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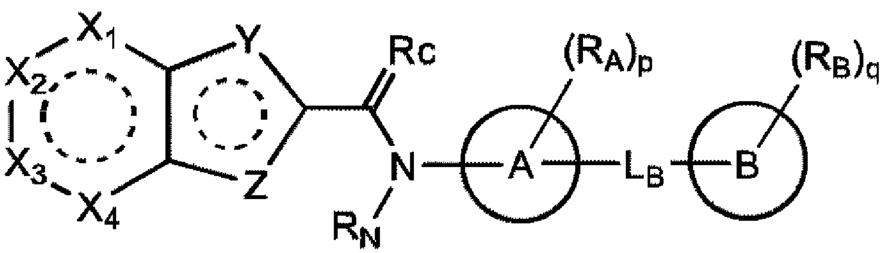
(72) Inventeurs/Inventors:
PARK, CHAN HEE, KR;
LEE, SANG HWI, KR;
IM, JUNHWAN, KR;
LEE, SOON OK, KR;
...

(73) Propriétaire/Owner:

(54) Titre : DERIVES HETEROCYCLIQUES POUR TRAITER DES MALADIES ASSOCIEES A L'ACTIVATION DE LA PROTEINE STAT3

(54) Title: HETEROCYCLIC DERIVATIVES FOR TREATING DISEASES ASSOCIATED WITH ACTIVATION OF STAT3 PROTEIN



(I)

(57) Abrégé/Abstract:
A heterocyclic derivative represented by formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, which has an inhibitory effect on the activation of STAT3 protein, and is useful for the prevention or treatment of diseases associated with the activation of STAT3 protein, is provided.

(72) **Inventeurs(suite)/Inventors(continued)**: KIM, JONGMIN, KR; KO, KWANG SEOK, KR; KIM, BYUNGHO, KR; KONG, MINJUNG, KR; KIM, MI SUN, KR; MOON, HYUNG JO, KR

(73) **Propriétaires(suite)/Owners(continued)**:C&C RESEARCH LABORATORIES, KR

(74) **Agent**: SMART & BIGGAR LP

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(71) Applicant: C&C RESEARCH LABORATORIES [KR/KR]; 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR).

(72) Inventors: PARK, Chan Hee; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **LEE, Sang Hwi**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **IM, Junhwan**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **LEE, Soon Ok**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **KIM, Jongmin**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **KO, Kwang Seok**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **KIM, Byungho**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **KONG, Minjung**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **KIM, Mi Sun**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR). **MOON, Hyung Jo**; C&C Research Laboratories, 2066, Seobu-ro, Jangan-gu, Suwon-si, Gyeonggi-do 16419 (KR).

(74) Agent: FIRSTLAW P.C.; 60 Mabang-Ro, Seocho-Ku, Seoul 06775 (KR).

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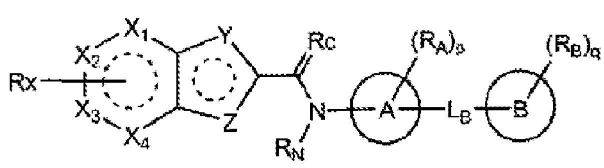

(I)

(57) Abstract: A heterocyclic derivative represented by formula (I), or a pharmaceutically acceptable salt or a stereoisomer thereof, which has an inhibitory effect on the activation of STAT3 protein, and is useful for the prevention or treatment of diseases associated with the activation of STAT3 protein, is provided.

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HETEROCYCLIC DERIVATIVES FOR TREATING DISEASES ASSOCIATED WITH ACTIVATION OF STAT3 PROTEIN

FIELD OF THE INVENTION

The present invention relates to novel heterocyclic compounds, uses thereof for the prevention or treatment of diseases associated with the activation of STAT proteins, particularly, STAT3 protein and pharmaceutical compositions comprising same.

BACKGROUND OF THE INVENTION

Signal transducer and activator of transcription (STAT) proteins are transcription factors which transduce signals from various extracellular cytokines and growth factors to a nucleus. Seven (7) subtypes of STAT proteins (i.e., STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6) are currently known, and generally they consist of about 750 - 850 amino acids. In addition, each subtype of STAT proteins contains several conserved domains which play an important role in exhibiting the function of STAT proteins. Specifically, five (5) domains from N-terminus to C-terminus of STAT proteins have been reported including coiled-coiled domain, DNA binding domain, linker domain, SH2 domain and transactivation domain (TAD)). Further, X-ray crystalline structures of STAT1, STAT3, STAT4 and STAT5 have been reported since 1998 (Becker S *et al.*, *Nature*, 1998, 394; Vinkemeier U *et al.*, *Science*, 1998, 279; Chen X *et al.*, *Cell*, 1998, 93; D. Neculai *et al.*, *J. Biol. Chem.*, 2005, 280). In general, receptors to which cytokines and growth factors bind are categorized into Class I and Class II. IL-2, IL-3, IL-5, IL-6, IL-12, G-CSF, GM-CSF, LIF, thrombopoietin, etc., bind to Class I receptors, while INF-α, INF-γ, IL-10, etc., bind to Class II receptors (Schindler C *et al.*, *Annu. Rev. Biochem.*, 1995, 64; Novick D *et al.*, *Cell*, 1994, 77; Ho AS *et al.*, *Proc. Natl. Acad. Sci.*, 1993, 90). Among them, the cytokine receptors involved in the activation of STAT proteins can be classified depending on their structural forms of extracellular domains into a gp-130 family, an IL-2 family, a growth factor family, an interferon family and a receptor tyrosine kinase family. Interleukin-6 family cytokines are representative multifunctional cytokines which mediate various physiological activities. When interleukin-6 cytokine binds to IL-6 receptor which is present on the cell membrane surface, it attracts gp-130 receptor to form an IL-6-gp-130 receptor complex. At the same time, JAK kinases (JAK1, JAK2, JAK3 and Tyk2) in the cytoplasm are recruited to a cytoplasmic region of gp130 to be phosphorylated and activated. Subsequently, latent cytoplasmic STAT proteins are attracted to a receptor, phosphorylated by JAK kinases and activated.

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Tyrosine-705 adjacent to the SH2 domain located in the C-terminus of STAT proteins is phosphorylated, and the activated tyrosine-705 of each STAT protein monomer binds to the SH2 domain of another monomer in a reciprocal manner, thereby forming a homo- or heterodimer. The dimers are translocalized into a nucleus and bind to a specific DNA binding promoter to promote the transcription. Through its transcription process, various proteins (Myc, Cyclin D1/D2, Bcl-xL, Mcl, survivin, VEGF, HIF-1, immune suppressors, etc.) associated with cell proliferation, survival, angiogenesis and immune evasion are produced (Stark et al., *Annu. Rev. Biochem.*, 1997, 67; Levy et al., *Nat. Rev. Mol. Cell Biol.*, 2002, 3).

In particular, STAT3 protein is known to play a crucial role in the acute inflammatory response and the signal transduction pathway of IL-6 and EGF (Akira *et al.*, *Cell*, 1994, 76; Zhong *et al.*, *Science*, 1994, 264). According to the recent clinical report, STAT3 protein is constantly activated in patients with solid cancers occurring in prostate, stomach, breast, lung, pancreas, kidney, uterine, ovary, head and neck, etc., and also in patients with blood cancer such as acute and chronic leukemia, multiple myeloma, etc. Further, it has been reported that the survival rate of a patient group with activated STAT3 is remarkably lower than that of a patient group with inactivated STAT3 (Masuda *et al.*, *Cancer Res.*, 2002, 62; Benekli *et al.*, *Blood*, 2002, 99; Yuichi *et al.*, *Int. J. Oncology*, 2007, 30). Meanwhile, STAT3 was identified to be an essential factor for the growth and maintenance of murine embryonic stem cells in a study employing a STAT3 knockout mouse model. Also, a study with a tissue-specific STAT3-deficient mouse model reveals that STAT3 plays an important role in cell growth, apoptosis, and cell motility in a tissue-specific manner (Akira *et al.*, *Oncogene* 2000, 19). Moreover, since apoptosis induced by anti-sensing STAT3 was observed in various cancer cell lines, STAT3 is considered as a promising new anticancer target. STAT3 is also considered as a potential target in the treatment of patients with diabetes, immune-related diseases, hepatitis C, macular degeneration, human papillomavirus infection, non-Hodgkin's lymphoma, tuberculosis, etc. Meanwhile, newly identified Th17 cells have been reported through a number of recent articles to be associated with various autoimmune diseases (Jacek Tabarkiewicz et al., Arch. Immunol. Ther. Exp., 2015, 11). Based on these reports, a control of the differentiation and function of Th17 cells is considered as a good target in the treatment of related diseases. In particular, since STAT3-dependent IL-6 and IL-23 signal transductions are known as important factors in the differentiation of Th17 cells (Xuexian O. Yang et al., J. Biol. Chem., 2007, 282; Harris T J et al., J. Immunol., 2007, 179), an inhibition of the function of STAT3 is expected to be effective in the treatment of diseases associated with Th17 cells such as systemic lupus erythematosus, uveitis, rheumatoid arthritis, autoimmune thyroid disease, inflammatory bowel disease, psoriasis and psoriatic arthritis (Jacek Tabarkiewicz et al., Arch. Immunol. Ther. Exp., 2015, 11).

Recently, IL-6 and IL-23 antibodies are under clinical studies on the treatment of arthritis and psoriasis associated with Th17 cells and exhibit a clinical efficacy (Nishimoto

N. et al., Arthritis Rheum., 2004, 50; Gerald G. et al., N. Engl. J. Med., 2007, 356). This also confirms that the inhibition of STAT3 signal transduction is an effective therapeutic method for such diseases.

In contrast, while having intracellular response pathways of identical cytokines and growth factors to those of STAT3, STAT1 increases inflammation and congenital and acquired immunities to inhibit the proliferation of cancer cells or cause pro-apoptotic responses, unlike STAT3 (Valeria Poli *et al., Review, Landes Bioscience*, 2009).

In order to develop STAT3 inhibitors, the following methods can be considered: i) inhibition of the phosphorylation of STAT3 protein by IL-6/gp-130/JAK kinase, ii) inhibition of the dimerization of activated STAT3 proteins, and iii) inhibition of the binding of STAT3 dimer to nuclear DNA. Small molecular STAT3 inhibitors are currently under development. Specifically, OPB-31121 and OPB-51602 are under clinical studies on patients with solid cancers or blood cancers by Otsuka Pharmaceutical Co., Ltd. Further, S3I-201 (Siddiquee *et al., Proc. Natl. Acad. Sci.*, 2007, 104), S3I-M2001 (Siddiquee *et al., Chem. Biol.*, 2007, 2), LLL-12 (Lin *et al., Neoplasia*, 2010, 12), Stattic (Schust *et al., Chem. Biol.* 2006, 13), STA-21 (Song *et al., Proc. Natl. Acad. Sci.,* 2005, 102), SF-1-066 (Zhang *et al., Biochem. Pharm.*, 2010, 79) and STX-0119 (Matsuno *et al., ACS Med. Chem. Lett.*, 2010, 1), etc. have been reported to be effective in a cancer cell growth inhibition experiment and in animal model (in vivo Xenograft model). Furthermore, although peptide compounds mimicking the sequence of amino acid of pY-705 (STAT3) adjacent to the binding site to SH2 domain or the amino acid sequence of gp-130 receptor in which JAK kinases bind were studied (Coleman *et al., J. Med. Chem.,* 2005, 48), the development of the peptide compounds has not been successful due to the problems such as solubility and membrane permeability.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide novel heterocyclic derivatives for the inhibition of the activation of STAT3 protein.

It is another object of the present invention to provide uses of the heterocyclic derivatives for the prevention or treatment of diseases associated with the activation of STAT3 protein.

In accordance with one aspect of the present invention, there is provided a compound of formula (I), a pharmaceutically acceptable salt or a stereoisomer thereof:

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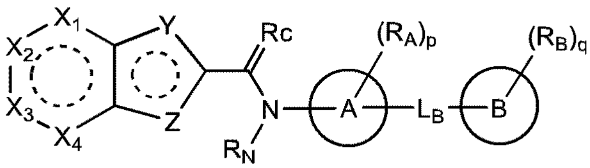
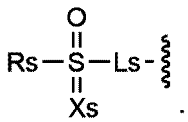


(I)

wherein

one of X_1, X_2, X_3 and X_4 is -C(-Rx)=, and the others are each independently -C(-Rx')= or -N=;

one of Y and Z is -S- or -NH-, and the other is -CH= or -N=;

Rx is  ;

Xs is =O or =NH;

Ls is -C(-Rs')(-Rs")-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl or 5- to 10-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

Rs' and Rs" are each independently hydrogen, halogen, C_{1-6}alkyl, carbamoyl-C_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl or diC_{1-6}alkylamino-C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen, halogen, nitro, amino, C_{1-6}alkoxy, haloC_{1-6}alkoxy, or C_{1-6}alkylsulfonyl;

A and B are each independently a monocyclic- or bicyclic-saturated or unsaturated C_{3-10}carbocycle or 5- to 12-membered heterocycle;

Rc is =O, =NH, =N(-C_{1-6}alkyl), or =N(-OH);

R_N is hydrogen or C_{1-6}alkyl, or R_N is linked to R_A to form a chain;

L_B is -[C(-R_L)(-R_L')]$_m$-, -[C(-R_L)(-R_L')]$_n$-O-, -O-, -NH-, -N(C_{1-6}alkyl)-, -S(=O)$_2$-, -C(=O)-, or -C(=CH_2)-, wherein m is an integer of 0 to 3, n is an integer of 1 to 3, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form a chain;

R_A is hydrogen, halogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{1-6}alkylamino, diC_{1-6}alkylamino, C_{1-6}alkylthio, C_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, C_{2-8}alkynyl, C_{1-6}alkoxycarbonylamino-C_{1-6}alkoxy, aminoC_{1-6}alkoxy or 3- to 6-membered heterocyclyl, or R_A is linked to R_N to form a chain;

R_B is hydrogen, halogen, hydroxy, cyano, nitro, amino, oxo, aminosulfonyl, sulfonylamido, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{3-8}cyclcoalkyloxy, C_{2-8}alkenyl, C_{2-8}alkenyloxy, C_{2-8}alkynyl, C_{2-8}alkynyloxy, C_{1-6}alkylamino-C_{1-6}alkoxy, diC_{1-6}alkylamino-C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, carbamoyl-C_{1-6}alkoxy, C_{1-}

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$_6$alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclyl-C_{1-6}alkyl, 5- to 10-membered heterocyclyl-C_{1-6}alkoxy, or 5- to 10-membered heterocyclyl-oxy;

p is an integer of 0 to 4, and, when p is 2 or higher, R_A moieties are the same as or different from each other;

q is an integer of 0 to 4, and, when q is 2 or higher, R_B moieties are the same as or different from each other; and

each of said chains is independently a saturated or unsaturated C_{2-10} hydrocarbon chain not containing or containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy; and

each of said heterocycle and heterocyclyl moieties independently contains at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$-.

In accordance with another aspect of the present invention, there is provided a use of a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein.

In accordance with a further aspect of the present invention, there is provided a pharmaceutical composition for preventing or treating diseases associated with the activation of STAT3 protein, comprising a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof as active ingredients.

In accordance with a still further aspect of the present invention, there is provided a method for preventing or treating diseases associated with the activation of STAT3 protein in a mammal, which comprises administering a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof to the mammal.

In one aspect, there is provided a pharmaceutical composition comprising the compound, pharmaceutically acceptable salt or stereoisomer thereof of the invention and a non-toxic pharmaceutically acceptable additive.

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In another aspect, there is provided a use of the compound, pharmaceutically acceptable salt or stereoisomer thereof of the invention for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis; or the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

In another aspect, there is provided use of the compound, pharmaceutically acceptable salt or stereoisomer thereof of the invention for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis; or the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

In another aspect, there is provided the compound, pharmaceutically acceptable salt or stereoisomer thereof of the invention for use in preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis; or the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and

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tuberculosis.

The heterocyclic derivative represented by formula (I) above, or a pharmaceutically acceptable salt or a stereoisomer thereof has an excellent inhibitory effect on the activation of STAT3 protein, and thus it can be used for the prevention or treatment of diseases associated with the activation of STAT3 protein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be further described in detail herein below.

In the specification of the present invention, the term "halogen" refers to fluoro, chloro, bromo or iodo, unless specified otherwise.

The term "alkyl" refers to a linear or branched hydrocarbon moiety, unless specified otherwise.

The terms "haloalkyl", "haloalkoxy", "halophenyl", etc., respectively refer to alkyl,

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alkoxy; and phenyl substituted with at least one halogen.

The term "carbocycle" refers to an aromatic or non-aromatic hydrocarbon ring, which may be saturated or unsaturated, and a monocyclic or polycyclic radical. The term "carbocyclyl" refers to a radical of "carbocycle", and is used as a term inclusive of "cycloalkyl" and "aryl". The term "cycloalkyl" refers to a saturated hydrocarbon radical, which may be monocyclic or polycyclic. The term "aryl" refers to an aromatic hydrocarbon ring, which may be monocyclic or polycyclic.

The terms "carbocycle", "carbocyclyl", "cycloalkyl" and "aryl" may refer to, for example, a monocycle or polycycle having 3 to 20 carbon atoms, and will be indicated as "C_{3-20} carbocycle", "C_{3-20} carbocyclyl", "C_{3-20} cycloalkyl", and "C_{3-20} aryl", respectively.

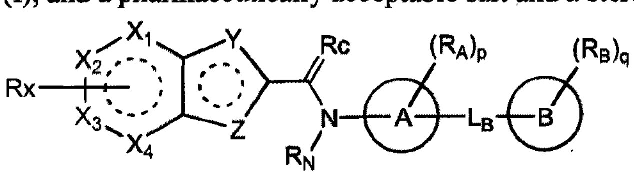
The term "heterocycle" refers to an aromatic or non-aromatic ring having at least one heteroatom, which may be saturated or unsaturated, and a monocycle or polycycle. The term "heterocyclyl" refers to a radical of "heterocycle", which is used as a term inclusive of "heterocycloalkyl" and "heteroaryl". The term "heterocycloalkyl" refers to a saturated ring radical having at least one heteroatom, which may be monocyclic or polycyclic. The term "heteroaryl" refers to an aromatic ring radical having at least one heteroatom, which may be monocyclic or polycyclic.

The term "heteroatom" may be selected from N, O and S.

The terms "heterocycle", "heterocyclyl", "heterocycloalkyl" and "heteroaryl" may refer to, for example, a mono- or polycycle having 3 to 20 heteroatoms and/or carbon atoms, and will be indicated as "3- to 20-membered heterocycle", "3- to 20-membered heterocyclyl", "3- to 20-membered heterocycloalkyl", and "3- to 20-membered heteroaryl".

The term "chain" refers to a saturated or unsaturated C_{2-10} hydrocarbon chain not containing any heteroatoms in the chain, for example, ethylene, propylene, butylene and -CH_2-CH=CH-; or a saturated or unsaturated C_{2-10} hydrocarbon chain containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, for example, -CH_2-O-CH_2-, -CH_2-O-CH_2-O-CH_2-, -CH_2-CH=CH-NH- and -CH_2-CH_2-S(=O)$_2$-CH_2-O-, unless specified otherwise. The chain may be substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy.

In accordance with one aspect of the present invention, there is provided a compound selected from the group consisting of a heterocyclic derivative represented by formula (I), and a pharmaceutically acceptable salt and a stereoisomer thereof:



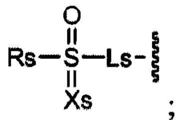
(I)

wherein

one of X_1, X_2, X_3 and X_4 is -C(-Rx)=, and the others are each independently -C(-

Rx')= or -N=;

one of Y and Z is -S- or -NH-, and the other is -CH= or -N=;

Rx is  ;

Xs is =O or =NH;

Ls is -C(-Rs')(-Rs'')- or -N(-Rs')-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl or 5- to 10-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

Rs' and Rs'' are each independently hydrogen, halogen, C_{1-6}alkyl, carbamoyl-C_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl or diC_{1-6}alkylamino-C_{1-6}alkyl, or Rs' and Rs'' are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen, halogen, nitro, amino, C_{1-6}alkoxy, haloC_{1-6}alkoxy, or C_{1-6}alkylsulfonyl;

A and B are each independently a monocyclic- or bicyclic-saturated or unsaturated C_{3-10}carbocycle or 5- to 12-membered heterocycle;

Rc is =O, =NH, =N(-C_{1-6}alkyl), or =N(-OH);

R_N is hydrogen or C_{1-6}alkyl, or R_N is linked to R_A to form a chain;

L_B is -[C(-R_L)(-R_L')]$_m$-, -[C(-R_L)(-R_L')]$_n$-O-, -O-, -NH-, -N(C_{1-6}alkyl)-, -S(=O)$_2$-, -C(=O)-, or -C(=CH_2)-, wherein m is an integer of 0 to 3, n is an integer of 1 to 3, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form a chain;

R_A is hydrogen, halogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{1-6}alkylamino, diC_{1-6}alkylamino, C_{1-6}alkylthio, C_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, C_{2-8}alkynyl, C_{1-6}alkoxycarbonylamino-C_{1-6}alkoxy, aminoC_{1-6}alkoxy or 3- to 6-membered heterocyclyl, or R_A is linked to R_N to form a chain;

R_B is hydrogen, halogen, hydroxy, cyano, nitro, amino, oxo, aminosulfonyl, sulfonylamido, C_{1-6}alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{3-8}cyclcoalkyloxy, C_{2-8}alkenyl, C_{2-8}alkenyloxy, C_{2-8}alkynyl, C_{2-8}alkynyloxy, C_{1-6}alkylamino-C_{1-6}alkoxy, diC_{1-6}alkylamino-C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, carbamoyl-C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclyl-C_{1-6}alkyl, 5- to 10-membered heterocyclyl-C_{1-6}alkoxy, or 5- to 10-membered heterocyclyl-oxy;

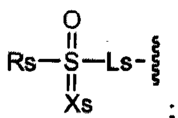
p is an integer of 0 to 4, and, when p is 2 or higher, R_A moieties are the same as or different from each other;

q is an integer of 0 to 4, and, when q is 2 or higher, R_B moieties are the same as or different from each other; and

each of said chains is independently a saturated or unsaturated C_{2-10} hydrocarbon chain not containing or containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy; and

each of said heterocycle and heterocyclyl moieties independently contains at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$-.

In a preferred embodiment of the compound of formula (I),
one of X_2 and X_3 is -C(-Rx)=, and the other is -C(-Rx')= or -N=;
X_1 and X_4 are each independently -C(-Rx')= or -N=;
one of Y and Z is -S- or -NH-, and the other is -CH=;
Rx and Rx' are the same as defined above in formula (I); and
Rc, R_N, A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

In a preferred embodiment of the compound of formula (I),
one of X_2 and X_3 is -C(-Rx)=, and the other is -C(-Rx')= or -N=;
X_1 and X_4 are each independently -C(-Rx')= or -N=;
one of Y and Z is -S- or -NH-, and the other is -CH=;
Rx is 

;
Xs is =O or =NH;
Ls is -C(-Rs')(-Rs")- or -N(-Rs')-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl or 5- to 6-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

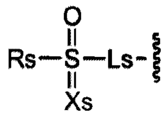
Rs' and Rs" are each independently hydrogen, halogen or C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen or halogen;

each of said chains is independently a saturated or unsaturated C_{2-7} hydrocarbon chain not containing or containing at least one heteroatom selected from the group consisting of O, N and S; and

Rc, R_N, A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

In a preferred embodiment of the compound of formula (I),
one of X_2 and X_3 is -C(-Rx)=, and the other is -C(-Rx')= or -N=;
X_1 and X_4 are each independently -C(-Rx')= or -N=;
one of Y and Z is -S- or -NH-, and the other is -CH=;



Rx is ;

Xs is =O or =NH;

Ls is -C(-Rs')(-Rs")- or -N(-Rs')-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl or 5- to 6-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

Rs' and Rs" are each independently hydrogen, halogen or C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen or halogen;

each of said chains is independently a saturated or unsaturated C_{2-7} hydrocarbon chain not containing or containing at least one heteroatom selected from the group consisting of O, N and S;

Rc and R_N are the same as defined above in formula (I);

A is benzene or a 5- to 10-membered heteroaryl containing 1 to 3 nitrogen atoms;

B is a monocyclic- or bicyclic-saturated or unsaturated C_{6-10}carbocycle or 5- to 10-membered heterocycle;

L_B is -[C(-R_L)(-R_L')]$_m$-, -O-, -NH-, or -N(C_{1-6}alkyl)-, wherein m is 0 or 1, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form C_{2-5}alkylene;

R_A is halogen, C_{1-6}alkoxycarbonylamino-C_{1-6}alkoxy, aminoC_{1-6}alkoxy, or 3- to 6-membered heterocyclyl;

R_B is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyloxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxycarbonyl, C_{3-10}carbocyclyl-oxy, or 3- to 10-membered heterocyclyl-C_{1-3}alkoxy; and

each of said heteroaryl, heterocycle and heterocyclyl moieties independently contains 1 to 3 heteroatoms selected from the group consisting of O, N and S.

