,6-Dichloropyrazine (1.0 g, 6.7 mmol) dissolved in 20 mL of THF was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.07 g, 80 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.09 (1H, s), 8.05 (1H, s), 5.40 (1H, m), 1.98 (2H, m), 1.80 (4H, m), 1.65 (2H, m)

Preparation Example 239: 2-chloro-4-ethoxy-pyrimidine

2,4-Dichloropyrimidine (3.0 g, 20.1 mmol) was dissolved in 40 mL of EtOH. NaOEt (1.0 M in EtOH, 20 mL, 20 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.41 g, 44 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.27 (1H, d), 6.64 (1H, d), 4.45 (2H, q), 1.40 (3H, t)

Preparation Example 240: 2-chloro-4-isopropoxy-pyrimidine

Cs_2CO_3 (7.15 g, 21.9 mmol) and 50 mL of propan-2-ol were added to 2,4-dichloropyrimidine (3.0 g, 20.1 mmol), and the mixture was stirred for 24 hours under reflux. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (2.24 g, 65 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.25 (1H, d), 6.58 (1H, d), 5.40 (1H, m), 1.37 (6H, d)

Preparation Example 241: 2-chloro-4-propoxy-pyrimidine

Propan-1-ol (1.33 g, 22.1 mmol) was dissolved in 60 mL of THF. NaH (60 wt% in mineral oil, 0.96 g, 24.1 mmol) was added thereto, and the mixture was stirred at room

temperature for 30 minutes. 2,4-Dichloropyrimidine (3.0 g, 22.1 mmol) was added thereto, and the mixture was stirred at room temperature for 24 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (2.06 g, 59 %).

¹H-NMR (CDCl₃) δ 8.27 (1H, d), 6.65 (1H, d), 4.34 (2H, t), 1.81 (2H, m), 1.03 (3H, t)

Preparation Example 242: 2-chloro-4-isobutoxy-pyrimidine

2-Methylpropan-1-ol (1.64 g, 22.1 mmol) was dissolved in 60 mL of THF. NaH (60 wt% in mineral oil, 0.96 g, 24.1 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,4-Dichloropyrimidine (3.0 g, 22.1 mmol) was added thereto, and the mixture was stirred at room temperature for 24 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound.

¹H-NMR (CDCl₃) δ 8.27 (1H, d), 6.65 (1H, d), 4.15 (2H, d), 2.09 (1H, m), 1.00 (6H, d)

Preparation Example 243: 2-chloro-4-ethoxy-6-methyl-pyrimidine

Cs₂CO₃ (6.6 g, 20.2 mmol) and 46 mL of EtOH were added to 2,4-dichloro-6-methyl-pyrimidine (3.0 g, 18.4 mmol), and the mixture was stirred for 48 hours under reflux. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.88 g, 59 %).

¹H-NMR (CDCl₃) δ 6.47 (1H, s), 4.41 (2H, q), 2.42 (3H, s), 1.39 (3H, t)

Preparation Example 244: 2-chloro-4-isopropoxy-6-methyl-pyrimidine

Cs₂CO₃ (6.6 g, 20.2 mmol) and 46 mL of propan-2-ol were added to 2,4-dichloro-6-methyl-pyrimidine (3.0 g, 18.4 mmol), and the mixture was stirred for 16 hours under reflux. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.18 g, 34 %).

¹H-NMR (CDCl₃) δ 6.41 (1H, s), 5.38 (1H, m), 2.40 (3H, s), 1.34 (6H, d)

Preparation Example 245: 2-chloro-4-methyl-6-propoxy-pyrimidine

Cs_2CO_3 (6.6 g, 20.2 mmol) and 46 mL of propan-1-ol were added to 2,4-dichloro-6-methyl-pyrimidine (3.0 g, 18.4 mmol), and the mixture was stirred for 16 hours under reflux. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.72 g, 50 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.48 (1H, s), 4.31 (2H, t), 2.42 (3H, s), 1.79 (2H, m), 1.00 (3H, t)

Preparation Example 246: 2-chloro-4-isobutoxy-6-methyl-pyrimidine

2-Methylpropan-1-ol (3.5 g, 21.4 mmol) was dissolved in 50 mL of THF. NaH (60 wt% in mineral oil, 1.03 g, 25.7 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,4-Dichloro-6-methyl-pyrimidine (3.0 g, 18.4 mmol) dissolved in 20 mL of THF was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et_2O . The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (1.75 g, 41 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.49 (1H, s), 4.13 (2H, d), 2.42 (3H, s), 2.07 (1H, m), 1.00 (6H, d)

Preparation Example 247: 2-chloro-4-(2-methoxyethoxy)-6-methyl-pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (1.63 g, 10.0 mmol) and 2-methoxyethanol (0.76 g, 10.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.03 g, 51 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.59 (1H, s), 4.56 (2H, m), 3.75 (2H, m), 3.45 (3H, s), 2.45 (3H, s)

Preparation Example 248: 2-chloro-4-(3-methoxy-propoxy)-6-methyl-pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (1.63 g, 10.0 mmol) and 3-methoxypropanol (0.90 g, 10.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.05 g, 48 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.52 (1H, s), 4.47 (2H, t), 3.54 (2H, t), 3.38 (3H, s), 2.48 (3H, s), 2.06 (2H, m)

Preparation Example 249: 2-chloro-6-pyrrolidin-1-yl-pyrazine

2,6-Dichloropyrazine (2.0 g, 13.4 mmol) was dissolved in 13 mL of DMSO. Pyrrolidine (1.05 g, 14.7 mmol) and DIPEA (2.92 mL, 16.7 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 24 hours. The reaction solution was diluted with water, extracted with EtOAc and purified by column chromatography to obtain the title compound (2.36 g, 96 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.74 (1H, s), 7.71 (1H, s), 3.49 (4H, m), 2.03 (4H, m)

Preparation Example 250: 6-chloro-*N*-isopropyl-pyrazin-2-amine

Propan-2-amine (1.7 mL, 20.1 mmol), 1 mL of TEA and 2 mL of THF were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was stirred at 60°C for 24 hours. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.35 g, 59 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.75 (1H, s), 7.71 (1H, s), 4.61 (1H, brs), 4.00 (1H, m), 1.26 (6H, d)

Preparation Example 251: 6-chloro-*N*-isobutyl-pyrazin-2-amine

2-Methylpropan-1-amine (2 mL, 20.1 mmol), 1 mL of TEA and 3 mL of THF were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was stirred at 60°C for 24 hours. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.95 g, 78 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.77 (1H, s), 7.75 (1H, s), 4.97 (1H, brs), 3.17 (2H, m), 1.90 (1H, m), 0.99 (6H, d)

Preparation Example 252: 6-chloro-*N*-cyclopentyl-pyrazin-2-amine

Cyclopentanamine (1.48 g, 17.4 mmol), 1 mL of TEA and 3 mL of THF were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was stirred at 60°C for 24 hours. After filtering solids, the filtrate was purified by column chromatography to obtain the title compound (1.84 g, 69 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.77 (1H, s), 7.74 (1H, s), 4.80 (1H, brs), 4.09 (1H, m), 2.07 (2H, m), 1.74 (2H, m), 1.67 (2H, m), 1.48 (2H, m)

Preparation Example 253: 6-chloro-*N,N*-diethyl-pyrazin-2-amine

2,6-Dichloropyrazine (2.0 g, 13.4 mmol) was dissolved in 13 mL of DMSO. Diethylamine (1.53 mL, 14.7 mmol) and DIPEA (2.92 mL, 16.7 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 24 hours. The reaction solution was diluted with water, extracted with EtOAc and purified by column chromatography to obtain the title compound (1.44 g, 58 %).

¹H-NMR (CDCl₃) δ 7.80 (1H, s), 7.70 (1H, s), 3.51 (4H, q), 1.21 (6H, t)

Preparation Example 254: 6-chloro-*N,N*-dimethyl-pyrazin-2-amine

2,6-Dichloropyrazine (2.0 g, 13.4 mmol) was dissolved in 13 mL of DMSO. Dimethylamine hydrochloride (1.31 g, 16.08 mmol) and DIPEA (5.2 mL, 30 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 24 hours. The reaction solution was diluted with water, extracted with EtOAc and purified by column chromatography to obtain the title compound (1.82 g, 86 %).

¹H-NMR (CDCl₃) δ 7.87 (1H, s), 7.77 (1H, s), 3.13 (6H, s)

Preparation Example 255: 2-chloro-*N*-isobutyl-pyrimidin-4-amine

15 mL of THF, 2-methylpropan-1-amine (2.6 mL, 26.1 mmol) and DIPEA (5.3 mL, 30 mmol) were added to 2,4-dichloropyrimidin (3.0 g, 20.1 mmol), the mixture was stirred at 65°C for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (2.57 g, 69 %).

¹H-NMR (CDCl₃) δ 8.03 (1H, m), 6.23 (1H, d), 5.40 (1H, brs), 3.07 (2H, m), 1.89 (1H, m), 0.98 (6H, d)

Preparation Example 256: 5-chloro-3-(cyclobutoxy)-2-methyl-pyrazine

Step A: 3,5-dichloro-2-methyl-pyrazine

110 mL of THF was added to 2,2,6,6-tetramethylpiperidine (3.3 mL, 20 mmol) and cooled to -78°C. *n*-BuLi (2.5 M hexane solution, 8 mL, 20 mmol) was added thereto, and the mixture was stirred at -78°C for 30 minutes. 2,6-Dichloropyrazine (2.0 g, 13.4 mmol) dissolved in 20 mL was added thereto, and the mixture was stirred at -78°C for 90 minutes. Iodomethane (3.8 mL, 60 mmol) was added thereto, and the mixture was stirred at room temperature for 3 hours. Solids were removed by filtration, and the filtrate was purified by column chromatography to obtain the title compound (0.77 g, 35 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, s), 2.65 (3H, s)

Step B: 5-chloro-3-(cyclobutoxy)-2-methyl-pyrazine

3,5-Dichloro-2-methyl-pyrazine (0.62 g, 3.8 mmol) obtained in Step A and cyclobutanol (0.3 g, 4.18 mmol) was reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.54 g, 71 %).

¹H-NMR (CDCl₃) δ 7.98 (1H, s), 5.20 (1H, m), 2.48 (2H, m), 2.43 (3H, s), 2.15 (2H, m), 1.86 (1H, m), 1.70 (1H, m)

Preparation Example 257: 2-chloro-6-isobutyl-pyrazine

50 mL of THF, 5 mL of NMP and Fe(acac)₃ (0.24 g, 0.67 mmol) were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was cooled to 0°C. Isobutylmagnesium bromide (2.0 M Et₂O solution, 12 mL, 24 mmol) was slowly added thereto. The reaction solution was stirred at room temperature for 24 hours. After addition of water, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.32 g, 14 %).

¹H-NMR (CDCl₃) δ 8.43 (1H, s), 8.31 (1H, s), 2.66 (2H, d), 2.13 (1H, m), 0.95 (6H, d)

Preparation Example 258: 2-chloro-6-cyclopentyl-pyrazine

13 mL of toluene, SPhos (1.37 g, 3.3 mmol) and Pd(OAc)₂ (0.38 g, 1.67 mmol) were added to 2,6-dichloropyrazine (1.0 g, 6.7 mmol). Cyclopentylzinc bromide (0.5 M THF solution, 20 mL, 10 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.19 g, 15 %).

¹H-NMR (CDCl₃) δ 8.39 (1H, s), 8.36 (1H, s), 3.18 (1H, m), 2.10 (2H, m), 1.85 (4H, m), 1.71 (2H, m)

Preparation Example 259: 2-chloro-4-isobutyl-pyrimidine

40 mL of THF, Pd(PPh₃)₄ (1.0 g, 0.9 mmol) and triisobutylaluminum (1.0 M hexane solution, 16 mL, 16 mmol) were added to 2,4-dichloropyrimidine (2.0 g, 13.4 mmol), and the

mixture was stirred for 20 hours under reflux. After cooling and addition of water, the reaction solution was extracted with Et₂O. The organic layer was purified by column chromatography to obtain the title compound (0.32 g, 14 %).

¹H-NMR (CDCl₃) δ 8.49 (1H, d), 7.08 (1H, d), 2.63 (2H, d), 2.14 (1H, m), 0.95 (6H, d)

Preparation Example 260: 2-butyl-6-chloro-pyrazine

50 mL of THF, 5 mL of NMP and Fe(acac)₃ (0.24 g, 0.67 mmol) were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was cooled to 0°C. Butylmagnesium chloride (0.9 M THF solution, 16 mL, 14.4 mmol) was slowly added thereto. The reaction solution was stirred at room temperature for 24 hours. After addition of water, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.38 g, 17 %).

¹H-NMR (CDCl₃) δ 8.42 (1H, s), 8.35 (1H, s), 2.79 (2H, t), 1.73 (2H, m), 1.39 (2H, m), 0.95 (3H, t)

Preparation Example 261: 2-chloro-6-isopentyl-pyrazine

50 mL of THF, 5 mL of NMP and Fe(acac)₃ (0.24 g, 0.67 mmol) were added to 2,6-dichloropyrazine (2.0 g, 13.4 mmol), and the mixture was cooled to 0°C. Isopentylmagnesium bromide (0.9 M THF solution, 16 mL, 14.4 mmol) was slowly added thereto. The reaction solution was stirred at room temperature for 24 hours. After addition of water, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.36 g, 15 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, s), 8.35 (1H, s), 2.79 (2H, m), 1.62 (3H, m), 0.95 (6H, d)

Preparation Example 262: 2-chloro-6-cyclobutyl-pyrazine

Magnesium (0.326 g, 13.4 mL) and 13.4 mL of THF were added to a dried flask. Bromocyclobutane (1.81 g, 13.4 mmol) was slowly added thereto, and the mixture was stirred for 1 hour under reflux. The reaction solution was cooled to 0°C. Fe(acac)₃ (0.24 g, 16 mmol) dissolved in 2 mL of THF was added thereto, and the mixture was stirred for 5 minutes. 2,6-Dichloropyrazine (2.0 g, 13.4 mmol) dissolved in 20 mL of THF and 2 mL of NMP was

added thereto, and the mixture was stirred for 2 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (0.05 g, 2 %).

¹H-NMR (CDCl₃) δ 8.40 (1H, s), 8.33 (1H, s), 3.68 (1H, m), 2.38 (4H, m), 2.10 (1H, m), 1.96 (1H, m)

Preparation Example 263: 4-chloro-6,7-dihydro-5H-cyclopenta[d]pyrimidine

Step A: 2-aminocyclopentene-1-carboxylic acid methyl ester

2-Oxocyclopentancarboxylic acid methyl ester (9.86 g, 69.3 mmol) was dissolved in 140 mL of MeOH. Ammonium formate (21.9 g, 350 mmol) was added thereto, and the mixture was stirred for 24 hours under reflux. The reaction solution was cooled to room temperature. Small amount of SiO₂ was added, and the reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (9.49 g, 97 %).

¹H-NMR (DMSO-d₆) δ 6.76 (2H, brs), 3.53 (3H, s), 2.39 (4H, m), 1.70 (2H, m)

Step B: 2-formamidocyclopentene-1-carboxylic acid methyl ester

21 mL of formic acid was cooled to 0°C. 30 mL of acetic anhydride was added, and 2-aminocyclopentene-1-carboxylic acid methyl ester (4.76 g, 33.7 mmol) obtained in Step A was then added thereto little by little. The reaction solution was stirred at room temperature for 16 hours. The organic layer extracted with EtOAc was purified by column chromatography to obtain the title compound (4.95 g, 87 %).

¹H-NMR (DMSO-d₆) δ 10.28 (0.5H, brs), 9.72 (0.5H, brs), 8.57 (0.5H, brs), 8.28 (0.5H, brs), 3.68 (3H, s), 3.05 (1H, m), 2.88 (1H, m), 2.46 (2H, m), 1.86 (2H, m)

Step C: 6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ol

Ammonium formate (9.94 g, 157 mmol) was dissolved in 15 mL of formamide. 2-Formamidocyclopentene-1-carboxylic acid methyl ester (4.94 g, 29.2 mmol) obtained in Step B was added thereto, and the mixture was stirred at 150°C for 4 hours. After cooling to room temperature, the reaction solution was stirred for 16 hours. The formed precipitate was dried to obtain the title compound (1.56 g, 39 %).

¹H-NMR (DMSO-d₆) δ 12.28 (1H, brs), 8.02 (1H, s), 2.75 (2H, t), 2.62 (2H, t), 1.95

(2H, m)

Step D: 4-chloro-6,7-dihydro-5H-cyclopenta[d]pyrimidine

11 mL of phosphorus oxychloride was added to 6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-ol (1.56 g, 11.4 mmol) obtained in Step C, and the mixture was stirred for 4 hours under reflux. The reaction solution was cooled to room temperature. DCM was added thereto, and water was then added thereto. The water layer was extracted with DCM, and the organic layer was purified by column chromatography to obtain the title compound (1.67 g, 95 %).

¹H-NMR (DMSO-d₆) δ 8.78 (1H, s), 3.03 (2H, t), 2.99 (2H, t), 2.10 (2H, m)

Preparation Example 264: 2-chloro-4-(cyclobutoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine

Step A: 2,4-dichloro-6,7-dihydro-5H-cyclopenta[d]pyrimidine

12 mL of EtOH and 0.6 mL of concentrated HCl were added to 2-oxocyclopentancarboxylic acid methyl ester (5.2 g, 36.6 mmol) and urea (2.42 g, 40.2 mmol), and the mixture was stirred for 3 hours under reflux. The reaction solution was cooled to room temperature. The formed solids were dissolved in 12 mL of 5% NaOH aqueous solution, and the reaction solution was stirred for 2 hours under reflux. The reaction solution was cooled to 0°C and adjusted to pH 3. The formed solids were filtered to obtain 6,7-dihydro-5H-cyclopenta[d]pyrimidin-2,4-diol (3.34 g, 60 %). This compound was dissolved in 7 mL of phosphorus oxychloride, and the mixture was stirred for 4 hours under reflux. The reaction solution was cooled to room temperature. After addition of cold water, the reaction solution was extracted with DCM to obtain the title compound (0.98 g, 24 %).

¹H-NMR (CDCl₃) δ 3.08 (2H, t), 2.99 (2H, t), 2.22 (2H, m)

Step B: 2-chloro-4-(cyclobutoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidine

Cyclobutanol (0.34 g, 4.75 mmol) was dissolved in 30 mL of THF and cooled to 0°C. NaH (60 wt% in mineral oil, 0.21 g, 5.18 mmol) was added thereto, and the mixture was stirred for 30 minutes. 2,4-Dichloro-6,7-dihydro-5H-cyclopenta[d]pyrimidine (0.82 g, 4.32 mmol) obtained in Step A was dissolved in 13 mL of THF and added thereto. The mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted

with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.59 g, 61 %).

¹H-NMR (CDCl₃) δ 5.28 (1H, m), 2.93 (2H, m), 2.82 (2H, m), 2.48 (2H, m), 2.13 (4H, m), 1.84 (1H, m), 1.67 (1H, m)

Preparation Example 265: 2-chloro-4-(cyclobutoxy)-5,6-dimethyl-pyrimidine

Step A: 2,4-dichloro-5,6-dimethyl-pyrimidine

5,6-Dimethyl-1H-pyrimidin-2,4-dione (2.5 g, 17.8 mmol) was dissolved in 12 mL of phosphorus oxychloride, and the mixture was stirred for 4 hours under reflux. The reaction solution was cooled to at room temperature and added to cold water. The formed precipitate was dried to obtain the title compound (3.08 g, 98 %).

¹H-NMR (DMSO-d₆) δ 2.51 (3H, s), 2.30 (3H, s)

Step B: 2-chloro-4-(cyclobutoxy)-5,6-dimethyl-pyrimidine

Cyclobutanol (0.45 g, 6.21 mmol) was dissolved in 40 mL of THF and cooled to 0°C. NaH (60 wt% in mineral oil, 0.27 g, 6.77 mmol) was added thereto, and the mixture was stirred for 30 minutes. 2,4-Dichloro-5,6-dimethyl-pyrimidine (1.0 g, 5.64 mmol) obtained in Step A was dissolved in 15 mL of THF and added thereto. The mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.84 g, 70 %).

¹H-NMR (CDCl₃) δ 5.24 (1H, m), 2.48 (2H, m), 2.40 (3H, s), 2.13 (2H, m), 2.08 (3H, s), 1.84 (1H, m), 1.68 (1H, m)

Preparation Example 266: (6-bromo-2-pyridyl)methanol

6-Bromopyridin-2-carbaldehyde (1.86 g, 10.0 mmol) was dissolved in 30 mL of MeOH and cooled to 0°C. NaBH₄ (0.38 g, 10.0 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 30 minutes. After addition of water, the organic layer extracted with EtOAc was purified by column chromatography to obtain the title compound (1.86 g, 99 %).

¹H-NMR (CDCl₃) δ 7.56 (1H, t), 7.40 (1H, m), 7.28 (1H, m), 4.75 (2H, d), 3.02 (1H, t)

Preparation Example 267: 2-bromo-6-(cyclopropylmethoxymethyl)pyridine

(6-Bromo-2-pyridyl)methanol (0.376 g, 2.0 mmol) obtained in Preparation Example 266 was dissolved in 8 mL of THF. NaH (60 wt% in mineral oil, 0.088 g, 2.2 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. Bromomethylcyclopropane (0.297 g, 2.2 mmol) and Bu₄NI (0.074 g, 0.2 mmol) were sequentially added thereto, and the mixture was stirred at room temperature. The reaction solution was adjusted to pH 4 by the addition of water. The organic layer extracted with DCM was purified by column chromatography to obtain the title compound (0.283 g, 58 %).