In a preferred embodiment of the compound of formula (I),

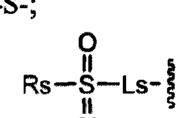
X_1 and X_4 are -CH=;

X_2 is -C(-Rx)=;

X_3 is -N= or -C(-Rx')-;

Y is -C=;

Z is -S-;



Rx is ;

Ls is -C(-CH_3)(-CH_3)-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl, or a 5- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of O, N and S;

Rx' is hydrogen, halogen, nitro, amino, C_{1-6}alkoxy, haloC_{1-6}alkoxy, or C_{1-6}alkylsulfonyl;

Rc is =O;

R_N is hydrogen; and

A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

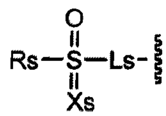
In a preferred embodiment of the compound of formula (I),

X_1, X_3 and X_4 are -CH=;

X_2 is -C(-Rx)=;

Y is -C=;

Z is -S-;

Rx is  ;

Ls is -C(-Rs')(-Rs")-;

Xs is =O or =NH;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl, or a 5- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of O, N and S;

Rs' and Rs" are each independently hydrogen, halogen, C_{1-6}alkyl, carbamoylC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl or diC_{1-6}alkylamino-C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, wherein the chain is a saturated or unsaturated C_{2-10} hydrocarbon chain not containing or containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy;

Rc is =O;

R_N is hydrogen; and

A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

In a preferred embodiment of the compound of formula (I),

X_1, X_3 and X_4 are -CH=;

X_2 is -C(-Rx)=;

Y is -C=;

Z is -S-;

Rx is the same as defined above in formula (I);

Rc is =O;

R_N is hydrogen; and

A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

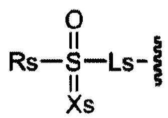
In a preferred embodiment of the compound of formula (I),

X_1, X_2 and X_4 are -CH=;

X_3 is -C(-Rx)=;

Y is -C=;

Z is -S- or -NH-;

Rx is  ;

Xs is =O;

Ls is -C(-CH_3)(-CH_3)-;

Rs is methyl;

Rc is =O;

R_N is hydrogen; and

A, B, L_B, R_A, R_B, p and q are the same as defined above in formula (I).

In a preferred embodiment of the compound of formula (I), if A is 5-membered heterocycle, m is an integer of 1 to 3. The 5-membered heterocycle is preferably a 5-membered aromatic ring unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-10}alkyl and haloC_{1-10}alkyl. The 5-membered heterocycle contains at least one heteroatom selected from the group consisting of N, S and O.

Preferable examples of the compound according to the present invention are listed below, and a pharmaceutically acceptable salt and a stereoisomer thereof are also included in the scope of the present invention:

1) *N*-(3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

2) *N*-(3-chloro-5-(2-(3-propoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

3) *N*-(3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

4) *N*-(3-bromo-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

5) *N*-(3-chloro-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

6) *N*-(3-methoxy-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

7) *N*-(3-chloro-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-

5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

8) *N*-(3-chloro-5-(2-(3-(2-morpholinoethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

9) *N*-(3-bromo-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

10) *N*-(3-(2-(3-(but-2-yn-1-yloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

11) *N*-(3-chloro-5-(2-(3-isobutoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

12) *N*-(3-chloro-5-(2-(3-(2,2,2-trifluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

13) *N*-(3-chloro-5-(2-(3-(2,2-difluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

14) *N*-(3-(2-(3-(allyloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

15) *N*-(3-chloro-5-(2-(3-cyclopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

16) *N*-(3-chloro-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

17) *N*-(3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

18) *N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

19) *N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

20) *N*-(3-bromo-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

21) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

22) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

23) 6-chloro-*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

24) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

25) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

26) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

27) *N*-(3-chloro-5-(2-(5-chlorothiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

28) *N*-(3-chloro-5-(2-(5-isopropylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

29) *N*-(3-chloro-5-(2-(5-methoxythiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

30) *N*-(3-chloro-5-(2-(2-methoxythiophen-3-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

31) *N*-(3-chloro-5-(2-(1-methyl-1*H*-pyrrol-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

32) *N*-(3-chloro-5-(2-(4-methylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

33) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxamide;

34) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

35) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide;

36) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((S-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxamide;

37) *N*-(3-chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

38) *N*-(3-chloro-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

39) *N*-(3-bromo-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

40) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide;

41) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

42) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

43) *N*-(3-chloro-5-(4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

44) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

45) 6-chloro-*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

46) *N*-(3-(4-chlorophenoxy)-5-methoxyphenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

47) *N*-(3-chloro-5-(3-chloro-5-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

48) *N*-(3-chloro-5-(3-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

49) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

50) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

51) *N*-(3-chloro-5-(3-chloro-4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

52) *N*-(3-chloro-5-(3,4-difluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

53) *N*-(3-chloro-5-(3-fluoro-5-methoxyphenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

54) *N*-(3-chloro-5-(4-chloro-3-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

55) *N*-(3-chloro-5-(2-(3-chloro-5-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

56) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

57) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

58) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

59) *N*-(3-(azetidin-1-yl)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

60) *N*-(3-chloro-5-((6-chloropyridin-3-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

61) *N*-(3-chloro-5-((5-chloropyridin-2-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

62) *N*-(2-chloro-6-(3,5-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

63) *N*-(6-chloro-4-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

64) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

65) *N*-(2-chloro-6-((6-chloropyridin-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

66) *N*-(4-chloro-6-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

67) *N*-(2-chloro-6-(4-(trifluoromethyl)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

68) *N*-(2-chloro-6-(4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

69) *N*-(2-bromo-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

70) *N*-(2-chloro-6-(3-chloro-5-methoxyphenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

71) *N*-(2-chloro-6-(3-chloro-4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

72) *N*-(2-chloro-6-(4-chloro-3-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

73) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxamide;

74) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxamide;

75) *N*-(2-chloro-6-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

76) *N*-(6-chloro-2-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

77) *N*-(2-(4-chlorophenoxy)-6-fluoropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

78) *N*-(2-(bicyclo[2.2.1]hept-5-en-2-yloxy)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

79) *N*-(2-chloro-6-(3,4-difluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

80) *N*-(2-chloro-6-(3-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

81) *N*-(2-chloro-6-(3-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

82) *N*-(2-chloro-6-(3,4-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

83) *N*-(2-chloro-6-(4-chloro-2-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

84) *N*-(2-chloro-6-(4-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

85) *N*-(2-chloro-6-((5-chloropyridin-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

86) *N*-(2-chloro-6-((4-chlorobenzyl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

87) *N*-(3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

88) *N*-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

89) *N*-(3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

90) *N*-(2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

91) *N*-(4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

92) *N*-(3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

93) *tert*-butyl (2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate;

94) *N*-(3-(2-aminoethoxy)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

95) *N*-(5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-yl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

96) (8-chloro-6-(4-chlorophenoxy)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophen-2-yl)methanone;

97) *N*-(3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

98) *N*-(3-chloro-5-((2,4-difluorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

99) *N*-(3-chloro-5-((4-chlorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

100) *N*-(2-chloro-6-((4-chlorophenyl)(methyl)amino)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

101) *N*-(2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

102) *N*-(2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

103) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboximidamide 2,2,2-trifluoroacetate;

104) *N*-(2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

105) *N*-(2-(4-(*tert*-butyl)piperidin-1-yl)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

106) *N*-(2-chloro-6-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

107) *N*-(2-chloro-6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

108) *N*-(2-chloro-6-(octahydroisoquinolin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

109) *N*-(2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

110) *N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-5-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

111) *N*-(2-chloro-6-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

112) *N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

113) *N*-(2-chloro-6-((3,5-dimethylisoxazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

114) *N*-(2-chloro-6-((5-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

115) *N*-(2-chloro-6-((2-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

116) *N*-(2-chloro-6-((4,5-dimethylisoxazol-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

117) *N*-(2-chloro-6-((5-(trifluoromethyl)thiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

118) methyl 3-((6-chloro-4-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)pyridin-2-yl)oxy)isoxazole-5-carboxylate;

119) *N*-(2-chloro-6-((4-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

120) *N*-(2-chloro-6-((5-methylthiophen-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide; and

121) *N*-(2-chloro-6-((2-chlorothiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide.

The above-listed names of the compounds are described in accordance with the nomenclature method provided by ChemBioDraw Ultra software (Version 13.0.0.3015) of PerkinElmer.

The present invention provides a pharmaceutically acceptable salt of a heterocyclic derivative represented by formula (I) above. The pharmaceutically acceptable salt should have low toxicity to humans, and should not have any negative impact on the biological activities and physicochemical properties of parent compounds. Examples of the pharmaceutically acceptable salt may include an acid addition salt between a pharmaceutically usable free acid and a basic compound represented by formula (I), an alkaline metal salt (sodium salt, etc.) and an alkaline earth metal salt (potassium salt, etc.), an organic base addition salt between an organic base and carboxylic acid represented by formula (I), amino acid addition salt, etc.

Examples of a suitable form of salts according to the present invention may be a salt with an inorganic acid or organic acid, wherein the inorganic acid may be hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, bromic acid, etc., and the organic acid may be acetic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, fumaric acid, maleic acid, malonic acid, phthalic acid, succinic acid, lactic acid, citric acid, gluconic acid, tartaric acid, salicylic acid, malic acid, oxalic acid, benzoic acid, embonic acid, aspartic acid, glutamic acid, etc. The organic base which may be used for the preparation of the organic base addition salt may include tris(hydroxymethyl)methylamine, dicyclohexylamine, etc. Amino acids which may be used for the preparation of amino acid addition base may include natural amino acids such as alanine, and glycine.

The salts may be prepared using a conventional method. For example, the salts may be prepared by dissolving the compound represented by formula (I) in a water-miscible solvent such as methanol, ethanol, acetone, and 1,4-dioxane, adding a free acid or a free base, and then crystallizing the resultant thereafter.

Additionally, the compounds of the present invention may have a chiral carbon center, and thus they may be present in the form of an R or S isomer, a racemic compound, an individual enantiomer or a mixture, an individual diastereomer or a mixture, and all these stereoisomers and a mixture thereof may belong to the scope of the present invention.

Additionally, the compounds of the present invention may also include a hydrate or solvate of the heterocyclic derivative represented by formula (I). The hydrate or solvate may be prepared using a known method, and they are preferred to be non-toxic and water-soluble, and in particular, they are preferably water or a hydrate or solvate having 1-5 molecules of alcoholic solvent (especially ethanol, etc.) bound thereto.

The present invention also provides a use of a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein.

Further, the present invention provides method for preventing or treating diseases associated with the activation of STAT3 protein in a mammal, which comprises administering a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof to the mammal.

Further, the present invention provides a pharmaceutical composition for preventing or treating diseases associated with the activation of STAT3 protein, comprising a compound selected from the group consisting of a heterocyclic derivative represented by formula (I) above, and a pharmaceutically acceptable salt and a stereoisomer thereof as active ingredients.

Specifically, the diseases associated with the activation of STAT3 protein is selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

More specifically, the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

In particular, a heterocyclic derivative represented by formula (I) above, or a pharmaceutically acceptable salt or a stereoisomer thereof has an excellent inhibitory effect on the activation of STAT3 protein, and thus the present invention also provides a composition for the inhibition of STAT3 protein comprising the same as an active ingredient.

The pharmaceutical composition of the present invention, in addition to the heterocyclic derivative represented by formula (I) above, the pharmaceutically acceptable salt thereof, or the stereoisomer thereof, may further include as active ingredients, common and non-toxic pharmaceutically acceptable additives, for example, a carrier, an excipient, a diluent, an adjuvant, etc., to be formulated into a preparation according to a conventional method.

The pharmaceutical composition of the present invention may be formulated into various forms of preparations for oral administration such as tablets, pills, powders, capsules, syrups, or emulsions, or for parenteral administration such as intramuscular, intravenous or subcutaneous injections, etc., and preferably in the form of a preparation for oral administration.

Examples of the additives to be used in the pharmaceutical composition of the present invention may include sweeteners, binders, solvents, solubilization aids, wetting agents, emulsifiers, isotonic agents, absorbents, disintegrating agents, antioxidants, preservatives, lubricants, fillers, flavoring agents, etc. For example, they may include, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine, silica, talc, stearic acid, stearin, magnesium stearate, magnesium alluminosilicate, starch, gelatin, gum tragacanth, alginic acid, sodium alginate, methylcellulose, sodium carboxymethylcellulose, agar, water, ethanol, polyethylene glycol, polyvinylpyrrolidone, sodium chloride, calcium chloride, orange essence, strawberry essence, vanilla flavor, etc.

The pharmaceutical composition of the present invention may be formulated into a preparation for oral administration by adding additives to active ingredients, wherein the additives may include cellulose, calcium silicate, corn starch, lactose, sucrose, dextrose, calcium phosphate, stearic acid, magnesium stearate, calcium stearate, gelatin, talc, surfactants, suspension agents, emulsifiers, diluents, etc.

The pharmaceutical composition of the present invention may be formulated into a preparation for injection by adding additives to the active ingredients, for example, water, a saline solution, a glucose solution, an aqueous glucose solution analog, alcohol, glycol, ether, oil, fatty acid, fatty acid ester, glyceride, surfactants, suspension agents, emulsifiers, etc.

The compound of the present invention may be administered preferably in an amount ranging from 0.1 to 2,000 mg/day based on an adult subject with 70 kg body weight. The compound of the present invention may be administered once daily or a few divided doses. The dosage of the compound of the present invention may vary depending on the health conditions, age, body weight, sex of the subject, administration route, severity of illness, etc., and the scope of the present invention will not be limited to the dose suggested above.

Example

Hereinafter, the present invention is described more specifically by the following examples, but these are provided only for illustration purposes and the present invention is not limited thereto.

The definition of the abbreviations used in the following examples is as follows.

[Table 1]

Abbreviation	Full name
$AlCl_3$	Aluminum chloride
AcOH	Acetic acid
AIBN	2,2'-Azobis(2-methylpropionitrile)
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BBr_3	Boron tribromide
Brine	Brine is water saturated or nearly saturated with a brine salt (generally, sodium chloride)

n-BuLi	*n*-butyllithium
tert-BuLi	*tert*-butyllithium
tert-BuOH	*tert*-buthyl alcohol
CH_3CN	Acetonitrile
$CHCl_3$	Chloroform
$CHBr_3$	Bromoform
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
CH_3I	Methyl iodide
$(COCl)_2$	Oxalyl chloride
Cs_2CO_3	Cesium carbonate
CuI	Copper (I) iodide
Cu_2O	Copper (I) oxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DEAD	Diethyl azodicarboxylate
DIPEA	*N,N*-diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulfoxide
DMSO-d_6	Dimethylsulfoxide-d_6
EtOAc	Ethyl acetate
EtOH	Ethyl alcohol
Et_2O	Diethyl ether
HATU	2-(7-Aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBr	Hydrogen bromide
HCl	Hydrogen chloride
n-Hex	*n*-Hexane
H_2O	Water
H_2O_2	Hydrogen peroxide
K_2CO_3	Potassium carbonate
KOH	Potassium hydroxide
$LiAlH_4$	Lithium aluminum hydride
$LiOHH_2O$	Lithium hydroxide, monohydrate
MeOH	Methyl alcohol
Na_2CO_3	Sodium carbonate
Na_2SO_4	Sodium sulfate
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
$NaHSO_4$	Sodium bisulfate
NaH_2PO_4	Sodium phosphate monobasic acid
$NaIO_4$	Sodium periodate

NaN_3	Sodium azide
NaOH	Sodium hydroxide
NaOMe	Sodium methoxide
NaO*t*-Bu	Sodium *tert*-butoxide
NH_4Cl	Ammonium chloride
$Pd(dba)_2$	Bis(dibenzylideneacetone)palladium(0)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
$Pd(OAc)_2$	Palladium(II) acetate
PCl_3	Phosphorus trichloride
PCl_5	Phosphorus pentachloride
PPh_3	Triphenylphosphine
$RuCl_3H_2O$	Ruthenium(III) chloride hydrate
$SOCl_2$	Thionyl chloride
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
TFA	Trifluoroacetic acid
XPhos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Zn	Zinc
$ZnBr_2$	Zinc bromide
$ZnCl_2$	Zinc chloride

Intermediate 1) Synthesis of 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 1-(bromomethyl)-2,4-difluoro-5-methylbenzene

Paraformaldehyde (247.0 mg, 7.81 mmol) was dissolved in 33% solution of HBr in AcOH (4.0 mL), and 2,4-difluoro-1-methylbenzene (1.0 g, 7.81 mmol) and $ZnBr_2$ (880.0 mg, 3.91 mmol) were added. The reaction mixture was stirred at 120°C for 4 hours, cooled to room temperature, sat. $NaHCO_3$ was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 1-(bromomethyl)-2,4-difluoro-5-methylbenzene (1.1 g, 64%) as a colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.20 (t, 1H, *J*=8.4Hz), 6.77 (t, 1H, *J*=9.5Hz), 4.46 (s, 2H), 2.24 (s, 3H)

(b) Synthesis of 1,5-difluoro-2-methyl-4-((methylsulfonyl)methyl)benzene

1-(Bromomethyl)-2,4-difluoro-5-methylbenzene (260.0 mg, 1.18 mmol) was dissolved in anhydrous EtOH (6.0 mL) and sodium methanesulfinate (120.0 mg, 1.18

mmol) was added. The reaction mixture was refluxed for 2 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was recrystallized with Et_2O to obtain 1,5-difluoro-2-methyl-4-((methylsulfonyl)methyl)benzene (160.0 mg, 61%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.32 (t, 1H, *J*=8.3Hz), 6.86 (t, 1H, *J*=9.5Hz), 4.24 (s, 2H), 2.82 (s, 3H), 2.27 (s, 3H)

(c) Synthesis of 1,5-difluoro-2-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene

1,5-Difluoro-2-methyl-4-((methylsulfonyl)methyl)benzene (3.4 g, 15.40 mmol) was dissolved in anhydrous DMF (22.4 mL), and NaO*t*-Bu (3.7 g, 38.60 mmol) and CH_3I (4.8 mL, 77.20 mmol) were added at 0°C. The reaction mixture was stirred at 0°C, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 4 : 1) to obtain 1,5-difluoro-2-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (370.0 mg, 10%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.38 (t, 1H, *J*=9.2Hz), 6.75 (t, 1H, *J*=9.2Hz), 2.70-2.81 (m, 3H), 1.90 (s, 3H), 1.74 (d, 6H, *J*=7.2Hz)

(d) Synthesis of 1-(bromomethyl)-2,4-difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzene

1,5-Difluoro-2-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (370.0 mg, 1.49 mmol) was dissolved in anhydrous 1,2-dichloroethane (15.0 mL), and *N*-bromosuccinimide (265.0 mg, 1.49 mmol) and AIBN (25.0 mg, 0.15 mmol) were added. The reaction mixture was refluxed at 100°C for 15 hours, cooled to room temperature, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica column chromatography (*n*-Hex:EtOAc=4:1) to obtain 1-(bromomethyl)-2,4-difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzene (367.0 mg, 66%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.60 (t, 1H, *J*=8.5Hz), 6.88 (dd, 1H, *J*=12.4, 9.2Hz), 4.28 (s, 2H), 2.74 (s, 3H), 1.93 (d, 6H, *J*=2.6Hz)

(e) Synthesis of 2,4-difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde

1-(Bromomethyl)-2,4-difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzene (367.0 mg, 1.12 mmol) was dissolved in anhydrous CH_3CN (11.0 mL), and 4-methylmorpholine *N*-oxide (263.0 mg, 2.24 mmol) and molecular sieves (1.0 g) were added. The reaction mixture was stirred at room temperature for 90 minutes, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized with CH_2Cl_2 and *n*-Hex to obtain 2,4-difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (200.0

mg, 66%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.07 (t, 1H, *J*=8.6Hz), 7.56 (dd, 1H, *J*=12.6, 10.6Hz), 2.90 (s, 3H), 1.87 (d, 6H, *J*=2.5Hz)

(f) Synthesis of methyl 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate

2,4-Difluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (170.0 mg, 0.65 mmol) was dissolved in anhydrous DMF (11.0 mL), and methyl 2-mercaptoacetate (58.0 μL, 0.65 mmol) and K_2CO_3 (179.6 mg, 1.30 mmol) were added. The reaction mixture was stirred at 80°C for 5 hours, cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain methyl 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (165.0 mg, 77%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.08 (d, 1H, *J*=7.6Hz), 8.03 (s, 1H), 7.60 (d, 1H, *J*=12.8Hz), 3.96 (s, 3H), 2.77 (s, 3H), 2.00 (d, 6H, *J*=2.6Hz)

(g) Synthesis of 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

Methyl 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (165.0 mg, 0.50 mmol) was dissolved in THF (3.4 mL) and H_2O (1.6 mL), and LiOH·H_2O (210.0 mg, 4.99 mmol) was added. The reaction mixture was stirred at room temperature for 1 hour, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized with CH_2Cl_2 and *n*-Hex to obtain 6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (150.0 mg, quant) as a white solid.

LC/MS ESI (-): 315 (M-1)

Intermediate 2) Synthesis of 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of methyl 5-methylbenzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 2-fluoro-5-methylbenzaldehyde (300.0 mg, 2.17 mmol) as a starting material to obtain methyl 5-methylbenzo[*b*]thiophene-2-carboxylate (164.0 mg, 37%).

LC/MS (ESI+): 207 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.29 (d, 1H, *J*=8.4Hz), 7.67 (s, 1H), 7.30 (dd, 1H, *J*=8.3, 1.3Hz), 3.94 (s, 3H), 2.48 (s, 3H)

(b) Synthesis of methyl 5-(bromomethyl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-d was repeated except for using methyl 5-methylbenzo[*b*]thiophene-2-carboxylate (100.0 mg, 0.49 mmol) as a starting material to obtain methyl 5-(bromomethyl)benzo[*b*]thiophene-2-carboxylate (46.5 mg, 34%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.89 (s, 1H), 7.85 (d, 1H, *J*=8.4Hz), 7.50 (d, 1H, *J*=8.5Hz), 4.63 (s, 2H), 3.95 (s, 3H)

(c) Synthesis of methyl 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-b was repeated except for using methyl 5-(bromomethyl)benzo[*b*]thiophene-2-carboxylate (45.0 mg, 0.16 mmol) as a starting material to obtain methyl 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (45.0 mg, quant).

LC/MS (ESI+): 285 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.91-7.93 (m, 2H), 7.51 (d, 1H, *J*=8.4Hz), 4.37 (s, 2H), 3.96 (s, 3H), 2.80 (s, 3H)

(d) Synthesis of 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (45.0 mg, 0.16 mmol) as a starting material to obtain 5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid (39.3 mg, 90%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.50 (brs, 1H), 8.15 (s, 1H), 8.08 (d, 1H, *J*=8.5Hz), 8.03 (s, 1H), 7.53 (d, 1H, *J*=8.5Hz), 4.62 (s, 2H), 2.94 (s, 3H)

Intermediate 3) Synthesis of 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of methyl 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate

Methyl 5-(bromomethyl)benzo[*b*]thiophene-2-carboxylate (263.0 mg, 0.92 mmol) and sodium triflinate (216.0 mg, 1.38 mmol) were dissolved in propionitrile (4.6 mL). The reaction mixture was refluxed for 16 hours and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 4 : 1) to obtain methyl 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (171.8 mg, 55%) as a white solid.

LC/MS (ESI+): 339 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.94-7.96 (m, 2H), 7.49 (dd, 1H, *J*=8.5, 1.6Hz), 4.61 (s, 2H), 3.97 (s, 3H)

(b) Synthesis of 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (210.0 mg, 0.62 mmol) as a starting material to obtain 5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid (151.8 mg) without purification.

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.62 (brs, 1H), 8.20 (s, 1H), 8.15 (d, 1H, *J*=8.5Hz), 8.12 (s, 1H), 7.58 (dd, 1H, *J*=8.5, 1.6Hz), 5.41 (s, 2H)

Intermediate 4) Synthesis of 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 2-methyl-4-((methylsulfonyl)methyl)-1-nitrobenzene

The synthesis procedure of Intermediate 1-b was repeated except for using 4-(bromomethyl)-2-methyl-1-nitrobenzene (2.0 g, 8.69 mmol) as a starting material to obtain 2-methyl-4-((methylsulfonyl)methyl)-1-nitrobenzene (1.7 g, 86%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.02 (d, 1H, *J*=8.1Hz), 7.40-7.42 (m, 2H), 4.29 (s, 2H), 2.86 (s, 3H), 2.64 (s, 3H)

(b) Synthesis of 4-(fluoro(methylsulfonyl)methyl)-2-methyl-1-nitrobenzene

2-Methyl-4-((methylsulfonyl)methyl)-1-nitrobenzene (760.0 mg, 3.32 mmol) and *N*-fluoro-*N*-(phenylsulfonyl)benzene sulfonamide (2.1 g, 6.64 mmol) were dissolved in anhydrous THF (16.6 mL), and 1.6M solution of *n*-BuLi in *n*-Hex (4.2 mL, 6.64 mmol) was slowly added dropwise at -78°C. The reaction mixture was stirred for 9 hours, H_2O was added at room temperature, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 4-(fluoro(methylsulfonyl)methyl)-2-methyl-1-nitrobenzene (175.0 mg, 21%) as a brown solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.05 (d, 1H, *J*=8.9Hz), 7.94 (m, 1H), 7.54 (m, 1H), 6.09 (d, 1H, *J*=46.8Hz), 3.04 (d, 3H, *J*=1.6Hz), 2.65 (s, 3H)

(c) Synthesis of 2-(bromomethyl)-4-(fluoro(methylsulfonyl)methyl)-1-nitrobenzene

The synthesis procedure of Intermediate 1-d was repeated except for using 4-(fluoro(methylsulfonyl)methyl)-2-methyl-1-nitrobenzene (168.0 mg, 0.68 mmol) as a starting material to obtain 2-(bromomethyl)-4-(fluoro(methylsulfonyl)methyl)-1-nitrobenzene (129.5 mg).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.05 (d, 1H, *J*=8.9Hz), 7.95 (m, 1H), 7.93 (m, 1H), 6.10 (d, 1H, *J*=46.8Hz), 4.84 (s, 2H), 2.65 (s, 3H)

(d) Synthesis of 5-(fluoro(methylsulfonyl)methyl)-2-nitrobenzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 2-(bromomethyl)-4-(fluoro(methylsulfonyl)methyl)-1-nitrobenzene (127.0 mg) as a starting material to obtain 5-(fluoro(methylsulfonyl)methyl)-2-nitrobenzaldehyde (13.5 mg, 2 steps yield: 8%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.44 (s, 1H), 8.23 (d, 1H, *J*=8.5Hz), 8.13 (d, 1H, *J*=1.9Hz), 7.97 (dd, 1H, *J*=8.5, 2.0Hz), 6.21 (d, 1H, *J*=47.0Hz), 3.10 (d, 3H, *J*=1.7Hz)

(e) Synthesis of methyl 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 5-(fluoro(methylsulfonyl)methyl)-2-nitrobenzaldehyde (10.0 mg, 0.04 mmol) as a starting material to obtain methyl 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (11.0 mg, quant).

LC/MS (ESI+): 303 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.08 (s, 1H), 7.98 (d, 1H, *J*=8.6Hz), 7.63 (dd, 1H, *J*=8.5, 1.6Hz), 6.17 (d, 1H, *J*=46.2Hz), 3.97 (s, 3H), 3.02 (d, 3H, *J*=1.4Hz)

(f) Synthesis of 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylate (11.0 mg, 0.04 mmol) as a starting material to obtain 5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxylic acid (6.7 mg, 64%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 8.23 (s, 1H), 8.17-8.20 (m, 2H), 7.59 (dd, 1H, *J*=8.5, 1.6Hz), 6.93 (d, 1H, *J*=45.2Hz), 3.19 (d, 3H, *J*=1.2Hz)

Intermediate 5) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 2-methyl-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene

The synthesis procedure of Intermediate 1-c was repeated except for using 2-methyl-4-((methylsulfonyl)methyl)-1-nitrobenzene (500.0 mg, 2.18 mmol) as a starting material to obtain 2-methyl-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene (308.0 mg, 55%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.00 (d, 1H, *J*=9.2Hz), 7.62-7.63 (m, 2H), 2.65 (s, 3H), 2.61 (s, 3H), 1.88 (s, 6H)

(b) Synthesis of 2-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene

The synthesis procedure of Intermediate 1-d was repeated except for using 2-methyl-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene (270.0 mg, 1.05 mmol) as a starting material to obtain 2-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene (272.0 mg).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.07 (d, 1H, *J*=8.7Hz), 7.84 (d, 1H, *J*=2.2Hz), 7.77 (dd, 1H, *J*=8.7, 2.2Hz), 4.86 (s, 2H), 2.63 (s, 3H), 1.91 (s, 6H)

(c) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)-2-nitrobenzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 2-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-yl)-1-nitrobenzene (270.0 mg) as a starting material to obtain 5-(2-(methylsulfonyl)propan-2-yl)-2-nitrobenzaldehyde (139.0 mg, 2 step yield: 49%).

LC/MS (ESI+): 272 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.46 (s, 1H), 8.10-8.18 (m, 3H), 2.66 (s, 3H), 1.93 (s, 6H)

(d) Synthesis of methyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 5-(2-(methylsulfonyl)propan-2-yl)-2-nitrobenzaldehyde (137.0 mg, 0.51 mmol) as a starting material to obtain methyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (140.0 mg, 89%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.12 (d, 1H, *J*=1.8Hz), 8.08 (s, 1H), 7.90 (d, 1H, *J*=8.7Hz), 7.79 (dd, 1H, *J*=8.7, 1.9Hz), 3.96 (s, 3H), 2.55 (s, 3H), 1.93 (s, 6H)

(e) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (155.0 mg, 0.50 mmol) as a starting material to obtain 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (115.0 mg, 78%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.55 (brs, 1H), 8.25 (s, 1H), 8.14 (s, 1H), 8.07 (d, 1H, *J*=8.7Hz), 7.76 (dd, 1H, *J*=8.8, 1.7Hz), 2.73 (s, 3H), 1.83 (s, 6H)

Intermediate 6) Synthesis of 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 2-methyl-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene

2-Methyl-4-((methylsulfonyl)methyl)-1-nitrobenzene (500.0 mg, 2.18 mmol), 1,2-dibromoethane (0.3 mL, 3.27 mmol) and tetra-*n*-butylammonium bromide (70.3 mg, 0.22 mmol) were dissolved in toluene (22.0 mL), and 10N NaOH aqueous solution (0.7 mL, 6.54 mmol) was slowly added. The reaction mixture was heated at 40°C for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 4 : 1) to obtain 2-methyl-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene (92.0 mg, 17%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.00 (d, 1H, *J*=8.4Hz), 7.58 (m, 1H), 7.53 (m, 1H), 2.79 (s, 3H), 2.62 (s, 3H), 1.89-1.92 (m, 2H), 1.30-1.33 (m, 2H)

(b) Synthesis of 2-(bromomethyl)-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene

The synthesis procedure of Intermediate 1-d was repeated except for using 2-methyl-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene (95.0 mg, 0.37 mmol) as a starting material to obtain 2-(bromomethyl)-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene (102.0 mg).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.05 (d, 1H, *J*=8.4Hz), 7.79 (d, 1H, *J*=2.0Hz), 7.69 (dd, 1H, *J*=8.4, 2.0Hz), 4.83 (s, 2H), 2.80 (s, 3H), 1.90-1.95 (m, 2H), 1.34-1.37 (m, 2H)

(c) Synthesis of 5-(1-(methylsulfonyl)cyclopropyl)-2-nitrobenzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 2-(bromomethyl)-4-(1-(methylsulfonyl)cyclopropyl)-1-nitrobenzene (100.0 mg) as a starting material to obtain 5-(1-(methylsulfonyl)cyclopropyl)-2-nitrobenzaldehyde (40.6 mg, 2 steps yield: 41%).

LC/MS (ESI+): 270 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.43 (s, 1H), 8.16 (d, 1H, *J*=8.2Hz), 8.03-8.07 (m, 2H), 2.80 (s, 3H), 1.96-1.99 (m, 2H), 1.35-1.39 (m, 2H)

(d) Synthesis of methyl 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 5-(1-(methylsulfonyl)cyclopropyl)-2-nitrobenzaldehyde (40.0 mg, 0.15 mmol) as a starting material to obtain methyl 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylate (35.9 mg, 78%).

LC/MS (ESI+): 311 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.04-8.07 (m, 2H), 7.88 (m, 1H), 7.67 (m, 1H), 3.96 (s, 3H), 2.77 (s, 3H), 1.90-1.91 (m, 2H), 1.34-1.36 (m, 2H)

(e) Synthesis of 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylate (33.0 mg, 0.11 mmol) as a starting material to obtain 5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxylic acid (21.9 mg, 70%).

LC/MS ESI (+): 297 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.57 (brs, 1H), 8.19 (s, 1H), 8.10 (s, 1H), 8.07 (d, 1H, *J*=8.5Hz), 7.67 (d, 1H, *J*=8.9Hz), 2.88 (s, 3H), 1.67-1.70 (m, 2H), 1.35-1.38 (m, 2H)

Intermediate 7) Synthesis of 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 1-(2-chloro-4-fluoro-5-methylphenyl)ethan-1-one

$AlCl_3$ (5.8 g, 43.3 mmol) was dissolved in 1,2-dichloroethane (34.6 mL), and acetyl chloride (3.1 mL, 43.3 mmol) was added dropwise at 0°C. 4-Chloro-2-fluoro-1-methylbenzene (5.0 g, 34.6 mmol) was added. The reaction mixture was stirred at 0°C for 1 hour and then at 60°C for 16 hours. 1N HCl aqueous solution was added dropwise, and the reaction mixture was extracted with EtOAc. The organic extract was washed with sat. $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 1-(2-chloro-4-fluoro-5-methylphenyl)ethan-1-one (4.9 g, 75%) as a yellow oil.

LC/MS ESI (+): 187 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.48 (d, 1H, *J*=8.1Hz), 7.10 (d, 1H, *J*=9.1Hz), 2.64 (s, 3H), 2.27 (s, 3H)

(b) Synthesis of 2-(2-chloro-4-fluoro-5-methylphenyl)propan-2-ol

1-(2-Chloro-4-fluoro-5-methylphenyl)ethan-1-one (4.9 g, 26.00 mmol) was dissolved in THF (260.0 mL), and 3.0M solution of methylmagnesium bromide in Et_2O (26.0 mL) was added dropwise at -8°C. The reaction mixture was stirred for 16 hours, 1N HCl aqueous solution was added dropwise at 0°C to quench the reaction, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 2 : 1) to obtain 2-(2-chloro-4-fluoro-5-methylphenyl)propan-2-ol (4.3 g, 82%) as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.50 (d, 1H, *J*=8.4Hz), 7.04 (d, 1H, *J*=9.1Hz), 2.44 (s, 1H), 2.25 (d, 3H, *J*=1.7Hz), 1.70 (s, 6H)

(c) Synthesis of 2-(2-chloro-4-fluoro-5-methylphenyl)propane-2-thiol

2-(2-Chloro-4-fluoro-5-methylphenyl)propan-2-ol (4.3 g, 21.40 mmol) and Lawesson's reagent (5.2 g, 12.80 mmol) were dissolved in toluene (107.0 mL), and H_2O (0.5 mL) was added. The reaction mixture was stirred at 50°C for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with sat. $NaHCO_3$ aqueous solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : DCM = 4 : 1) to obtain 2-(2-chloro-4-fluoro-5-methylphenyl)propane-2-thiol (2.7 g, 59%) as a pale yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.31 (d, 1H, *J*=8.1Hz), 7.08 (d, 1H, *J*=9.1Hz), 2.89 (s, 1H), 2.24 (s, 3H), 1.92 (s, 6H)

(d) Synthesis of (2-(2-chloro-4-fluoro-5-methylphenyl)propan-2-yl)(methyl)sulfane

NaOH (357.0 mg, 8.92 mmol) was dissolved in EtOH (34.3 mL), and dimethyl sulfate (1.0 mL, 10.29 mmol) was added dropwise. 2-(2-Chloro-4-fluoro-5-methylphenyl)propane-2-thiol (1.5 g, 6.86 mmol) was added, and the reaction mixture was stirred at room temperature for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : DCM = 6 : 1) to obtain (2-(2-chloro-4-fluoro-5-methylphenyl)propan-2-yl)(methyl)sulfane (1.5 g, 93%) as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.27 (d, 1H, *J*=7.7Hz), 7.08 (d, 1H, *J*=9.2Hz), 2.25 (d, 3H, *J*=1.7Hz), 1.81-1.83 (m, 9H)

(e) Synthesis of 1-chloro-5-fluoro-4-methyl-2-(2-(methylsulfonyl)propan-2-yl)benzene

(2-(2-Chloro-4-fluoro-5-methylphenyl)propan-2-yl)(methyl)sulfane (1.5 g, 6.36 mmol) was dissolved in AcOH (31.8 mL) and 35 wt% H_2O_2 aqueous solution (6.4 mL) was added dropwise. The reaction mixture was stirred at room temperature for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with sat. $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 4 : 1) to obtain 1-chloro-5-fluoro-4-methyl-2-(2-(methylsulfonyl)propan-2-yl)benzene (1.6 g, 95%) as a white solid.

LC/MS ESI (+): 265 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.55 (d, 1H, *J*=8.1Hz), 7.09 (d, 1H, *J*=9.0Hz), 2.76 (s, 3H), 2.27 (s, 3H), 2.03 (s, 6H)

(f) Synthesis of 1-(bromomethyl)-4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-

2-yl)benzene

The synthesis procedure of Intermediate 1-d was repeated except for using 1-chloro-5-fluoro-4-methyl-2-(2-(methylsulfonyl)propan-2-yl)benzene (1.7 g, 6.35 mmol) as a starting material to obtain 1-(bromomethyl)-4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzene (2.2 g).

LC/MS ESI (+): 343 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.77 (d, 1H, *J*=7.9Hz), 7.18 (d, 1H, *J*=9.1Hz), 4.47 (s, 2H), 2.77 (s, 3H), 2.06 (s, 6H)

(g) Synthesis of 4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 1-(bromomethyl)-4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzene (2.2 g) as a starting material to obtain 4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (1.0 g, 2 step yield: 57%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.29 (s, 1H), 8.22 (d, 1H, *J*=7.4Hz), 7.34 (d, 1H, *J*=9.6Hz), 2.78 (s, 3H), 2.09 (s, 6H)

(h) Synthesis of methyl 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 4-chloro-2-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (1.0 g, 3.59 mmol) as a starting material to obtain methyl 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (1.1 g, 91%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.03 (s, 1H), 7.94 (s, 1H), 3.96 (s, 3H), 2.79 (s, 3H), 2.14 (s, 6H)

(i) Synthesis of 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (1.1 g, 3.26 mmol) as a starting material to obtain 6-chloro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (998.0 mg, 92%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.67 (brs, 1H), 8.44 (s, 1H), 8.26 (s, 1H), 8.14 (s, 1H), 2.88 (s, 3H), 2.04 (s, 6H)

Intermediate 8) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylic acid

(a) Synthesis of 2-(bromomethyl)-4-methyl-5-nitropyridine

The synthesis procedure of Intermediate 1-d was repeated except for using 2,4-

dimethyl-5-nitropyridine (2.5 g, 16.43 mmol) as a starting material to obtain 2-(bromomethyl)-4-methyl-5-nitropyridine (1.1 g, 28%).

LC/MS ESI (+): 231 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 9.11 (s, 1H), 7.74 (s, 1H), 4.75 (s, 2H), 2.59 (s, 3H)

(b) Synthesis of 4-methyl-2-((methylsulfonyl)methyl)-5-nitropyridine

The synthesis procedure of Intermediate 1-**b** was repeated except for using 2-(bromomethyl)-4-methyl-5-nitropyridine (1.1 g, 4.76 mmol) as a starting material to obtain 4-methyl-2-((methylsulfonyl)methyl)-5-nitropyridine (980.0 mg, 89%).

LC/MS ESI (+): 231 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 9.15 (s, 1H) 7.50 (s, 1H), 4.46 (s, 2H), 2.98 (s, 3H), 2.69 (s, 3H)

(c) Synthesis of 4-methyl-2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridine

4-Methyl-2-((methylsulfonyl)methyl)-5-nitropyridine (980.0 mg, 4.25 mmol) was dissolved in anhydrous DMF (21.2 mL), and 60wt% NaH (426.0 mg, 10.64 mmol) and CH_3I (0.8 mL, 12.75 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 16 hours, H_2O was added at 0°C, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 2 : 1) to obtain 4-methyl-2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridine (290.0 mg, 26%) as a white solid.

LC/MS ESI (+): 259 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 9.14 (s, 1H) 7.65 (s, 1H), 2.82 (s, 3H), 2.69 (s, 3H), 1.92 (s, 6H)

(d) Synthesis of (*E*)-*N*,*N*-dimethyl-2-(2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridin-4-yl)ethene-1-amine

4-Methyl-2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridine (250.0 mg, 0.97 mmol) was dissolved in anhydrous DMF (1.2 mL) and *N*,*N*-dimethylformamide dimethylacetal (1.3 mL, 9.68 mmol) was added. The reaction mixture was stirred for 1 hour, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain (*E*)-*N*,*N*-dimethyl-2-(2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridin-4-yl)ethene-1-amine (250.0 mg, 82%) as a red solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.93 (s, 1H) 7.58 (s, 1H), 7.35 (d, 1H, *J*=13.2Hz), 5.98 (d, 1H, *J*=13.2Hz), 3.05 (s, 6H), 2.95 (s, 3H), 1.87 (s, 6H)

(e) Synthesis of 2-(2-(methylsulfonyl)propan-2-yl)-5-nitroisonicotinaldehyde

(*E*)-*N*,*N*-dimethyl-2-(2-(2-(methylsulfonyl)propan-2-yl)-5-nitropyridin-4-yl)ethene-1-amine (250.0 mg, 0.80 mmol) was dissolved in THF (4.0 mL) and H_2O (4.0 mL), and sodium metaperiodate (512.0 mg, 2.39 mmol) was added. The reaction mixture was stirred at 40°C for 5 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 2-(2-(methylsulfonyl)propan-2-yl)-5-nitroisonicotinaldehyde (130.0 mg, 60%) as a yellow solid.

LC/MS ESI (+): 273 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.55 (s, 1H) 9.41 (s, 1H), 8.06 (s, 1H), 2.87 (s, 3H), 1.95 (s, 6H)

(f) Synthesis of methyl 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 2-(2-(methylsulfonyl)propan-2-yl)-5-nitroisonicotinaldehyde (130.0 mg, 0.48 mmol) as a starting material to obtain methyl 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylate (110.0 mg, 74%).

LC/MS ESI (+): 314 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 9.16 (s, 1H) 8.10 (s, 1H), 8.07 (s, 1H), 4.00 (s, 3H), 2.82 (s, 3H), 1.98 (s, 6H)

(g) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylate (110.0 mg, 7.64 mmol) as a starting material to obtain 5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxylic acid (100.0 mg, 95%).

LC/MS ESI (+): 300 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 9.37 (s, 1H) 8.28 (s, 1H), 8.16 (s, 1H), 2.86 (s, 3H), 1.86 (s, 6H)

Intermediate 9) Synthesis of 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 2-fluoro-1-methyl-4-((methylsulfonyl)methyl)benzene

The synthesis procedure of Intermediate 1-b was repeated except for using 4-(bromomethyl)-2-fluoro-1-methylbenzene (1.0 g, 4.92 mmol) as a starting material to obtain 2-fluoro-1-methyl-4-((methylsulfonyl)methyl)benzene (813.0 mg, 82%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.23 (t, 1H, *J*=8.1Hz), 7.07-7.10 (m, 2H), 4.20 (s, 2H), 2.78 (s, 3H), 2.29 (s, 3H)

(b) Synthesis of 2-fluoro-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene

The synthesis procedure of Intermediate 1-c was repeated except for using 2-fluoro-1-methyl-4-((methylsulfonyl)methyl)benzene (813.0 mg, 4.02 mmol) as a starting material to obtain 2-fluoro-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (620 mg, 67%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.26-7.32 (m, 2H), 7.21 (t, 1H, *J*=8.4Hz), 2.54 (s, 3H), 2.28 (s, 3H), 1.82 (s, 6H)

(c) Synthesis of 1-(bromomethyl)-2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzene

The synthesis procedure of Intermediate 1-d was repeated except for using 2-fluoro-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (620.0 mg, 2.69 mmol) to obtain 1-(bromomethyl)-2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzene (680.0 mg, 79%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.35-7.46 (m, 3H), 4.51 (s, 2H), 2.58 (s, 3H), 1.84 (s, 6H)

(d) Synthesis of 2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 1-(bromomethyl)-2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzene (650.0 mg, 2.10 mmol) as a starting material to obtain 2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (330.0 mg, 64%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.23 (s, 1H), 7.88 (t, 1H, *J*=8.3Hz), 7.60-7.64 (m, 2H), 2.78 (s, 3H), 1.78 (s, 6H)

(e) Synthesis of methyl 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 2-fluoro-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (350.0 mg, 1.43 mmol) as a starting material to obtain methyl 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (265.0 mg, 59%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.33 (s, 1H), 8.22 (s, 1H), 8.04 (d, 1H, *J*=8.6Hz), 7.73 (dd, 1H, *J*=8.6, 1.7Hz), 3.90 (s, 3H), 2.74 (s, 3H), 1.84 (s, 6H)

(f) Synthesis of 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (265.0 mg, 0.85

mmol) as a starting material to obtain 6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (230.0 mg, 91%).

LC/MS ESI (-): 297 (M-1)

Intermediate 10) Synthesis of 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-ol

4-Bromo-1-fluoro-2-methylbenzene (1.0 g, 5.29 mmol) was dissolved in anhydrous THF (26.0 mL), and 1.6M solution of *n*-BuLi in THF (3.5 mL, 5.55 mmol) and tetrahydro-4*H*-pyran-4-one (556.0 mg, 5.55 mmol) were added at -78°C. The reaction mixture was stirred at 0°C for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-ol (800.0 mg, 72%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.31 (dd, 1H, *J*=7.3, 2.2Hz), 7.26 (m, 1H), 6.99 (t, 1H, *J*=8.9Hz), 3.84-3.98 (m, 4H), 2.29 (s, 3H), 2.08-2.18 (m, 2H), 1.65-1.69 (m, 3H)

(b) Synthesis of 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-thiol

The synthesis procedure of Intermediate 7-c was repeated except for using 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-ol (800.0 mg, 3.80 mmol) as a starting material to obtain 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-thiol (450.0 mg, 52%).