¹H-NMR (CDCl₃) δ 7.56 (1H, t), 7.47 (1H, m), 7.37 (1H, m), 4.63 (2H, s), 3.41 (2H, d), 1.10 (1H, m), 0.56 (2H, m), 0.24 (2H, m)

Preparation Example 268: (6-bromo-2-pyridyl)-cyclopropyl-methanol

6-Bromopyridin-2-carbaldehyde (0.93 g, 5.0 mmol) was dissolved in 20 mL of THF. Cyclopropyl magnesium bromide (0.5 M in THF, 11 mL, 5.5 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 15 minutes. After addition of ammonium chloride aqueous solution, the organic layer extracted with DCM was purified by column chromatography to obtain the title compound (1.09 g, 96 %).

¹H-NMR (CDCl₃) δ 7.55 (1H, t), 7.40 (1H, d), 7.37 (1H, d), 4.09 (1H, m), 3.62 (1H, d), 1.12 (1H, m), 0.55 (4H, m)

Preparation Example 269: 2-bromo-6-(cyclobutoxymethyl)pyridine

(6-Bromo-2-pyridyl)methanol (0.38 g, 2.0 mmol) obtained in Preparation Example 266 was dissolved in 5 mL of DCM. 2-Bromo-6-(chloromethyl)pyridine obtained by the addition of 1.2 mL of SOCl₂ and cyclobutanol (0.145 g, 2.0 mmol) were reacted in the same manner as in Preparation Example 267 to obtain the title compound (0.365 g, 75 %).

¹H-NMR (CDCl₃) δ 7.55 (1H, t), 7.43 (1H, d), 7.38 (1H, d), 4.51 (2H, s), 4.06 (1H, m), 2.23 (2H, m), 2.00 (2H, m), 1.73 (1H, m), 3.53 (1H, m)

Preparation Example 270: 2,6-dichloro-4-(cyclobutoxy)pyridine

2-Chloro-6-cyclobutoxy-pyridine (0.88 g, 4.8 mmol) was dissolved in 50 mL of DCM. mCPBA (4.45 g, 17.8 mmol) was added thereto, and the mixture was stirred at room temperature for 3 days. The precipitate was removed by filtration, and the filtrate was washed

with 1N NaOH aqueous solution and extracted with chloroform. The organic layer was dried with anhydrous magnesium sulfate for concentration. 15 mL of POCl₃ was added thereto, and the mixture was stirred at 90°C for 3 hours. The reaction solution was concentrated under reduced pressure. Cold water and 1N NaOH aqueous solution were sequentially added thereto, and the reaction solution was extracted with DCM. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.956 g, 91 %).

¹H-NMR (CDCl₃) δ 6.67 (2H, s), 4.66 (1H, m), 2.46 (2H, m), 2.19 (2H, m), 1.90 (1H, m), 1.70 (1H, m)

Preparation Example 271: 2-chloro-6-(cyclobutoxy)-4-methyl-pyridine

Step A: 2-(cyclobutoxy)-4-methyl-pyridine

2-Chloro-4-methyl-pyridine (0.89 g, 7.0 mmol) and cyclobutanol (0.05 g, 7.0 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.827 g, 72 %).

¹H-NMR (CDCl₃) δ 8.03 (1H, m), 6.71 (1H, m), 6.54 (1H, m), 5.19 (1H, m), 2.49 (2H, m), 2.32 (3H, s), 2.16 (2H, m), 1.86 (1H, m), 1.70 (1H, m)

Step B: 2-chloro-6-(cyclobutoxy)-4-methyl-pyridine

2-(Cyclobutoxy)-4-methyl-pyridine (0.0827 g, 5.07 mmol) obtained in Step A was reacted in the same manner as in Preparation Example 270 to obtain the title compound (0.405 g, 40 %).

¹H-NMR (CDCl₃) δ 6.75 (1H, m), 6.44 (1H, m), 5.18 (1H, m), 2.49 (2H, m), 2.30 (3H, s), 2.12 (2H, m), 1.85 (1H, m), 1.70 (1H, m)

Preparation Example 272: 2-*tert*-butoxy-6-chloro-pyridine

45 mL of toluene and potassium *tert*-butoxide (2.77 g, 24.6 mmol) were added to 2,6-dichloropyridine (3.04 g, 20.5 mmol), and the mixture was stirred for 24 hours under reflux. Solids were filtered through Celite, and the filtrate was purified by column chromatography to obtain the title compound (1.57 g, 41 %).

¹H-NMR (CDCl₃) δ 7.44 (1H, t), 6.82 (1H, d), 6.54 (1H, d), 1.58 (9H, s)

Preparation Example 273: 2-chloro-6-ethoxy-pyridine

EtOH (2.8 mL, 47 mmol) was added to 80 mL of THF, and the mixture was cooled to 0°C. Sodium (0.57 g, 25 mmol) was slowly added thereto, and the mixture was stirred at 40°C for 30 minutes. 2,6-Dichloropyridine (3.51 g, 23.7 mmol) was added thereto, and the mixture was stirred at 50°C for 16 hours. After addition of water, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (2.27 g, 61 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, t), 6.87 (1H, d), 6.62 (1H, d), 4.36 (2H, q), 1.38 (3H, t)

Preparation Example 274: 2-chloro-6-(2,2,2-trifluoroethoxy)pyridine

2,2,2-Trifluoroethanol (2.42 g, 24 mmol) was dissolved in 67 mL of THF. NaH (55 wt% in mineral oil, 1.06 g, 24 mmol) was added thereto, and the mixture was stirred at room temperature for 45 minutes. 2,6-Dichloropyridine (3.0 g, 20 mmol) was added thereto, and the mixture was stirred at 70°C for 16 hours. After addition of water, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (2.17 g, 51 %).

¹H-NMR (CDCl₃) δ 7.60 (1H, t), 7.00 (1H, d), 6.79 (1H, d), 4.73 (2H, m)

Preparation Example 275: 2-chloro-6-(2,2,2-trifluoro-1-methyl-ethoxy)pyridine

1,1,1-Trifluoro-2-propanol (2.76 g, 24 mmol) was dissolved in 67 mL of THF. NaH (55 wt% in mineral oil, 1.06 g, 24 mmol) was added thereto, and the mixture was stirred at room temperature for 45 minutes. 2,6-Dichloropyridine (3.0 g, 20 mmol) was added thereto, and the mixture was stirred at 70°C for 16 hours. After addition of water, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (3.58 g, 79 %).

¹H-NMR (CDCl₃) δ 7.57 (1H, t), 6.97 (1H, d), 6.73 (1H, d), 5.72 (1H, m), 1.50 (3H, d)

Preparation Example 276: 2-butoxy-6-chloro-pyridine

Butan-1-ol (1.87 g, 25.2 mmol) was dissolved in 50 mL of DMF and cooled to 0°C. NaH (55 wt% in mineral oil, 1.10 g, 25.2 mmol) was added thereto, and the mixture was stirred at room temperature for 45 minutes. 2,6-dichloropyridine (3.55 g, 24.0 mmol) was added thereto, and the mixture was stirred for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O and purified by column

chromatography to obtain the title compound (4.05 g, 91 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, t), 6.87 (1H, d), 6.63 (1H, d), 4.28 (2H, t), 1.74 (2H, m), 1.46 (2H, m), 0.97 (3H, t)

Preparation Example 277: 2-chloro-6-cyclobutyl-pyridine

2,6-Dichloropyridine (1.98 g, 13.4 mmol) and Fe(acac)₃ (0.24 g, 0.67 mmol) were dissolved in 49 mL of THF and 5 mL of NMP, and cooled to 0°C. Cyclobutylmagnesium bromide (0.9 M THF solution, 18 mL, 16 mmol) was slowly added thereto, and the mixture was stirred at 0°C for 6 hours. After termination of the reaction by the addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.43 g, 19 %).

¹H-NMR (CDCl₃) δ 7.54 (1H, t), 7.12 (1H, d), 7.08 (1H, d), 3.63 (1H, m), 2.33 (4H, m), 2.05 (1H, m), 1.90 (1H, m)

Preparation Example 278: 2-bromo-6-(cyclobutylidenemethyl)pyridine

35 mL of THF was added to 2-bromo-6-(diethoxyphosphorylmethyl)pyridine (2.2 g, 7.14 mmol), and the mixture was cooled to 0°C. LiHMDS (1.0 M THF solution, 8.6 mL, 8.6 mmol) was added thereto, and the mixture was stirred at 0°C for 30 minutes. Cyclobutanone (0.50 g, 7.14 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (1.02 g, 64 %).

¹H-NMR (CDCl₃) δ 7.42 (1H, t), 7.20 (1H, d), 7.04 (1H, d), 6.19 (1H, m), 3.13 (2H, m), 2.91 (2H, m), 2.14 (2H, m)

Preparation Example 279: 2-bromo-6-(cyclopentylidenemethyl)pyridine

35 mL of THF was added to 2-bromo-6-(diethoxyphosphorylmethyl)pyridine (2.2 g, 7.14 mmol), and the mixture was cooled to 0°C. LiHMDS (1.0 M THF solution, 8.6 mL, 8.6 mmol) was added thereto, and the mixture was stirred at 0°C for 30 minutes. Cyclopentanone (0.6 g, 7.14 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was

extracted with EtOAc and purified by column chromatography to obtain the title compound (1.17 g, 69 %).

¹H-NMR (CDCl₃) δ 7.43 (1H, t), 7.20 (1H, d), 7.13 (1H, d), 6.41 (1H, m), 2.73 (2H, m), 2.52 (2H, m), 1.81 (2H, m), 1.68 (2H, m)

Preparation Example 280: 1-bromo-3-(cyclopropylmethoxy)benzene

3-Bromophenol (0.865 g, 5.0 mmol) and bromomethylcyclopropane (1.01 g, 7.5 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (1.09 g, 96 %).

¹H-NMR (CDCl₃) δ 7.13 (1H, m), 7.06 (2H, m), 6.88 (1H, m), 3.82 (2H, d), 1.28 (1H, m), 0.65 (2H, m), 0.35 (2H, m)

Preparation Example 281: 1-bromo-3-(cyclobutoxy)benzene

3-Bromophenol (0.865 g, 5.0 mmol) and bromocyclobutane (1.01 g, 7.5 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (1.04 g, 91 %).

¹H-NMR (CDCl₃) δ 7.10 (1H, t), 7.05 (1H, m), 6.95 (1H, m), 6.74 (1H, m), 4.60 (1H, m), 2.44 (2H, m), 2.14 (2H, m), 1.85 (1H, m), 1.69 (1H, m)

Preparation Example 282: 4-bromo-2-(cyclopropylmethoxy)-1-methoxy-benzene

20 mL of DMF was added to 5-bromo-2-methoxy-phenol (1.8 g, 8.87 mmol), bromomethylcyclopropane (1.44 g, 10.7 mmol), K₂CO₃ (1.84 g, 13.3 mmol) and Bu₄NI (0.33 g, 0.88 mmol), and the mixture was stirred at 80°C. After termination of the reaction, the reaction solution was cooled to room temperature. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (2.21 g, 97 %).

¹H-NMR (CDCl₃) δ 7.02 (1H, m), 6.97 (1H, d), 6.74 (1H, d), 3.85 (3H, s), 3.82 (2H, d), 1.33 (1H, m), 0.65 (2H, m), 0.35 (2H, m)

Preparation Example 283: 4-bromo-2-(cyclopropylmethoxy)-1-fluoro-benzene

5-Bromo-2-fluoro-phenol (0.955 g, 5.0 mmol) and bromomethylcyclopropane (0.81 g, 6.0 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title

compound (1.22 g, 99 %).

¹H-NMR (CDCl₃) δ 7.06 (1H, m), 6.95 (2H, m), 3.85 (2H, d), 1.30 (1H, m), 0.66 (2H, m), 0.36 (2H, m)

Preparation Example 284: 1-bromo-3-(cyclobutoxy)-5-fluoro-benzene

3-Bromo-5-fluoro-phenol (0.955 g, 5.0 mmol) and bromocyclobutane (0.81 g, 6.0 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (1.19 g, 97 %).

¹H-NMR (CDCl₃) δ 6.84 (1H, m), 6.76 (1H, m), 6.46 (1H, m), 4.57 (1H, m), 2.44 (2H, m), 2.15 (2H, m), 1.88 (1H, m), 1.70 (1H, m)

Preparation Example 285: 1-bromo-3-cyclobutylsulfonyl-benzene

20 mL of THF and 20 mL of MeOH were added to 1-bromo-3-cyclobutylsulfonyl-benzene (0.73 g, 3.0 mmol) obtained in Preparation Example 293. Oxone (9.2 g, 30 mmol) dissolved in 40 mL of water was added thereto, and the mixture was stirred at room temperature for 5 hours. After termination of the reaction, water was added thereto, and the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.81 g, 98 %).

¹H-NMR (CDCl₃) δ 8.01 (1H, d), 7.79 (2H, m), 7.44 (1H, t), 3.85 (1H, m), 2.60 (2H, m), 2.20 (2H, m), 1.98 (2H, m)

Preparation Example 286: 1-bromo-3-(isopropoxymethyl)benzene

10 mL of 2-propanol and iron(II) sulfate heptahydrate (2.78 g, 6 mmol) were added to 1-bromo-3-(bromomethyl)benzene (2.5 g, 10 mmol), and the mixture was stirred for 36 hours under reflux. Solids were filtered through Celite and purified by column chromatography to obtain the title compound (1.5 g, 65 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, m), 7.39 (1H, m), 7.27 (1H, m), 7.19 (1H, t), 4.47 (2H, s), 3.67 (1H, m), 1.22 (6H, d)

Preparation Example 287: 1-bromo-3-(ethoxymethyl)benzene

10 mL of EtOH and iron(II) sulfate heptahydrate (2.78 g, 6 mmol) were added to 1-bromo-3-(bromomethyl)benzene (2.5 g, 10 mmol) and the mixture was stirred for 36 hours

under reflux. Solids were filtered through Celite and purified by column chromatography to obtain the title compound (1.54 g, 71 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, m), 7.40 (1H, m), 7.26 (1H, m), 7.21 (1H, t), 4.47 (2H, s), 3.53 (2H, q), 1.26 (3H, t)

Preparation Example 288: 1-bromo-3-(cyclobutoxy)-2-methyl-benzene

Step A: 3-bromo-2-methyl-phenol

31 mL of 1N sulfuric acid aqueous solution was added to 3-bromo-2-methyl-aniline (4.04 g, 21.7 mmol), and the mixture was cooled to 0°C. Sodium nitrite (6.0 M aqueous solution, 4.3 mL) was slowly added thereto. After 15 minutes, 10 mL of sulfuric acid was added thereto, and the mixture was stirred for 1 hour under reflux. The reaction solution was cooled to room temperature. After addition of water, the reaction solution was extracted with Et₂O. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (2.34 g, 58 %).

¹H-NMR (CDCl₃) δ 7.14 (1H, d), 6.92 (1H, t), 6.71 (1H, d), 4.83 (1H, brs), 2.34 (3H, s)

Step B: 1-bromo-3-(cyclobutoxy)-2-methyl-benzene

3-Bromo-2-methyl-phenol (0.2 g, 1 mmol) obtained in Step A was dissolved in 3.6 mL of DMF. Bromocyclobutane (0.17 g, 1.28 mmol) and Cs₂CO₃ (0.7 g, 2.14 mmol) were added thereto, and the mixture was stirred at 50°C for 24 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.2 g, 83 %).

¹H-NMR (CDCl₃) δ 7.12 (1H, d), 6.95 (1H, t), 6.61 (1H, d), 4.60 (1H, m), 2.44 (2H, m), 2.30 (3H, s), 2.16 (2H, m), 1.86 (1H, m), 1.69 (1H, m)

Preparation Example 289: 4-bromo-2-(cyclobutoxy)thiazole

Cyclobutanol (0.065 g, 0.9 mmol) was dissolved in 8 mL of THF. NaH (55 wt% in mineral oil, 0.04 g, 0.9 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,4-Dibromothiazole (0.2 g, 0.82 mmol) was added thereto, and the mixture was stirred for 16 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc and purified by column chromatography to

obtain the title compound (0.13 g, 68 %).

¹H-NMR (CDCl₃) δ 6.56 (1H, s), 5.17 (1H, m), 2.48 (2H, m), 2.20 (2H, m), 1.84 (1H, m), 1.65 (1H, m)

Preparation Example 290: 4-bromo-2-(cyclopropylmethoxy)thiazole

Cyclopropylmethanol (0.14 g, 2.0 mmol) was dissolved in 16 mL of THF. NaH (55 wt% in mineral oil, 0.086 g, 2.0 mmol) was added thereto, and the mixture was stirred at room temperature for 30 minutes. 2,4-Dibromothiazole (0.4 g, 1.64 mmol) was added thereto, and the mixture was stirred for 24 hours. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (0.23 g, 60 %).

¹H-NMR (CDCl₃) δ 6.57 (1H, s), 4.25 (2H, d), 1.30 (1H, m), 0.65 (2H, m), 0.37 (2H, m)

Preparation Example 291: 4-bromo-3-(cyclopropylmethoxymethyl)-5-methyl-isoxazole

Step A: 3-(cyclopropylmethoxymethyl)-5-methyl-isoxazole

5-Methylisoxazol-3-carboxylic acid methyl ester (1.5 g, 10.5 mmol) was dissolved in 27 mL of EtOH. NaBH₄ (0.8 g, 21 mmol) was slowly added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was neutralized by the addition of HCl aqueous solution, extracted with EtOAc and dried with anhydrous magnesium sulfate for concentration. The obtained concentrate was dissolved in 20 mL of DCM. 1.4 mL of SOCl₂ was added thereto, and the mixture was stirred at room temperature for 16 hours and concentrated. The mixed solution of cyclopropylmethanol (0.31 g, 4.2 mmol), NaH (55 wt% in mineral oil, 0.19 g, 4.2 mmol) and DMF (20 mL) was added thereto, and the mixture was stirred at room temperature for 72 hours. The reaction solution was concentrated under reduced pressure. After addition of ammonium chloride aqueous solution, the reaction solution was extracted with EtOAc and purified by column chromatography to obtain the title compound (0.074 g, 4 %).

¹H-NMR (CDCl₃) δ 6.05 (1H, s), 4.56 (2H, s), 3.31 (2H, d), 2.42 (3H, s), 1.07 (1H, m), 0.55 (2H, m), 0.21 (2H, m)

Step B: 4-bromo-3-(cyclopropylmethoxymethyl)-5-methyl-isoxazole

3-(Cyclopropylmethoxymethyl)-5-methyl-isoxazole (0.074 g, 0.44 mmol) obtained in Step A was dissolved in 1.5 mL of DMF. *N*-bromosuccinimide (0.078 g, 0.44 mmol) was added thereto, and the mixture was stirred at room temperature for 48 hours. The reaction solution was concentrated under reduced pressure. After addition of water, the reaction solution was extracted with Et₂O and purified by column chromatography to obtain the title compound (0.069 g, 55 %).

¹H-NMR (CDCl₃) δ 4.57 (2H, s), 3.35 (2H, d), 2.42 (3H, s), 1.10 (1H, m), 0.54 (2H, m), 0.23 (2H, m)

Preparation Example 292: 4-bromo-5-(cyclobutoxy)-3-methyl-isothiazole

Cyclobutanol (0.32 g, 4.4 mmol) and 4,5-dibromo-3-methyl-isothiazole (1.03 g, 4.0 mmol, WO2013 132376A1) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.120 g, 12 %).

¹H-NMR (CDCl₃) δ 4.68 (1H, m), 2.52 (2H, m), 2.45 (3H, s), 2.35 (2H, m), 1.94 (1H, m), 1.72 (1H, m)

Preparation Example 293: 1-bromo-3-cyclobutylsulfanyl-benzene

3-Bromo-benzenethiol (3 g, 15.87 mmol) and bromocyclobutane (2.25 mL, 23.80 mmol) were reacted in the same manner as in Preparation Example 17 to obtain the title compound (3.36 g, 87 %).

¹H-NMR (CDCl₃) δ 7.33 (1H, s), 7.26 (1H, m), 7.12 (2H, m), 3.89 (1H, m), 2.47 (2H, m), 2.07 (3H, m), 2.04 (1H, m).

Preparation Example 294: 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine

4-Bromo-phenylamine (1 g, 5.81 mmol), bis(pinacolato)diboron (1.6 g, 6.39 mmol) and potassium acetate (1.43 g, 14.53 mmol) were dissolved in 20 mL of 1,4-dioxane and charged with N₂ gas for 5 minutes. PdCl₂(dppf)-DCM (0.425 g, 0.58 mmol) was added thereto, and the mixture was stirred at 80°C for 16 hours. The reaction solution was filtered through Celite, diluted with water and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title

compound (0.764 g, 60 %).

¹H-NMR (CDCl₃) δ 7.60 (2H, d), 6.66 (2H, d), 3.82 (2H, br), 1.31 (12H, s).