^{1}H-NMR (400MHz, DMSO-d_6): δ, 7.40 (dd, 1H, *J*=7.4, 2.4Hz), 7.32 (m, 1H), 7.10 (t, 1H, *J*=8.9Hz), 3.76-3.82 (m, 2H), 3.65-3.69 (m, 2H), 3.26 (s, 1H), 2.24 (s, 3H), 2.08-2.18 (m, 4H)

(c) Synthesis of 4-(4-fluoro-3-methylphenyl)-4-(methylthio)tetrahydro-2*H*-pyran

The synthesis procedure of Intermediate 7-d was repeated except for using 4-(4-fluoro-3-methylphenyl)tetrahydro-2*H*-pyran-4-thiol (450.0 g, 1.99 mmol) as a starting material to obtain 4-(4-fluoro-3-methylphenyl)-4-(methylthio)tetrahydro-2*H*-pyran (300.0 mg, 63%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 7.33 (d, 1H, *J*=7.4Hz), 7.25 (m, 1H), 7.09 (t, 1H, *J*=9.0Hz), 3.77-3.82 (m, 2H), 3.57-3.62 (m, 2H), 2.24 (s, 3H), 2.04-2.12 (m, 4H), 1.60 (s, 3H)

(d) Synthesis of 4-(4-fluoro-3-methylphenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran

The synthesis procedure of Intermediate 7-e was repeated except for using 4-(4-

fluoro-3-methylphenyl)-4-(methylthio)tetrahydro-2*H*-pyran (300.0 mg, 1.25 mmol) as a starting material to obtain 4-(4-fluoro-3-methylphenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran (300.0 mg, 89%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.39 (dd, 1H, *J*=7.0, 2.4Hz), 7.33 (m, 1H), 7.10 (t, 1H, *J*=8.8Hz), 3.98-4.02 (m, 2H), 3.40 (t, 2H, *J*=11.7Hz), 2.55-2.63 (m, 2H), 2.42-2.47 (m, 5H), 2.33 (s, 3H)

(e) Synthesis of 4-(3-(bromomethyl)-4-fluorophenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran

The synthesis procedure of Intermediate 1-d was repeated except for using 4-(4-fluoro-3-methylphenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran (300.0 mg, 1.10 mmol) as a starting material to obtain 4-(3-(bromomethyl)-4-fluorophenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran (340.0 mg, 88%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.59 (dd, 1H, *J*=6.9, 2.6Hz), 7.50 (m, 1H), 7.19 (t, 1H, *J*=8.9Hz), 4.54 (s, 2H), 3.98-4.02 (m, 2H), 3.36-3.42 (m, 2H), 2.55-2.65 (m, 2H), 2.42-2.50 (m, 5H)

(f) Synthesis of 2-fluoro-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 4-(3-(bromomethyl)-4-fluorophenyl)-4-(methylsulfonyl)tetrahydro-2*H*-pyran (350.0 mg, 1.00 mmol) as a starting material to obtain 2-fluoro-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzaldehyde (220.0 mg, 76%).

LC/MS ESI (-): 285 (M-1)

(g) Synthesis of methyl 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 2-fluoro-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzaldehyde (110.0 mg, 0.38 mmol) as a starting material to obtain methyl 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxylate (124.0 mg, 91%).

^{1}H-NMR (400MHz, $CDCl_3$): δ, 8.06-8.09 (m, 2H), 7.97 (d, 1H, *J*=8.7Hz), 7.66 (dd, 1H, *J*=8.7, 1.9Hz), 4.03-4.06 (m, 2H), 3.97 (s, 3H), 3.43 (t, 2H, *J*=11.6Hz), 2.56-2.72 (m, 4H), 2.49 (s, 3H)

(h) Synthesis of 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxylate (124.0 mg, 0.35 mmol) as a starting material to obtain 5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-

4-yl)benzo[*b*]thiophene-2-carboxylic acid (104.0 mg, 87%).

LC/MS ESI (-): 339 (M-1)

Intermediate 11) Synthesis of 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylic acid

(a) Synthesis of 2-(3-bromo-4-methylphenyl)propan-2-ol

The synthesis procedure of Intermediate 7-b was repeated except for using 1-(3-bromo-4-methylphenyl)ethan-1-one (1.0 g, 4.69 mmol) as a starting material to obtain 2-(3-bromo-4-methylphenyl)propan-2-ol (1.0 g, 96%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.67 (d, 1H, *J*=1.8Hz), 7.31 (dd, 1H, *J*=7.9, 1.8Hz), 7.20 (d, 1H, *J*=7.9Hz), 2.38 (s, 3H), 1.70 (s, 1H), 1.56 (s, 6H)

(b) Synthesis of 2-(3-bromo-4-methylphenyl)propane-2-thiol

The synthesis procedure of Intermediate 7-c was repeated except for using 2-(3-bromo-4-methylphenyl)propan-2-ol (1.0 g, 4.50 mmol) as a starting material to obtain 2-(3-bromo-4-methylphenyl)propane-2-thiol (1.0 g, 92%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.40 (d, 1H, *J*=8.0Hz), 7.18 (d, 1H, *J*=8.0Hz), 2.37 (s, 3H), 2.24 (s, 1H), 1.79 (s, 6H)

(c) Synthesis of (2-(3-bromo-4-methylphenyl)propan-2-yl)(methyl)sulfane

The synthesis procedure of Intermediate 7-d was repeated except for using 2-(3-bromo-4-methylphenyl)propane-2-thiol (1.0 g, 4.08 mmol) as a starting material to obtain (2-(3-bromo-4-methylphenyl)propan-2-yl)(methyl)sulfane (872.7 mg, 83%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.65 (d, 1H, *J*=2.0Hz), 7.36 (dd, 1H, *J*=8.0, 2.0Hz), 7.18 (d, 1H, *J*=8.0Hz), 2.37 (s, 3H), 1.79 (s, 3H), 1.66 (s, 6H)

(d) Synthesis of 2-bromo-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene

The synthesis procedure of Intermediate 7-e was repeated except for using (2-(3-bromo-4-methylphenyl)propan-2-yl)(methyl)sulfane (871.0 mg, 3.36 mmol) as a starting material to obtain 2-bromo-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (973.7 mg, quant).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.51 (d, 1H, *J*=8.1Hz), 7.27 (d, 1H, *J*=8.1Hz), 2.56 (s, 3H), 2.41 (s, 3H), 1.82 (s, 6H)

(e) Synthesis of 2-bromo-1-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-yl)benzene

The synthesis procedure of Intermediate 1-d was repeated except for using 2-bromo-1-methyl-4-(2-(methylsulfonyl)propan-2-yl)benzene (972.0 mg, 3.34 mmol) as a starting material to obtain 2-bromo-1-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-

yl)benzene (894.4 mg, 72%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.82 (d, 1H, *J*=2.0Hz), 7.61 (dd, 1H, *J*=8.2, 2.0Hz), 7.50 (d, 1H, *J*=8.2Hz), 4.59 (s, 2H), 2.59 (s, 3H), 1.84 (s, 6H)

(f) Synthesis of 2-bromo-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 2-bromo-1-(bromomethyl)-4-(2-(methylsulfonyl)propan-2-yl)benzene (890.0 mg, 2.41 mmol) as a starting material to obtain 2-bromo-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (475.9 mg, 65%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.36 (s, 1H), 7.94 (d, 1H, *J*=8.3Hz), 7.92 (d, 1H, *J*=1.8Hz), 7.74 (dd, 1H, *J*=8.3, 1.2Hz), 2.62 (s, 3H), 1.88 (s, 6H)

(g) Synthesis of methyl (*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(2-bromo-4-(2-(methylsulfonyl)propan-2-yl)phenyl)acrylate

2-Bromo-4-(2-(methylsulfonyl)propan-2-yl)benzaldehyde (441.0 mg, 1.45 mmol), methyl 2-(((benzyloxy)carbonyl)amino)-2-(dimethoxyphosphoryl)acetate (622.0 mg, 1.88 mmol) and DBU (330.0 mg, 2.17 mmol) were dissolved in CH_2Cl_2 (14.5 mL). The reaction mixture was stirred at room temperature for 30 minutes, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain methyl (*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(2-bromo-4-(2-(methylsulfonyl)propan-2-yl)phenyl)acrylate (570.0 mg, 77%).

LC/MS ESI (+): 510 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.51 (s, 2H), 7.32-7.37 (m, 4H), 7.26-7.29 (m, 2H), 6.55 (brs, 1H), 5.04 (s, 2H), 3.87 (s, 3H), 2.53 (s, 3H), 1.82 (s, 6H)

(h) Synthesis of methyl 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylate

Methyl (*Z*)-2-(((benzyloxy)carbonyl)amino)-3-(2-bromo-4-(2-(methylsulfonyl)propan-2-yl)phenyl)acrylate (570.0 mg, 1.12 mmol), CuI (42.5 mg, 0.22 mmol), L-proline (51.4 mg, 0.45 mmol) and K_2CO_3 (463.0 mg, 3.35 mmol) were dissolved in 1,4-dioxane (5.6 mL). The reaction mixture was stirred at 100°C for 2 days, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain methyl 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylate (227.0 mg, 69%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 12.02 (s, 1H), 7.67-7.69 (m, 2H), 7.37 (dd, 1H, *J*=8.6, 1.8Hz), 7.16 (d, 1H, *J*=1.5Hz), 3.88 (s, 3H), 2.68 (s, 3H), 1.80 (s, 6H)

(i) Synthesis of 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylic acid hydrochloride

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylate (227.0 mg, 0.77 mmol) as a starting material to obtain 6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxylic acid hydrochloride (170.0 mg, 79%).

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.02 (brs, 1H), 11.82 (s, 1H), 7.64-7.67 (m, 2H), 7.35 (dd, 1H, *J*=8.8, 1.6Hz), 7.07 (d, 1H, *J*=1.6Hz), 2.67 (s, 3H), 1.80 (s, 6H)

Intermediate 12) Synthesis of 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of 2-(4-fluoro-3-methylphenyl)propan-2-ol

The synthesis procedure of Intermediate 7-b was repeated except for using 1-(4-fluoro-3-methylphenyl)ethan-1-one (1.0 g, 6.57 mmol) as a starting material to obtain 2-(4-fluoro-3-methylphenyl)propan-2-ol (872.0 mg, 79%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.31 (dd, 1H, *J*=7.4, 2.1Hz), 7.25 (m, 1H), 6.95 (t, 1H, *J*=8.9Hz), 2.28 (s, 3H), 1.71 (s, 1H), 1.57 (s, 6H)

(b) Synthesis of 2-(4-fluoro-3-methylphenyl)propane-2-thiol

The synthesis procedure of Intermediate 7-c was repeated except for using 2-(4-fluoro-3-methylphenyl)propan-2-ol (872.0 mg, 5.18 mmol) as a starting material to obtain 2-(4-fluoro-3-methylphenyl)propane-2-thiol (955.0 mg, 85%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.37 (dd, 1H, *J*=7.1, 2.3Hz), 7.32 (m, 1H), 6.93 (t, 1H, *J*=8.9Hz), 2.28 (s, 3H), 2.24 (s, 1H), 1.81 (s, 6H)

(c) Synthesis of (2-(4-fluoro-3-methylphenyl)propan-2-yl)(2-methoxyethyl)sulfane

2-(4-Fluoro-3-methylphenyl)propane-2-thiol (400.0 mg, 2.17 mmol) was dissolved in anhydrous DMF(16.3 mL), and 1-bromo-2-methoxyethane (392.0 mg, 2.82 mmol) and Cs_2CO_3 (1.4 g, 4.34 mmol) were added. The reaction mixture was stirred at 70°C for 5 hours, cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain (2-(4-fluoro-3-methylphenyl)propan-2-yl)(2-methoxyethyl)sulfane (420.0 mg, 80%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.34 (dd, 1H, *J*=7.4, 2.3Hz), 7.29 (m, 1H), 6.92 (t, 1H, *J*=8.9Hz), 3.32 (t, 2H, *J*=6.7Hz), 3.26 (s, 3H), 2.43 (t, 2H, *J*=6.7Hz), 2.27 (s, 3H), 1.68 (s, 6H)

(d) Synthesis of 1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)-2-

methylbenzene

The synthesis procedure of Intermediate 7-e was repeated except for using (2-(4-fluoro-3-methylphenyl)propan-2-yl)(2-methoxyethyl)sulfane (420.0 mg, 1.73 mmol) as a starting material to obtain 1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)-2-methylbenzene (410.0 mg, 86%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.32-7.40 (m, 2H), 7.02 (t, 1H, *J*=8.9Hz), 3.64 (t, 2H, *J*=6.7Hz), 3.29 (s, 3H), 2.91 (t, 2H, *J*=6.7Hz), 2.30 (s, 3H), 1.82 (s, 6H)

(e) Synthesis of 2-(bromomethyl)-1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzene

The synthesis procedure of Intermediate 1-d was repeated except for using 1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)-2-methylbenzene (410.0 mg, 1.49 mmol) as a starting material to to obtain 2-(bromomethyl)-1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzene (40.0 mg, 8%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.65 (dd, 1H, *J*=7.0, 2.6Hz), 7.58 (m, 1H), 7.10 (t, 1H, *J*=9.0Hz), 4.52 (s, 2H), 3.64 (t, 2H, *J*=6.5Hz), 3.29 (s, 3H), 2.93 (t, 2H, *J*=6.5Hz), 1.84 (s, 6H)

(f) Synthesis of 2-fluoro-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzaldehyde

The synthesis procedure of Intermediate 1-e was repeated except for using 2-(bromomethyl)-1-fluoro-4-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzene (60.0 mg, 0.17 mmol) as a starting material to obtain 2-fluoro-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzaldehyde (36.0 mg, 74%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.30 (s, 1H), 7.99 (dd, 1H, *J*=6.4, 2.7Hz), 7.93 (m, 1H), 7.17 (t, 1H, *J*=9.2Hz), 3.62 (t, 2H, *J*=6.4Hz), 3.23 (s, 3H), 2.87 (t, 2H, *J*=6.4Hz), 1.80 (s, 6H)

(g) Synthesis of methyl 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using 2-fluoro-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzaldehyde (36.0 mg, 0.13 mmol) as a starting material to obtain methyl 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (30.0 mg, 67%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.10 (s, 1H), 8.07 (s, 1H), 7.90 (d, 1H, *J*=8.7Hz), 7.78 (dd, 1H, *J*=8.7, 2.0Hz), 3.96 (s, 3H), 3.63 (t, 2H, *J*=6.4Hz), 3.25 (s, 3H), 2.91 (t, 2H, *J*=6.4Hz), 1.93 (s, 6H)

(h) Synthesis of 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylate (30.0 mg, 0.08 mmol) as a starting material to obtain 5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (27.0 mg, 94%).

LC/MS ESI (-): 341 (M-1)

Intermediate 13) Synthesis of 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of (4-fluoro-3-methylbenzyl)(methyl)sulfane

4-(Bromomethyl)-1-fluoro-2-methylbenzene (1.0 g, 4.92 mmol) and sodium methanethiolate (380.0 mg, 5.42 mmol) were dissolved in DMF (24.6 mL). The reaction mixture was stirred at room temperature for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : CH_2Cl_2 = 4 : 1) to obtain (4-fluoro-3-methylbenzyl)(methyl)sulfane (709.0 mg, 85%) as a colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.12 (d, 1H, *J*=7.3Hz), 7.06 (m, 1H), 6.93 (m, 1H), 3.61 (s, 2H), 2.26 (s, 3H), 1.99 (s, 3H)

(b) Synthesis of (*E*)-*N*-((4-fluoro-3-methylbenzyl)(methyl)-λ^4-sulfanylidene)-4-nitrobenzenesulfonamide

(4-Fluoro-3-methylbenzyl)(methyl)sulfane (600.0 mg, 3.52 mmol), 4-nitrobenzenesulfonamide (869.0 mg, 4.39 mmol) and (diacetoxyiodo)benzene (1.7 g, 5.37 mmol) were dissolved in CH_3CN (35.8 mL). The reaction mixture was stirred at 90°C for 16 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, CH_3CN : H_2O) to obtain (*E*)-*N*-((4-fluoro-3-methylbenzyl)(methyl)-λ^4-sulfanylidene)-4-nitrobenzenesulfonamide (606.0 mg, 46%).

LC/MS ESI (+): 371 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.18 (d, 2H, *J*=8.9Hz), 7.88 (d, 2H, *J*=8.9Hz), 7.01-7.05 (m, 2H), 6.91 (m, 1H), 4.16 (d, 1H, *J*=12.8Hz), 4.07 (d, 1H, *J*=12.8Hz), 2.66 (s, 3H), 2.20 (d, 3H, *J*=1.9Hz)

(c) Synthesis of *N*-((4-fluoro-3-methylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide

(*E*)-*N*-((4-fluoro-3-methylbenzyl)(methyl)-λ^4-sulfanylidene)-4-nitrobenzene sulfonamide (600,0 mg, 1.62 mmol), $RuCl_3 \cdot H_2O$ (36.5 mg, 0.16 mmol) and $NaIO_4$ (520.0 mg, 2.43 mmol) were dissolved in a mixture of CH_2Cl_2/H_2O (16.3 mL, 10/3 v/v). The reaction mixture was stirred at room temperature for 16 hours, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 2) to obtain *N*-((4-fluoro-3-methylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (546.0 mg, 87%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.32 (d, 2H, *J*=9.0Hz), 8.14 (d, 2H, *J*=9.0Hz), 7.30 (dd, 1H, *J*=6.9, 1.9Hz), 7.25 (m, 1H), 7.08 (m, 1H), 4.69 (s, 2H), 3.09 (s, 3H), 2.31 (d, 3H, *J*=1.8Hz)

(d) Synthesis of *N*-((3-(bromomethyl)-4-fluorobenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide

The synthesis procedure of Intermediate 1-d was repeated except for using *N*-((4-fluoro-3-methylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (546.0 mg, 1.41 mmol) as a starting material to obtain *N*-((3-(bromomethyl)-4-fluorobenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (657.0 mg, quant).

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.32 (d, 2H, *J*=9.0Hz), 8.13 (d, 2H, *J*=9.0Hz), 7.52 (m, 1H), 7.43 (m, 1H), 7.17 (m, 1H), 4.72 (s, 2H), 4.51 (s, 2H), 3.13 (s, 3H)

(e) Synthesis of *N*-((4-fluoro-3-formylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide

The synthesis procedure of Intermediate 1-e was repeated except for using *N*-((3-(bromomethyl)-4-fluorobenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (657.0 mg, 1.41 mmol) as a starting material to obtain *N*-((4-fluoro-3-formylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (357.7 mg, 63%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 10.38 (s, 1H), 8.33 (d, 2H, *J*=8.8Hz), 8.14 (d, 2H, *J*=8.8Hz), 7.92 (dd, 1H, *J*=6.2, 2.4Hz), 7.82-7.86 (m, 1H), 7.34 (m, 1H), 4.75-4.83 (m, 2H), 3.14 (s, 3H)

(f) Synthesis of methyl 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 1-f was repeated except for using *N*-((4-fluoro-3-formylbenzyl)(methyl)(oxo)-λ^6-sulfanylidene)-4-nitrobenzene sulfonamide (306.0 mg, 0.77 mmol) as a starting material to obtain methyl 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylate (139.0 mg, 65%).

LC/MS ESI (+): 284 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.91-7.93 (m, 2H), 7.51 (dd, 1H, *J*=8.5, 1.7Hz), 4.52 (d, 1H, *J*=13.1Hz), 4.36 (d, 1H, *J*=13.1Hz), 3.97 (s, 3H), 3.77 (s, 1H), 2.97 (s, 3H)

(g) Synthesis of 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylate (137.0 mg, 0.48 mmol) as a starting material to obtain 5-((*S*-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxylic acid (93.4 mg, 46%).

LC/MS ESI (+): 270 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 8.13 (s, 1H), 8.06 (d, 1H, *J*=8.3Hz), 8.04 (s, 1H), 7.57 (dd, 1H, *J*=8.4, 1.4Hz), 4.55-4.57 (m, 3H), 2.86 (d, 3H, *J*=3.5Hz)

Intermediate 14) Synthesis of 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of methyl 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylate

Tetrahydrothiophene 1,1-dioxide (124.0 mg, 1.03 mmol) was dissolved in anhydrous THF (7.3 mL), and 1M solution of lithium bis(trimethylsilyl)amide in THF (1.5 mL, 1.55 mmol) was added dropwise at -20°C. The reaction mixture was stirred at room temperature for 30 minutes, and $ZnCl_2$ (211.0 mg, 1.55 mmol) was added -20°C. The reaction mixture was slowly warmed to room temperature, methyl 5-bromobenzo[*b*]thiophene-2-carboxylate (200.0 mg, 0.74 mmol), $Pd(OAc)_2$ (8.3 mg, 0.04 mmol) and XPhos (35.2 mg, 0.07 mmol) were added, and stirred at 65°C for 5 hours. The reaction mixture was cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain methyl 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylate (60.0 mg, 26%) as an off-white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.89-7.91 (m, 2H), 7.49 (dd, 1H, *J*=8.4, 2.0Hz), 4.30 (m, 1H), 3.95 (s, 3H), 2.95-3.35 (m, 3H), 2.22-2.58 (m, 3H)

(b) Synthesis of 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylate (70.0 mg, 0.23 mmol) as a starting material to obtain 5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxylic acid (60.0 mg, 90%) as a white solid.

LC/MS ESI (-): 295 (M-1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 13.55 (s, 1H), 8.13 (s, 1H), 8.08 (d, 1H, *J*=8.5Hz), 8.02 (s, 1H), 7.51 (d, 1H, *J*=8.4Hz), 4.50 (m, 1H), 3.17-3.36 (m, 2H), 2.38-2.46 (m, 2H), 2.13-2.28 (m, 2H)

Intermediate 15) Synthesis of 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylic acid

(a) Synthesis of methyl 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylate

The synthesis procedure of Intermediate 14-a was repeated except for using methyl 5-bromobenzo[*b*]thiophene-2-carboxylate (95.0 mg, 0.35 mmol) and tetrahydro-2*H*-thiopyrane 1,1-dioxide (66.0 mg, 0.49 mmol) as a starting material to obtain methyl 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylate (26.0 mg, 23%) as an off-white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.95 (s, 1H), 7.89 (d, 1H, *J*=8.5Hz), 7.53 (d, 1H, *J*=8.5Hz), 4.15 (m, 1H), 3.95 (s, 3H), 3.09-3.29 (m, 2H), 1.56-2.59 (m, 6H)

(b) Synthesis of 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylic acid

The synthesis procedure of Intermediate 1-g was repeated except for using methyl 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylate (26.0 mg, 0.08 mmol) as a starting material to obtain 5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxylic acid (22.0 mg, 88%) as a white solid.

LC/MS ESI (-): 309 (M-1)

Example 1) Synthesis of *N*-(3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 3-chloro-5-nitrobenzoyl chloride

3-Chloro-5-nitrobenzoic acid (5.0 g, 24.81 mmol) was dissolved in $SOCl_2$ (10.0 mL, 137.00 mmol), and a catalytic amount of anhydrous DMF was added. The reaction mixture was refluxed at 110°C for 2 hours and concentrated under reduced pressure to obtain 3-chloro-5-nitrobenzoyl chloride (5.3 g, quant.) as a yellow liquid without purification.

(b) Synthesis of (3-chloro-5-nitrophenyl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone

3-Chloro-5-nitrobenzoyl chloride (5.0 g, 22.70 mmol) was dissolved in anhydrous Et_2O (230.0 mL), and (3-methoxy-5-(trifluoromethoxy)phenyl)boronic acid (5.4 g, 22.70 mmol), $Pd(dba)_2$ (1.3 g, 2.27 mmol), PPh_3 (1.2 g, 4.54 mmol) and copper thiophene-2-

carboxylate (4.3 g, 22.70 mmol) were added. The reaction mixture was stirred at room temperature for 15 hours, filtered through Celite™, and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain (3-chloro-5-nitrophenyl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone (4.2 g, 41%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.46 (s, 1H), 8.10 (s, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 7.05 (s, 1H), 3.90 (s, 3H)

(c) Synthesis of 1-chloro-3-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)-5-nitrobenzene

(3-Chloro-5-nitrophenyl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone (4.0 g, 10.65 mmol) was dissolved in 1,2-dibromoethane (106.0 mL) and PCl_5 (11.1 g, 53.24 mmol) was added. The reaction mixture was stirred at 110°C for 24 hours and cooled to room temperature. The reaction mixture was poured into a solution of $NaHCO_3$ in ice water, vigorously stirred, and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 20 : 1) to obtain 1-chloro-3-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)-5-nitrobenzene (1.4 g, 30%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.24 (s, 1H), 7.91 (s, 1H), 7.08 (s, 1H), 7.05 (s, 1H), 6.81 (s, 1H), 3.84 (s, 3H)

(d) Synthesis of 1-chloro-3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-nitrobenzene

1M solution of $TiCl_4$ in CH_2Cl_2 (0.6 mL, 0.63 mmol) was added to 1.2M solution of dimethylzinc in toluene (7.8 mL, 9.41 mmol) at -40°C, and stirred for 1 hour. 1-Chloro-3-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)-5-nitrobenzene (1.4 g, 3.14 mmol) in CH_2Cl_2 (11.4 mL) was slowly added dropwise at -40°C, and the reaction mixture was warmed to 0°C and stirred for 18 hours. H_2O was added, and the reaction mixture was extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 1-chloro-3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-nitrobenzene (750.0 mg, 61%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00 (s, 1H), 7.48 (s, 1H), 6.62-6.65 (m, 3H), 3.78 (s, 3H), 1.70 (s, 6H)

(e) Synthesis of 3-(2-(3-chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenol

1-Chloro-3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-

Date Reçue/Date Received 2022-04-12

nitrobenzene (450.0 mg, 1.15 mmol) was dissolved in anhydrous CH_2Cl_2 (8.0 mL) and 1M solution of BBr_3 in CH_2Cl_2 (3.5 mL, 3.46 mmol) was slowly added dropwise at 0°C. The reaction mixture was stirred at room temperature for 8 hours, H_2O was added at 0°C, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 3 : 1) to obtain 3-(2-(3-chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenol (380.0 mg, 88%) as a colorless oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00 (s, 1H), 7.48 (s, 1H), 6.64 (s, 1H), 6.61 (s, 1H), 6.55 (s, 1H), 5.00 (s, 1H), 1.69 (s, 6H)

(f) Synthesis of 1-chloro-3-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-nitrobenzene

3-(2-(3-Chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenol (370.0 mg, 0.98 mmol) was dissolved in anhydrous DMF (9.8 mL), and K_2CO_3 (406.0 mg, 2.94 mmol) and iodoethane (158.0 mL, 1.97 mmol) were added. The reaction mixture was stirred at 40°C for 15 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 1-chloro-3-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-nitrobenzene (386.0 mg, 97%) as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.00 (s, 1H), 7.48 (s, 1H), 6.60-6.63 (m, 3H), 3.98 (q, 2H, *J*=7.0Hz), 1.69 (s, 6H), 1.40 (t, 3H, *J*=7.0Hz)

(g) Synthesis of 3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline

1-Chloro-3-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-nitrobenzene (380.0 mg, 0.94 mmol) was dissolved in a mixture of $MeOH/H_2O$ (10.0 mL, 9/1 v/v), and Zn (616.0 mg, 9.43 mmol) and NH_4Cl (504.0 mg, 9.43 mmol) were added at room temperature. The reaction mixture was ultrasonificated at 40°C for 40 minutes, cooled to room temperature, filtered through Celite, and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline (350.0 mg, 98%) as a white solid.

LC/MS ESI (+): 374 (M+H1)

(h) Synthesis of *N*-(3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

5-(2-(Methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (38.8 mg, 0.13 mmol), 3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline (48.6 mg, 0.13 mmol) and HATU (53.0 mg, 0.14 mmol) were dissolved in anhydrous DMF (1.3

mL) and DIPEA (44.0 μL, 0.24 mmol) was added. The reaction mixture was stirred at 40°C for 3 hours, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN : 0.1% formic acid in H_2O) to obtain *N*-(3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (35.0 mg, 41%) as a white solid.

LC/MS ESI (+): 654 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.88 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.52 (s, 1H), 7.04 (s, 1H), 6.77 (s, 2H), 6.72 (s, 1H), 4.01 (q, 2H, *J*=6.9 Hz), 2.73 (s, 3H), 1.84 (s, 6H), 1.64 (s, 6H), 1.29 (t, 3H, *J*=6.9 Hz)

Compounds from **Examples 2 to 16** were synthesized through the synthesis route of Example 1, and data of these compounds are listed as follows.

[Table 2]

Ex.	Compound	Analysis data
2	*N*-(3-chloro-5-(2-(3-propoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 668 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.88 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.53 (s, 1H), 7.04 (s, 1H), 6.78 (s, 2H), 6.72 (s, 1H), 3.93 (t, 2H, *J*=6.4Hz), 2.73 (s, 3H), 1.85 (s, 6H), 1.67-1.73 (m, 2H) 1.64 (s, 6H), 0.96 (t, 3H, *J*=8.8Hz)
3	*N*-(3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 606 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.50 (s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.72 (t, 2H, *J*=9.6Hz), 7.63 (s, 1H), 7.31 (t, 1H, *J*=8.0Hz), 7.01 (d, 1H, *J*=8.0Hz), 6.78 (d, 2H, *J*=6.4Hz), 6.70 (s, 1H), 3.75 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H), 1.65 (s, 6H)
4	*N*-(3-bromo-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 770 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 8.04 (s, 1H), 7.75 (d, 1H, *J*=8.8Hz), 7.59 (s, 1H), 7.27 (s, 1H), 7.23 (s, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 6.81 (t, 1H, *J*=51.9 Hz), 2.73 (s, 3H), 1.85 (s, 6H), 1.68 (s, 6H)

5	*N*-(3-chloro-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 724 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.4Hz), 7.92 (t, 1H, *J*=1.6Hz), 7.75 (dd, 1H, *J*=8.8, 2.0Hz), 7.56 (s, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 6.81 (tt, 1H, *J*=51.6, 3.2Hz), 2.74 (s, 3H), 1.86 (s, 6H), 1.69 (s, 6H)
6	*N*-(3-methoxy-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 636 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.48 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.73 (d, 1H, *J*=8.8Hz), 7.41 (s, 1H), 7.19 (s, 1H), 6.79 (d, 2H, *J*=8.8Hz), 6.71 (s, 1H), 6.56 (s, 1H), 3.75 (s, 3H), 3.73 (s, 3H) 2.73 (s, 3H), 1.84 (s, 6H), 1.62 (s, 6H)
7	*N*-(3-chloro-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 640 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.88 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.52 (s, 1H), 7.04 (s, 1H), 6.81 (s, 2H), 6.73 (s, 1H), 3.76 (s, 3H), 2.73 (s, 3H) 1.85 (s, 6H), 1.64 (s, 6H)
8	*N*-(3-chloro-5-(2-(3-(2-morpholinoethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 739 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.10 (d, 1H, *J*=8.7Hz), 7.89 (s, 1H), 7.74 (d, 1H, *J*=8.7Hz), 7.54 (s, 1H), 7.05 (s, 1H), 6.83 (s, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 4.07-4.10 (m, 2H), 3.54-3.55 (m, 4H), 2.73 (s, 3H), 2.43-2.64 (m, 6H), 1.85 (s, 6H), 1.64 (s, 6H)
9	*N*-(3-bromo-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 712 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 8.03 (s, 1H), 7.74 (d, 1H, *J*=8.6Hz), 7.59 (s, 1H), 7.17 (s, 1H), 6.77 (s, 1H), 6.73 (s, 1H), 6.71 (s, 1H), 4.65 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H), 1.64 (s, 6H), 1.24 (d, 6H, *J*=6.0Hz)
10	*N*-(3-(2-(3-(but-2-yn-1-yloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 676 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.36 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.4Hz), 7.91 (t, 1H, *J*=2.0Hz), 7.75 (dd, 1H, *J*=8.8, 2.0Hz), 7.55 (s, 1H), 7.06 (s, 1H), 6.85

		(s, 1H), 6.84 (s, 1H), 6.80 (s, 1H), 4.78 (s, 2H), 2.75 (s, 3H), 1.86 (s, 6H), 1.80 (s, 3H), 1.66 (s, 6H)
11	*N*-(3-chloro-5-(2-(3-isobutoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 680 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.90 (s, 1H), 7.74 (dd, 1H, *J*=8.8, 2.0Hz), 7.54 (s, 1H), 7.06 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 6.73 (s, 1H), 3.76 (d, 2H, *J*=6.4Hz), 2.74 (s, 3H), 1.99 (m, 1H), 1.86 (s, 6H), 1.66 (s, 6H), 0.97 (d, 6H, *J*=6.8Hz)
12	*N*-(3-chloro-5-(2-(3-(2,2,2-trifluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 706 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.90 (s, 1H), 7.75 (dd, 1H, *J*=8.8, 2.0Hz), 7.55 (s, 1H), 7.06 (s, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 6.85 (s, 1H), 4.82-4.88 (m, 2H), 2.75 (s, 3H), 1.86 (s, 6H), 1.67 (s, 6H)
13	*N*-(3-chloro-5-(2-(3-(2,2-difluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 688 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.90 (s, 1H), 7.75 (dd, 1H, *J*=8.8, 1.6Hz), 7.55 (s, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.81 (s, 1H), 6.38 (tt, 1H, *J*=54.4, 3.6Hz), 4.38 (td, 2H, *J*=14.4, 3.6Hz), 2.74 (s, 3H), 1.86 (s, 6H), 1.67 (s, 6H)
14	*N*-(3-(2-(3-(allyloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 664 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.4Hz), 7.90 (s, 1H), 7.75 (d, 1H, *J*=8.8Hz), 7.54 (s, 1H), 7.05 (s, 1H), 6.84 (s, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 6.00 (m, 1H), 5.37 (d, 1H, *J*=18.0Hz), 5.27 (d, 1H, *J*=9.6Hz), 4.60 (d, 2H, *J*=5.2Hz), 2.74 (s, 3H), 1.84 (s, 6H), 1.66 (s, 6H)
15	*N*-(3-chloro-5-(2-(3-cyclopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 664 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.91 (s, 1H), 7.75 (d, 1H, *J*=8.8Hz), 7.55 (s, 1H), 7.07 (s, 1H), 6.95 (s, 1H), 6.87 (s, 1H), 6.79 (s, 1H), 3.89 (s, 1H), 2.74 (s, 3H), 1.86 (s, 6H) , 1.66 (s, 6H), 0.65-0.79 (m, 4H)

16	*N*-(3-chloro-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 640 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.35 (s, 1H), 8.10 (d, 1H, *J*=8.4Hz), 8.03 (s, 1H), 7.91 (m, 1H), 7.51-7.54 (m, 2H), 7.05 (s, 1H), 6.77 (s, 1H), 6.73 (m, 1H), 6.72 (s, 1H), 4.60-4.66 (m, 3H), 2.93 (s, 3H), 1.64 (s, 6H), 1.24 (d, 6H, *J*=6.0Hz)

Example 17) Synthesis of *N*-(3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 1-chloro-3-(2-(4-methoxyphenyl)propan-2-yl)-5-nitrobenzene

1-(2-Bromopropan-2-yl)-3-chloro-5-nitrobenzene (30.0 mg, 0.11 mmol) and anisole (0.1 mL, 1.07 mmol) were dissolved in 1,2-dichloroethane (1.1 mL) and $AlCl_3$ (44.0 mg, 0.33 mmol) was added. The reaction mixture was stirred at room temperature for 12 hours, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 1-chloro-3-(2-(4-methoxyphenyl)propan-2-yl)-5-nitrobenzene (40.0 mg, 90%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.03 (s, 1H), 8.01 (s, 1H), 7.49 (s, 1H), 7.11 (d, 2H, *J*=8.4Hz), 6.84 (d, 2H, *J*=8.6Hz), 3.81 (s, 3H), 1.70 (s, 6H)

(b) Synthesis of 3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)aniline

The synthesis procedure of Example 1-g was repeated except for using 1-chloro-3-(2-(4-methoxyphenyl)propan-2-yl)-5-nitrobenzene (84.2 mg, 0.24 mmol) as a starting material to obtain 3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)aniline (20.0 mg, 56%).

LC/MS ESI (+): 276 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.14 (d, 2H, *J*=8.4Hz), 6.81 (d, 2H, *J*=8.6Hz), 6.64 (s, 1H), 6.49 (s, 1H), 6.36 (s, 1H), 3.79 (s, 3H), 3.62 (s, 2H), 1.59 (s, 6H)

(c) Synthesis of *N*-(3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)aniline (81.0 mg, 0.27 mmol) as a starting material to obtain *N*-(3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (40.0 mg, 27%).

LC/MS ESI (+): 556 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 8.10 (d, 1H, *J*=8.4Hz), 7.87 (s, 1H), 7.75 (dd, 1H, *J*=8.4, 1.6Hz), 7.54 (s, 1H), 7.17 (d, 2H, *J*=8.8Hz), 7.00 (s, 1H), 6.88 (d, 2H, *J*=8.8Hz), 3.74 (s, 3H), 2.74 (s, 3H), 1.86 (s, 6H), 1.64 (s, 6H)

Compounds from **Example 18 to Example 36** were synthesized through the synthesis route of Example 17, and data of these compounds are listed as follows.

[Table 3]

Ex.	**Compound**	**Analysis data**
18	*N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 544 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.64 (brs, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.08 (d, 1H, *J*=8.7Hz), 7.87 (s, 1H), 7.73 (d, 1H, *J*=8.7Hz), 7.52 (s, 1H), 7.27-7.30 (m, 2H), 7.11-7.15 (m, 2H), 7.02(s, 1H), 2.73(s, 3H), 1.85 (s, 6H), 1.65 (s, 6H)
19	*N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 562 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.66 (s, 1H), 8.32 (s, 1H), 8.22 (d, 1H, *J*=7.7Hz), 8.02 (d, 1H, *J*=13.1Hz), 7.86 (s, 1H), 7.49 (s, 1H), 7.28 (dd, 2H, *J*=8.7, 5.5Hz), 7.13 (t, 2H, *J*=8.8Hz), 7.03 (s, 1H), 2.88 (s, 3H), 1.92 (s, 6H), 1.64 (s, 6H)
20	*N*-(3-bromo-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 588 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.61 (s, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 8.00 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.56 (s, 1H), 7.26-7.30 (m, 2H), 7.11-7.15 (m, 3H), 2.73 (s, 3H), 1.84 (s, 6H), 1.64 (s, 6H)
21	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 532 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.60 (s, 1H), 8.34 (s, 1H), 8.09 (d, 1H, *J*=8.4Hz), 8.02 (s, 1H), 7.89 (m, 1H), 7.50-7.53 (m, 2H), 7.37 (d, 2H, *J*=8.6Hz), 7.27 (d, 2H, *J*=8.6Hz), 7.03 (m, 1H), 4.64 (s, 2H), 2.93 (s, 3H), 1.65 (s, 6H)
22	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 560 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.63 (s, 1H), 8.33 (s, 1H), 8.19 (m, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.88 (m, 1H), 7.74 (dd, 1H, *J*=8.5, 1.6Hz), 7.50 (m, 1H), 7.37 (d, 2H, *J*=8.5Hz), 7.27 (d, 2H, *J*=8.7Hz), 7.03 (m, 1H), 2.73 (s,

		3H), 1.85 (s, 6H), 1.64 (s, 6H)
23	6-chloro-*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 594 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.36 (s, 1H), 8.31 (s, 1H), 8.28 (s, 1H), 7.87 (m, 1H), 7.47 (m, 1H), 7.37 (d, 2H, *J*=8.7Hz), 7.27 (d, 2H, *J*=8.7Hz), 7.04 (m, 1H), 2.89 (s, 3H), 2.05 (s, 6H), 1.64 (s, 6H)
24	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 586 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.36 (s, 1H), 8.16 (m, 1H), 8.12 (m, 1H), 7.89 (m, 1H), 7.56 (m, 1H), 7.50 (m, 1H), 7.37 (d, 2H, *J*=8.7Hz), 7.27 (d, 2H, *J*=8.7Hz), 7.03 (m, 1H), 5.42 (s, 2H), 1.64 (s, 6H)
25	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 550 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.39 (m, 1H), 8.21 (d, 1H, *J*=8.8Hz), 8.13 (s, 1H), 7.89 (m, 1H), 7.59 (d, 1H, *J*=8.8Hz), 7.49 (m, 1H), 7.37 (d, 2H, *J*=8.7Hz), 7.27 (d, 2H, *J*=8.7Hz), 7.03 (m, 1H), 6.94 (d, 1H, *J*=45.0Hz), 3.20 (s, 3H), 1.65 (s, 6H)
26	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide	LC/MS ESI (+): 561 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.83 (s, 1H), 9.39 (s, 1H), 8.38 (s, 1H), 8.26 (s, 1H), 7.89 (s, 1H), 7.51 (s, 1H), 7.38 (d, 2H, *J*=8.4Hz), 7.28 (d, 2H, *J*=8.4Hz), 7.08 (s, 1H), 2.87 (s, 3H), 1.88 (s, 6H), 1.66 (s, 6H)
27	*N*-(3-chloro-5-(2-(5-chlorothiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 566 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 7.90 (m, 1H), 7.74 (dd, 1H, *J*=8.8, 1.9Hz), 7.63 (m, 1H), 7.13 (m, 1H), 6.99 (d, 1H, *J*=3.9Hz), 6.86 (d, 1H, *J*=3.9Hz), 2.74 (s, 3H), 1.85 (s, 6H), 1.71 (s, 6H)
28	*N*-(3-chloro-5-(2-(5-isopropylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 574 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.67 (s, 1H), 8.37 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.5Hz), 7.88 (s, 1H), 7.75 (d, 1H, *J*=8.7Hz), 7.67 (s, 1H), 7.09 (s, 1H), 6.75 (d, 1H *J*=3.4Hz), 6.67 (d, 1H *J*=3.3Hz), 3.08 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H), 1.70 (s, 6H), 1.22 (d, 6H, *J*=6.8Hz)

29	*N*-(3-chloro-5-(2-(5-methoxythiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 562 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.36 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.6Hz), 7.87 (s, 1H), 7.76 (d, 1H, *J*=8.7Hz), 7.64 (s, 1H), 7.08 (s, 1H), 6.58 (d, 1H *J*=3.8Hz), 6.10 (d, 1H *J*=3.8Hz), 3.79 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H), 1.66 (d, 6H)
30	*N*-(3-chloro-5-(2-(2-methoxythiophen-3-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 562 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.62 (s, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.6Hz), 7.84 (t, 1H, *J*=1.6Hz), 7.75 (d, 1H, *J*=1.6Hz), 7.55 (s, 1H), 6.97 (d, 1H *J*=1.6Hz), 6.80 (d, 2H *J*=2.0Hz), 3.63 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H), 1.62 (s, 6H)
31	*N*-(3-chloro-5-(2-(1-methyl-1*H*-pyrrol-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*] thiophene-2-carboxamide	LC/MS ESI (+): 529 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.35 (s, 1H), 8.19 (s, 1H), 8.09 (d, 1H, *J*=8.4Hz), 7.88 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.50 (s, 1H), 6.80 (s, 1H), 6.62 (d, 1H, *J*=1.6Hz), 6.10 (m, 1H), 5.94 (t, 1H, *J*=1.6Hz), 3.09 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H), 1.61 (s, 6H)
32	*N*-(3-chloro-5-(2-(4-methylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 546 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.88 (s, 1H), 7.74 (dd, 1H, *J*=8.4, 1.6Hz), 7.64 (s, 1H), 7.08 (s, 1H), 6.95 (s, 1H) 6.78 (s, 1H), 2.73 (s, 3H), 2.17 (s, 3H) 1.85 (s, 6H), 1.70 (s, 6H)
33	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 558 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.32 (s, 1H), 8.16 (s, 1H), 8.09 (d, 1H, *J*=8.4Hz), 7.87 (m, 1H), 7.66 (dd, 1H, *J*=8.2, 1.4Hz), 7.50 (m, 1H), 7.37 (d, 2H, *J*=8.6Hz), 7.27 (d, 2H, *J*=8.6Hz), 7.03 (m, 1H), 2.89 (s, 3H), 1.68-1.71 (m, 2H), 1.64 (s, 6H), 1.37-1.40 (m, 2H)
34	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 602 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 8.15 (d, 1H, *J*=8.7Hz), 7.88 (s, 1H), 7.73 (d, 1H, *J*=8.5Hz), 7.50 (s, 1H), 7.37 (d, 2H, *J*=8.5Hz), 7.27 (d, 2H, *J*=8.5Hz), 7.04 (s, 1H), 3.91 (d, 2H, *J*=10.8Hz), 3.20 (t, 2H, *J*=11.8Hz), 2.73 (d,

		2H, *J*=12.7Hz), 2.65 (s, 3H), 2.33 (t, 2H, *J*=12.0Hz), 1.64 (s, 6H)
35	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide	LC/MS ESI (+): 543 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.85 (s, 1H), 10.34 (s, 1H), 7.95 (m, 1H), 7.68-7.70 (m, 2H), 7.55 (m, 1H), 7.35-7.40 (m, 4H), 7.28 (d, 2H, *J*=8.7Hz), 7.00 (m, 1H), 2.68 (s, 3H), 1.81 (s, 6H), 1.65 (s, 6H)
36	*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((S-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 531 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.58 (s, 1H), 8.34 (m, 1H), 8.07 (d, 1H, *J*=8.4Hz), 8.04 (m, 1H), 7.89 (m, 1H), 7.55 (dd, 1H, *J*=8.4, 1.6Hz), 7.51 (m, 1H), 7.37 (d, 2H, *J*=8.7Hz), 7.27 (d, 2H, *J*=8.7Hz), 7.03 (m, 1H), 4.47-4.56 (m, 3H), 2.80 (s, 3H), 1.65 (s, 6H)

Example 37) Synthesis of *N*-(3-chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 1-chloro-3-nitro-5-(4-(trifluoromethoxy)phenoxy)benzene

1-Bromo-3-chloro-5-nitrobenzene (200.0 mg, 0.84 mmol), 4-(trifluoromethoxy)phenol (220.0 mg, 1.69 mmol), CuI (80.6 mg, 0.42 mmol), *N,N*-dimethylglycine (87.2 mg, 0.42 mmol) and Cs_2CO_3 (826.9 mg, 2.53 mmol) were dissolved in anhydrous 1,4-dioxane (5.0 mL). The reaction mixture was stirred at 120°C for 15 hours, cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex) to obtain 1-chloro-3-nitro-5-(4-(trifluoromethoxy)phenoxy)benzene (160.0 mg, 61%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.65 (s, 1H), 7.26-7.30 (m, 3H), 7.09 (d, 2H, *J*=8.8Hz)

(b) Synthesis of 3-chloro-5-(4-(trifluoromethoxy)phenoxy)aniline

The synthesis procedure of Example 1-g was repeated except for using 1-chloro-3-nitro-5-(4-(trifluoromethoxy)phenoxy)benzene (160.0 mg, 0.52 mmol) as a starting material to obtain 3-chloro-5-(4-(trifluoromethoxy)phenoxy)aniline (130.0 mg, 79%) as an off-white oil.

LC/MS ESI (+): 304 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.31 (d, 2H, *J*=8.7 Hz), 6.95 (d, 2H, *J*=8.7 Hz), 6.41 (s, 1H), 6.34 (s, 1H), 6.16 (s, 1H), 3.76 (brs, 2H)

(c) Synthesis of *N*-(3-chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-**h** was repeated except for using 3-chloro-5-(4-(trifluoromethoxy)phenoxy)aniline (130.0 mg, 0.42 mmol) and 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (150.0 mg, 0.55 mmol) as starting materials, to obtain *N*-(3-chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (75.0 mg, 47%) as a white solid.

LC/MS ESI (+): 584 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.74 (brs, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 7.79 (s, 1H), 7.74 (d, 1H, *J*=8.7Hz), 7.46 (d, 2H, *J*=8.7Hz), 7.40 (t, 1H, *J*=1.8 Hz), 7.26 (d, 2H, *J*=8.9Hz), 6.96 (t, 1H, *J*=1.8 Hz), 2.73(s, 3H), 1.85 (s, 6H)

Compounds from **Example 38 to Example 61** were synthesized through the synthesis route of Example 37, and data of these compounds are listed as follows.