Preparation Example 295: 4-(6-cyclobutoxy-pyridin-2-yl)-phenylamine

2-Bromo-6-cyclobutoxy-pyridine (0.251 g, 1.37 mmol) obtained in Preparation Example 186 and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenylamine (0.2 g, 0.91 mmol) obtained in Preparation Example 294 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.17 g, 77 %).

¹H-NMR (CDCl₃) δ 7.85 (2H, d), 7.55 (1H, t), 7.21 (1H, d), 6.72 (2H, d), 6.51 (1H, d), 5.26 (1H, m), 3.79 (2H, br), 2.51 (2H, m), 2.18 (2H, m), 1.86 (1H, m), 1.72 (1H, m).

Preparation Example 296: 4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-[3-(4-methoxyphenoxy)-isoxazol-5-ylmethyl]-amine

4-(6-Cyclobutoxy-pyridin-2-yl)-phenylamine (0.17 g, 0.71 mmol) obtained in Preparation Example 295 and 3-[(4-methoxyphenyl)methoxy]isoxazol-5-carbaldehyde (0.122 g, 0.71 mmol) obtained in Preparation Example 61 were dissolved in 2.3 mL of DCE. Sodium triacetoxyborohydride (0.225 g, 1.06 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of sodium bicarbonate aqueous solution, the reaction solution was extracted with DCM and purified by column chromatography. The obtained compound was dissolved in 2 ml of methanol. NaBH₄ (0.053 g, 1.41 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. The reaction solution was diluted with water and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain the title compound (0.1 g, 30 %).

¹H-NMR (CDCl₃) δ 7.87 (2H, d), 7.54 (1H, t), 7.34 (2H, d), 7.20 (1H, d), 6.90 (2H, d), 6.69 (2H, d), 6.53 (1H, d), 5.81 (1H, s), 5.25 (1H, m), 4.40 (2H, d), 3.80 (3H, s), 2.52 (2H, m), 2.18 (2H, m), 1.83 (1H, m), 1.72 (1H, m).

Preparation Example 297: 1-bromo-3-(cyclopentoxy)benzene

The title compound was obtained by the method disclosed in WO 2014/209034 A1.

¹H NMR (CDCl₃) δ 7.11 (1H, t), 7.02 (2H, m), 6.80 (1H, dd), 4.72 (1H, m), 1.94-1.73 (6H, m), 1.62 (2H, m)

Preparation Example 298: 3,6-dichloro-2-cyclobutoxy-pyridine**Step A: 6-chloro-2-cyclobutoxy-3-nitro-pyrimidine**

2,6-Dichloro-3-nitro-pyrimidine (1.93 g, 10.0 mmol) and cyclobutanol (0.645 g, 9.0 mmol) were reacted in the same manner as in Preparation Example 227 to obtain the title compound (1.92 g, 93 %).

¹H-NMR (CDCl₃) δ 8.27 (1H, d), 7.04 (2H, t), 5.39 (1H, m), 2.56 (2H, m), 2.30 (2H, m), 1.93 (1H, m), 1.78 (1H, m)

Step B: 3,6-dichloro-2-cyclobutoxy-pyrimidine

Methanol (60 mL) was added to nickel(II) chloride hexahydrate (NiCl₂ 6H₂O)(1.0 g, 4.21 mmol), and sodium borohydride (0.30 g, 7.93 mmol) was then added thereto little by little. The mixture was stirred for 30 minutes, and 6-chloro-2-cyclobutoxy-3-nitro-pyrimidine (1.92 g, 8.40 mmol) obtained in Step A was added thereto. Sodium borohydride (0.65 g, 17.2 mmol) was slowly added thereto for 10 minutes, and the mixture was stirred for 30 minutes. The reaction product was filtered through Celite, and the filtrate was concentrated under reduced pressure and extracted with water and EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography to obtain 6-chloro-2-cyclobutoxy-pyridin-3-ylamine (1.37 g, 82 %).

6-Chloro-2-cyclobutoxy-pyridin-3-ylamine (0.60 g, 3.0 mmol), copper chloride(II) (0.484 g, 3.6 mmol) and tBuONO (0.464 g, 4.5 mmol) were reacted in the same manner as in Step C of Preparation Example 84 to obtain the title compound (0.341 g, 52 %).

¹H-NMR (CDCl₃) δ 7.58 (1H, d), 6.87 (1H, d), 5.26 (1H, m), 2.53 (2H, m), 2.24 (2H, m), 1.88 (1H, m), 1.74 (1H, m)

Preparation Example 299: 2-chloro-6-cyclobutylsulfanyl-pyridine

The title compound was obtained by the method disclosed in WO 2014/209034 A1.

¹H NMR (CDCl₃) δ 7.40 (1H, t), 6.98 (2H, m), 4.30 (1H, m), 2.56 (2H, m), 2.08 (4H, m)

Preparation Example 300: 2-chloro-6-cyclopropylmethoxy-4-methyl-pyridine

Cyclopropylmethanol (0.979 g, 13.58 mmol) and 2,6-dichloro-4-methyl-pyridine (2 g,

12.34 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.62 g, 66 %).

¹H-NMR (CDCl₃) δ 6.75 (1H, s), 6.43 (1H, s), 5.18 (1H, m), 2.48 (2H, m), 2.30 (3H, s), 2.14 (2H, m), 1.84 (1H, m), 1.68 (1H, m).

Preparation Example 301: 2-chloro-6-isopropoxy-pyrazine

Isopropanol (1.85 ml, 24.16 mmol) and 2,6-dichloropyrazine (3 g, 20.13 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (2.77 g, 79 %).

¹H-NMR (CDCl₃) δ 8.04-8.09 (2H, d), 5.28 (1H, m), 1.36 (6H, d).

Preparation Example 302: 2-chloro-6-ethoxy-pyrazine

Ethanol (1.17 ml, 24.16 mmol) and 2,6-dichloropyrazine (3 g, 20.13 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (2.63 g, 82 %).

¹H-NMR (CDCl₃) δ 8.12 (2H, d), 4.39 (2H, q), 1.40 (3H, t).

Preparation Example 303: {(R)-1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid methyl ester

Step A: 2-((R)-1-tert-butoxycarbonyl-pyrrolidin-3-yl)-malonic acid diethyl ester

(R)-3-hydroxy-pyrrolidin-1-carboxylic acid tert-butyl ester (1 g, 5.34 mmol) was dissolved in 18 mL of MC. Et₃N (2.22 ml, 16.02 mmol) was added thereto at 0°C, and MsCl (0.62 ml, 8.01 mmol) was then added thereto. The mixture was stirred at room temperature for 16 hours. The reaction solution was diluted with water and extracted with MC. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography to obtain (R)-3-methanesulfonyloxy-pyrrolidin-1-carboxylic acid tert-butyl ester. At another flask, diethyl malonate (1.7 ml, 11.3 mmol) was dissolved in 10 ml of ethanol. NaOEt (21%wt, 4.2 ml, 11.3 mmol) was added thereto, and the mixture was stirred at 40°C for 1 hour. The obtained (R)-3-methanesulfonyloxy-pyrrolidin-1-carboxylic acid tert-butyl ester (1.5 g, 5.65 mmol) was dissolved in 8 ml of ethanol and added thereto. The mixture was stirred at 80°C for 16 hours. The reaction solution was adjusted to pH 2 by the use of 6N HCl aqueous solution and extracted with ether. The organic layer was dried with anhydrous

magnesiumsulfate and purified by column chromatography to obtain the title compound (0.785 g, 44 %).

¹H-NMR (CDCl₃) δ 4.21 (4H, m), 3.63 (1H, m), 3.47 (1H, m), 3.25 (2H, m), 3.01 (1H, m), 2.80 (1H, m), 2.06 (1H, m), 1.62 (1H, m), 1.42 (9H, s), 1.26 (6H, m).

Step B: (R)-3-carboxymethyl-pyrrolidin-1-carboxylic acid tert-butyl ester

2-((R)-1-tert-butoxycarbonyl-pyrrolidin-3-yl)-malonic acid diethyl ester (0.785 g, 2.38 mmol) obtained in Step A was dissolved in 8 mL of THF. 6N NaOH (2 ml, 11.9 mmol) was added thereto, and the mixture was stirred at 40°C for 16 hours. The reaction solution was adjusted to pH 2 by the use of 6N HCl aqueous solution and extracted with EtOAc. The organic layer was dried with anhydrous magnesiumsulfate and concentrated under reduced pressure to obtain 2-((R)-1-tert-butoxycarbonyl-pyrrolidin-3-yl)-malonic acid. The obtained compound was dissolved in 4.5 ml of toluene. 0.06 ml of DMSO was added thereto, and the mixture was stirred for 4 hours under reflux. After addition of 10% citric acid, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography to obtain the title compound (0.29 g, 53 %).

¹H-NMR (CDCl₃) δ 3.62 (1H, m), 3.45 (1H, m), 3.29 (1H, m), 2.96 (1H, m), 2.56 (1H, m), 2.44 (2H, d), 2.07 (1H, m), 1.57 (1H, m), 1.44 (9H, s).

Step C: (R)-1-(2,6-difluoro-4-nitro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester

(R)-3-carboxymethyl-pyrrolidin-1-carboxylic acid tert-butyl ester (0.29 g, 1.26 mmol) obtained in Step B was dissolved in 10 ml of MC. 0.25 M CH₂N₂ (10 ml, 2.53 mmol) was added thereto at 0°C, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure to obtain (R)-3-methoxycarbonylmethyl-pyrrolidin-1-carboxylic acid tert-butyl ester. The obtained compound was dissolved in 5 ml of MC. HCl (1.58 mL, 6.32 mmol, 4 M 1,4-dioxane solution) was added thereto at 0°C, and the mixture was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure to obtain hydrochloric acid salt of (R)-pyrrolidin-3-yl-acetic acid methyl ester. The obtained compound and 3,4,5-trifluoronitrobenzene (0.163 ml, 1.42 mmol) were reacted in the same manner as in Step A of Preparation Example 84 to obtain the title compound (0.38 g, 98 %).

¹H-NMR (CDCl₃) δ 7.73 (2H, m), 3.91-3.75 (3H, m), 3.71 (3H, s), 3.48 (1H, m), 2.64 (1H, m), 2.48 (2H, m), 2.18 (1H, m), 1.65 (1H, m).

Step D: [(R)-1-(4-amino-2,6-difluoro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester

(R)-1-(2,6-difluoro-4-nitro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester (0.38 g, 1.26 mmol) obtained in Step C was dissolved in 4 mL of EtOAc. 0.04 g of 10 wt% Pd/C was added thereto, and the mixture was stirred for 24 hours under hydrogen atmosphere. Solids were filtered and concentrated under reduced pressure to obtain the title compound (0.315 g, 92 %).

¹H-NMR (CDCl₃) δ 6.17 (2H, m), 3.66 (3H, s), 3.41 (1H, m), 3.28 (2H, m), 2.98 (1H, m), 2.66 (1H, m), 2.45 (2H, m), 2.13 (1H, m), 1.60 (1H, m).

Step E: [(R)-1-(4-bromo-2,6-difluoro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester

[(R)-1-(4-amino-2,6-difluoro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester (0.315 g, 1.16 mmol) obtained in Step D was dissolved in 3 mL of CH₃CN. CSA (0.345 g, 1.40 mmol), *tert*-butyl nitrite (0.166 mL, 1.40 mmol), TBAB (0.751 g, 2.33 mmol) and CuBr₂ (0.003 g, 0.01 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. Solids were filtered and concentrated under reduced pressure. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography to obtain the title compound (0.2 g, 51 %).

¹H-NMR (CDCl₃) δ 6.93 (2H, m), 3.68 (3H, s), 3.59 (2H, m), 3.47 (1H, m), 3.23 (1H, m), 2.61 (1H, m), 2.45 (2H, m), 2.11 (1H, m), 1.59 (1H, m).

Step F: {(R)-1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid methyl ester

[(R)-1-(4-bromo-2,6-difluoro-phenyl)-pyrrolidin-3-yl]-acetic acid methyl ester (0.225 g, 0.67 mmol) obtained in Step E was reacted in the same manner as in Preparation Example 294 to obtain the title compound (0.09 g, 33 %).

¹H-NMR (CDCl₃) δ 7.16 (2H, m), 3.71 (5H, m), 3.60 (1H, m), 3.32 (1H, m), 2.61 (1H, m), 2.44 (2H, d), 2.11 (1H, m), 1.61 (1H, m), 1.30 (12H, s)

Preparation Example 304: 3-[8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiochroman-2-yl]propanoic acid ethyl ester

Step A: 4-bromo-2-fluoro-benzenethiol

The title compound was obtained by the method disclosed in WO 2006/21759 A1.

^1H NMR (CDCl_3) δ 7.24 (2H, m), 7.16 (2H, m), 3.58 (1H, s)

Step B: 6-bromo-8-fluoro-4-oxo-thiochroman-2-carboxylic acid

4-Bromo-2-fluoro-benzenethiol (3.0 g, 14.48 mmol) and furan-2,5-dione (1.4 g, 14.48 mmol) were dissolved in 50 mL of toluene and heated to 50°C. TEA (0.1 mL) was slowly added thereto, and the mixture was stirred at 50°C for 1 hour. The reaction solution was concentrated under reduced pressure, dissolved in 50 mL of DCM and cooled to 0°C. AlCl_3 (2.9 g, 21.73 mmol) was added thereto, and the mixture was stirred at room temperature for 1 hour. After slowly adding cold concentrated HCl solution dropwise, the reaction solution was extracted with DCM. The organic solvent was dried with MgSO_4 , concentrated under reduced pressure and solidified with Et_2O to obtain the title compound (2.3 g, 52 %).

^1H -NMR ($\text{DMSO}-d_6$) δ 7.89 (2H, m), 4.55 (1H, t), 3.14 (2H, m)

Step C: 6-bromo-8-fluoro-4-oxo-thiochroman-2-carboxylic acid methyl ester

6-Bromo-8-fluoro-4-oxo-thiochroman-2-carboxylic acid (2.3 g, 7.54 mmol) obtained in Step B was dissolved in 50 mL of methanol. Concentrated sulfuric acid (0.8 mL) was added thereto, and the mixture was stirred for 18 hours under reflux. The reaction solution was concentrated under reduced pressure, extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (1.5 g, 62 %).

^1H -NMR (CDCl_3) δ 8.08 (1H, m), 7.37 (1H, dd), 4.15 (1H, t), 3.76 (3H, s), 3.18 (2H, d)

Step D: 6-bromo-8-fluoro-thiochroman-2-carboxylic acid methyl ester

6-Bromo-8-fluoro-4-oxo-thiochroman-2-carboxylic acid methyl ester (1.5 g, 4.70 mmol) obtained in Step C was dissolved in 20 mL of TFA. Triethylsilane (1.5 mL, 9.40 mmol) was added thereto, and the mixture was stirred at room temperature for 3 hours. The reaction solution was concentrated under reduced pressure, extracted with EtOAc, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.34 g, 24 %).

¹H-NMR (CDCl₃) δ 7.06 (2H, m), 4.01 (1H, m), 3.78 (3H, s), 3.01~2.93 (1H, m), 2.84~2.77 (1H, m), 2.34~2.20 (2H, m)

Step E: 6-bromo-8-fluoro-thiochroman-2-carboxylic acid

6-Bromo-8-fluoro-thiochroman-2-carboxylic acid methyl ester (0.340 g, 1.11 mmol) obtained in Step D was dissolved in each 5 mL of THF, MeOH and 1N NaOH aqueous solution, and the mixture was stirred at room temperature for 2 hours. After removing of organic solvent, the reaction solution was adjusted to pH 3 by the use of 1N HCl aqueous solution and extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO₄ and concentrated under reduced pressure to obtain the title compound (0.280 g, 86 %).

Step F: (6-bromo-8-fluoro-thiochroman-2-yl)-methanol

6-Bromo-8-fluoro-thiochroman-2-carboxylic acid (0.28 g, 0.96 mmol) obtained in Step E was dissolved in 10 mL of THF and cooled to -20°C. Isobutyl chloroformate (0.14 mL, 1.06 mmol) and NMM (0.12 mL, 1.10 mmol) was added thereto, and the mixture was stirred at the same temperature for 1.5 hours. At another reactor, NaBH₄ (0.073 g, 1.92 mmol) was dissolved in 4 mL of THF and 1 mL of MeOH and cooled to -78°C. The above reaction solution was filtered through Celite and added thereto. The mixture was stirred at room temperature for 2 hours. The reaction solution was extracted with EtOAc, dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.175 g, 66 %).

¹H-NMR (CDCl₃) δ 7.06 (2H, m), 3.77 (2H, m), 3.49 (1H, m), 2.90~2.73 (2H, m), 2.22 (1H, m), 1.88 (2H, m)

Step G: (E)-3-(6-bromo-8-fluoro-thiochroman-2-yl)prop-2-enoic acid ethyl ester

Oxalyl chloride (0.1 mL, 0.95 mmol) was added to 5 mL of DCM and cooled to -78°C. DMSO (0.11 mL, 1.57 mmol) was slowly added thereto, and the mixture was stirred for 0.5 hour. The solution in which (6-bromo-8-fluoro-thiochroman-2-yl)-methanol (0.175 g, 0.63 mmol) obtained in Step F was dissolved in 2 mL of DCM, and TEA (0.35 mL, 2.52 mmol) were sequentially added thereto, and the mixture was stirred at room temperature for 1 hour. (Carbethoxymethylene)triphenylphosphorane (0.263 g, 0.76 mmol) was added thereto, and the mixture was stirred at room temperature for 18 hours. After addition of water, the reaction solution was extracted with DCM to separate an organic layer. The organic layer was dried

with MgSO₄ and purified by column chromatography to obtain the title compound (0.180 g, 83 %).

¹H-NMR (CDCl₃) δ 7.06 (2H, m), 6.91 (1H, m), 6.03 (1H, d), 4.19 (2H, q), 4.01 (1H, m), 2.82 (2H, m), 2.28 (1H, m), 1.95 (1H, m), 1.28 (3H, t)

Step H: 3-(6-bromo-8-fluoro-thiochroman-2-yl)propanoic acid ethyl ester

(E)-3-(6-bromo-8-fluoro-thiochroman-2-yl)-acetic acid ethyl ester (0.180 g, 0.52 mmol) obtained in Step G was dissolved in 10 mL of DME. *p*-Toluenesulfonyl hydrazide (0.680 g, 3.65 mmol) was added thereto little by little and heated to 90°C. Sodium acetate (0.427 g, 5.20 mmol, 1.4 M aqueous solution) was added thereto, and the mixture was stirred for 18 hours under reflux. After addition of water, the reaction solution was extracted with DCM. The organic layer was dried with MgSO₄ and purified by column chromatography to obtain the title compound (0.030 g, 17 %).

¹H-NMR (CDCl₃) δ 7.02 (2H, m), 4.14 (2H, q), 3.29 (1H, m), 2.83 (2H, m), 2.49 (2H, m), 2.21 (1H, m), 2.03 (1H, m), 1.94 (1H, m), 1.78 (1H, m), 1.25 (3H, t)

Step I: 3-[8-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiochroman-2-yl]propanoic acid ethyl ester

3-(6-Bromo-8-fluoro-thiochroman-2-yl)-propionic acid ethyl ester (0.070 mg, 0.21 mmol) obtained in Step H was reacted in the same manner as in Step D of Preparation Example 1 to obtain the title compound (0.046 g, 57 %).

¹H-NMR (CDCl₃) δ 7.27 (2H, m), 4.14 (2H, q), 3.30 (1H, m), 2.88 (2H, m), 2.51 (2H, m), 2.22 (1H, m), 2.00 (2H, m), 1.82 (1H, m), 1.32 (12H, s), 1.26 (3H, t)

Preparation Example 305: 1-iodo-2,3-dipropoxy-benzene

7 mL of DMF was added to 3-iodo benzene-1,2-diol (0.28 g, 1.18 mmol), 1-iodopropane (0.3 mL, 2.96 mmol) and K₂CO₃ (0.49 g, 3.54 mmol), and the mixture was stirred at 80°C for 16 hours. The reaction solution was concentrated under reduced pressure and purified by column chromatography to obtain the title compound (0.24 g, 64 %).

¹H-NMR (CDCl₃) δ 7.32 (1H, m), 6.85 (1H, m), 6.74 (1H, t), 3.94 (4H, m), 1.83 (4H, m), 1.07 (6H, m)

Preparation Example 306: 2-(cyclopropylmethoxy)-6-iodo-3-methoxy-pyridine**Step A: 2-bromo-6-iodo-3-methoxy-pyridine**

The title compound was obtained by the method disclosed in WO 2006/21759 A1.

$^1\text{H-NMR}$ (MeOH-d_4) δ 7.64 (1H, d), 7.08 (1H, d), 3.83 (3H, s)

Step B: 2-(cyclopropylmethoxy)-6-iodo-3-methoxy-pyridine

Cyclopropyl methanol (0.54 mL, 6.62 mmol) was dissolved in dry DMF (5 mL). NaH (60 %)(0.248 g, 6.21 mmol) was slowly added dropwise thereto at 0°C, and the mixture was stirred for 30 minutes. 2-Bromo-6-iodo-3-methoxy-pyridine (1.3 g, 4.14 mmol) obtained in Step A was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was purified by column chromatography to obtain the title compound (0.89 g, 70 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.20 (1H, d), 6.73 (1H, d), 4.19 (2H, d), 3.84 (3H, s), 1.31 (1H, m), 0.60 (2H, m), 0.38 (2H, m)

Preparation Example 307: 2-(cyclobutoxy)-6-iodo-3-methoxy-pyridine

2-Bromo-6-iodo-3-methoxy-pyridine (1.5 g, 4.78 mmol) and cyclobutanol (0.6 mL, 7.17 mmol) were reacted in the same manner as in Preparation Example 306 to obtain the title compound (0.92 g, 63 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.19 (1H, d), 6.72 (1H, d), 5.22 (1H, m), 3.83 (3H, s), 2.48 (2H, m), 2.21 (2H, m), 1.83 (1H, m), 1.67 (1H, m)

Preparation Example 308: 6-(cyclobutoxy)-1H-indole

1H-indol-6-ol (0.1 g, 0.75 mmol) and bromocyclobutane (0.203 g, 1.50 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (0.068 g, 28 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.99 (1H, brs), 7.48 (1H, d), 7.07 (1H, m), 6.77 (1H, m), 6.73 (1H, m), 6.46 (1H, m), 4.66 (1H, m), 2.46 (2H, m), 2.20 (2H, m), 1.85 (1H, m), 1.70 (1H, m)

Preparation Example 309: 6-(cyclobutoxy)-1H-indazole

1H-indazol-6-ol (0.5 g, 3.72 mmol) and bromocyclobutane (0.7 mL, 1.50 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (0.4 g,

57 %).

¹H-NMR (CDCl₃) δ 10.07 (1H, brs), 7.96 (1H, m), 7.60 (1H, m), 6.78 (1H, m), 6.73 (1H, m), 4.68 (1H, m), 2.50 (2H, m), 2.22 (2H, m), 1.89 (1H, m), 1.74 (1H, m)

Preparation Example 310: 5-(cyclobutoxy)-1H-indole

1H-indol-5-ol (0.1 g, 0.75 mmol) and bromocyclobutane (0.203 g, 1.50 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (0.021 g, 19 %).

¹H-NMR (CDCl₃) δ 8.06 (1H, s), 7.27 (1H, m), 7.16 (1H, t), 7.00 (1H, m), 6.81 (1H, m), 6.45 (1H, m), 4.66 (1H, m), 2.47 (2H, m), 2.19 (2H, m), 1.85 (1H, m), 1.69 (1H, m)

Preparation Example 311: 6-(cyclopropylmethoxy)-1H-indole

1H-indol-6-ol (0.05 g, 0.38 mmol) and bromomethylcyclopropane (0.061 g, 0.45 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (0.018 g, 24 %).

¹H-NMR (CDCl₃) δ 7.99 (1H, s), 7.50 (1H, d), 7.09 (1H, m), 6.89 (1H, m), 6.81 (1H, m), 6.47 (1H, m), 3.83 (2H, d), 1.31 (1H, m), 0.64 (2H, m), 0.36 (2H, m)

Preparation Example 312: 2-chloro-4-(4-chloro-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.16 g, 7.78 mmol) and 4-chloro-phenol (1.0 g, 7.78 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.735 g, 39 %).

¹H-NMR (CDCl₃) δ 8.45 (1H, d), 7.40 (2H, m), 7.10 (2H, m), 6.83 (1H, d)

Preparation Example 313: 2-chloro-4-phenoxy-pyrimidine

2,4-Dichloro-pyrimidine (1.6 g, 10.62 mmol) and phenol (1.0 g, 10.62 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.9 g, 86 %).

¹H-NMR (CDCl₃) δ 8.43 (1H, d), 7.46 (2H, m), 7.31 (1H, m), 7.15 (2H, m), 6.77 (1H, d)

Preparation Example 314: 2-chloro-4-(4-fluoro-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.3 g, 8.92 mmol) and 4-fluoro-phenol (1.0 g, 8.92 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.1 g, 55 %).

¹H-NMR (CDCl₃) δ 8.44 (1H, d), 7.12 (4H, d), 6.81 (1H, d)

Preparation Example 315: 2-chloro-4-(4-pyridin-3-yloxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.57 g, 10.51 mmol) and pyridin-3-ol (1.0 g, 10.51 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.52 g, 24 %).

¹H-NMR (CDCl₃) δ 8.56 (1H, dd), 8.53 (1H, d), 8.50 (1H, d), 7.57 (1H, m), 7.40 (1H, m), 6.93 (1H, d)

Preparation Example 316: 2-chloro-4-(4-fluoro-phenoxy)-pyrazine

2,6-Dichloro-pyrazine (1.3 g, 8.92 mmol) and 4-fluoro-phenol (1.0 g, 8.92 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.1 g, 55 %).

¹H-NMR (CDCl₃) δ 8.29 (2H, s), 7.12 (4H, m)

Preparation Example 317: 2-chloro-4-(4-methoxy-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.2 g, 8.05 mmol) and 4-methoxy-phenol (1.0 g, 8.05 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.5 g, 79 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, d), 7.07 (2H, m), 6.94 (2H, m), 6.74 (1H, d), 3.83 (3H, s)

Preparation Example 318: 2-chloro-4-(4-fluoro-phenoxy)-6-methyl-pyrimidine

2,4-Dichloro-6-methyl-pyrimidine (1.45 g, 8.92 mmol) and 4-fluoro-phenol (1.0 g, 8.92 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.7 g, 80 %).

¹H-NMR (CDCl₃) δ 7.11 (4H, m), 6.61 (1H, d)

Preparation Example 319: 2-chloro-4-p-tolyloxy-pyrimidine

2,4-Dichloro-pyrimidine (1.38 g, 9.24 mmol) and 4-methyl-phenol (1.0 g, 9.24 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.4 g, 69 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, d), 7.24 (2H, m), 7.05 (2H, m), 6.75 (1H, d), 2.38 (3H, s)

Preparation Example 320: 2-chloro-4-(3,4-difluoro-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.14 g, 7.69 mmol) and 3,4-difluoro-phenol (1.0 g, 7.69 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.8 g, 43 %).

¹H-NMR (CDCl₃) δ 8.47 (1H, d), 7.24 (1H, m), 7.04 (1H, m), 6.93 (1H, m), 6.85 (1H, d)

Preparation Example 321: 2-[2,6-difluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy-methyl]-cyclopropanecarboxylic acid ethyl ester

2,6-Difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.2 g, 0.78 mmol) obtained in Step B of Preparation Example 16, 2-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester (0.17 g, 1.17 mmol), triphenylphosphine (0.51 g, 1.95 mmol) and diisopropyl azodicarboxylate (0.39 g, 1.95 mmol) were reacted in the same manner as in Preparation Example 62 to obtain the title compound (0.25 g, 84 %).

¹H-NMR (CDCl₃) δ 7.30 (2H, m), 4.13 (3H, m), 4.03 (1H, m), 1.86 (1H, m), 1.64 (1H, m), 1.32 (12H, s), 1.26 (4H, m), 0.93 (1H, m)

Preparation Example 322: 2-[2-chloro-6-fluoro-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenoxy-methyl]-cyclopropanecarboxylic acid ethyl ester

2-Chloro-6-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (0.75 g, 2.8 mmol), 2-hydroxymethyl-cyclopropanecarboxylic acid ethyl ester (0.48 g, 6.9 mmol), triphenylphosphine (1.80 g, 6.9 mmol) and diisopropyl azodicarboxylate (1.39 g, 6.9 mmol) were reacted in the same manner as in Preparation Example 62 to obtain the title compound (0.82 g, 75 %).

¹H-NMR (CDCl₃) δ 7.58 (1H, s), 7.41 (1H, d), 4.13 (3H, m), 3.99 (1H, m), 1.89 (1H, m), 1.65 (1H, m), 1.32 (12H, s), 1.25 (4H, m), 0.95 (1H, m)

Preparation Example 323: 1-bromo-3-cyclobutylmethoxy-benzene

3-Bromo-phenol (1.2 g, 6.94 mmol), Cs₂CO₃ (4.52 g, 13.9 mmol) and bromomethyl-cyclobutane (0.86 mL, 7.63 mmol) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (1.70 g, 99 %).

¹H-NMR (CDCl₃) δ 7.12 (1H, m), 7.06 (2H, m), 6.83 (1H, m), 3.90 (2H, d), 2.76 (1H, m), 2.14 (2H, m), 1.96 (4H, m)

Preparation Example 324: 2-chloro-6-cyclobutylmethoxy-pyridine

6-Chloro-pyridin-2-ol (2.0 g, 15.4 mmol), K₂CO₃ (4.27 g, 30.1 mmol) and bromomethyl-cyclobutane (1.91 mL, 17.0 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (2.30 g, 75 %).

¹H-NMR (CDCl₃) δ 7.50 (1H, t), 6.87 (1H, d), 6.64 (1H, d), 4.26 (2H, d), 2.76 (1H, m), 2.12 (2H, m), 1.94 (4H, m)

Preparation Example 325: 2-bromo-4-cyclobutylmethoxy-1-methyl-benzene

3-Bromo-4-methyl-phenol (0.5 g, 2.67 mmol), Cs₂CO₃ (1.74 g, 5.35 mmol) and bromomethyl-cyclobutane (0.33 mL, 2.94 mmol) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.65 g, 95 %).

¹H-NMR (CDCl₃) δ 7.09 (2H, m), 6.76 (1H, m), 3.88 (2H, d), 2.76 (1H, m), 2.31 (3H, s), 2.13 (2H, m), 1.95 (4H, m)

Preparation Example 326: 4-bromo-1-chloro-2-cyclopropylmethoxy-benzene

5-Bromo-2-chloro-phenol (0.5 g, 2.41 mmol), Cs₂CO₃ (1.60 g, 4.82 mmol) and bromomethyl-cyclopropane (0.26 mL, 2.65 mmol) were reacted in the same manner as in Preparation Example 28 to obtain the title compound (0.60 g, 95 %).

¹H-NMR (CDCl₃) δ 7.22 (1H, d), 7.02 (2H, m), 3.87 (2H, d), 1.32 (1H, m), 0.67 (2H, m), 0.40 (2H, m)

Preparation Example 327: 4-bromo-2-cyclopropylmethoxy-1-methyl-benzene

5-Bromo-2-methyl-phenol (0.5 g, 2.67 mmol), Cs₂CO₃ (1.70 g, 5.35 mmol) and bromomethyl-cyclopropane (0.29 mL, 2.94 mmol) were reacted in the same manner as in

Preparation Example 28 to obtain the title compound (0.63 g, 98 %).

$^1\text{H-NMR}$ (CDCl_3) δ 6.97 (2H, m), 6.89 (1H, s), 3.79 (2H, d), 2.18 (3H, s), 1.26 (1H, m), 0.63 (2H, m), 0.35 (2H, m)

Preparation Example 328: 7-bromo-5-chloro-2-methyl-benzofuran

Step A: 2-bromo-4-chloro-1-prop-2-ynyloxy-benzene

2-Bromo-4-chloro-phenol (1.0 g, 4.82 mmol), 3-bromo-propyne (0.79 g, 5.30 mmol) and K_2CO_3 (1.47 g, 10.6 mmol) were reacted in the same manner as in Preparation Example 12 to obtain the title compound (1.1 g, 93 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.55 (1H, d), 7.24 (1H, m), 6.99 (1H, d), 4.76 (2H, d), 2.55 (1H, t)

Step B: 7-bromo-5-chloro-2-methyl-benzofuran

2-Bromo-4-chloro-1-prop-2-ynyloxy-benzene (1.1 g, 4.48 mmol) obtained in Step A and cesium fluoride (0.95 g, 6.27 mmol) were dissolved in 7.5 mL of diethyl-phenyl-amine, and stirred at 210°C for 4 hours. The reaction solution was cooled to room temperature and diluted with hexane. After washing with 1N HCl three times, the organic layer was separated. The organic layer was dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.65 g, 59 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.37 (2H, d), 6.39 (1H, s), 2.49 (3H, s)

Preparation Example 329: 2-chloro-4-cyclobutoxy-5-fluoro-pyrimidine

2,4-Dichloro-5-fluoro-pyrimidine (0.50 g, 2.99 mmol) and cyclobutanol (0.26 mL, 3.29 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.57 g, 89 %).

$^1\text{H-NMR}$ (400HMz, CDCl_3); δ 8.17 (d, 1H), 5.37-5.29 (m, 1H), 2.55-2.48 (m, 2H), 2.30-2.20 (m, 2H), 1.94-1.86 (m, 1H), 1.77-1.67 (m, 1H)

Preparation Example 330: 2-chloro-4-cyclopropylmethoxy-5-fluoro-pyrimidine

2,4-Dichloro-5-fluoro-pyrimidine (0.50 g, 2.99 mmol) and cyclopropylmethanol (0.27 mL, 3.29 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.52 g, 81 %).

$^1\text{H-NMR}$ (400HMz, CDCl_3); δ 8.19-8.18 (d, 1H), 4.32-4.31 (d, 2H), 1.37-1.30 (m, 1H),

0.70-0.65 (m, 2H), 0.43-0.39 (m, 2H)

Preparation Example 331: 2-chloro-5-fluoro-4-isobutoxy-pyrimidine

2,4-Dichloro-5-fluoro-pyrimidine (0.50 g, 2.99 mmol) and 2-methyl-propan-1-ol (0.30 ml, 3.29 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.51 g, 79 %).

¹H-NMR (400HMz, CDCl₃); δ 8.18 (d, 1H), 4.25-4.10 (d, 2H), 2.21-2.11 (m, 1H), 1.05-1.03 (d, 6H)

Preparation Example 332: 2-chloro-6-(3-methoxy-propoxy)-pyridine

2,6-Dichloropyridine (0.50 g, 3.38 mmol) and 3-methoxy-propan-1-ol (0.40 ml, 4.05 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.37 g, 51 %).

¹H-NMR (400HMz, CDCl₃); δ 8.18 (d, 1H), 4.25-4.10 (d, 2H), 2.21-2.11 (m, 1H), 1.05-1.03 (d, 6H)

Preparation Example 333: 2-chloro-6-(tetrahydro-thiopyran-4-yloxy)-pyridine

2,6-Dichloropyridine (0.50 g, 3.38 mmol) and tetrahydro-2H-thiopyran-4-ol (0.44 g, 3.72 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.36 g, 44 %).

¹H-NMR (400HMz, CDCl₃); δ 8.18 (d, 1H), 4.25-4.10 (d, 2H), 2.21-2.11 (m, 1H), 1.05-1.03 (d, 6H)

Preparation Example 334: 2-chloro-5-fluoro-4-propoxy-pyrimidine

2,4-Dichloro-5-fluoro-pyrimidine (0.40 g, 2.40 mmol) and propan-1-ol (0.20 ml, 2.64 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.35 g, 77 %).

¹H-NMR (500HMz, CDCl₃); δ 8.17-8.16 (d, 1H), 4.43-4.41 (t, 2H), 1.89-1.82 (m, 1H), 1.05-1.02 (t, 3H)

Preparation Example 335: 2-chloro-4-(3-methyl-butoxy)-pyrimidine

2,4-Dichloropyrimidine (0.50 g, 3.36 mmol) and 3-methylbutan-1-ol (0.40 ml, 3.69

mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.59 g, 87 %).

¹H-NMR (500HMz, CDCl₃); δ 8.27-8.25 (d, 1H), 6.63-6.62 (d, 1H), 4.41-4.39 (t, 2H), 1.80-1.75 (m, 1H), 1.70-1.65 (q, 2H), 0.96-0.94 (d, 6H)

Preparation Example 336: 2-chloro-4-(3-methoxy-propoxy)-pyrimidine

2,4-Dichloropyrimidine (0.50 g, 3.36 mmol) and 3-methoxypropan-1-ol (0.35 ml, 3.69 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.34 g, 50 %).

¹H-NMR (500HMz, CDCl₃); δ 8.28-8.27 (d, 1H), 6.65-6.64 (d, 1H), 4.48-4.45 (t, 2H), 3.52-3.50 (t, 2H), 3.34 (s, 3H), 2.05-2.02 (m, 2H)

Preparation Example 337: 5-bromo-4-cyclopropylmethoxymethyl-2-methyl-thiazole

Step A: 4-cyclopropylmethoxymethyl-2-methyl-thiazole

Cyclopropyl-methanol (0.65 ml, 7.93 mmol) and 4-chloromethyl-2-methyl-thiazole (0.78 g, 5.28 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.83 g, 80 %).

¹H-NMR(400HMz CDCl₃); δ 7.06 (s, 1H), 4.61 (s, 2H), 3.46-3.40 (d, 2H), 2.71 (s, 3H), 1.15-1.09 (m, 1H), 0.58-0.53 (m, 2H), 0.25-0.21 (m, 2H)

Step B: 5-bromo-4-cyclopropylmethoxymethyl-2-methyl-thiazole

4-Cyclopropylmethoxymethyl-2-methyl-thiazole (0.52 g, 2.64 mmol) and 1,3-dibromo-5,5-dimethyl-imidazolin-2,4-dione (0.74 g, 2.64 mmol) were reacted in the same manner as in Step B of Preparation Example 6 to obtain the title compound (0.66 g, 96 %).

¹H-NMR(400HMz CDCl₃); δ 4.46 (s, 2H), 3.39-3.38 (d, 2H), 2.66 (s, 3H), 1.16 -1.09 (m, 1H), 0.57-0.53 (m, 2H), 0.25-0.22 (m, 2H)

Preparation Example 338: 4-bromo-2-cyclobutoxymethyl-thiophene

4-Bromo-2-chloromethyl-thiophene (0.30 g, 1.42 mmol) and cyclobutanol (0.14 ml, 1.84 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.065 g, 19 %).

¹H-NMR(400HMz CDCl₃); δ 7.17-7.16 (d, 1H), 6.90 (d, 1H), 4.52 (s, 2H), 4.06-3.99 (m, 1H), 2.24-2.16 (m, 2H), 2.01-1.92 (m, 2H), 1.75-1.68 (m, 1H), 1.52-1.47 (m, 1H)

Preparation Example 339: 4-(4-bromo-2,6-difluoro-phenoxy)-butanoic acid ethyl ester

4-Bromo-2,6-difluoro-phenol (19.5 g, 93.3 mmol) obtained in Step A of Preparation Example 16 and 4-bromo-butyric acid ethyl ester (21.82 g, 112 mmol) were reacted in the same manner as in Step C of Preparation Example 16 to obtain the title compound (30.0 g, 99 %).

¹H-NMR (CDCl₃) δ 7.09 (2H, m), 4.16 (4H, m), 2.57 (2H, t), 2.08 (2H, m), 1.28 (3H, t)

Preparation Example 340: 2-chloro-4-(6-methyl-pyridin-3-yloxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.36 g, 9.16 mmol) and 6-methyl-pyridin-3-ol (1.0 g, 9.16 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.850 g, 42 %).

¹H-NMR (CDCl₃) δ 8.47 (1H, d), 8.38 (1H, d), 7.44 (1H, m), 7.24 (1H, m), 6.89 (1H, d)

Preparation Example 341: 2-chloro-4-(4-ethyl-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.22 g, 8.18 mmol) and 4-ethyl-phenol (1.0 g, 8.18 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.5 g, 78 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, d), 7.26 (2H, m), 7.06 (2H, m), 6.74 (1H, d), 2.67 (2H, q), 1.27 (3H, t)

Preparation Example 342: 2-chloro-4-(3-fluoro-phenoxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.3 g, 8.92 mmol) and 3-fluoro-phenol (1.0 g, 8.92 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.2 g, 59 %).

¹H-NMR (CDCl₃) δ 8.47 (1H, d), 7.40 (1H, m), 7.04~6.91 (3H, m), 6.84 (1H, d)

Preparation Example 343: 2-chloro-4-(3,4-difluoro-phenoxy)-6-methyl-

pyrimidine

2,4-Dichloro-6-methyl-pyrimidine (1.25 g, 7.69 mmol) and 3,4-difluoro-phenol (1.0 g, 7.69 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.1 g, 55 %).

¹H-NMR (CDCl₃) δ 7.22 (1H, q), 7.03 (1H, m), 6.90 (1H, m), 6.67 (1H, s), 2.51 (3H, s)

Preparation Example 344: 2-chloro-4-(pyridin-2-yloxy)-pyrimidine

2,4-Dichloro-pyrimidine (1.57 g, 10.51 mmol) and pyridin-2-ol (1.0 g, 10.51 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.1 g, 4 %).

¹H-NMR (CDCl₃) δ 8.52 (1H, d), 8.38 (1H, m), 7.85 (1H, m), 7.25 (1H, m), 7.15 (1H, d), 7.03 (1H, d)

Preparation Example 345: 2-chloro-4-[4-(trifluoromethyl)phenoxy]pyrimidine

2,4-Dichloropyrimidine (2.0 g, 13.4 mmol) and 4-(trifluoromethyl)phenol (2.17 g, 13.4 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (2.62 g, 71 %).

¹H-NMR (CDCl₃) δ 8.50 (1H, d), 7.72 (2H, d), 7.30 (2H, d), 6.89 (1H, d)

Preparation Example 346: 2-chloro-4-[3-(trifluoromethyl)phenoxy]pyrimidine

2,4-Dichloropyrimidine (2.0 g, 13.4 mmol) and 3-(trifluoromethyl)phenol (2.17 g, 13.4 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (2.7 g, 73 %).