[Table 4]

Ex.	Compound	Analysis data
38	*N*-(3-chloro-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 568 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.77 (s, 1H), 8.34 (s, 1H), 8.21 (d, 1H, *J*=1.5Hz), 8.10 (d, 1H, *J*=8.7Hz), 7.82 (s, 1H), 7.81 (d, 2H, *J*=8.7Hz), 7.75 (dd, 1H, *J*=8.8, 1.8Hz), 7.47 (m, 1H), 7.30 (d, 2H, *J*=8.5Hz), 7.05 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
39	*N*-(3-bromo-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 576 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.4Hz), 7.90 (s, 1H), 7.75 (d, 1H, *J*=8.4Hz), 7.52 (d, 2H, *J*=8.8Hz), 7.42 (s, 1H), 7.18 (d, 2H, *J*=8.8Hz), 7.04 (s, 1H), 2.74 (s, 3H), 1.86 (s, 6H)
40	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide	LC/MS ESI (+): 517 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.90 (s, 1H), 10.42 (s, 1H), 7.79 (m, 1H), 7.70 (d, 1H, *J*=8.7Hz), 7.67 (s, 1H), 7.52 (d, 2H, *J*=8.9Hz), 7.45 (m, 1H), 7.40 (m, 1H), 7.36 (dd, 1H,

		J=8.7, 1.8Hz), 7.19 (d, 2H, *J*=8.9Hz), 6.89 (m, 1H), 2.68 (s, 3H), 1.80 (s, 6H)
41	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 506 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.33 (s, 1H), 8.09 (d, 1H, *J*=8.3Hz), 8.03 (s, 1H), 7.76 (m, 1H), 7.54 (s, 1H), 7.44 (d, 2H, *J*=8.8Hz), 7.36 (m, 1H), 7.18 (d, 2H, *J*=8.8Hz), 6.92 (m, 1H), 4.64 (s, 2H), 2.93 (s, 3H)
42	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 560 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.35 (s, 1H), 8.15-8.18 (m, 2H), 7.75 (m, 1H), 7.56 (m, 1H), 7.51 (d, 2H, *J*=8.9Hz), 7.35 (m, 1H), 7.18 (d, 2H, *J*=8.9Hz), 6.92 (m, 1H), 5.41 (s, 2H)
43	*N*-(3-chloro-5-(4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 518 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.72 (brs, 1H), 8.33 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 7.74-7.76 (m, 2H), 7.30-7.34 (m, 3H), 7.20-7.23 (m, 2H), 6.86 (s, 1H), 2.74 (s, 3H), 1.85 (s, 6H)
44	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 552 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.74 (s, 1H), 8.31 (s, 1H), 8.24 (d, 1H, *J*=7.6Hz), 8.02 (d, 1H, *J*=13.1Hz), 7.75 (s, 1H), 7.51 (d, 2H, *J*=8.6Hz), 7.34 (s, 1H), 7.18 (d, 2H, *J*=8.6Hz), 6.93 (s, 1H), 2.87 (s, 3H), 1.92 (s, 6H)
45	6-chloro-*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 568 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.74 (s, 1H), 8.38 (s, 1H), 8.31 (s, 1H), 8.28 (s, 1H), 7.75 (m, 1H), 7.51 (d, 2H, *J*=8.9Hz), 7.34 (m, 1H), 7.18 (d, 2H, *J*=8.9Hz), 6.93 (m, 1H), 2.89 (s, 3H), 2.05 (s, 6H)
46	*N*-(3-(4-chlorophenoxy)-5-methoxyphenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 530 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.53 (brs, 1H), 8.34 (s, 1H), 8.19 (s, 1H), 8.08 (d, 1H, *J*=8.7Hz), 7.73 (d, 1H, *J*=8.7Hz), 7.47 (d, 2H, *J*=8.7Hz), 7.30 (s, 1H), 7.11 (d, 2H, *J*=8.9Hz), 7.04 (s, 1H), 6.44 (s, 1H), 3.77 (s, 3H), 2.73(s, 3H), 1.85 (s, 6H)
47	*N*-(3-chloro-5-(3-chloro-5-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 552 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6); δ 10.76 (s, 1H), 8.35 (s, 1H), 8.22 (d, 1H, *J*=1.6Hz), 8.10 (d, 1H, *J*=8.7Hz), 7.81 (m, 1H), 7.75 (dd, 1H,

		J=8.7, 1.8Hz), 7.44 (m, 1H), 7.32 (dt, 1H, J=8.6, 2.0Hz), 7.08-7.12 (m, 2H), 7.03 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
48	*N*-(3-chloro-5-(3-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 584 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.78 (brs, 1H), 8.34 (s, 1H), 8.22 (s, 1H), 8.10 (d, 1H, J=8.8Hz), 7.80 (s, 1H), 7.75 (d, 1H, J=8.8Hz), 7.59 (t, 1H, J=8.0Hz), 7.44 (s, 1H) 7.15-7.26 (m, 3H), 6.98 (s, 1H), 2.74 (s, 3H), 1.86 (s, 6H)
49	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 534 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, J=8.7Hz), 7.73-7.76 (m, 2H), 7.51 (d, 2H, J=8.9Hz), 7.36 (m, 1H), 7.18 (d, 2H, J=8.9Hz), 6.91 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
50	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide	LC/MS ESI (+): 535 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.91 (brs, 1H), 9.38 (s, 1H), 8.36 (s, 1H), 8.27 (s, 1H), 7.76 (s, 1H), 7.52 (d, 2H, J=8.8Hz), 7.36 (s, 1H), 7.19 (d, 2H, J=8.8Hz), 6.96 (s, 1H), 2.87 (s, 3H), 1.87 (s, 6H)
51	*N*-(3-chloro-5-(3-chloro-4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 552 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.71 (brs, 1H), 8.34 (s, 1H), 8.21 (d, 1H, J=1.6Hz), 8.10 (d, 1H, J=8.7Hz), 7.73-7.77 (m, 2H), 7.49-7.54 (m, 2H), 7.34 (m, 1H), 7.20 (m, 1H), 6.93 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
52	*N*-(3-chloro-5-(3,4-difluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 536 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.70 (s, 1H), 8.34 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, J=8.7Hz), 7.73-7.77 (m, 2H), 7.55 (m, 1H), 7.42 (m, 1H), 7.36 (m, 1H), 7.04 (m, 1H), 6.93 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
53	*N*-(3-chloro-5-(3-fluoro-5-methoxyphenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 548 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.75 (s, 1H), 8.35 (s, 1H), 8.21 (s, 1H), 8.10 (d, 1H, J=8.7Hz), 7.73-7.78 (m, 2H), 7.40 (s, 1H), 6.96 (s, 1H), 6.73 (m, 1H), 6.57-6.61 (m, 2H), 3.78 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H)
54	*N*-(3-chloro-5-(4-chloro-3-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 552 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.72 (s, 1H), 8.34 (s, 1H), 8.21 (d, 1H, J=1.4Hz), 8.10 (d, 1H, J=8.7Hz), 7.79 (m, 1H), 7.75 (dd, 1H,

		J=8.8, 1.8Hz), 7.66 (t, 1H, *J*=8.7Hz), 7.41 (m, 1H), 7.35 (dd, 1H, *J*=10.4, 2.7Hz), 6.99-7.04 (m, 2H), 2.73 (s, 3H), 1.85 (s, 6H)
55	*N*-(3-chloro-5-(2-(3-chloro-5-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 564 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.71 (s, 1H), 8.34 (s, 1H), 8.20 (d, 1H, *J*=1.6 Hz), 8.09 (d, 1H, *J*=8.7Hz), 7.79 (t, 1H, *J*=1.8H), 7.74 (dd, 1H, *J*=8.7, 1.8Hz), 7.39 (t, 1H, *J*=1.9H), 6.96 (t, 1H, *J*=1.9H), 6.91 (t, 1H, *J*=1.9H), 6.77 (t, 1H, *J*=1.9H), 6.70 (t, 1H, *J*=2.1H), 3.79 (s, 3H), 2.72 (s, 3H) 1.84 (s, 6H)
56	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 576 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.32 (s, 1H), 8.27 (s, 1H), 8.16 (d, 1H, *J*=8.7Hz), 7.76 (s, 1H), 7.73 (d, 1H, *J*=9.1Hz), 7.51 (d, 2H, *J*=8.8Hz), 7.36 (s, 1H), 7.18 (d, 2H, *J*=8.8Hz), 6.93 (s, 1H), 3.91 (d, 2H, *J*=9.7Hz), 3.20 (t, 2H, *J*=11.7Hz), 2.74 (d, 2H, *J*=13.3Hz), 2.65 (s, 3H), 2.33 (t, 2H, *J*=12.3Hz)
57	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 578 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.72 (s, 1H), 8.33 (s, 1H), 8.22 (s, 1H), 8.11 (d, 1H, *J*=8.6Hz), 7.74-7.77 (m, 2H), 7.52 (d, 2H, *J*=8.9Hz), 7.37 (s, 1H), 7.19 (d, 2H, *J*=8.9Hz), 6.93 (s, 1H), 3.49 (t, 2H, *J*=6.3Hz), 3.11-3.14 (m, 5H), 1.85 (s, 6H)
58	*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 534 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.69 (s, 1H), 8.30-8.33 (s, 2H), 8.02 (d, 1H, *J*=8.6Hz), 7.76 (s, 1H), 7.74 (d, 1H, *J*=8.6Hz), 7.51 (d, 2H, *J*=8.9Hz), 7.37 (s, 1H), 7.18 (d, 2H, *J*=8.9Hz), 6.92 (s, 1H), 2.73 (s, 3H), 1.84 (s, 6H)
59	*N*-(3-(azetidin-1-yl)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 555 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.41 (s, 1H), 8.34 (s, 1H), 8.18 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.74 (d, 1H, *J*=8.8Hz), 7.45 (d, 2H, *J*=8.8Hz), 7.08 (d, 2H, *J*=9.2Hz), 6.76-6.78 (m, 2H), 5.89 (s, 1H), 3.82 (t, 4H, *J*=6.4Hz), 2.74 (s, 3H), 2.33-2.34 (m, 2H), 1.85 (s, 6H)
60	*N*-(3-chloro-5-((6-chloropyridin-3-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.33-8.37 (m, 2H), 8.22 (s, 1H), 8.10 (d, 1H, *J*=8.6Hz), 7.71-7.79 (m, 3H), 7.62 (d, 1H,

		J=8.7Hz), 7.39 (s, 1H), 7.03 (s, 1H), 2.73 (s, 3H), 1.85 (s, 6H)
61	*N*-(3-chloro-5-((5-chloropyridin-2-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.36 (s, 1H), 8.28 (d, 1H, *J*=2.6Hz), 8.22 (s, 1H), 8.10 (d, 1H, *J*=8.7Hz), 7.03 (dd, 1H, *J*=8.7, 2.7Hz), 7.74-7.80 (m, 2H), 7.55 (s, 1H), 7.21 (d, 1H, *J*=8.7Hz), 7.09 (s, 1H), 2.73 (s, 3H), 1.85 (s, 6H)

Example 62) Synthesis of *N*-(2-chloro-6-(3,5-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 2-chloro-6-(3,5-dichlorophenoxy)pyridine-4-amine

2,6-Dichloropyridine-4-amine (200.0 mg, 1.22 mmol) and 3,5-dichlorophenol (400.0 mg, 2.45 mmol) were dissolved in sulfolane (6.1 mL) and K_2CO_3 (339.0 mg, 2.45 mmol) was added. The reaction mixture was stirred at 160°C for 16 hours, cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with 1N NaOH aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN : 0.1% formic acid in H_2O) to obtain 2-chloro-6-(3,5-dichlorophenoxy)pyridine-4-amine (121.0 mg, 34%) as a white solid.

LC/MS ESI (+): 289 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 7.46 (s, 1H), 7.24 (d, 2H, *J*=1.8Hz), 6.63 (brs, 2H), 6.35 (d, 1H, *J*=1.6Hz), 6.00 (d, 1H, *J*=1.6Hz)

(b) Synthesis of *N*-(2-chloro-6-(3,5-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

5-(2-(Methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (50.0 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (1.6 mL), and DMF (1.2 μL, 0.01 mmol) and $(COCl)_2$ (16.1 μL, 0.18 mmol) were added. The reaction mixture was stirred at 25°C for 2 hours and concentrated under reduced pressure to obtain 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carbonyl chloride. To the residue, 2-chloro-6-(3,5-dichlorophenoxy)pyridine-4-amine (50.9 mg, 0.17 mmol) and pyridine (550.0 μL) were added, stirred at 30°C for 16 hours, and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN : 0.1% formic acid in H_2O) to obtain *N*-(2-chloro-6-(3,5-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (62.0 mg, 65%) as a white solid.

LC/MS ESI (+): 569 (M+1)

[1]H-NMR (400MHz, DMSO-d_6): δ 11.14 (brs, 1H), 8.42 (s, 1H), 8.26 (d, 1H, *J*=2.8Hz), 8.13 (d, 1H, *J*=8.7Hz), 7.77 (dd, 1H, *J*=8.7, 1.8Hz), 7.71 (d, 1H, *J*=1.3Hz), 7.56 (t, 1H, *J*=1.8Hz), 7.44 (d, 2H, *J*=1.8Hz), 7.39 (d, 1H, *J*=1.4Hz), 2.74 (s, 3H), 1.86 (s, 6H)

Compounds from **Example 63 to Example 86** were synthesized through the synthesis route of Example 62, and data of these compounds are listed as follows.

[Table 5]

Ex.	Compound	Analysis data
63	*N*-(6-chloro-4-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) [1]H-NMR(400MHz, DMSO-d_6): δ 11.59 (s, 1H), 8.60 (s, 1H), 8.13 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.74-7.77 (m, 2H), 7.59 (d, 2H, *J*=8.8Hz), 7.33 (d, 2H, *J*=8.8Hz), 6.94 (s, 1H), 2.75 (s, 3H), 1.86 (s, 6H)
64	*N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) [1]H-NMR(400MHz, DMSO-d_6): δ 11.10 (s, 1H), 8.39 (s, 1H), 8.26 (s, 1H), 8.12 (d, 1H, *J*=8.8Hz), 7.79 (d, 1H, *J*=8.8Hz), 7.67 (s, 1H), 7.53 (d, 2H, *J*=8.8Hz), 7.33 (s, 1H), 7.27 (d, 2H, *J*=8.8Hz), 2.75 (s, 3H), 1.86 (s, 6H)
65	*N*-(2-chloro-6-((6-chloropyridin-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 536 (M+1) [1]H-NMR(400MHz, DMSO-d_6): δ 11.18 (brs, 1H), 8.39-8.41 (m, 2H), 8.25 (s, 1H), 8.11 (d, 1H, *J*=8.7Hz), 7.83 (d, 1H, *J*=8.6Hz), 7.76 (d, 1H, *J*=8.7Hz), 7.63-7.67 (m, 2H), 7.44 (s, 1H), 2.74 (s, 3H), 1.86 (s, 6H)
66	*N*-(4-chloro-6-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) [1]H-NMR(400MHz, DMSO-d_6): δ 11.27 (s, 1H), 8.54 (s, 1H), 8.15 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 8.04 (s, 1H), 7.75 (dd, 1H, *J*=8.8, 1.6Hz), 7.51 (d, 2H, *J*=8.8Hz), 7.28 (d, 2H, *J*=8.8Hz), 6.93 (s, 1H), 2.74 (s, 3H), 1.85 (s, 6H)
67	*N*-(2-chloro-6-(4-(trifluoromethyl)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 569 (M+1) [1]H-NMR(400MHz, DMSO-d_6): δ 11.15 (s, 1H), 8.42 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H, *J*=8.8Hz), 7.86 (d, 2H, *J*=8.8Hz), 7.79 (dd, 1H, *J*=8.4, 2.0Hz), 7.73 (s, 1H), 7.43-7.46 (m, 3H), 2.75 (s, 3H), 1.87 (s, 6H)

68	*N*-(2-chloro-6-(4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 519 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.41 (s, 1H), 8.27 (d, 1H, *J*=1.6 Hz), 8.14 (d, 1H, *J*=8.8Hz), 7.79 (dd, 1H, *J*=8.7, 1.9Hz), 7.68 (d, 1H, *J*=1.2Hz), 7.27-7.35 (m, 5H), 2.76 (s, 3H) 1.87 (s, 6H)
69	*N*-(2-bromo-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (-): 577 (M-1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.06 (s, 1H), 8.41 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, *J*=8.8Hz), 7.83 (d, 1H, *J*=1.6Hz), 7.77 (dd, 1H, *J*=8.8, 2.0Hz), 7.54 (d, 2H, *J*=8.8Hz), 7.37 (s, 1H), 7.27 (d, 2H, *J*=8.8Hz), 2.75 (s, 3H), 1.87 (s, 6H)
70	*N*-(2-chloro-6-(3-chloro-5-methoxyphenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 565 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.15 (brs, 1H), 8.40 (s, 1H), 8.23 (d, 1H, *J*=1.6Hz), 8.10 (d, 1H, *J*=8.7Hz), 7.75 (dd, 1H, *J*=8.7, 1.9Hz), 7.69 (d, 1H, *J*=1.4Hz), 7.30 (d, 1H, *J*=1.4Hz), 6.96 (s, 1H), 6.91 (s, 1H), 6.81 (s, 1H), 3.79 (s, 3H), 2.70 (s, 3H), 1.85 (s, 6H)
71	*N*-(2-chloro-6-(3-chloro-4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 553 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.08 (brs, 1H), 8.39 (s, 1H), 8.24 (d, 1H, *J*=1.6Hz), 8.10 (d, 1H, *J*=8.7Hz), 7.76 (dd, 1H, *J*=8.7, 1.9Hz), 7.66 (s, 1H), 7.58 (dd, 1H, *J*=6.3, 2.9Hz), 7.52 (t, 1H, *J*=9.0Hz), 7.33(d, 1H, *J*=1.4Hz), 7.27 (m, 1H), 2.70 (s, 3H), 1.85 (s, 6H)
72	*N*-(2-chloro-6-(4-chloro-3-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 553 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.18 (brs, 1H), 8.40 (s, 1H), 8.25 (s, 1H), 8.12 (d, 1H, *J*=8.7Hz), 7.77 (dd, 1H, *J*=8.7, 1.8Hz), 7.66-7.71 (m, 2H), 7.46 (dd, 1H, *J*=10.2, 2.7Hz), 7.37 (s, 1H), 7.15 (m, 1H), 2.74 (s, 3H), 1.85 (s, 6H)
73	*N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxamide	C/MS ESI (+): 533 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.07 (s, 1H), 8.38 (s, 1H), 8.11 (d, 1H, *J*=8.5Hz), 8.05 (s, 1H), 7.67 (s, 1H), 7.52-7.55 (m, 3H), 7.33 (s, 1H), 7.26 (d, 2H, *J*=8.9Hz), 4.55 (m, 1H), 3.20-3.26 (m, 2H), 2.38-2.44 (m, 2H), 2.12-2.28 (m, 2H)
74	*N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-	LC/MS ESI (+): 547 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.07 (s, 1H),

	dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxamide	8.39 (s, 1H), 8.09 (d, 1H, *J*=8.5Hz), 8.03 (s, 1H), 7.67 (s, 1H), 7.51-7.54 (m, 3H), 7.33 (s, 1H), 7.26 (d, 2H, *J*=8.9Hz), 4.60 (m, 1H), 3.25-3.33 (m, 2H), 1.67-2.41 (m, 6H)
75	*N*-(2-chloro-6-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 536 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 12.11 (brs, 1H), 8.59 (s, 1H), 8.15 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 7.76 (d, 1H, *J*=8.7Hz), 7.66 (s, 1H), 7.56 (d, 2H, *J*=8.8Hz), 7.34 (d, 2H, *J*=8.8Hz), 2.75 (s, 3H), 1.85 (s, 6H)
76	*N*-(6-chloro-2-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 536 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 12.00 (brs, 1H), 8.56 (s, 1H), 8.17 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 7.98 (s, 1H), 7.75 (d, 1H, *J*=10.2Hz), 7.52 (d, 2H, *J*=8.8Hz), 7.33 (d, 2H, *J*=8.8Hz), 2.74 (s, 3H), 1.85 (s, 6H)
77	*N*-(2-(4-chlorophenoxy)-6-fluoropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 519 (M+1) ^{1}H-NMR(400MHz, DMSO-d6): δ 11.17 (s, 1H), 8.41 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, *J*=8.4Hz), 7.78 (d, 1H, J=8.4Hz), 7.54 (d, 2H, *J*=8.8Hz), 7.32 (s, 1H), 7.28 (d, 2H, *J*=8.8Hz), 7.21 (s, 1H), 2.75 (s, 3H), 1.86 (s, 6H)
78	*N*-(2-(bicyclo[2.2.1]hept-5-en-2-yloxy)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 517 (M+1) ^{1}H-NMR(400MHz, DMSO-d6): δ 10.89 (s, 1H), 8.37 (s, 1H), 8.24 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.77 (d, 1H, J=8.7Hz), 7.41 (s, 1H), 7.14 (s, 1H), 6.38 (m, 1H), 6.01 (m, 1H), 5.40 (m, 1H), 3.25 (s, 1H), 2.86 (s, 1H), 2.73 (s, 3H), 2.22 (m, 1H), 1.85 (s, 6H), 1.42 (m, 2H), 0.92 (d, 1H, *J*=13.0Hz)
79	*N*-(2-chloro-6-(3,4-difluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 537 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.41 (s, 1H), 8.26 (s, 1H), 8.15 (d, 1H, *J*=8.8Hz), 7.80 (d, 1H, *J*=8.8Hz), 7.69 (s, 1H), 7.55-7.57 (m, 2H), 7.36 (s, 1H), 7.14-7.15 (m, 1H), 2.75 (s, 3H) 1.86 (s, 6H)
80	*N*-(2-chloro-6-(3-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 535 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.08 (brs, 1H), 8.31 (s, 1H), 8.17 (s, 1H), 8.04 (d, 1H, *J*=8.8Hz), 7.69 (d, 1H, *J*=8.8Hz), 7.61 (s, 1H), 7.43 (t, 1H, *J*=8.0Hz), 7.26-7.31 (m, 3H), 7.13 (d, 1H, *J*=8.6Hz), 2.67 (s, 3H), 1.89 (s, 6H)

81	*N*-(2-chloro-6-(3-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 585 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.05 (s, 1H), 8.33 (s, 1H), 8.19 (d, 1H, *J*=1.6Hz), 8.05 (d, 1H, *J*=8.7Hz), 7.70 (dd, 1H, *J*=8.7, 1.6Hz), 7.62 (d, 1H, *J*=1.2Hz), 7.53 (t, 1H, *J*=7.2Hz), 7.32 (s, 1H), 7.21-7.26 (m, 3H), 2.67 (s, 3H), 1.79 (s, 6H)
82	*N*-(2-chloro-6-(3,4-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 569 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.34 (s, 1H), 8.19 (d, 1H, *J*=1.6Hz), 8.06 (d, 1H, *J*=8.7Hz), 7.71 (dd, 1H, *J*=8.7, 1.6Hz), 7.67 (d, 1H, *J*=8.8Hz), 7.53 (d, 1H, *J*=1.6Hz), 7.32 (d, 1H, *J*=2.4Hz), 7.3 (d, 1H, *J*=2.4Hz), 7.21 (dd, 1H, *J*=8.0, 2.4Hz), 2.67 (s, 3H), 1.79 (s, 6H)
83	*N*-(2-chloro-6-(4-chloro-2-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 553 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.04 (s, 1H), 8.33 (s, 1H), 8.18 (s, 1H), 8.06 (d, 1H, *J*=8.7Hz), 7.71 (dd, 1H, *J*=8.7, 1.6Hz), 7.61 (s, 1H), 7.41 (d, 2H, *J*=8.8Hz), 7.29 (d, 2H, *J*=8.8Hz), 2.67 (s, 3H), 1.78 (s, 6H)
84	*N*-(2-chloro-6-(4-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 585 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.11 (s, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, *J*=8.8Hz), 7.77 (d, 1H, *J*=8.8Hz), 7.68 (s, 1H,) 7.50 (s, 1H), 7.48 (s, 1H), 7.35-7.37 (m, 3H), 2.74 (s, 3H), 1.85 (s, 6H)
85	*N*-(2-chloro-6-((5-chloropyridin-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 536 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.09 (s, 1H), 8.34 (s, 1H), 8.31 (d, 1H, *J*=2.4Hz), 8.19 (s, 1H), 8.01-8.07 (m, 2H), 7.71 (d, 1H, *J*=8.8Hz), 7.68 (d, 1H, *J*=1.2Hz), 7.41 (s, 1H), 7.23 (d, 1H, *J*=8.8Hz), 2.62 (s, 3H), 1.79 (s, 6H)
86	*N*-(2-chloro-6-((4-chlorobenzyl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 549 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 10.91 (s, 1H), 8.32 (s, 1H), 8.18 (s, 1H), 8.05 (d, 1H, *J*=8.8Hz), 7.70 (d, 1H, *J*=8.8Hz), 7.38-7.44 (m, 5H) 7.24 (s, 1H), 5.26 (s, 2H), 2.67 (s, 3H), 1.78 (s, 6H)

Example 87) Synthesis of *N*-(3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-

(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 3-(2-(3-chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenyl trifluoromethanesulfonate

3-(2-(3-Chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenol (100.0 mg, 0.27 mmol) was dissolved in CH_2Cl_2 (2.7 mL), and pyridine (109.0 μL, 1.35 mmol) and Tf_2O (45.0 μL, 0.27 mmol) were slowly added dropwise at 0°C. The reaction mixture was stirred at 0°C for 2 hours, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 3-(2-(3-chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenyl trifluoromethanesulfonate (120.0 mg, 88%) as a colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.13 (t, 1H, *J*=1.9Hz), 7.99 (t, 1H, *J*=1.9Hz), 7.45 (t, 1H, *J*=1.8Hz), 7.08-7.10 (m, 2H), 7.04 (t, 1H, *J*=1.9Hz), 1.75 (s, 6H)

(b) Synthesis of 1-chloro-3-nitro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)benzene

3-(2-(3-Chloro-5-nitrophenyl)propan-2-yl)-5-(trifluoromethoxy)phenyl trifluoromethanesulfonate (280.0 mg, 0.55 mmol) was dissolved in anhydrous DMF (5.5 mL), and 1-(trimethylsilyl)-1-propyne (123.0 μL, 0.83 mmol), $Pd(PPh_3)_4$ (64.0 mg, 0.06 mmol), CuI (21.0 mg, 0.11 mmol) and DIPEA (480.0 μL, 2.75 mmol) were added at room temperature. The reaction mixture was stirred at 90°C for 15 hours, cooled to room temperature, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : CH_2Cl_2 = 4 : 1) to obtain 1-chloro-3-nitro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)benzene (120.0 mg, 55%) as a colorless liquid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.08 (t, 1H, *J*=1.9Hz), 7.99 (t, 1H, *J*=1.9Hz), 7.46 (t, 1H, *J*=1.8Hz), 7.11-7.13 (m, 2H), 6.94 (s, 1H), 2.04 (s, 3H), 1.70 (s, 6H)

(c) Synthesis of 3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline

The synthesis procedure of Example 1-g was repeated except for using 1-chloro-3-nitro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)benzene (120.0 mg, 0.32 mmol) as a starting material to obtain 3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline (93.0 mg, 84%).