¹H-NMR (CDCl₃) δ 8.50 (1H, d), 7.57 (2H, m), 7.44 (1H, m), 7.38 (1H, m), 6.88 (1H, d)

Preparation Example 347: 2-chloro-4-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (3.0 g, 18.4 mmol) and 4-(trifluoromethyl)phenol (2.98 g, 18.4 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (3.2 g, 62 %).

¹H-NMR (CDCl₃) δ 7.70 (2H, d), 7.27 (2H, d), 6.70 (1H, s), 2.52 (3H, s)

Preparation Example 348: 2-chloro-4-methyl-6-[3-(trifluoromethyl)phenoxy]pyrimidine

2,6-Dichloro-4-methyl-pyrimidine (3.0 g, 18.4 mmol) and 3-(trifluoromethyl)phenol (2.98 g, 18.4 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (3.0 g, 57 %).

¹H-NMR (CDCl₃) δ 7.56 (2H, m), 7.42 (1H, m), 7.36 (1H, m), 6.69 (1H, s), 2.52 (3H, s)

Preparation Example 349: 2-chloro-4-cyclobutoxy-6-trifluoromethyl-pyrimidine

2,6-Dichloro-6-trifluoromethyl-pyrimidine (0.40 g, 1.85 mmol) and cyclobutanol (0.17 ml, 2.22 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.40 g, 86 %).

¹H-NMR (400HMz CDCl₃); δ 7.08 (s, 1H), 6.83 (s, 1H), 5.24-5.15 (m, 1H), 2.52 (m, 2H), 2.17-2.11 (m, 2H), 1.87-1.84 (m, 1H), 1.73-1.65 (m, 1H)

Preparation Example 350: 4-bromo-benzo[b]thiophene

3-Bromo-benzenethiol (0.5 g, 2.64 mmol) was dissolved in 8 mL of DMF. Bromoacetaldehyde diethyl acetal (0.52 g, 2.64 mmol) and K₂CO₃ (0.548 g, 3.97 mmol) were added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of water, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesiumsulfate and concentrated under reduced pressure to obtain 1-bromo-3-(2,2-diethoxy-ethylsulfanyl)-benzene. The obtained compound was dissolved in 8 ml of MC. 0.7 g of PPA (polyphosphoric acid) was added thereto, and the mixture was stirred for 4 hours under reflux. After addition of Na₂CO₃ aqueous solution, the reaction solution was extracted with MC. The organic layer was dried with anhydrous magnesiumsulfate and purified by column chromatography to obtain the mixture of 4-bromo-benzo[b]thiophene and 6-bromo-benzo[b]thiophene (1:1, 0.33 g, 58 %).

¹H-NMR (CDCl₃) δ 8.01 (1H, s), 7.80 (1H, d), 7.66 (1H, d), 7.50 (4H, m), 7.41 (1H, d), 7.29 (1H, d), 7.19 (1H, t)

Preparation Example 351: [1-(4-benzo[b]thiophen-4-yl-2,6-difluoro-phenyl)-

piperidin-4-yl]-acetic acid ethyl ester

The mixture of 4-bromo-benzo[b]thiophene and 6-bromo-benzo[b]thiophene (0.19 g, 0.89 mmol) obtained in Preparation Example 350 and 2-[1-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-4-piperidyl]acetic acid ethyl ester (0.365 g, 0.89 mmol) obtained in Preparation Example 220 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.11 g, 29%).

¹H-NMR (CDCl₃) δ 7.87 (1H, d), 7.46 (2H, s), 7.39 (1H, t), 7.29 (1H, d), 7.04 (2H, m), 4.14 (2H, q), 3.32 (2H, m), 3.16 (2H, m), 2.29 (2H, d), 1.96 (1H, m), 1.77 (2H, m), 1.46 (2H, m), 1.26 (3H, t)

Preparation Example 352: 2-chloro-4-cyclobutoxy-6-trifluoromethyl-pyrimidine

Cyclobutanol (0.365 g, 5.07 mmol) and 2,4-dichloro-6-trifluoromethyl-pyrimidine (1 g, 4.61 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.603 g, 51 %).

¹H-NMR (CDCl₃) δ 6.93 (1H, s), 5.30 (1H, m), 2.50 (2H, m), 2.18 (2H, m), 1.87 (1H, m), 1.71 (1H, m)

Preparation Example 353: 2-chloro-4-propoxy-6-trifluoromethyl-pyrimidine

Propanol (0.304 g, 5.07 mmol) and 2,4-dichloro-6-trifluoromethyl-pyrimidine (1 g, 4.61 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (0.602 g, 54 %).

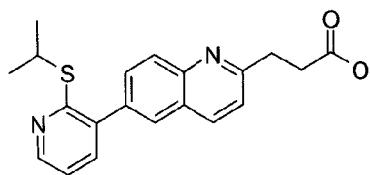
¹H-NMR (CDCl₃) δ 6.97 (1H, s), 4.41 (2H, t), 1.83 (2H, m), 1.02 (3H, t)

Preparation Example 354: 2-chloro-4-(4-fluoro-phenoxy)-6-trifluoromethyl-pyrimidine

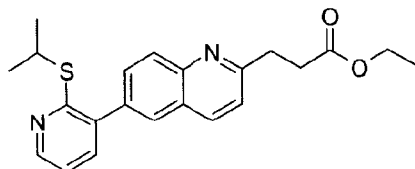
4-Fluoro-phenol (0.568 g, 5.07 mmol) and 2,4-dichloro-6-trifluoromethyl-pyrimidine (1 g, 4.61 mmol) were reacted in the same manner as in Preparation Example 226 to obtain the title compound (1.07 g, 79 %).

¹H-NMR (CDCl₃) δ 7.15 (5H, m)

Example 1: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-quinolin-2-yl]-propionic acid



Step A: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-quinolin-2-yl]-propionic acid ethyl ester



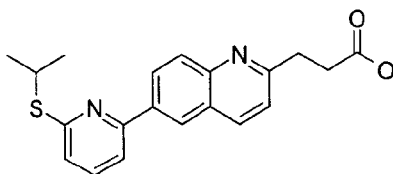
3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-propionic acid ethyl ester (0.06 g, 0.17 mmol) obtained in Preparation Example 1 and 3-iodo-2-isopropylsulfanyl-pyridine (0.047 g, 0.17 mmol) obtained in Preparation Example 9 were dissolved in 0.25 mL of 2M sodium carbonate and 2 mL of DME, and charged with nitrogen for 5 minutes. $\text{PdCl}_2(\text{PPh}_3)_2$ (0.006 g, 0.008 mmol) was added thereto, and the mixture was stirred for 4 hours under reflux. After addition of water, the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.040 g, 63 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.53 (1H, d), 8.15~8.08 (2H, m), 7.82 (1H, s), 7.78 (1H, d), 7.50 (1H, d), 7.39 (1H, d), 7.12 (1H, m), 4.15~4.10 (3H, m), 3.34 (2H, t), 2.97 (2H, t), 1.40 (6H, d), 1.30 (3H, t)

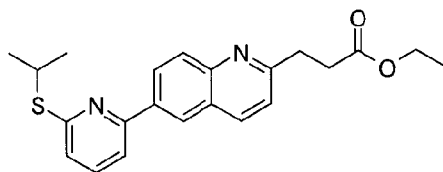
Step B: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-quinolin-2-yl]-propionic acid

3-[6-(2-Isopropylsulfanyl-pyridin-3-yl)-quinolin-2-yl]-propionic acid ethyl ester (0.040 g, 0.10 mmol) obtained in Step A was dissolved in each 0.3 mL of THF, MeOH and 1N NaOH aqueous solution, and the mixture was stirred at room temperature for 2 hours. After removing organic solvent, the reaction solution was adjusted to pH 3 by the use of 1N HCl aqueous solution and extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO_4 and concentrated under reduced pressure to obtain the title compound (0.030 g, 86 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.51 (1H, d), 8.26 (1H, d), 8.11 (1H, d), 7.92~7.80 (2H, m), 7.46 (1H, d), 7.40 (1H, d), 7.10 (1H, m), 4.15 (1H, m), 3.38 (2H, t), 2.98 (2H, t), 1.35 (6H, d)

Example 2: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-quinolin-2-yl]-propionic acid

Step A: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-quinolin-2-yl]-propionic acid ethyl ester



3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-quinolin-2-yl]-propionic acid ethyl ester (0.06 g, 0.17 mmol) obtained in Preparation Example 1 and 2-chloro-6-isopropylsulfanyl-pyridine (0.032 g, 0.17 mmol) obtained in Preparation Example 10 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.021 g, 33 %).

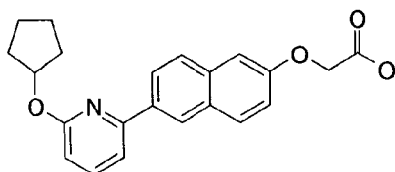
¹H-NMR (CDCl₃) δ 8.50 (1H, s), 8.43 (1H, d), 8.20 (1H, d), 8.14 (1H, d), 7.65~7.60 (2H, m), 7.40 (1H, d), 7.16 (1H, m), 4.31~4.17 (3H, m), 3.34 (2H, t), 2.96 (2H, t), 1.54 (6H, d), 1.29 (3H, t)

Step B: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-quinolin-2-yl]-propionic acid

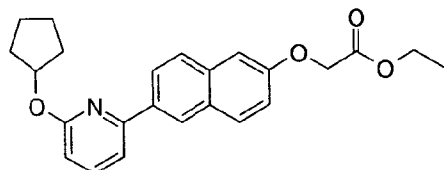
3-[6-(6-Isopropylsulfanyl-pyridin-2-yl)-quinolin-2-yl]-propionic acid ethyl ester (0.021 g, 0.06 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.016 g, 83 %).

¹H-NMR (CDCl₃) δ 8.51~8.46 (2H, m), 8.32 (1H, d), 8.11 (1H, d), 7.65~7.55 (2H, m), 7.41 (1H, d), 7.15 (1H, m), 4.20 (1H, m), 3.39 (2H, t), 2.98 (2H, t), 1.50 (6H, d)

Example 3: [6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid



Step A: [6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester



[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester (0.06 g, 0.17 mmol) obtained in Preparation Example 2 and 2-chloro-6-cyclopentyloxy-pyridine (0.033 g, 0.17 mmol) obtained in Preparation Example 12 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.013 g, 20 %).

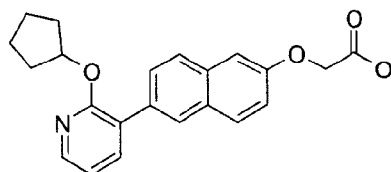
¹H-NMR (CDCl₃) δ 8.43 (1H, s), 8.17 (1H, d), 7.86 (1H, d), 7.77 (1H, t), 7.62 (1H, d), 7.42 (1H, d), 7.25 (1H, d), 7.12 (1H, s), 6.63 (1H, d), 5.60 (1H, m), 4.75 (2H, s), 4.30 (2H, q), 2.20~1.60 (8H, m), 1.22 (3H, t)

Step B: [6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid

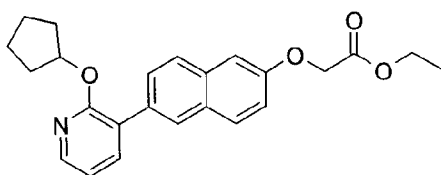
[6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester (0.013 g, 0.03 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.010 g, 83 %).

¹H-NMR (CDCl₃) δ 8.48 (1H, s), 8.22 (1H, d), 7.94 (1H, d), 7.83 (1H, d), 7.70 (1H, t), 7.47 (1H, d), 7.25 (1H, d), 7.20 (1H, s), 6.70 (1H, d), 5.63 (1H, m), 4.87 (2H, s), 2.20~1.70 (8H, m)

Example 4: [6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid



Step A: [6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester



[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester (0.06 g, 0.17 mmol) obtained in Preparation Example 2 and 2-cyclopentyloxy-3-iodo-pyridine (0.049 g, 0.17 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.030 g, 45 %).

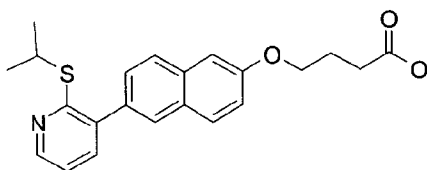
¹H-NMR (CDCl₃) δ 8.21 (1H, d), 8.00 (1H, s), 7.85~7.70 (4H, m), 7.24 (1H, d), 7.18 (1H, s), 6.99 (1H, t), 5.60 (1H, m), 4.80 (2H, s), 4.36 (2H, q), 2.10~1.60 (8H, m), 1.35 (3H, t)

Step B: [6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid

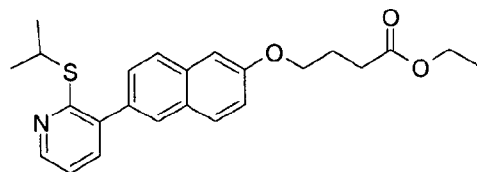
[6-(2-Cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid ethyl ester (0.030 g, 0.08 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.018 g, 67 %).

¹H-NMR (CDCl₃) δ 8.24 (1H, d), 7.97 (1H, s), 7.85~7.70 (4H, m), 7.30 (1H, d), 7.20 (1H, s), 7.00 (1H, t), 5.57 (1H, m), 4.87 (2H, s), 2.10~1.65 (8H, m)

Example 5: 4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid



Step A: 4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester



4-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester (0.05 g, 0.13 mmol) obtained in Preparation Example 3 and 3-iodo-2-

isopropylsulfanyl-pyridine (0.036 g, 0.13 mmol) obtained in Preparation Example 9 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.035 g, 66 %).

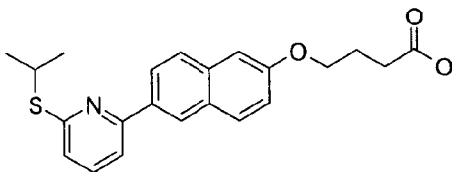
$^1\text{H-NMR}$ (CDCl_3) δ 8.50 (1H, d), 7.82~7.75 (3H, m), 7.62~7.48 (2H, m), 7.20 (2H, m), 7.10 (1H, m), 4.25~4.05 (5H, m), 2.63 (2H, t), 2.22 (2H, t), 1.39 (6H, d), 1.30 (3H, t)

Step B: 4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid

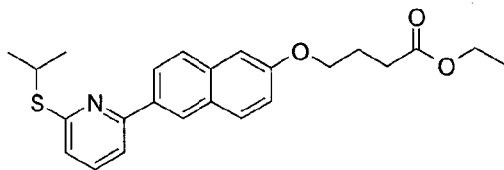
4-[6-(2-Isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester (0.035 g, 0.09 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.025 g, 78 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.46 (1H, d), 7.80~7.75 (3H, m), 7.52 (1H, d), 7.45 (1H, d), 7.15 (2H, m), 7.05 (1H, m), 4.18 (2H, t), 4.07 (1H, m), 2.65 (2H, t), 2.22 (2H, t), 1.34 (6H, d)

Example 6: 4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid



Step A: 4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester



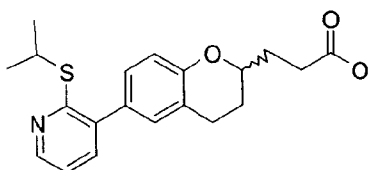
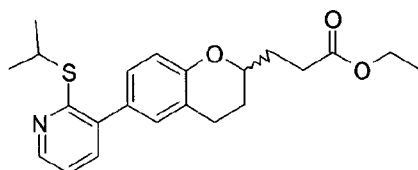
4-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester (0.05 g, 0.13 mmol) obtained in Preparation Example 3 and 2-chloro-6-isopropylsulfanyl-pyridine (0.024 g, 0.13 mmol) obtained in Preparation Example 10 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.012 g, 23 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.46 (1H, s), 8.20 (1H, d), 7.90~7.80 (2H, m), 7.60 (2H, m), 7.22~7.12 (3H, m), 4.35~4.15 (5H, m), 2.61 (2H, t), 2.22 (2H, t), 1.54 (6H, d), 1.30 (3H, t)

Step B: 4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid

4-[6-(6-Isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid ethyl ester (0.012 g, 0.03 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.010 g, 88 %).

¹H-NMR (CDCl₃) δ 8.41 (1H, s), 8.15 (1H, d), 7.84~7.77 (2H, m), 7.53 (2H, m), 7.16~7.12 (2H, m), 7.09 (1H, d), 4.24~4.12 (3H, m), 2.65 (2H, t), 2.21 (2H, t), 1.49 (6H, d)

Example 7: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid**Step A: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid ethyl ester**

3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 4 and 3-iodo-2-isopropylsulfanyl-pyridine (0.046 g, 0.16 mmol) obtained in Preparation Example 9 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.040 g, 66 %).

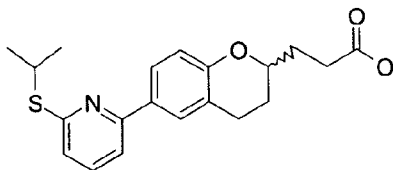
¹H-NMR (CDCl₃) δ 8.40 (1H, d), 7.35 (1H, d), 7.18 (1H, d), 7.08 (1H, s), 7.00 (1H, t), 6.82 (1H, d), 4.17 (2H, q), 4.15~4.00 (2H, m), 2.95~2.80 (2H, m), 2.70~2.50 (2H, m), 2.05 (3H, m), 1.80 (1H, m), 1.35 (6H, d), 1.28 (3H, t)

Step B: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid

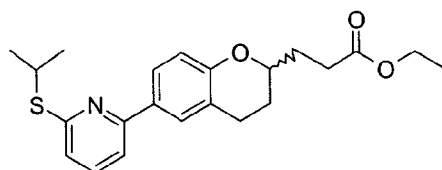
3-[6-(2-Isopropylsulfanyl-pyridin-3-yl)-chroman-2-yl]-propionic acid ethyl ester (0.040 g, 0.10 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.028 g, 76 %).

$^1\text{H-NMR}$ (CDCl_3) δ 8.38 (1H, d), 7.33 (1H, d), 7.14 (1H, d), 7.07 (1H, s), 7.00 (1H, t), 6.83 (1H, d), 4.15~4.00 (2H, m), 2.95~2.75 (2H, m), 2.70~2.50 (2H, m), 2.05~1.90 (3H, m), 1.80 (1H, m), 1.34 (6H, d)

Example 8: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-chroman-2-yl]-propionic acid



Step A: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-chroman-2-yl]-propionic acid ethyl ester



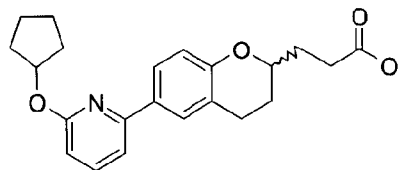
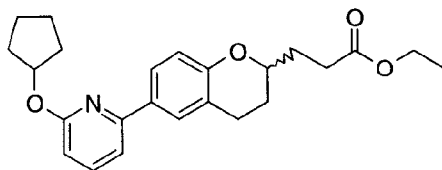
3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 4 and 2-chloro-6-isopropylsulfanyl-pyridine (0.031 g, 0.16 mmol) obtained in Preparation Example 10 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.020 g, 33 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.79~7.72 (2H, m), 7.49 (1H, t), 7.33 (1H, d), 7.02 (1H, d), 6.84 (1H, d), 4.20~4.05 (4H, m), 2.97~2.80 (2H, m), 2.70~2.50 (2H, m), 2.10~2.00 (3H, m), 1.82 (1H, m), 1.45 (6H, d), 1.26 (3H, t)

Step B: 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-chroman-2-yl]-propionic acid

3-[6-(6-Isopropylsulfanyl-pyridin-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.020 g, 0.05 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.014 g, 75 %).

$^1\text{H-NMR}$ (CDCl_3) δ 7.78~7.73 (2H, m), 7.46 (1H, t), 7.32 (1H, d), 7.01 (1H, d), 6.85 (1H, d), 4.14~4.07 (2H, m), 2.97~2.82 (2H, m), 2.75~2.60 (2H, m), 2.08~2.00 (3H, m), 1.80 (1H, m), 1.45 (6H, m)

Example 9: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-chroman-2-yl]-propionic acid**Step A: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-chroman-2-yl]-propionic acid ethyl ester**

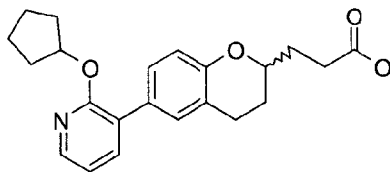
3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 4 and 2-chloro-6-cyclopentyloxy-pyridine (0.033 g, 0.16 mmol) obtained in Preparation Example 12 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.013 g, 21 %).

¹H-NMR (CDCl₃) δ 7.77~7.70 (2H, m), 7.54 (1H, t), 7.20 (1H, d), 6.85 (1H, d), 6.54 (1H, d), 5.50 (1H, m), 4.13 (2H, q), 4.08 (1H, m), 3.00~2.50 (4H, m), 2.10~1.55 (12H, m), 1.24 (3H, t)

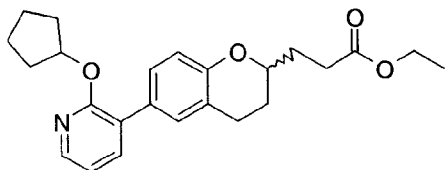
Step B: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-chroman-2-yl]-propionic acid

3-[6-(6-Cyclopentyloxy-pyridin-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.013 g, 0.03 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.010 g, 83 %).

¹H-NMR (CDCl₃) δ 7.72~7.65 (2H, m), 7.45 (1H, t), 7.11 (1H, d), 6.79 (1H, d), 6.49 (1H, d), 5.45 (1H, m), 4.04 (1H, m), 2.95~2.50 (4H, m), 2.10~1.65 (12H, m)

Example 10: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-chroman-2-yl]-propionic acid

Step A: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-chroman-2-yl]-propionic acid ethyl ester



3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman-2-yl]-propionic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 4 and 2-cyclopentyloxy-3-iodo-pyridine (0.049 g, 0.16 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.030 g, 48 %).

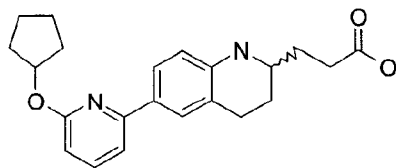
¹H-NMR (CDCl₃) δ 8.07 (1H, d), 7.56 (1H, d), 7.32~7.26 (2H, m), 6.85 (1H, t), 6.80 (1H, d), 5.49 (1H, m), 4.15 (2H, q), 4.10 (1H, m), 2.95~2.55 (4H, m), 2.10~1.55 (12H, m), 1.26 (3H, t)

Step B: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-chroman-2-yl]-propionic acid

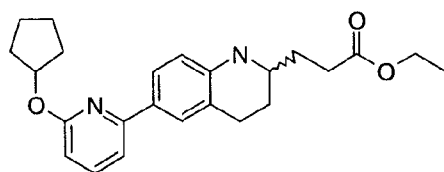
3-[6-(2-Cyclopentyloxy-pyridin-3-yl)-chroman-2-yl]-propionic acid ethyl ester (0.030 g, 0.08 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.018 g, 67 %).

¹H-NMR (CDCl₃) δ 8.09 (1H, d), 7.56 (1H, d), 7.31~7.26 (2H, m), 6.88 (1H, t), 6.81 (1H, d), 5.49 (1H, m), 4.08 (1H, m), 2.95~2.60 (4H, m), 2.10~1.65 (12H, m)

Example 11: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid



Step A: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester



3-[6-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester (0.1 g, 0.30 mmol) obtained in Preparation Example 6 and 2-chloro-6-cyclopentyloxy-pyridine (0.06 g, 0.30 mmol) obtained in Preparation Example 12 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.035 g, 30 %).

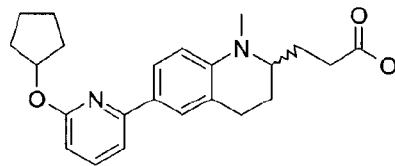
¹H-NMR (CDCl₃) δ 7.68 (2H, m), 7.51 (1H, t), 7.15 (1H, d), 6.56~6.48 (2H, m), 5.51 (1H, m), 4.16 (2H, q), 4.05 (1H, brs), 3.40 (1H, m), 2.90~2.80 (2H, m), 2.55~2.40 (2H, m), 2.10~1.60 (12H, m), 1.25 (3H, t)

Step B: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid

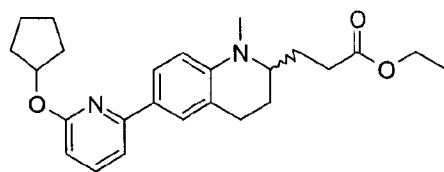
3-[6-(6-Cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester (0.012 g, 0.03 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.010 g, 91 %).

¹H-NMR (CDCl₃) δ 7.68 (2H, m), 7.52 (1H, t), 7.16 (1H, d), 6.60~6.48 (2H, m), 5.52 (1H, m), 3.42 (1H, m), 2.90~2.80 (2H, m), 2.60~2.50 (2H, m), 2.05~1.60 (12H, m)

Example 12: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid



Step A: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester



3-[6-(6-Cyclopentyloxy-pyridin-2-yl)-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester (0.012 g, 0.03 mmol) obtained in Step A of Example 11 was dissolved in 5 mL of DCE. Formaldehyde (0.005 g, 0.06 mmol) and acetic acid (0.002 g, 0.036 mmol) were added thereto, and the mixture was stirred at room temperature for 1 hour. Sodium triacetoxyborohydride (0.013 g, 0.06 mmol) was added to the reaction solution, and the reaction was carried out at room temperature for 16 hours. After addition of 50 mL of water, the reaction solution was extracted with DCM, dried with MgSO_4 and purified by column chromatography to obtain the title compound (0.007 g, 58 %).

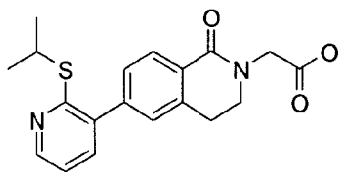
$^1\text{H-NMR}$ (CDCl_3) δ 7.79 (1H, d), 7.68 (1H, s), 7.54 (1H, t), 7.16 (1H, d), 6.61 (1H, d), 6.47 (1H, d), 5.52 (1H, m), 4.13 (2H, q), 3.32 (1H, m), 3.01 (3H, s), 2.95~2.75 (2H, m), 2.50~2.30 (2H, m), 2.10~1.60 (12H, m), 1.24 (3H, t)

Step B: 3-[6-(6-cyclopentyloxy-pyridin-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid

3-[6-(6-Cyclopentyloxy-pyridin-2-yl)-1-methyl-1,2,3,4-tetrahydro-quinolin-2-yl]-propionic acid ethyl ester (0.007 g, 0.02 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.006 g, 92 %).

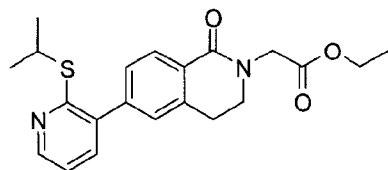
$^1\text{H-NMR}$ (CDCl_3) δ 7.80 (1H, d), 7.68 (1H, s), 7.54 (1H, t), 7.18 (1H, d), 6.65 (1H, d), 6.47 (1H, d), 5.52 (1H, m), 3.36 (1H, m), 3.02 (3H, s), 2.95~2.70 (2H, m), 2.55~2.30 (2H, m), 2.10~1.60 (12H, m)

Example 13: [6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid



Step A: [6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl]-acetic acid

yl]-acetic acid ethyl ester



[1-Oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 7 and 3-iodo-2-isopropylsulfanyl-pyridine (0.047 g, 0.16 mmol) obtained in Preparation Example 9 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.020 g, 33 %).

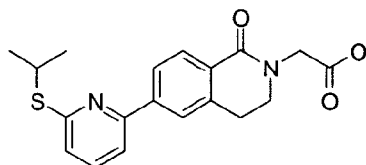
¹H-NMR (CDCl₃) δ 8.46 (1H, d), 8.15 (1H, d), 7.41~7.35 (2H, m), 7.25 (1H, d), 7.04 (1H, t), 4.36 (2H, s), 4.22 (2H, q), 4.07 (1H, m), 3.73 (2H, t), 3.10 (2H, t), 1.37 (6H, d), 1.26 (3H, t)

Step B: [6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid

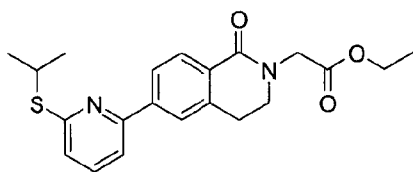
[6-(2-Isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester (0.020 g, 0.05 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.012 g, 63 %).

¹H-NMR (CDCl₃) δ 8.47 (1H, d), 8.13 (1H, d), 7.43~7.35 (2H, m), 7.25 (1H, d), 7.05 (1H, t), 4.40 (2H, s), 4.13 (1H, m), 3.74 (2H, t), 3.13 (2H, t), 1.36 (6H, d)

Example 14: [6-(6-isopropylsulfanyl-pyridin-2-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid



Step A: [6-(6-isopropylsulfanyl-pyridin-2-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester



[1-Oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 7 and 2-chloro-6-isopropylsulfanyl-pyridine (0.031 g, 0.16 mmol) obtained in Preparation Example 10 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.014 g, 23 %).

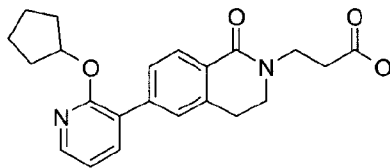
¹H-NMR (CDCl₃) δ 8.17 (1H, d), 7.98 (1H, d), 7.89 (1H, s), 7.55 (1H, t), 7.47 (1H, d), 7.12 (1H, d), 4.36 (2H, s), 4.30~4.15 (3H, m), 3.72 (2H, t), 3.17 (2H, t), 1.47 (6H, d), 1.28 (3H, t)

Step B: [6-(6-isopropylsulfanyl-pyridin-2-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid

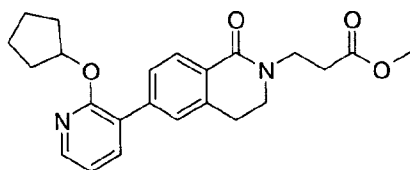
[6-(6-Isopropylsulfanyl-pyridin-2-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-acetic acid ethyl ester (0.014 g, 0.04 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.010 g, 78 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, d), 7.98 (1H, d), 7.89 (1H, s), 7.53 (1H, t), 7.45 (1H, d), 7.12 (1H, d), 4.40 (2H, s), 4.15 (1H, m), 3.75 (2H, t), 3.16 (2H, t), 1.48 (6H, d)

Example 15: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid



Step A: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester



3-[1-Oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 8 and 2-cyclopentyloxy-3-iodo-pyridine (0.048 g, 0.16 mmol) obtained in Preparation Example 11 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.015 g, 23 %).

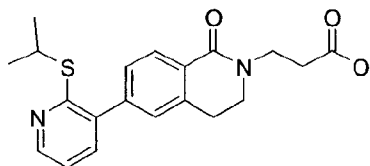
¹H-NMR (CDCl₃) δ 8.17 (1H, d), 8.09 (1H, d), 7.62 (1H, d), 7.53 (1H, d), 7.37 (1H, s), 6.93 (1H, t), 5.53 (1H, m), 3.85 (2H, t), 3.77~3.70 (5H, m), 3.00 (2H, t), 2.74 (2H, t), 2.00~1.60 (8H, m)

Step B: 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid

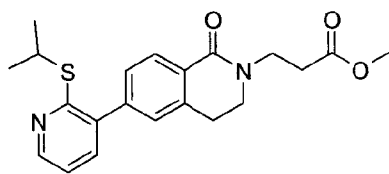
3-[6-(2-Cyclopentyloxy-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester (0.015 g, 0.04 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.020 g, 56 %).

¹H-NMR (CDCl₃) δ 8.17 (1H, d), 8.06 (1H, d), 7.62 (1H, d), 7.52 (1H, d), 7.37 (1H, s), 6.93 (1H, t), 5.52 (1H, m), 3.85 (2H, t), 3.71 (2H, t), 3.05 (2H, t), 2.82 (2H, t), 2.00~1.60 (8H, m)

Example 16: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid



Step A: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1*H*-isoquinolin-2-yl]-propionic acid methyl ester



3-[1-Oxo-6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid methyl ester (0.06 g, 0.16 mmol) obtained in Preparation Example 8 and 3-iodo-2-isopropylsulfanyl-pyridine (0.047 g, 0.16 mmol) obtained in Preparation Example 9 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.030 g, 46 %).

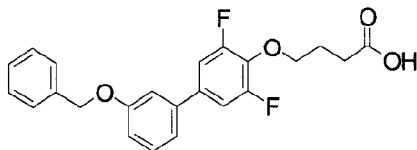
¹H-NMR (CDCl₃) δ 8.46 (1H, d), 8.11 (1H, d), 7.45~7.35 (2H, m), 7.25 (1H, d), 7.03 (1H, t), 4.07 (1H, m), 3.85 (2H, t), 3.75~3.65 (5H, m), 3.05 (2H, t), 2.75 (2H, t), 1.35 (6H, d)

Step B: 3-[6-(2-isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid

3-[6-(2-Isopropylsulfanyl-pyridin-3-yl)-1-oxo-3,4-dihydro-1H-isoquinolin-2-yl]-propionic acid methyl ester (0.030 g, 0.08 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (0.020 g, 69 %).

¹H-NMR (CDCl₃) δ 8.46 (1H, d), 8.10 (1H, d), 7.45~7.35 (2H, m), 7.25 (1H, d), 7.05 (1H, t), 4.05 (1H, m), 3.90 (2H, t), 3.75 (2H, t), 3.05 (2H, t), 2.80 (2H, t), 1.34 (6H, d)

Example 17: 4-(3'-benzyloxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid



Step A: 4-(3'-benzyloxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester

2N Na₂CO₃ (0.5 mL) and 1,4-dioxane (5 mL) were added to 1-benzyloxy-3-iodobenzene (42 mg, 0.135 mmol) obtained in Preparation Example 17, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (50 mg, 0.135 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.5 mg, 0.0068 mmol), and the mixture was stirred 2 hours under reflux. After termination of the reaction, the reaction solution was cooled and filtered through Celite. After addition of water, the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with

MgSO₄, concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (20 mg, 35%).

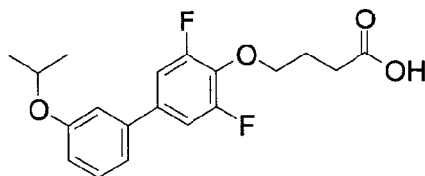
¹H NMR (400 MHz, CDCl₃) δ 7.48-7.43(m, 2H), 7.43-7.37(m, 2H), 7.37-7.31(m, 2H), 7.13-7.06(m, 4H), 6.99-6.95(m, 1H), 4.12(s, 2H), 4.21(t, 2H), 4.16(q, 2H), 2.58(t, 2H), 2.15-2.06(m, 2H), 1.27(t, 3H)

Step B: 4-(3'-benzyloxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid

4-(3'-Benzyloxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester (20 mg, 0.047 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (18 mg, 96%).

¹H NMR (400 MHz, CDCl₃) δ 7.48-7.43(m, 2H), 7.43-7.36(m, 2H), 7.37-7.31(m, 2H), 7.13-7.06(m, 4H), 6.99-6.95(m, 1H), 4.12(s, 2H), 4.21(t, 2H), 4.16(q, 2H), 2.66(t, 2H), 2.15-2.05(m, 2H), 1.27(t, 3H)

Example 18: 4-(3,5-difluoro-3'-isopropoxy-biphenyl-4-yloxy)-butyric acid



Step A: 4-(3,5-difluoro-3'-isopropoxy-biphenyl-4-yloxy)-butyric acid ethyl ester

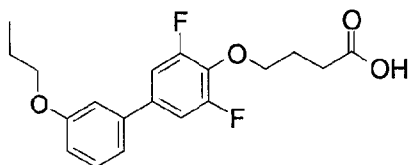
2 N Na₂CO₃ (0.5 mL) and 1,4-dioxane (5 mL) were added to 1-iodo-3-isopropoxybenzene (35 mg, 0.135 mmol) obtained in Preparation Example 18, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (50 mg, 0.135 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.5 mg, 0.0068 mmol), and the mixture was stirred for 2 hours under reflux. After termination of the reaction, the reaction solution was cooled and filtered through Celite. After addition of water, the reaction solution was extracted with EtOAc to separate an organic layer. The organic layer was dried with MgSO₄, concentrated under reduced pressure and purified by column chromatography (eluent, EtOAc/Hex = 1/10) to obtain the title compound (32 mg, 63 %).

¹H NMR (400 MHz, CDCl₃) δ 7.40-7.34(m, 1H), 7.29-6.97(m, 4H), 6.96-7.182(m, 1H), 4.70-4.52(m, 1H), 4.28-4.08(m, 4H), 2.69-2.52(m, 2H), 2.20-2.03(m, 2H), 1.37(d, 6H), 1.25(t, 3H)

Step B: 4-(3,5-difluoro-3'-isopropoxy-biphenyl-4-yloxy)-butyric acid

4-(3,5-Difluoro-3'-isopropoxy-biphenyl-4-yloxy)-butyric acid ethyl ester (32 mg, 0.085 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (28 mg, 95 %).

¹H NMR (400 MHz, CDCl₃) δ 7.32(t, 1H), 7.15-7.07(m, 2H), 7.07-7.03(m, 1H), 7.03-7.00(m, 1H), 6.91-6.86(m, 1H), 4.66-4.56(m, 1H), 4.22(t, 2H), 2.67(t, 2H), 2.16-2.07(m, 2H), 1.36(d, 6H)

Example 19: 4-(3,5-difluoro-3'-propoxy-biphenyl-4-yloxy)-butyric acid**Step A: 4-(3,5-difluoro-3'-propoxy-biphenyl-4-yloxy)-butyric acid ethyl ester**

1-Iodo-3-propoxy-benzene (35 mg, 0.135 mmol) obtained in Preparation Example 19, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (50 mg, 0.135 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.5 mg, 0.0068 mmol) were reacted in the same manner as in Step A of Example 18 to obtain the title compound (42 mg, 83%).

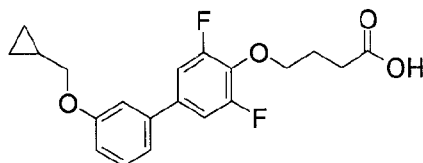
¹H NMR (400 MHz, CDCl₃) δ 7.32(t, 1H), 7.16-7.09(m, 2H), 7.09-7.04(m, 1H), 7.04-7.00(m, 1H), 6.92-6.87(m, 1H), 4.20(t, 2H), 4.16(q, 2H), 3.97(t, 2H), 2.57(t, 2H), 2.15-2.04(m, 2H), 1.89-1.78(m, 2H), 1.28(t, 3H), 1.06(t, 3H)

Step B: 4-(3,5-difluoro-3'-propoxy-biphenyl-4-yloxy)-butyric acid

4-(3,5-Difluoro-3'-propoxy-biphenyl-4-yloxy)-butyric acid ethyl ester (42 mg, 0.11 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (37 mg, 95 %).

¹H NMR (400 MHz, CDCl₃) δ 7.32(t, 1H), 7.16-7.09(m, 2H), 7.09-7.00(m, 2H), 6.93-6.87(m, 1H), 4.22(t, 2H), 3.97(t, 2H), 2.67(t, 2H), 2.19-2.06(m, 2H), 1.89-1.78(m, 2H), 1.05(t, 3H)

Example 20: 4-(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid



Step A: 4-(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester

1-Cyclopropylmethoxy-3-iodo-benzene (37 mg, 0.135 mmol) obtained in Preparation Example 20, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (50 mg, 0.135 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.5 mg, 0.0068 mmol) were reacted in the same manner as in Step A of Example 18 to obtain the title compound (20 mg, 38 %).

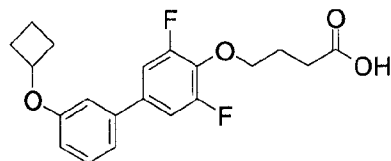
¹H NMR (400 MHz, CDCl₃) δ 7.32(t, 1H), 7.16-7.09(m, 2H), 7.09-7.05(m, 1H), 7.05-7.02(m, 1H), 6.92-6.87(m, 1H), 4.20(t, 2H), 4.16(q, 2H), 3.85(d, 2H), 2.59(t, 2H), 2.15-2.05(m, 2H), 1.35-1.21(m, 1H), 1.27(t, 3H), 0.71-0.62(m, 2H), 0.41-0.34(m, 2H)

Step B: 4-(3'-cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid

4-(3'-Cyclopropylmethoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester (20 mg, 0.05 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (18.4 mg, 99 %).

¹H NMR (400 MHz, CDCl₃) δ 7.32(t, 1H), 7.15-7.09(m, 2H), 7.09-7.05(m, 1H), 7.05-7.02(m, 1H), 6.92-6.87(m, 1H), 4.22(t, 2H), 3.85(d, 2H), 2.67(t, 2H), 2.15-2.06(m, 2H), 1.33-1.21(m, 1H), 0.70-0.62(m, 2H), 0.41-0.33(m, 2H)

Example 21: 4-(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid



Step A: 4-(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester

1-Cyclobutoxy-3-iodo-benzene (37 mg, 0.135 mmol) obtained in Preparation Example 21, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl

ester (50 mg, 0.135 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.5 mg, 0.0068 mmol) were reacted in the same manner as in Step A of Example 18 to obtain the title compound (30 mg, 57 %).

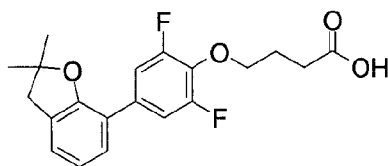
¹H NMR (400 MHz, CDCl₃) δ 7.31(t, 1H), 7.14-7.07(m, 2H), 7.07-7.04(m, 1H), 6.96-6.92(m, 1H), 6.83-6.79(m, 1H), 4.73-4.64(m, 1H), 4.20(t, 2H), 4.16(q, 2H), 2.59(t, 2H), 2.52-2.41(m, 2H), 2.26-2.13(m, 2H), 2.13-2.04(m, 2H), 1.93-1.82(m, 1H), 1.78-1.67(m, 1H), 1.28(t, 3H)

Step B: 4-(3'-cyclobutoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid

4-(3'-Cyclobutoxy-3,5-difluoro-biphenyl-4-yloxy)-butyric acid ethyl ester (30 mg, 0.077 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (27 mg, 97 %).