LC/MS ESI (+): 368 (M+1)

(d) Synthesis of *N*-(3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-

(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)aniline (55.0 mg, 0.15 mmol) as a starting material to obtain *N*-(3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (23.5 mg, 33%).

LC/MS ESI (+): 648 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.65 (s, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 7.90 (s, 1H), 7.74 (d, 1H, *J*=8.8Hz), 7.50 (s, 1H), 7.19-7.22 (m, 3H), 7.07 (s, 1H), 2.73 (s, 3H), 2.03 (s, 3H), 1.85 (s, 6H), 1.65 (s, 6H)

Example 88) Synthesis of *N*-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 4-(4-chlorophenyl)-4-methyl-3-oxopentanenitrile

2-(4-Chlorophenyl)-2-methylpropanic acid (500.0 mg, 2.52 mmol) was dissolved in THF (10.0 mL), carbonyldiimidazole (490.0 mg, 3.02 mmol) was added, and stirred for 2 hours. To the reaction mixture was added a solution prepared by dissolving CH_3CN (0.2 mL, 8.31 mmol) in THF (10.0 mL), adding 1.6M solution of *n*-BuLi in THF (4.7 mL, 7.56 mmol) slowly dropwise at -78°C and stirring for 1 hour. The resulting mixure was stirred at -78°C for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : CH_2Cl_2 = 1 : 2) to obtain 4-(4-chlorophenyl)-4-methyl-3-oxopentanenitrile (333.0 mg, 59%) as an off-white oil.

LC/MS ESI (-): 220 (M-1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.38 (d, 2H, *J*=8.4Hz), 7.19 (d, 2H, *J*=8.8Hz), 3.30 (s, 2H), 1.53 (s, 6H)

(b) Synthesis of 1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazole-5-amine

tert-Butylhydrazine chloride (463.0 mg, 3.72 mmol) was dissolved in EtOH (1.9 mL), and NaOH (119.0 g, 2.97 mmol) was added. 4-(4-Chlorophenyl)-4-methyl-3-oxopentanenitrile (330.0 mg, 1.49 mmol) in EtOH (1.0 mL) was added to the reaction mixture dropwise. The reaction mixture was stirred at 80°C for 12 hours, H_2O was added, and extracted with EtOAc. The organic extract was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazole-5-amine (130.0 mg, 30%) as a whilte solid.

LC/MS ESI (+): 292 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.25 (d, 2H, *J*=9.2Hz), 7.19 (d, 2H, *J*=8.8Hz), 5.24 (s, 1H), 3.41 (s, 2H), 1.62 (s, 9H), 1.59 (s, 6H)

(c) Synthesis of *N*-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazole-5-amine (100.0 mg, 0.34 mmol) as a starting material to obtain *N*-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (78.0 mg, 40%).

LC/MS ESI (+): 572 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.35 (s, 1H), 8.27 (s, 1H), 8.26 (s, 1H), 8.10 (d, 1H, *J*=8.8Hz), 7.76 (d, 1H, *J*=8.8Hz), 7.30-7.35 (m, 4H), 6.08 (s, 1H), 2.74 (s, 3H), 1.85 (s, 6H), 1.63 (s, 6H), 1.57 (s, 9H).

Example 89) Synthesis of *N*-(3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

N-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (30.0 mg, 0.05 mmol) was dissolved in formic acid (4.0 mL). The reaction mixture was stirred at 80°C for 12 hours and concentrated under reduced pressure, basified with sat. $NaHCO_3$ aqueous solution (pH=9) and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN : 0.1% formic acid in H_2O) to obtain *N*-(3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (17.0 mg, 67%) as a white solid.

LC/MS ESI (+): 516 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 12.30 (s, 1H), 11.23 (s, 1H), 8.44 (s, 1H), 8.13 (s, 1H), 8.09 (d, 1H, *J*=8.8Hz), 7.74 (d, 1H, *J*=8.8Hz), 7.38 (d, 2H, *J*=8.4Hz), 7.29 (d, 2H, *J*=8.4Hz), 6.50 (s, 1H), 2.74 (s, 3H), 1.86 (s, 6H), 1.67 (s, 6H)

Example 90 and Example 91) Synthesis of *N*-(2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide and *N*-(4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 4,6-dichloro-*N*-methoxy-*N*-methylisonicotinamide

4,6-Dichloroisonicotinic acid (3.0 g, 15.6 mmol) was dissolved in anhydrous CH_2Cl_2 (100.0 mL), and $(COCl)_2$ (2.1 mL, 23.40 mmol) and anhydrous DMF were added dropwise in a catalytic amount, followed by stirring at 0°C for 1 hour. The reaction mixture was dried under reduced pressure for 1 hour, the residue was dissolved in anhydrous CH_2Cl_2 (100.0 mL), and *N,O*-dimethylhydroxyamine (4.6 g, 46.80 mmol) and pyridine (7.5 mL, 93.60 mmol) were added at 0°C. The reaction mixture was stirred at 0°C for 1 hour, H_2O was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 1 : 4) to obtain 4,6-dichloro-*N*-methoxy-*N*-methylisonicotinamide (3.5 g, 83%) as a white solid.

LC/MS ESI (+): 235 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.56 (brs, 1H), 7.44 (s, 1H), 3.80 (s, 3H), 3.36 (s, 3H)

(b) Synthesis of (4,6-dichloropyridin-2-yl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone

1-Bromo-3-methoxy-5-(trifluoromethoxy)benzene (5.0 g, 18.45 mmol) was dissolved in THF (90.0 mL), 1.7M solution of *tert*-BuLi in pentane (11.4 mL, 19.30 mmol) was added dropwise at -78°C, and stirred for 1 hour. 4,6-Dichloro-*N*-methoxy-*N*-methylisonicotinamide (3.5 g, 14.88 mmol) in THF (10.0 mL) was slowly added, and the reaction mixture was stirred at 0°C for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : CH_2Cl_2 = 1 : 10) to obtain (4,6-dichloropyridin-2-yl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone (2.4 g, 44%) as a yellow solid.

LC/MS ESI (+): 366 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.63 (s, 1H), 7.61 (s, 1H), 7.59 (s, 1H), 7.01 (s, 1H), 3.89 (s, 3H)

(c) Synthesis of 2,4-dichloro-6-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)pyridine

The synthesis procedure of Example 1-c was repeated except for using (4,6-dichloropyridin-2-yl)(3-methoxy-5-(trifluoromethoxy)phenyl)methanone (2.4 g, 6.55 mmol) as a starting material to obtain 2,4-dichloro-6-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)pyridine (2.1 g, 76%).

LC/MS ESI (+): 420 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.37 (s, 1H), 7.13 (s, 1H), 7.06 (s, 1H), 6.77 (s, 1H), 3.84 (s, 3H)

(d) Synthesis of 2,4-dichloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine

The synthesis procedure of Example 1-d was repeated except for using 2,4-dichloro-6-(dichloro(3-methoxy-5-(trifluoromethoxy)phenyl)methyl)pyridine (2.1 g, 4.98 mmol) as a starting material to obtain 2,4-dichloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine (1.3 g, 69%) as an off-white oil.

LC/MS ESI (+): 380 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.19 (s, 1H), 6.94 (s, 1H), 6.73 (s, 1H), 6.70 (s, 1H), 6.62 (s, 1H), 3.79 (s, 3H), 1.69 (s, 6H)

(e) Synthesis of 2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-4-amine and (f) synthesis of 4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-2-amine

2,4-Dichloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine (50.0 mg, 0.13 mmol), NaN_3 (17.0 mg, 0.26 mmol), Cu_2O (18.7 mg, 0.131 mmol) and L-proline (19.5 mg, 0.17 mmol) were dissolved in anhydrous DMSO (1.0 mL). The reaction mixture was stirred at 100°C for 12 hours, cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-4-amine (14.0 mg, 30%) and 4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-2-amine (4.0 mg, 8%) as an off-white oil.

(e) LC/MS ESI (+): 361 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.72 (s, 1H), 6.96 (s, 1H), 6.37 (d, 1H, *J*=1.2Hz), 6.14 (d, 1H, *J*=1.2Hz), 4.13 (brs, 2H), 3.76 (s, 3H), 1.64 (s, 6H)

(f) LC/MS ESI (+): 361 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.72 (s, 1H), 6.71 (s, 1H), 6.59 (s, 1H), 6.48 (s, 1H), 6.32 (s, 1H), 4.43 (brs, 2H), 3.77 (s, 3H), 1.62 (s, 6H)

(g) Synthesis of *N*-(2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-4-amine (38.0 mg, 0.11 mmol) as a starting material to obtain *N*-(2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (20.0 mg, 30%) as a white solid.

LC/MS ESI (+): 641 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.99 (s, 1H), 8.39 (s, 1H), 8.24 (s, 1H), 8.13

(d, 1H, *J*=8.8Hz), 7.89 (s, 1H), 7.77 (d, 1H, *J*=8.8Hz), 7.56 (s, 1H), 6.84 (s, 1H), 6.83 (s, 1H), 6.77 (s, 1H), 3.79 (s, 3H), 2.75 (s, 3H), 1.86 (s, 6H), 1.68 (s, 6H)

(h) Synthesis of *N*-(4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridine-2-amine (20.0 mg, 0.06 mmol) as a starting material to obtain *N*-(4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (12.0 mg, 34%) as a white solid.

LC/MS ESI (+): 641 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 11.16 (s, 1H), 8.64 (s, 1H), 8.19 (s, 1H), 8.11 (d, 1H, *J*=8.8Hz), 8.09 (d, 1H, *J*=2.0Hz), 7.77 (dd, 1H, *J*=8.8, 2.0Hz), 7.20 (s, 1H), 6.86 (s, 1H), 6.79-6.81 (m, 2H), 3.78 (s, 3H), 2.76 (s, 3H), 1.86 (s, 6H), 1.74 (s, 6H)

Example 92) Synthesis of *N*-(3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 4-(3-bromo-5-chlorophenoxy)-2,2,6,6-tetramethylpiperidine

1-Bromo-3-chloro-5-nitrobenzene (200.0 mg, 0.42 mmol) was dissolved in anhydrous DMF (2.1 mL), and 2,2,6,6-tetramethylpiperidin-4-ol (66.0 mg, 0.42 mmol) and 60wt% NaH (50.4 mg, 1.26 mmol) were added. The reaction mixture was stirred at room temperature for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 4-(3-bromo-5-chlorophenoxy)-2,2,6,6-tetramethylpiperidine (160.0 mg, 54%) as an off-white oil.

LC/MS ESI (+): 346 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.93 (s, 1H), 6.81 (s, 1H), 4.60 (m, 1H), 2.02-2.06 (m, 2H), 1.20-1.30 (m, 14H)

(b) Synthesis of 3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)aniline

The synthesis procedure of Example 91-e was repeated except for using 4-(3-bromo-5-chlorophenoxy)-2,2,6,6-tetramethylpiperidine (34.0 mg, 0.10 mmol) as a starting material to obtain 3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)aniline (16.0 mg, 58%).

LC/MS ESI (+): 283 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.31 (s, 1H), 6.29 (s, 1H), 6.10 (s, 1H), 4.58 (m, 1H), 3.70 (brs, 2H), 2.03-2.05 (m, 2H), 1.18-1.23 (m, 14H)

(c) Synthesis of *N*-(3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)aniline (16.0 mg, 0.06 mmol) as a starting material to obtain *N*-(3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (9.0 mg, 28%) as a white solid.

LC/MS ESI (+): 563 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.53 (s, 1H), 8.28 (s, 1H), 8.16 (s, 1H), 8.03 (d, 1H, *J*=8.8Hz), 7.68 (dd, 1H, *J*=8.8, 2.0Hz), 7.41 (s, 1H), 7.33 (s, 1H), 6.73 (s, 1H), 4.66-4.71 (m, 1H), 1.88 (dd, 2H, *J*=12.4, 4.0Hz), 1.79 (s, 6H), 1.14 (s, 6H), 1.07-1.10 (m, 2H), 1.02 (s, 6H)

Example 93) Synthesis *tert*-butyl (2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate

(a) Synthesis of 1-(4-chlorophenoxy)-3-methoxy-5-nitrobenzene

The synthesis procedure of Example 40-a was repeated except for using 1-bromo-3-methoxy-5-nitrobenzene (500.0 mg 1.71 mmol) as a starting material to obtain 1-(4-chlorophenoxy)-3-methoxy-5-nitrobenzene (400.0 mg, 66%).

LC/MS ESI (+): 280 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.48 (t, 1H, *J*=2.2Hz), 7.37 (t, 1H, *J*=2.1Hz), 7.36 (d, 2H, *J*=8.8Hz), 7.00 (d, 2H, *J*=8.9Hz), 6.83 (t, 1H, *J*=2.1Hz), 3.87 (s, 3H)

(b) Synthesis of 3-(4-chlorophenoxy)-5-nitrophenol

The synthesis procedure of Example 1-e was repeated except for using 1-(4-chlorophenoxy)-3-methoxy-5-nitrobenzene (396.0 mg, 1.42 mmol) as a starting material to obtain 3-(4-chlorophenoxy)-5-nitrophenol (307.0 mg, 82%).

LC/MS ESI (+): 266 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.39 (t, 1H, *J*=2.2Hz), 7.35 (d, 2H, *J*=8.9Hz), 7.33 (t, 1H, *J*=2.1Hz), 6.98 (d, 2H, *J*=8.9Hz), 6.74 (t, 1H, *J*=2.2Hz)

(c) Synthesis of *tert*-butyl (2-(3-(4-chlorophenoxy)-5-nitrophenoxy)ethyl)carbamate

3-(4-Chlorophenoxy)-5-nitrophenol (297.0 mg, 1.11 mmol) was dissolved in anhydrous DMF (10.0 mL), K_2CO_3 (231.0 mg, 1.68 mmol) was added, stirred at room temperature for 10 minutes, and *tert*-butyl (2-bromoethyl)carbamate (300.0 mg, 1.34 mmol) was added. The reaction mixture was stirred at room temperature for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 6 : 1) to obtain *tert*-butyl (2-(3-(4-chlorophenoxy)-5-nitrophenoxy)ethyl)carbamate (435.0 mg, 95%).

LC/MS ESI (+): 409 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.44 (t, 1H, *J*=2.1Hz), 7.37 (t, 1H, *J*=2.1Hz), 7.36 (d, 2H, *J*=8.9Hz), 6.98 (d, 2H, *J*=8.9Hz), 6.79 (t, 1H, *J*=2.2Hz), 4.90 (brs, 1H), 4.04 (t, 2H, *J*=5.1Hz), 3.51-3.55 (m, 2H), 1.43 (s, 9H)

(d) Synthesis of *tert*-butyl (2-(3-amino-5-(4-chlorophenoxy)phenoxy)ethyl)carbamate

The synthesis procedure of Example 1-g was repeated except for using *tert*-butyl (2-(3-(4-chlorophenoxy)-5-nitrophenoxy)ethyl)carbamate (425.0 mg, 1.04 mmol) as a starting material to obtain *tert*-butyl (2-(3-amino-5-(4-chlorophenoxy)phenoxy)ethyl)carbamate (360.0 mg, 92%).

LC/MS ESI (+): 379 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.28 (d, 2H, *J*=8.9Hz), 6.96 (d, 2H, *J*=8.9Hz), 5.98 (t, 1H, *J*=2.0Hz), 5.91-5.94 (m, 2H), 3.92 (t, 2H, *J*=5.0Hz), 3.73 (brs, 2H), 3.46-3.50 (m, 2H), 1.44 (s, 9H)

(e) Synthesis of *tert*-butyl(2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate

The synthesis procedure of Example 1-h was repeated except for using *tert*-butyl (2-(3-amino-5-(4-chlorophenoxy)phenoxy)ethyl)carbamate (211.0 mg, 0.56 mmol) as a starting material to obtain *tert*-butyl (2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate (360.0 mg, 98%) as a white solid.

LC/MS ESI (+): 682 (M+Na)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.53 (brs, 1H), 8.33 (s, 1H), 8.19 (s, 1H), 8.08 (d, 1H, *J*=8.7Hz), 7.73 (d, 1H, *J*=8.7Hz), 7.47 (d, 2H, *J*=8.7Hz), 7.29 (s, 1H), 7.12 (d, 2H, *J*=8.9Hz), 7.02-7.04 (m, 2H), 6.44 (s, 1H), 3.94-3.97 (m, 2H), 3.28-3.32 (m, 2H), 2.73 (s, 3H), 1.85 (s, 6H), 1.38 (s, 9H)

Example 94) Synthesis of *N*-(3-(2-aminoethoxy)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

tert-Butyl (2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate (187.0 mg, 0.28 mmol) were dissolved in anhydrous CH_2Cl_2 (3.0 mL) and TFA (220.0 μL, 2.84 mmol) was added at 0°C. The reaction mixture was stirred at room temperature for 5 hours, sat. $NaHCO_3$ was added, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, CH_2Cl_2 : MeOH = 20 : 1) to obtain *N*-(3-(2-aminoethoxy)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (81.0 mg, 51%) as a white solid.

LC/MS ESI (+): 559 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.54 (brs, 1H), 8.35 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 7.74 (d, 1H, *J*=8.7Hz), 7.50 (d, 2H, *J*=8.7Hz), 7.32 (s, 1H), 7.12 (d, 2H, *J*=8.9Hz), 7.04 (s, 1H), 6.42 (s, 1H), 3.90-3.94(t, 2H, *J*=5.6Hz), 2.87-2.90 (t, 2H, *J*=5.6Hz), 2.51 (s, 3H), 2.00 (brs, 2H), 1.85 (s, 6H)

Example 95) Synthesis of *N*-(5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-yl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 3'-chloro-2,4-difluoro-5'-nitro-1,1'-biphenyl

1-Bromo-3-chloro-5-nitrobenzene (1.0 g, 4.23 mmol), (2, 4-difluorophenyl)boronic acid (0.7 g, 4.23 mmol), $Pd(PPh_3)_4$ (490.0 mg, 0.42 mmol) and Na_2CO_3 (1.4 g, 12.70 mmol) were added to a mixture of DME/H_2O (42.0 mL, 4/1 v/v). The reaction mixture was stirred at 90°C for 3 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 3'-chloro-2,4-difluoro-5'-nitro-1,1'-biphenyl (1.1 g, 96%) as a white solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.23 (s, 1H), 7.83 (s, 1H), 7.26-7.46 (m, 1H), 6.98-7.03 (m, 2H)

(b) Synthesis of 5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-amine

The synthesis procedure of Example 1-g was repeated except for using 3'-chloro-2,4-difluoro-5'-nitro-1,1'-biphenyl (1.1 g, 4.08 mmol) as a starting material to obtain 5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-amine (830.0 mg, 85%).

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.33-7.37 (m, 1H), 6.85-6.93 (m, 3H), 6.68 (m, 2H), 3.81 (brs, 2H)

(c) Synthesis of *N*-(5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-yl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-amine (40.0 mg, 0.17 mmol) as a starting material to obtain *N*-(5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-yl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide (30.8 mg, 41%).

LC/MS ESI (+): 492 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.76 (s, 1H), 8.40 (s, 1H), 8.11 (d, 1H, *J*=8.4Hz), 8.06 (s, 1H), 8.00 (m, 1H), 7.91 (m, 1H), 7.66 (m, 1H), 7.54 (d, 1H, *J*=8.4Hz), 7.43 (m, 1H), 7.37 (m, 1H), 7.25 (m, 1H), 4.65 (s, 2H), 2.94 (s, 3H)

Example 96) Synthesis of (8-chloro-6-(4-chlorophenoxy)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophen-2-yl)methanone

(a) Synthesis of 6-bromo-8-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine

2-Amino-4-bromo-6-chlorophenol (100.0 mg, 0.45 mmol), dibromoethane (0.1 mL, 1.12 mmol) and K_2CO_3(186.0 mg, 1.35 mmol) were dissolved in anhydrous DMF (1.5 mL). The reaction mixture was stirred at 125°C for 15 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 3 : 1) to obtain 6-bromo-8-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (70.0 mg, 63%) as a white solid.

LC/MS ESI (+): 248 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 6.84 (s, 1H), 6.61 (s, 1H), 4.31-4.33 (m, 2H), 3.42-3.45 (m, 2H), 3.97 (brs, 1H)

(b) Synthesis of 8-chloro-6-(4-chlorophenoxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine

6-Bromo-8-chloro-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (60.0 mg, 0.24 mmol), 4-chlorophenol (62 mg, 0.48 mmol), CuI (23.0 mg, 0.12 mmol), *N,N*-dimethylglycine (24.9 mg, 0.24 mmol) and Cs_2CO_3 (236.0 mg, 0.72 mmol) were added to anhydrous 1,4-dioxane (2.4 mL). The reaction mixture was stirred at 120°C for 15 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain 8-chloro-6-(4-chlorophenoxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (42.0 mg, 42%).