¹H NMR (400 MHz, CDCl₃) δ 7.31(t, 1H), 7.14-7.08(m, 2H), 7.08-7.03(m, 1H), 6.96-6.92(m, 1H), 6.83-6.78(m, 1H), 4.73-4.64(m, 1H), 4.22(t, 2H), 2.67(t, 2H), 2.51-2.42(m, 2H), 2.28-2.17(m, 2H), 2.17-2.07(m, 2H), 1.92-1.82(m, 1H), 1.78-1.64(m, 1H)

Example 22: 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid



Step A: 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid ethyl ester

7-Iodo-2,2-dimethyl-2,3-dihydro-benzofuran (35 mg, 0.13 mmol) obtained in Preparation Example 22, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (47 mg, 0.13 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.2 mg, 0.0065 mmol) were reacted in the same manner as in Step A of Example 18 to obtain the title compound (20 mg, 40%).

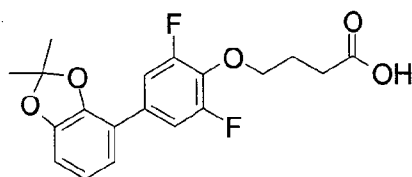
¹H NMR (400 MHz, CDCl₃) δ 7.35-7.27(m, 2H), 7.20(d, 1H), 7.11(d, 1H), 6.88(t, 1H), 4.23-4.12(m, 4H), 3.04(s, 2H), 2.58(t, 2H), 2.14-2.04(m, 2H), 1.51(s, 6H), 1.26(t, 3H)

Step B: 4-[4-(2,2-dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid

4-[4-(2,2-Dimethyl-2,3-dihydro-benzofuran-7-yl)-2,6-difluoro-phenoxy]-butyric acid ethyl ester (20 mg, 0.051 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (17 mg, 92%).

¹H NMR (400 MHz, CDCl₃) δ 7.34-7.27(m, 2H), 7.20(d, 1H), 7.11(d, 1H), 6.88(t, 1H), 4.20(t, 2H), 3.04(s, 2H), 2.67(t, 2H), 2.14-2.06(m, 2H), 1.51(s, 6H)

Example 23: 4-[4-(2,2-dimethyl-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid



Step A: 4-[4-(2,2-dimethyl-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid ethyl ester

4-Iodo-2,2-dimethyl-benzo[1,3]dioxole (40 mg, 0.145 mmol) obtained in Preparation Example 23, 4-[2,6-difluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy]butyric acid ethyl ester (53.6 mg, 0.145 mmol) obtained in Preparation Example 16 and PdCl₂(dppf)-DCM (5.9 mg, 0.0073 mmol) were reacted in the same manner as in Step A of Example 18 to obtain the title compound (19 mg, 33%).

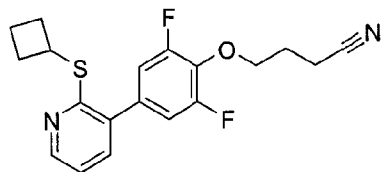
¹H NMR (400 MHz, CDCl₃) δ 7.32-7.24(m, 2H), 6.94-6.81(m, 2H), 6.74-6.70(m, 1H), 4.20(t, 2H), 4.15(q, 2H), 2.58(t, 2H), 2.13-2.05(m, 2H), 1.72(s, 6H), 1.26(t, 3H)

Step B: 4-[4-(2,2-dimethyl-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid

4-[4-(2,2-Dimethyl-benzo[1,3]dioxol-4-yl)-2,6-difluoro-phenoxy]-butyric acid ethyl ester (19 mg, 0.048 mmol) obtained in Step A was reacted in the same manner as in Step B of Example 1 to obtain the title compound (16 mg, 91%).

¹H NMR (400 MHz, CDCl₃) δ 7.32-7.22(m, 2H), 6.94-6.78(m, 2H), 6.74-6.68(m, 1H), 4.21(t, 2H), 2.65(t, 2H), 2.14-2.03(m, 2H), 1.72(s, 6H)

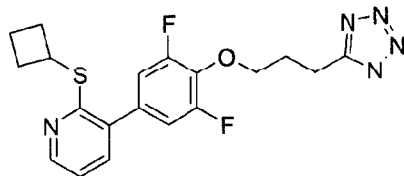
Example 24: 4-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-

phenoxy]butanenitrile

4-(2-Cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenol (0.06 g, 0.204 mmol) obtained in Preparation Example 24 was dissolved in DMF (3 mL), and 4-bromobutanenitrile (0.02 mL, 0.204 mmol) was added thereto. Cs_2CO_3 (0.133 g, 0.108 mmol) was added thereto, and the mixture was stirred at room temperature for 16 hours. After addition of brine aqueous solution, the reaction solution was extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/2.5) to obtain the title compound (0.056 g, 76%).

NMR: ^1H -NMR (CDCl_3) δ 8.41(1H, m), 7.32(1H, m), 7.01(3H, m), 4.43(1H, m), 4.30(2H, t), 2.69(2H, t), 2.52(2H, m), 2.15(2H, m), 2.04(4H, m)

Example 25: 2-cyclobutylsulfanyl-3-{3,5-difluoro-4-[3-(1H-tetrazol-5-yl)propoxy]phenyl}pyridin

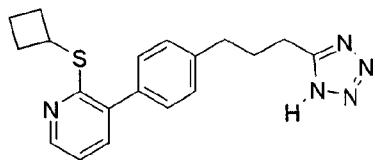


4-[4-(2-Cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]butanenitrile (0.056 g, 0.155 mmol) obtained in Example 24, sodium azide (0.029 g, 0.434 mmol) and ammonium chloride (0.024 g, 0.434 mmol) were dissolved in DMF (3 mL), and the mixture was stirred at 120°C for 16 hours. After termination of the reaction, the reaction solution was diluted with water and extracted with EtOAc. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, MeOH/DCM = 1/20) to obtain the title compound (0.004 g, 7.2%).

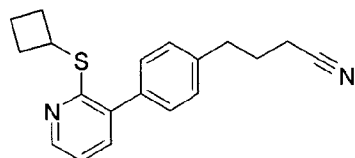
NMR: ^1H -NMR (CDCl_3) δ 8.42(1H, m), 7.32(1H, m), 7.03(3H, m), 4.43(1H, m), 4.31(2H, t), 3.34(2H, t), 2.53(2H, m), 2.32(2H, m), 2.06(4H, m)

Example 26: 2-cyclobutylsulfanyl-3-{4-[3-(1H-tetrazol-5-

yl)propyl]phenyl}pyridine



Step A: 4-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]butanenitrile



2-Cyclobutylsulfanyl-3-iodo-pyridine (0.038 g, 0.177 mmol) obtained in Preparation Example 13 and 4-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]butanenitrile (0.045 g, 0.166 mmol) obtained in Preparation Example 25 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.03 g, 55%).

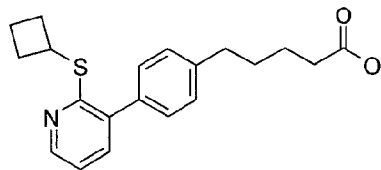
NMR: $^1\text{H-NMR}$ (CDCl_3) δ 8.39(1H, m), 7.34(3H, m), 7.26(2H, m), 7.00(1H, m), 4.22(1H, m), 2.83(2H, t), 2.48(2H, m), 2.37(2H, t), 2.03(6H, m)

Step B: 2-cyclobutylsulfanyl-3-{4-[3-(1H-tetrazol-5-yl)propyl]phenyl}pyridine

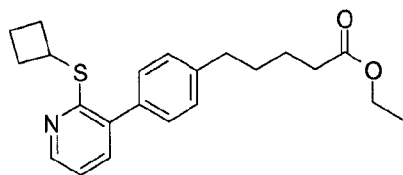
4-[4-(2-Cyclobutylsulfanyl-pyridin-3-yl)phenyl]butanenitrile (0.03 g, 0.097 mmol) obtained in Step A was reacted in the same manner as in Example 25 to obtain the title compound (0.001 g, 4.6%).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 8.39(1H, m), 7.34(3H, m), 7.26(2H, m), 7.03(1H, m), 4.41(1H, m), 3.00(2H, t), 2.77(2H, m), 2.49(2H, m), 2.20(2H, m), 2.01(4H, m)

Example 27: 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid



Step A: 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid ethyl ester



2-Cyclobutylsulfanyl-3-iodo-pyridine (0.08 g, 0.27 mmol) obtained in Preparation Example 13 and 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester (0.085 g, 0.25 mmol) obtained in Preparation Example 26 were reacted in the same manner as in Step A of Example 1 to obtain the title compound (0.063 g, 62%).

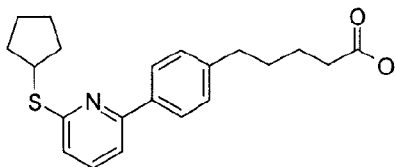
NMR: $^1\text{H-NMR}$ (CDCl_3) δ 8.37(1H, m), 7.33(3H, m), 7.26(2H, m), 7.00(1H, m), 4.41(1H, m), 4.12(2H, q), 2.68(2H, m), 2.48(2H, m), 2.33(2H, m), 1.99(4H, m), 1.71(4H, m), 1.24(3H, t)

Step B: 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid

5-[4-(2-Cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid ethyl ester (0.063 g, 0.17 mmol) obtained in Step A was dissolved in EtOH (2 mL). 1N NaOH (1 mL) was added thereto, and the mixture was stirred at room temperature for 3 hours. After termination of the reaction, the reaction solution was concentrated under reduced pressure, and residues were diluted with water. The water layer was adjusted to pH 2-3 by the use of 1N HCl and extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate and purified by column chromatography (eluent, EtOAc/Hex = 1/2) to obtain the title compound (0.044 g, 75%).

NMR: $^1\text{H-NMR}$ (CDCl_3) δ 8.37(1H, m), 7.31(3H, m), 7.26(2H, m), 7.00(1H, m), 4.41(1H, m), 2.68(2H, m), 2.48(2H, m), 2.40(2H, m), 1.99(4H, m), 1.72(4H, m)

Example 28: 5-[4-(6-cyclopentylsulfanyl-2-pyridyl)phenyl]pentanoic acid



2-Chloro-6-cyclopentylsulfanyl-pyridine (0.042 g, 0.196 mmol) obtained in Preparation Example 14 and 5-[4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)phenyl]pentanoic acid ethyl ester (0.061 g, 0.183 mmol) obtained in Preparation Example 26 were reacted in the same manner as in Example 1 to obtain the title compound (0.015 g,

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __3__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

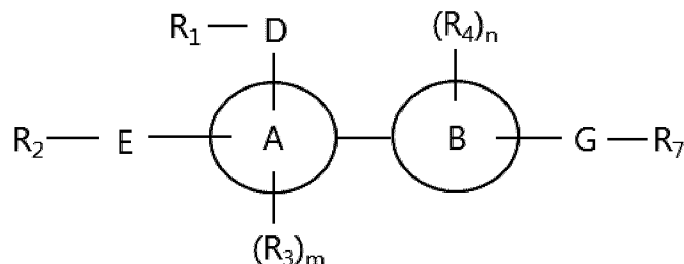
THIS IS VOLUME __1__ OF __3__

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS

1. A biaryl derivative of Formula 1, or a pharmaceutically acceptable salt or isomer thereof:

[Formula 1]



wherein,

A represents pyridinyl, pyrimidinyl, pyrazinyl, indolinyl or indolyl;

B represents naphthalenyl or phenyl;

D and E may independently not exist, or represent independently C, CH, CH_2 , N, NH, O or S;

R_1 and R_2 may independently not exist, or represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, oxo, alkylcycloalkyl, cycloalkylalkyl, haloalkyl, alkoxy, alkoxyalkyl, alkoxyaryl, cycloalkoxy, cycloalkylalkoxy, alkylheterocycloalkyl, aryl, alkylaryl, aralkyl, haloaryl, heteroaryl, alkylheteroaryl or haloalkylaryl;

R_1 and R_2 may be connected to each other, or with D and/or E to form a ring, or may form a fused ring with A; the ring is optionally substituted with alkyl, halogen, alkoxycarbonyl, cycloalkylalkyl, haloaryl or alkylaryl; and when D and E represent C, CH or N, R_1 and R_2 can represent two or three alkyl, oxo, cycloalkyl, alkoxy, alkylcycloalkyl, aryl or alkylaryl which may be the same or different;

R_3 and R_4 represent independently hydrogen, halogen, alkyl, cycloalkyl, heterocycloalkyl, alkoxy, nitrile, oxo, cycloalkoxy, aryloxy, heteroaryloxy, aminoalkyl, aminocycloalkyl, aminoaryl, alkylamine, cycloalkylamine, aminoheteroaryl, thioalkyl, thioaryl or thioheteroaryl;

m and n represent independently an integer of 0 to 5;

G represents $-(\text{CR}_5\text{R}_6)_p\text{-J-(CR}_5\text{R}_6)_q$, wherein J represents CH_2 , O, N, NH, S or a double bond; R_5 and R_6 represent independently hydrogen, halogen, alkyl or cycloalkyl, hydroxy or amine, or may be connected to each other to form cycloalkyl, and when J is N, each of R_5 and R_6 at two (CR_5R_6) s may be connected to form a ring, or may be substituted with alkyl; and p and q represent independently an integer of 0 to 6; and R_7 represents carboxylic acid or carboxylic acid isostere, provided that the carboxylic acid isostere is not tetrazole.

2. The biaryl derivative of claim 1, wherein

A represents pyridinyl, pyrimidinyl, pyrazinyl, indolinyl or indolyl;

B represents naphthalenyl or phenyl;

D and E may independently not exist, or represent independently C, CH, CH_2 , N, NH, O or S;

R_1 and R_2 may independently not exist, or represent independently hydrogen, halogen, $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl, 3- to 12-membered heterocycloalkyl, oxo, $\text{C}_1\text{-C}_{10}$ alkyl- $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl- $\text{C}_1\text{-C}_{10}$ alkyl, halo- $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkoxy- $\text{C}_1\text{-C}_{10}$ alkyl, $\text{C}_1\text{-C}_{10}$ alkoxy- $\text{C}_5\text{-C}_{12}$ aryl, $\text{C}_3\text{-C}_{10}$ cycloalkoxy, $\text{C}_3\text{-C}_{10}$ cycloalkyl- $\text{C}_1\text{-C}_{10}$ alkoxy, $\text{C}_1\text{-C}_{10}$ alkyl-3- to 12-membered heterocycloalkyl, $\text{C}_5\text{-C}_{12}$ aryl, $\text{C}_1\text{-C}_{10}$ alkyl- $\text{C}_5\text{-C}_{12}$ aryl, $\text{C}_5\text{-C}_{12}$ aryl- $\text{C}_1\text{-C}_{10}$ alkyl, halo- $\text{C}_5\text{-C}_{12}$ aryl, 3- to 12-membered heteroaryl, $\text{C}_1\text{-C}_{10}$ alkyl-3- to 12-membered heteroaryl or halo- $\text{C}_1\text{-C}_{10}$ alkyl- $\text{C}_5\text{-C}_{12}$ aryl, wherein the heterocycloalkyl and heteroaryl have at least one heteroatom selected from the group consisting of N, O and S;

R_1 and R_2 may be connected to each other, or with D and/or E to form $\text{C}_3\text{-C}_{10}$ cycloalkyl, $\text{C}_5\text{-C}_{12}$ aryl or 3- to 12-membered heterocycloalkyl having at least one heteroatom selected from the group consisting of N, O and S, or may form 3- to 15-membered heterocycle or heteroaryl having at least one heteroatom selected from the group consisting of N, O and S, fused with A; the cycloalkyl, aryl, heterocycloalkyl, heterocycle or heteroaryl is optionally substituted with $\text{C}_1\text{-C}_{10}$ alkyl, halogen, $\text{C}_1\text{-C}_{10}$ alkoxycarbonyl, $\text{C}_3\text{-C}_{10}$ cycloalkyl- $\text{C}_1\text{-C}_{10}$ alkyl, halo- $\text{C}_5\text{-C}_{12}$ aryl or $\text{C}_1\text{-C}_{10}$ alkyl- $\text{C}_5\text{-C}_{12}$

aryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three C₁-C₁₀ alkyl, oxo, C₃-C₁₀ cycloalkyl, C₁-C₁₀ alkoxy, C₁-C₁₀ alkyl-C₃-C₁₀ cycloalkyl, C₅-C₁₂ aryl or C₁-C₁₀ alkyl-C₅-C₁₂ aryl which may be the same or different;

R₃ and R₄ represent independently hydrogen, halogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₁-C₁₀ alkoxy, nitrile, oxo, C₃-C₁₀ cycloalkoxy, C₅-C₁₂ aryloxy, 3- to 12 membered heteroaryloxy, amino-C₁-C₁₀ alkyl, amino-C₃-C₁₀ cycloalkyl, amino-C₅-C₁₂ aryl, C₁-C₁₀ alkylamine, C₃-C₁₀ cycloalkylamine, amino-3- to 12-membered heteroaryl, thio-C₁-C₁₀ alkyl, thio-C₅-C₁₂ aryl or thio-3 to 12-membered heteroaryl;

m and n represent independently an integer of 0 to 3;

G represents -(CR₅R₆)_p-J-(CR₅R₆)_q, wherein J represents CH₂, O, N, NH, S or double bond; R₅ and R₆ represent independently hydrogen, halogen, C₁-C₁₀ alkyl or C₃-C₁₀ cycloalkyl, hydroxy or amine, or may be connected to each other to form C₃-C₁₀ cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)s may be connected to form 3- to 12-membered heteroaryl or 3- to 12-membered heterocycloalkyl having 1 or 2 N atoms, or may be substituted with C₁-C₁₀ alkyl; and p and q represent independently an integer of 0 to 6; and

R₇ represents carboxylic acid or carboxylic acid isostere, provided that the carboxylic acid isostere is not tetrazole.

3. The biaryl derivative of claim 1 or 2, wherein

R₁ and R₂ may independently not exist, or represent independently hydrogen, halogen, C₁-C₈ alkyl, C₃-C₈ cycloalkyl, 3- to 10 membered heterocycloalkyl, oxo, C₁-C₈ alkyl-C₃-C₈ cycloalkyl, C₃-C₈ cycloalkyl-C₁-C₈ alkyl, halo-C₁-C₈ alkyl, C₁-C₈ alkoxy, C₁-C₈ alkoxy-C₁-C₈ alkyl, C₁-C₈ alkoxy-C₆-C₁₀ aryl, C₃-C₈ cycloalkoxy, C₃-C₈ cycloalkyl-C₁-C₈ alkoxy, C₁-C₈ alkyl-3- to 10-membered heterocycloalkyl, C₆-C₁₀ aryl, C₁-C₈ alkyl-C₆-C₁₀ aryl, C₆-C₁₀ aryl-C₁-C₈ alkyl, halo-C₆-C₁₀ aryl, 5- to 10-membered heteroaryl, C₁-C₈ alkyl-5- to 10-membered heteroaryl or halo-C₁-C₈ alkyl-C₆-C₁₀ aryl, wherein the heterocycloalkyl and heteroaryl have 1 to 3 heteroatoms selected from the group consisting of N, O and S;

R₁ and R₂ may be connected to each other, or with D and/or E to form C₃-C₈ cycloalkyl, C₆-C₁₀ aryl or 3- to 12-membered heterocycloalkyl having 1 to 3 heteroatoms selected from the group consisting of N, O and S, or may form 3- to 14-membered heterocycle or heteroaryl having 1 to 4 heteroatoms selected from the group consisting of N, O and S, fused with A; the cycloalkyl, aryl, heterocycloalkyl, heterocycle or heteroaryl is optionally substituted with C₁-C₈ alkyl, halogen, C₁-C₈ alkoxycarbonyl, C₃-C₈ cycloalkyl-C₁-C₈ alkyl, halo-C₆-C₁₀ aryl or C₁-C₈ alkyl-C₆-C₁₀ aryl; and when D and E represent C, CH or N, R₁ and R₂ can represent two or three C₁-C₈ alkyl, oxo, C₃-C₈ cycloalkyl, C₁-C₈ alkoxy, C₁-C₈ alkyl-C₃-C₈ cycloalkyl, C₆-C₁₀ aryl or C₁-C₈ alkyl-C₆-C₁₀ aryl which may be the same or different.

4. The biaryl derivative of any one of claims 1 to 3, wherein R₃ and R₄ represent independently hydrogen, halogen, C₁-C₁₀ alkyl, C₃-C₁₀ cycloalkyl, 3- to 12-membered heterocycloalkyl, C₁-C₁₀ alkoxy, nitrile, oxo or C₃-C₁₀ cycloalkoxy.
5. The biaryl derivative of any one of claims 1 to 4, wherein G represents -(CR₅R₆)_p-J-(CR₅R₆)_q, wherein J represents CH₂, O, N, NH, S or a double bond; R₅ and R₆ represent independently hydrogen, halogen, C₁-C₈ alkyl or C₃-C₈ cycloalkyl, hydroxy or amine, or may be connected to each other to form C₃-C₈ cycloalkyl, and when J is N, each of R₅ and R₆ at two (CR₅R₆)_s may be connected to form 3- to 10-membered heteroaryl or 3- to 12-membered heterocycloalkyl having 1 or 2 N atoms, or may be substituted with C₁-C₈ alkyl; and p and q represent independently an integer of 0 to 5.
6. The biaryl derivative of any one of claims 1 to 5, wherein the carboxylic acid isostere of R₇ is selected from the group consisting of isoxazolol, pyrazolol, isothiazolol, thiazolidinedione, pyrrolidinedione, oxazolidinedione, imidazolidinedione, thiazolidinedione, imidazoledione, pyrroledione, phenol, pyridinol, dioxothiadiazolidineone, triazole, imidazole, sulfonic acid, sulfonamide, acetamide,

nitrile, hydroxyacetamidine, oxadiazoleone and oxadiazolethione.

7. A biaryl derivative, which is selected from the group consisting of:
- [6-(6-cyclopentyloxy-pyridin-2-yl)-naphthalen-2-yloxy]-acetic acid,
 - [6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yloxy]-acetic acid,
 - 4-[6-(2-isopropylsulfanyl-pyridin-3-yl)-naphthalen-2-yloxy]-butyric acid,
 - 4-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yloxy]-butyric acid,
 - 4-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]butanenitrile,
 - 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
 - 5-[4-(6-cyclopentylsulfanyl-2-pyridyl)phenyl]pentanoic acid,
 - 5-[4-(2-cyclopentylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
 - 5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]pentanoic acid,
 - 5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
 - 5-[4-(6-cyclopentoxy-2-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
 - 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
 - 5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
 - 5-[4-(2-cyclopentoxy-3-pyridyl)-2,6-difluoro-phenyl]pentanoic acid,
 - {2-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]ethoxy}acetic acid,
 - 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]hexanoic acid,
 - 5-[4-(6-cyclobutoxy-2-pyridyl)-phenyl]hexanoic acid,
 - 5-[4-(6-cyclobutoxy-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 - 5-[4-(2-ethylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 - 5-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,
 - 5-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]hexanoic acid,
 - 5-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 - 5-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 - 5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)-phenyl]hexanoic acid,
 - 5-[4-(2-cyclopentoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 - 5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)-phenyl]hexanoic acid,
 - 5-[4-(6-cyclopentylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,

5-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]hexanoic acid,
 5-[4-(6-cyclopentoxy-2-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 4-[4-(2-isopropoxy-3-pyridyl)phenyl]butanoic acid,
 5-[2,6-difluoro-4-(2-hydroxy-3-pyridyl)phenyl]hexanoic acid,
 5-[4-(2-cyclobutoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[4-(2-cyclopropylmethoxy-3-pyridyl)-2,6-difluoro-phenyl]hexanoic acid,
 5-[[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
N'-hydroxy-4-[4-(2-propylsulfanyl-3-pyridyl)phenyl]butaneamidine,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4*H*-1,2,4-oxadiazol-5-one,
 3-[3-[4-(2-propylsulfanyl-3-pyridyl)phenyl]propyl]-4*H*-1,2,4-oxadiazol-5-thione,
 5-[[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenoxy]methyl]isoxazol-3-ol,
 5-[(*E*)-3-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]allyl]thiazolidin-2,4-dione,
 5-[[4-[2-(cyclobutoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclobutylmethoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]anilino]methyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 4-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]methyl]pyridin-2-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[(*E*)-3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]allyl]-1,1-dioxo-1,2,5-thiadiazolidin-3-one,

5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]sulfanylmethyl]isoxazol-3-ol,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]methyl]isoxazol-3-ol,
 5-[3-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]propyl]-1,1-dioxo-1,2,5-
 thiadiazolidin-3-one,
 5-[[4-[2-(cyclopentoxy)-3-pyridyl]-*N*-methyl-anilino]methyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]propyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenoxy]ethyl]isoxazol-3-ol,
 5-[2-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]ethyl]isoxazol-3-ol,
 2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
 5-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 5-[4-[2-(cyclopentoxy)-3-pyridyl]-*N*-ethyl-2,6-difluoro-anilino]pentanoic acid,
 5-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)anilino]pentanoic acid,
 5-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)anilino]pentanoic acid,
 5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 5-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-anilino]pentanoic acid,
 2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 5-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-*N*-methyl-anilino]pentanoic acid,
 2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-tetrahydrofuran-3-yloxy-3-pyridyl)phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-3-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]acetic acid,
 6-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-
 carboxylic acid,
 6-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-6-azaspiro[2.5]octan-2-

carboxylic acid,

2-[1-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]azetidin-3-yl]acetic acid,
2-[1-[4-[6-(cyclopentoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
2-[1-[2,6-difluoro-4-(2-propylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-(2-cyclobutylsulfanyl-3-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(2-isopropoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(2-propoxy-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
2-[1-[4-[2-(cyclopropylmethoxy)-3-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrazol-4-yl]acetic acid,
2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,
2-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]pyrrolidin-3-yl]acetic acid,
3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]propanoic acid,
3-[1-[2,6-difluoro-4-(6-isopropylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]propanoic acid,
2-[2-[4-(2-cyclopentylsulfanyl-3-pyridyl)-2,6-difluoro-anilino]ethyl]cyclopropane
carboxylic acid,
2-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-3-piperidyl]acetamide,
2-[4-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]piperazin-1-yl]acetic acid,
3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrazol-4-yl]propanoic acid,
4-[5-(2-cyclopentylsulfanyl-3-pyridyl)indolin-1-yl]butanoic acid,
3-[1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]azetidin-3-yl]propanoic acid,
2-[(3R)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic
acid,
2-[(3R)-1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic acid,
2-[(3S)-1-[2,6-difluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]pyrrolidin-3-yl]acetic
acid,
2-[(3S)-1-[4-[2-(cyclopentoxy)-3-pyridyl]-2,6-difluoro-phenyl]pyrrolidin-3-yl]acetic acid,

2-[1-[2-fluoro-4-(2-isopropylsulfanyl-3-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[2-(cyclopentoxy)-3-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,
 3-[6-(6-isopropylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-phenoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-cyclopentylsulfanyl-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-phenoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(6-cyclobutoxy-pyridin-2-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-isopropoxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-(2-cyclopentyloxy-pyridin-3-yl)-naphthalen-2-yl]-propanoic acid,
 3-[6-[6-(2-fluoro-phenoxy)-pyridin-2-yl]-naphthalen-2-yl]-propanoic acid,
 5-[4-(2-isopropoxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-5-methyl-hexanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5-methyl-hexanoic acid,
 4-{1-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 4-{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-butyric acid,
 {2-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 {2-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-2,2-difluoro-ethoxy}-acetic acid,
 3-{2-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic

acid,

3-{2-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

5-[4-(2-cyclopentyloxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

3-{2-[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-cyclopropyl}-propanoic acid,

3-{2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

3-{2-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

3-{2-[4-(2-cyclopentylamino-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

5-[4-(2-cyclobutoxy-pyridin-3-yl)-phenyl]-5,5-difluoro-pentanoic acid,

5-[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-5,5-difluoro-pentanoic acid,

{4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-cyclohexyl}-acetic acid,

3-{2-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

3-{2-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

3-(2-{2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl}-cyclopropyl)-propanoic acid,

3-{2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-cyclopropyl}-propanoic acid,

5,5-difluoro-5-[4-(6-isopropylsulfanyl-pyridin-2-yl)-phenyl]-pentanoic acid,

4-{[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric acid,

4-{[2,6-difluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino}-butyric acid,

4-[[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[4-(6-cyclopentyloxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[2,6-difluoro-4-(2-propylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-ethylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino]-butyric acid,

2-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenylamino]-methyl]-cyclopropane carboxylic acid,

2-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-phenylamino]-methyl]-cyclopropane carboxylic acid,

4-[[2-fluoro-4-(2-isopropylsulfanyl-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-methyl-amino]-butyric acid,

4-[[2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclopentyloxy-5-methyl-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-methyl-amino]-butyric acid,

4-[[2,6-difluoro-4-(2-methoxy-pyridin-3-yl)-phenyl]-methyl-amino]-butyric acid,

4-[[2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl]-methyl-amino]-butyric acid,

4-[[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-ethyl-amino]-butyric acid,

4-[[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-ethyl-amino]-butyric acid,

4-[[2,6-difluoro-4-(2-isopropoxy-pyridin-3-yl)-phenyl]-ethyl-amino]-butyric acid,

(R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,

(E)-(R)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hex-2-enoic acid,

(S)-5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-hexanoic acid,

5-[2,6-difluoro-4-[2-(tetrahydro-furan-3-yloxy)-pyridin-3-yl]-phenyl]-hexanoic acid,

5-[2,6-difluoro-4-[2-(tetrahydro-pyran-4-yloxy)-pyridin-3-yl]-phenyl]-hexanoic acid,

5-{2,6-difluoro-4-[2-(oxetan-3-yloxy)-pyridin-3-yl]-phenyl}-hexanoic acid,
 4-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 6-[4-(2-cyclopentyloxy-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 6-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenyl]-heptanoic acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenylsulfanyl]-butyric acid,
 4-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[3-(6-cyclopentyloxy-pyridin-2-yl)-phenoxy]-butyric acid,
 4-[3-(2-cyclopentyloxy-pyridin-3-yl)-phenoxy]-butyric acid,
 5-[4-(2-cyclopentyloxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopentylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutylsulfanyl-pyridin-3-yl)-2-fluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclobutoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 5-[4-(2-cyclopropylmethoxy-pyridin-3-yl)-2,6-difluoro-phenyl]-pentanoic acid,
 4-[4-(2-cyclohexylsulfanyl-pyridin-3-yl)-2,6-difluoro-phenoxy]-butyric acid,
 3-[4-(2-cyclopentyloxy-pyridin-3-yl)-benzylsulfanyl]-propionic acid,
 2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropoxy-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutylsulfanyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propylsulfanyl-2-pyridyl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentoxo)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2-chloro-4-[6-(cyclopropylmethoxy)-2-pyridyl]-6-fluoro-phenyl]-4-piperidyl]acetic

acid,

2-[1-[4-[6-(cyclobutylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-*tert*-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[5-chloro-6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclopropanecarbonyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxymethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-ethoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoroethoxy)-2-pyridyl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(2,2,2-trifluoro-1-methyl-ethoxy)-2-pyridyl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-cyclopentyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-[cyclopropyl(methoxy)methyl]-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2-fluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-(6-butoxy-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,

2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-

piperidyl]acetic acid,
 2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]azetidin-3-yl]acetic acid,
 2-[1-[4-(6-ethoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-methoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-propoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutoxypyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-butoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentoxypyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(4-ethoxypyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isopropoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-propoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutoxypyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-pyrrolidin-1-ylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[6-(isopropylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[6-(diethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[6-(isobutylamino)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylamino)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(dimethylamino)pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[4-(isobutylamino)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutoxy)-5-methyl-pyrazin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-phenylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclopentylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutylpyrimidin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-butylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopentylpyrazin-2-yl)phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(cyclopropylmethoxy)-5-fluoro-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutyl-2-pyridyl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-(6-cyclobutylpyrazin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclobutylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[6-(cyclopentylmethyl)-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-(1-[2,6-difluoro-4-[7-(propan-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl]phenyl]piperidin-4-yl)acetic acid,
 2-[1-[4-(6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(cyclobutoxy)-5,6-dimethyl-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

4-[2-chloro-4-[6-(cyclobutoxy)-2-pyridyl]-6-fluoro-phenoxy]butanoic acid,
 4-[2,6-dichloro-4-[6-(cyclobutoxy)-2-pyridyl]phenoxy]butanoic acid,
 4-[4-[6-(cyclopropylmethoxymethyl)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[2-chloro-4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,
 4-[2-chloro-4-[2-(cyclobutoxy)-6-methyl-pyrimidin-4-yl]-6-fluoro-phenoxy]butanoic acid,
 4-[4-[6-chloro-4-(cyclobutoxy)-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclobutoxy)-4-methyl-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[2-chloro-4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-6-fluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenoxy]butanoic acid,
 5-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-phenyl]hexanoic acid,
 4-[2-chloro-4-(6-cyclopentyloxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyridin-2-yl)-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-cyclobutylsulfanyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-6-fluoro-4-(6-isopropylsulfanyl-pyridin-2-yl)-phenoxy]-butyric acid,
 5-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 5-({[4-(6-cyclobutoxy-pyridin-2-yl)-phenyl]-methyl-amino}-methyl)-isoxazol-3-ol,
 5-[4-(2-cyclobutoxy-6-methyl-pyrimidin-4-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 5-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-hexanoic acid,
 4-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[4-(2-cyclobutoxy-pyrimidin-4-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(4-cyclobutoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(2-cyclobutoxy-pyrimidin-4-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-chloro-4-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,

4-[2-chloro-4-(6-cyclobutoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-cyclopropylmethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-cyclopropylmethoxy-4-methyl-pyridin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 4-[2-chloro-6-fluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenoxy]-butyric acid,
 4-[2-chloro-4-(6-ethoxy-pyrazin-2-yl)-6-fluoro-phenoxy]-butyric acid,
 {(R)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[4-[6-(cyclopropylmethoxy)-5-methoxy-2-pyridyl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 4-[4-(6-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,
 5-[4-[6-(cyclobutoxy)-5-methoxy-2-pyridyl]phenyl]-5,5-difluoro-pentanoic acid,
 4-[2,6-difluoro-4-(5-fluoroindol-1-yl)phenoxy]butanoic acid,
 4-[2,6-difluoro-N-methyl-4-(6-pyrrolidin-1-yl-2-pyridyl)anilino]butanoic acid,
 4-[2,6-difluoro-4-(5-methoxyindol-1-yl)phenoxy]butanoic acid,
 4-[4-(5-cyanoindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,
 4-[2,6-difluoro-4-(4-fluoroindol-1-yl)phenoxy]butanoic acid,
 4-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenoxy]butanoic acid,

4-[4-[6-(cyclopropylmethoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-(7-chloroindol-1-yl)-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[4-[5-(cyclobutoxy)indol-1-yl]-2,6-difluoro-phenoxy]butanoic acid,
 4-[2,6-difluoro-4-(4-methoxyindol-1-yl)phenoxy]butanoic acid,
 4-[2,6-difluoro-4-(7-methoxyindol-1-yl)phenoxy]butanoic acid,
 2-[1-[4-(7-chloroindol-1-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 4-[4-[4-(cyclobutoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[4-(cyclobutoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclobutoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[4-(cyclopropylmethoxy)-6-methyl-pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[4-(cyclopropylmethoxy)pyrimidin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclopropylmethoxy)pyrazin-2-yl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 4-[4-[6-(cyclopropylmethoxy)-2-pyridyl]-2,6-difluoro-N-methyl-anilino]butanoic acid,
 2-[1-[2,6-difluoro-4-(6-propoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-cyclopentoxo-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-butoxy-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-propoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isopropoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-ethoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(4-isobutoxy-pyrimidin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isobutylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-cyclopentylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-isopropylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,
 2-[1-[2,6-difluoro-4-(6-diethylamino-pyrazin-2-yl)phenyl]pyrrolidin-3-yl]acetic acid,

2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(4-chlorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-pyrrolidin-3-yl]acetic
 acid,
 2-[1-[4-[4-phenoxy-pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(4-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(4-pyridin-3-yloxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[2,6-difluoro-4-[6-(4-fluorophenoxy)pyrazin-2-yl]phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(4-methoxyphenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 2-[1-[2,6-difluoro-4-[4-(4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-
 piperidyl]acetic acid,
 2-[1-[4-[4-(*p*-tolylloxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,
 2-[1-[4-[4-(3,4-difluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic
 acid,
 4-{[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric
 acid,
 4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 4-{[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-methyl-amino}-butyric
 acid,
 4-[4-(5-chloro-6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxy]-butyric acid,
 5-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenyl]-pentanoic acid,
 4-[4-(6-cyclobutoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,
 4-[4-(6-cyclobutylsulfanyl-pyridin-2-yl)-2-fluoro-phenoxy]-butyric acid,
 2-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-
 cyclopropane carboxylic acid,
 2-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane
 carboxylic acid,
 2-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenoxy-methyl]-cyclopropane
 carboxylic acid,

2-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclopropylmethoxy-pyridin-2-yl)-6-fluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-6-fluoro-phenoxyethyl]-cyclopropane carboxylic acid,

2-[2-chloro-4-(6-cyclobutoxy-pyridin-2-yl)-6-fluoro-phenoxyethyl]-cyclopropane carboxylic acid,

{1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[2,6-difluoro-4-(6-isopropoxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclobutoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(4-cyclopropylmethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-4-methyl-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,

{1-[4-(6-cyclobutoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-cyclobutoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(6-cyclopropylmethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-cyclopropylmethoxy-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(6-methoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(6-ethoxy-pyrazin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(6-isopropoxy-pyrazin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(4-isopropoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(4-isobutoxy-6-methyl-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(4-methyl-6-propoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-ethoxy-6-methyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-cyclobutoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[4-(4-cyclopropylmethoxy-5-fluoro-pyrimidin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 (1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-pyrrolidin-3-yl)-acetic acid,
 (1-{2,6-difluoro-4-[6-(tetrahydro-thiopyran-4-yloxy-pyridin-2-yl)-phenyl]-pyrrolidin-3-yl}-acetic acid,
 {1-[2,6-difluoro-4-(5-fluoro-4-isobutoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,
 {1-[2,6-difluoro-4-(5-fluoro-4-propoxy-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid

acid,

(1-{2,6-difluoro-4-[4-(3-methyl-butoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic

acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-

acetic acid,

(1-{2,6-difluoro-4-[4-(3-methoxy-propoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-

4-yl)-acetic acid,

(1-{2,6-difluoro-4-[4-(2-methoxy-ethoxy)-6-methyl-pyrimidin-2-yl]-phenyl}-piperidin-

4-yl)-acetic acid,

(1-{2,6-difluoro-4-[6-(3-methoxy-propoxy)-pyridin-2-yl]-phenyl}-piperidin-4-yl)-acetic

acid,

{(S)-1-[4-(6-cyclopropylmethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-pyrrolidin-3-yl}-

acetic acid,

2-[1-[2,6-difluoro-4-[4-[(6-methyl-3-pyridyl)oxy]pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[6-(4-ethylphenoxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[4-[4-(3-fluorophenoxy)pyrimidin-2-yl]-2,6-difluoro-phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(3,4-fluorophenoxy)-6-methyl-pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-(2-pyridyloxy)pyrimidin-2-yl]phenyl]-4-piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

2-[1-[2,6-difluoro-4-[4-methyl-6-[3-(trifluoromethyl)phenoxy]pyrimidin-2-yl]phenyl]-4-

piperidyl]acetic acid,

{1-[4-(6-cyclobutoxy-4-trifluoromethyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-

acetic acid,

{1-[4-(4-cyclobutoxy-6-trifluoromethyl-pyrimidin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-acetic acid,
 {1-[2,6-difluoro-4-(4-propoxy-6-trifluoromethyl-pyrimidin-2-yl)-phenyl]-piperidin-4-yl}-acetic acid,
 (1-{2,6-difluoro-4-[4-(4-fluoro-phenoxy)-6-trifluoromethyl-pyrimidin-2-yl]-phenyl}-piperidin-4-yl)-acetic acid,
 3-{1-[2,6-difluoro-4-(6-propoxy-pyridin-2-yl)-phenyl]-piperidin-4-yl}-propionic acid,
 3-{1-[4-(6-cyclobutyl-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid,
 and
 3-{1-[4-(6-ethoxy-pyridin-2-yl)-2,6-difluoro-phenyl]-piperidin-4-yl}-propionic acid, or a pharmaceutically acceptable salt or isomer thereof.

8. Use of the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined in any one of claims 1 to 7, for the manufacture of a medicament for the prevention or treatment of metabolic disease selected from the group consisting of diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and inflammatory disease.
9. The use of claim 8, wherein the complication of diabetes is selected from the group consisting of neurogenic disease, hyperlipidemia, hypertension, retinosis and renal failure.
10. Use of the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined in any one of claims 1 to 7, for the manufacture of a medicament for lowering blood glucose level.
11. A pharmaceutical composition as a GPR120 agonist, comprising the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined in any one of claims 1 to 7, and a pharmaceutically acceptable carrier.

12. The pharmaceutical composition of claim 11, which is for the prevention or treatment of metabolic disease selected from the group consisting of diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and inflammatory disease.
13. The pharmaceutical composition of claim 12, wherein the complication of diabetes is selected from the group consisting of neurogenic disease, hyperlipidemia, hypertension, retinosis and renal failure.
14. Use of the pharmaceutical composition as defined in claim 11, for the prevention or treatment of metabolic disease selected from the group consisting of diabetes, complications of diabetes, obesity, non-alcoholic fatty liver, steatohepatitis, osteoporosis and inflammatory disease.
15. The use of claim 14, wherein the complication of diabetes is selected from the group consisting of neurogenic disease, hyperlipidemia, hypertension, retinosis and renal failure.
16. A pharmaceutical composition for lowering blood glucose level, comprising the biaryl derivative or pharmaceutically acceptable salt or isomer thereof as defined in any one of claims 1 to 7 and a pharmaceutically acceptable carrier.
17. Use of the pharmaceutical composition as defined in claim 11, for lowering blood glucose level.