LC/MS ESI (+): 296 (M+1)

(c) Synthesis of (8-chloro-6-(4-chlorophenoxy)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophen-2-yl)methanone

The synthesis procedure of Example 1-h was repeated except for using 8-chloro-6-(4-chlorophenoxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine (20.0 mg, 0.07 mmol) as a starting material to obtain (8-chloro-6-(4-chlorophenoxy)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophen-2-yl)methanone (13.0 mg, 33%) as a white solid.

LC/MS ESI (+): 576 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 8.20 (s, 1H), 8.07 (d, 1H, *J*=8.6Hz), 7.88 (s, 1H), 7.75 (d, 1H, *J*=8.7Hz), 7.02-7.09 (m, 4H), 6.79 (d, 2H, *J*=8.3Hz), 4.46-4.51 (m, 2H), 4.10-4.16 (m, 2H), 2.74 (s, 3H), 1.84 (s, 6H)

Example 97) Synthesis of *N*-(3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of (3-chloro-5-nitrophenyl)(4-chlorophenyl)methanone

3-Chloro-5-nitrobenzoic acid (2.0 g, 9.92 mmol) and DMF (0.1 mL, 0.99 mmol) was dissolved in $SOCl_2$ (3.6 mL, 49.60 mmol). The reaction mixture was stirred at 80°C for 3 hours and concentrated under reduced pressure to obtain 3-chloro-5-nitrobenzoyl chloride. The residue was dissolved in chlorobenzene (20.0 mL), $AlCl_3$ (4.0 g, 29.80 mmol) was added at 0°C, and stirred at 50°C for 5 hours. H_2O was added at 0°C, and the reaction mixture was extracted with EtOAc. The organic extract was washed with sat. $NaHCO_3$ aqueous solution and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : DCM = 4 : 1) to obtain (3-chloro-5-nitrophenyl)(4-chlorophenyl)methanone (2.8 g, 96%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.46 (m, 1H), 8.44 (m, 1H), 8.08 (m, 1H), 7.75 (d, 2H, *J*=8.5Hz), 7.54 (d, 2H, *J*=8.5Hz)

(b) Synthesis of 1-chloro-3-(1-(4-chlorophenyl)vinyl)-5-nitrobenzene

Bromo(methyl)triphenylphosphorane (5.3 g, 19.10 mmol) was dissolved in THF (25.0 mL), 1.6M solution of *n*-BuLi in *n*-Hex (12.0 mL, 19.10 mmol) was added dropwise at 0°C, and stirred for 30 minutes. The reaction mixture was slowly added to a solution of (3-chloro-5-nitrophenyl)(4-chlorophenyl)methanone (2.8 g, 9.56 mmol) in THF (8.0 mL) at 0°C. The reaction mixture was stirred at room temperature for 12 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : DCM = 4 : 1) to obtain 1-chloro-3-(1-(4-chlorophenyl)vinyl)-5-nitrobenzene (1.8 g, 65%) as a color solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.18 (m, 1H), 8.07 (m, 1H), 7.61 (m, 1H), 7.36 (d, 2H, *J*=8.4Hz), 7.22 (d, 2H, *J*=8.4Hz), 5.63 (s, 1H), 5.60 (s, 1H)

(c) Synthesis of 1-chloro-3-(2,2-dibromo-1-(4-chlorophenyl)cyclopropyl)-5-nitrobenzene

1-Chloro-3-(1-(4-chlorophenyl)vinyl)-5-nitrobenzene (1.8 g, 6.19 mmol), $CHBr_3$ (735.0 μL, 8.42 mmol) and benzyl triethylammonium chloride (254.0 mg, 1.11 mmol) were dissolved in 1,2-dichloroethane (6.2 mL), and NaOH (9.4 g, 235.0 mmol) in H_2O (9.4

mL) was added. The reaction mixture was stirred at 40°C for 16 hours, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : DCM = 4 : 1) to obtain 1-chloro-3-(2,2-dibromo-1-(4-chlorophenyl)cyclopropyl)-5-nitrobenzene (2.2 g, 75%) as a yellow oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.22 (s, 1H), 8.11 (s, 1H), 7.79 (s, 1H), 7.44 (d, 2H, *J*=8.4Hz), 7.35 (d, 2H, *J*=8.4Hz), 2.50-2.55 (m, 2H)

(d) Synthesis of 3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)aniline

The synthesis procedure of Example 1-g was repeated except for using 1-chloro-3-(2,2-dibromo-1-(4-chlorophenyl)cyclopropyl)-5-nitrobenzene (2.2 g, 4.61 mmol) as a starting material to obtain 3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)aniline (1.2 g, 95%) as a yellow oil.

LC/MS ESI (+): 278 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.24 (d, 2H, *J*=8.4Hz), 7.15 (d, 2H, *J*=8.4Hz), 6.56 (s, 1H), 6.50 (s, 1H), 6.35 (s, 1H), 3.66 (brs, 2H), 1.20-1.28 (m, 4H)

(e) Synthesis of *N*-(3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)aniline (46.7 mg, 0.17 mmol) as a starting material to obtain *N*-(3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (44.1 mg, 47%).

LC/MS ESI (+): 558 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.64 (s, 1H), 8.34 (s, 1H), 8.20 (s, 1H), 8.10 (d, 1H, *J*=8.7Hz), 7.84 (m, 1H), 7.74 (dd, 1H, *J*=8.7, 1.8Hz), 7.54 (m, 1H), 7.38 (d, 2H, *J*=8.6Hz), 7.29 (d, 2H, *J*=8.6Hz), 7.02 (m, 1H), 2.73 (s, 3H), 1.85 (s, 6H), 1.30-1.32 (m, 4H)

Example 98) Synthesis of *N*-(3-chloro-5-((2,4-difluorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of *N*-(3-chloro-5-nitrophenyl)-2,4-difluoroaniline

1-Bromo-3-chloro-5-nitrobenzene (100.0 mg, 0.42 mmol), 2,4-difluoroaniline (35.6 μL, 0.35 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (18.3 mg, 0.02 mmol), BINAP (21.9 mg, 0.04 mmol) and NaO*t*-Bu (47.5 mg, 0.49 mmol) were added to anhydrous toluene (3.5 mL). The reaction mixture was allowed to react at 110°C for 30 minutes in a microwave at 150W. The reaction mixture was cooled to room temperature, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous

Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain *N*-(3-chloro-5-nitrophenyl)-2,4-difluoroaniline (76.6 mg, 76%) as a yellow solid.

LC/MS ESI (+): 285 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.58 (s, 1H), 7.31 (m, 1H), 7.11 (s, 1H), 6.91-7.00 (m, 2H), 5.79 (s, 1H)

(b) Synthesis of *N*-(3-chloro-5-nitrophenyl)-2,4-difluoro-*N*-methylaniline

N-(3-chloro-5-nitrophenyl)-2,4-difluoroaniline (167.1 mg, 0.59 mmol) was dissolved in DMF (6.0 mL), and 60wt% NaH (35.2 mg, 0.88 mmol) and CH_3I (73.1 μL, 1.17 mmol) were added at 0°C. The reaction mixture was stirred at room temperature for 1 hour, H_2O was added, and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 9 : 1) to obtain *N*-(3-chloro-5-nitrophenyl)-2,4-difluoro-*N*-methylaniline (172.4 mg, 98%) as a yellow solid.

^{1}H-NMR (400MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.34 (s, 1H), 7.27 (m, 1H), 6.97-7.02 (m, 2H), 6.82 (s, 1H), 3.31 (s, 3H)

(c) Synthesis of 5-chloro-N^1-(2,4-difluorophenyl)-N^1-methylbenzene-1,3-diamine

The synthesis procedure of Example 1-g was repeated except for using *N*-(3-chloro-5-nitrophenyl)-2,4-difluoro-*N*-methylaniline (172.4 mg, 0.58 mmol) as a starting material to obtain 5-chloro-N^1-(2,4-difluorophenyl)-N^1-methylbenzene-1,3-diamine (148.4 mg, 96%) as a red oil.

^{1}H-*N*MR (400MHz, $CDCl_3$): δ 7.22 (m, 1H), 6.87-6.94 (m, 2H), 6.14 (s, 1H), 6.06 (s, 1H), 5.79 (s, 1H), 3.60 (brs, 2H), 3.18 (s, 3H)

(d) Synthesis of *N*-(3-chloro-5-((2,4-difluorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 1-h was repeated except for using 5-chloro-N^1-(2,4-difluorophenyl)-N^1-methylbenzene-1,3-diamine (35.6 mg, 0.13 mmol) as a starting material to obtain *N*-(3-chloro-5-((2,4-difluorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (57.2 mg, 79%) as a white solid.

LC/MS ESI (+): 549 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.45 (s, 1H), 8.31 (s, 1H), 8.19 (s, 1H), 8.08 (d, 1H, *J*=8.7Hz), 7.73 (m, 1H), 7.41-7.53 (m, 3H), 7.21 (m, 1H), 6.93 (s, 1H), 6.48 (s, 1H), 3.23 (s, 3H), 2.72 (s, 3H), 1.84 (s, 6H)

Compounds from **Example 99 and Example 100** were synthesized through the synthesis route of Example 98, data of these compounds are listed as follows.

[Table 6]

Ex.	Compound	Analysis data
99	*N*-(3-chloro-5-((4-chlorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 547 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.51 (s, 1H), 8.32 (s, 1H), 8.20 (s, 1H), 8.09 (d, 1H, *J*=8.7Hz), 7.74 (dd, 1H, *J*=8.7, 1.4Hz), 7.52 (s, 1H), 7.42 (d, 2H, *J*=8.7Hz), 7.25 (s, 1H), 7.19 (d, 2H, *J*=8.7Hz), 6.73 (s, 1H), 3.27 (s, 3H), 2.73 (s, 3H), 1.85 (s, 6H)
100	*N*-(2-chloro-6-((4-chlorophenyl)(methyl)amino)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 548 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 10.68 (s, 1H), 8.33 (s, 1H), 8.20 (d, 1H, *J*=1.6Hz), 8.09 (d, 1H, *J*=8.7Hz), 7.74 (dd, 1H, *J*=8.7, 1.9Hz), 7.55 (d, 2H, *J*=8.7Hz), 7.40 (d, 2H, *J*=8.7Hz), 7.33 (d, 1H, *J*=1.3Hz), 6.88 (d, 1H, *J*=1.3Hz), 3.36 (s, 3H), 2.73 (s, 3H), 1.84 (s, 6H)

Example 101) Synthesis of *N*-(2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 4-amino-6-chloropyridin-2-ol

2,6-Dichloropyridine-4-amine (1.0 g, 6.13 mmol) was dissolved in *tert*-BuOH (30.7 mL) and KOH (516.0 mg, 9.20 mmol) was added. The reaction mixture was stirred at 150°C for 15 hours, H_2O was added, and extracted with EtOAc. The aqueous layer was acidified with 1N HCl aqueous solution and then extracted with EtOAc. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, MeOH : EtOAc = 1 : 10) to obtain 4-amino-6-chloropyridin-2-ol (120.0 mg, 14%) as an off-white solid.

LC/MS ESI (+): 145 (M+1)

(b) Synthesis of 4-chlorocyclohex-3-en-1-yl benzoate

4-Oxocyclohexyl benzoate (1.1 g, 4.76 mmol) was dissolved in toluene (55.0 mL) and PCl_5 (1.3 g, 6.05 mmol) was added at -40°C. The reaction mixture was stirred at room temperature for 2 hours, H_2O was added, and extracted with EtOAc. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 4) to obtain 4-chlorocyclohex-3-en-1-yl benzoate (850.0 mg, 65%) as an off-white oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 8.03 (d, 2H, *J*=8.0Hz), 7.57 (t, 1H, *J*=7.6Hz), 7.44 (t, 2H, *J*=7.6Hz), 5.76 (m, 1H), 5.31 (m, 1H), 2.34-2.61 (m, 4H), 2.05-2.10 (m, 2H)

(c) Synthesis of 4-chlorocyclohex-3-en-1-ol

4-Chlorocyclohex-3-en-1-yl benzoate (400.0 mg, 1.69 mmol) was dissolved in MeOH (8.4 mL) and 0.5M solution of NaOMe in MeOH (3.8 mL, 1.86 mmol) was added at 0°C. The reaction mixture was stirred for 2 hours, $NaHSO_4$ and NaH_2PO_4 buffer solution were added, and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 1) to obtain 4-chlorocyclohex-3-en-1-ol (90.0 mg, 40%) as an off-white oil.

^{1}H-NMR (400MHz, $CDCl_3$): δ 5.69 (m, 1H), 4.01 (m, 1H), 2.41-2.45 (m, 3H), 2.14 (m, 1H), 1.82-1.92 (m, 2H)

(d) Synthesis of 2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridine-4-amine

4-Amino-6-chloropyridin-2-ol (80.0 mg, 0.55mmol) was dissolved in THF (2.0 mL), and 2-4-chlorocyclohex-3-en-1-ol (81.0 mg, 0.61mmol), 2.2M solution of DEAD in toluene (377.0 μL, 0.83 mmol) and PPh_3 (189.0 mg, 0.72 mmol) were added. The reaction mixture was stirred at room temperature for 15 hours and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, *n*-Hex : EtOAc = 1 : 2) to obtain 2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridine-4-amine (51.0 mg, 36%) as a yellow oil.

LC/MS ESI (+): 259 (M+1)

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.21 (s, 1H), 5.82 (s, 1H), 5.72 (m, 1H), 5.27 (m, 1H), 4.14 (s, 2H), 2.43-2.51 (m, 4H), 1.98-2.02 (m, 2H)

(e) Synthesis of *N*-(2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 67-b was repeated except for using 2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridine-4-amine (40.0 mg, 0.15mmol) as a starting material to obtain *N*-(2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (35.0 mg, 42%).

LC/MS ESI (+): 539 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.96 (s, 1H), 8.40 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, J=8.8Hz), 7.78 (d, 1H, J=8.8Hz), 7.46 (s, 1H), 7.24 (s, 1H), 5.81 (m, 1H), 5.21 (m, 1H), 2.75 (s, 3H), 2.43-2.68 (m, 4H), 2.01-2.03 (m, 2H)

Example 102) Synthesis of *N*-(2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[b]thiophene-2-

carboxamide

(a) Synthesis of octahydroindolizin-7-ol

Hexahydroindolizin-7(1*H*)-one (220.0 mg, 1.58 mmol) was dissolved in THF (12.5 ml) and 1.0M $LiAlH_4$ in THF (3.95 ml, 3.95 mmol) was added thereto at room temperature. The mixture was stirred at 80°C for 30 min. and water was added at 0°C. The resulting reaction mixture was filtered through Celite and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated to obtain octahydroindolizin-7-ol (220.0 mg, 99%) as a colorless liquid.

LC/MS ESI (+): 142 (M+1)

^{1}H-NMR(400MHz, DMSO-d_6): δ 4.63-4.64 (m, 1H), 2.86-2.93 (m, 2H), 1.86-1.97 (m, 3H), 1.56-1.79 (m, 5H), 1.25-1.40 (m, 2H), 0.98-1.07 (m, 1H)

(b) Synthesis of 2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-amine

Octahydroindolizin-7-ol (200.0 mg, 1.42 mmol) and 2,6-dichloropyridin-4-amine (462.0 mg, 2.83 mmol) were dissolved in sulfolane (7.0 ml) and 60wt% NaH (113.0 mg, 2.83 mmol) was added thereto at room temperature. The mixture was stirred at 160°C for 1 hour and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN: 0.1% formic acid in H_2O) to obtain 2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-amine (200.0 mg, 52%) as a colorless liquid.

LC/MS ESI (+): 268 (M+1)

^{1}H-NMR(400MHz, DMSO-d_6): δ 6.28 (s, 2H), 6.18 (d, 1H, *J*=1.6Hz), 5.74-5.76 (m, 1H), 4.72-4.80 (m, 1H), 2.89-3.01 (m, 2H), 2.12-2.16 (m, 1H), 1.86-2.06 (m, 4H), 1.62-1.83 (m, 3H), 1.47-1.56 (m, 1H), 1.27-1.37 (m, 1H), 1.15-1.27 (m, 1H)

(c) Synthesis of *N*-(2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 62-b was repeated except for using 2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-amine (50.0 mg, 0.19 mmol) as a starting material to obtain *N*-(2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (11.1 mg, 10%)

LC/MS ESI (+): 548 (M+1)

^{1}H-NMR(400MHz, DMSO-d_6): δ 10.95 (s, 1H), 8.40 (s, 1H), 8.26 (d, 1H, *J*=1.6Hz), 8.12-8.16 (m, 1H), 7.78 (dd, 1H, *J*=8.8, 1.6Hz), 7.45 (d, 1H, *J*=1.6Hz), 7.20 (d, 1H, *J*=1.2Hz), 4.88-4.94 (m, 1H), 2.94-3.08 (m, 2H), 2.75 (s, 3H), 2.22-2.26 (m, 1H), 1.95-1.96 (m, 4H), 1.79-1.90 (m, 6H), 1.60-1.76 (m, 3H), 1.23-1.42 (m, 3H)

Example 103) Synthesis of *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-

(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboximidamide 2,2,2-trifluoroacetate

(a) Synthesis of 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

5-(2-(Methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxylic acid (111.0 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (3.6 mL), and $(COCl)_2$ (50.8 mg, 0.40 mmol) and DMF (cat.) were added dropwise. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to obtain 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carbonyl chloride. The residue was dissolved in 1,4-dioxane (3.7 mL), and 2N solution of NH_3 in MeOH (1.8 mL) was added dropwise. The reaction mixture was stirred at room temperature for 40 minutes, concentrated under reduced pressure. The residue was purified by reversed-phase chromatography (C18-silica gel, CH_3CN : H_2O) to obtain 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (110.0 mg, quant).

LC/MS ESI (+): 298 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 8.26 (brs, 1H), 8.11 (d, 1H, *J*=1.7Hz), 8.08 (s, 1H), 8.04 (d, 1H, *J*=8.7Hz), 7.70 (dd, 1H, *J*=8.7, 2.0Hz), 7.66 (brs, 1H), 2.71 (s, 3H), 1.83 (s, 6H)

(b) Synthesis of ethyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carbimidate

5-(2-(Methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (85.0 mg, 0.29 mmol) was dissolved in CH_2Cl_2 (6.0 mL) and 1.0M solution of triethyloxonium tetrafluoroborate in CH_2Cl_2 (109.0 mL, 0.57 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 16 hours, and extracted with CH_2Cl_2. The organic extract was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (amine silica gel, CH_2Cl_2 : MeOH = 9 : 1) to obtain ethyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carbimidate (63.9 mg, 69%).

LC/MS ESI (+): 326 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 9.15 (s, 1H), 8.17 (s, 1H), 8.12 (d, 1H, *J*=1.5Hz), 8.03 (d, 1H, *J*=8.7Hz), 7.70 (dd, 1H, *J*=8.9, 1.8Hz), 4.27 (q, 2H, *J*=7.1Hz), 2.72 (s, 3H), 1.83 (s, 6H), 1.33 (t, 3H, *J*=7.1Hz)

(c) Synthesis of *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboximidamide 2,2,2-trifluoroacetate

Ethyl 5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carbimidate (63.9 mg, 0.20 mmol) and 3-chloro-5-(4-chlorophenoxy)aniline (59.9 mg, 0.24 mmol) were dissolved in DMF (0.4 mL) and triethylamine (19.9 mg, 0.20 mmol) was added dropwise.

The reaction mixture was stirred at 60°C for 16 hours and then at 100°C for 16 hours. The reaction mixture was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN: 0.1% formic acid in H_2O) to obtain *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboximidamide 2,2,2-trifluoroacetate (2.4 mg, 2%) as white solid.

LC/MS ESI (+): 533 (M+1), Free form

^{1}H-NMR (400MHz, DMSO-d_6): δ 11.79 (brs, 2H), 8.31 (s, 1H), 8.26 (s, 1H), 8.18 (d, 1H, *J*=7.3Hz), 7.80 (d, 1H, *J*=8.6Hz), 7.49 (d, 2H, *J*=7.7Hz), 7.26 (brs, 1H), 7.18 (d, 2H, *J*=8.4Hz), 7.14 (brs, 1H), 6.96 (brs, 1H), 2.75 (s, 3H), 1.86 (s, 6H)

Example 104) Synthesis of *N*-(2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-amine

2,6-dichloropyridin-4-amine (50.0 mg, 0.31 mmol) and octahydropyrrolo[1,2-*a*]pyrazine (77.6 mg, 0.61 mmol) were dissolved in sulfolane (0.5 mL), followed by heating at 150°C for overnight. Octahydropyrrolo[1,2-*a*]pyrazine (100.0 mg, 0.80 mmol) was more added. The reaction mixture was stirred at 150°C for 1 day additionally and then cooled to room temperature and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2 : MeOH = 7 : 1) to obtain 2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-amine (66.0 mg, 85%) as a light-yellow amorphous.

^{1}H-NMR (400MHz, $CDCl_3$): δ 6.00 (s, 1H), 5.71 (s, 1H) 4.31 (d, 1H, *J*=11.9Hz), 4.07 (d, 1H, *J*=12.2Hz), 4.02 (s, 2H), 3.11-3.15 (m, 2H), 2.94-3.01 (m, 1H), 2.57-2.63 (m, 1H), 2.28-2.31 (m, 1H), 2.15-2.19 (m, 1H), 2.03-2.08 (m, 2H), 1.77-1.83 (m, 2H), 1.47-1.50 (m, 1H)

(b) Synthesis of *N*-(2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

The synthesis procedure of Example 62-b was repeated except for using 2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-amine (62.0 mg, 0.25 mmol) to obtain *N*-(2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide (28.4 mg, 22%).

LC/MS ESI (+): 533 (M+1)

^{1}H-NMR (400MHz, DMSO-d_6): δ 10.73 (s, 1H), 8.39 (s, 1H), 8.22 (m, 1H), 8.12

(d, 1H, *J*=8.7Hz), 7.76 (dd, 1H, *J*=8.7, 1.8Hz), 7.22 (s, 1H), 7.13 (s, 1H), 4.23 (d, 1H, *J*=11.1Hz), 4.08 (d, 1H, *J*=12.4Hz), 3.00-3.09 (m, 2H), 2.87-2.94 (m, 1H), 2.74 (s, 3H), 2.55-2.60 (m, 1H), 2.03-2.16 (m, 2H), 1.86-1.97 (m, 8H), 1.66-1.76 (m, 2H), 1.33-1.43 (m, 1H)

Compounds from **Example 105 and Example 108** were synthesized through the synthesis route of Example 104, data of these compounds are listed as follows.

[Table 7]

Ex.	Compound	Analysis data
105	*N*-(2-(4-(*tert*-butyl)piperidin-1-yl)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 548 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): 10.71 (s, 1H), 8.38 (s, 1H), 8.22 (m, 1H), 8.11 (d, 1H, *J*=8.8Hz), 7.76 (dd, 1H, *J*=8.8, 2.0Hz), 7.17 (s, 1H), 7.09 (s, 1H), 4.24 (d, 2H, *J*=12.8Hz), 2.74-2.79 (m, 5H), 1.85 (s, 6H), 1.74 (d, 2H, *J*=11.2Hz), 1.14-1.26 (m, 3H), 0.85 (s, 9H)
106	*N*-(2-chloro-6-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 547 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): 10.74 (s, 1H), 8.39 (s, 1H), 8.22 (s, 1H), 8.12 (d, 1H, *J*=8.8Hz), 7.76 (dd, 1H, *J*=8.8, 1.6Hz), 7.16 (d, 1H, *J*=8.8Hz), 4.04 (d, 1H, *J*=12.4Hz), 3.92 (d, 1H, *J*=11.6Hz), 2.88-2.94 (m, 1H), 2.81 (dd, 2H, *J*=5.6, 0.8Hz), 2.74 (s, 3H), 2.54-2.57 (m, 1H), 2.12-2.13 (m, 1H), 1.85-1.89 (m, 8H), 1.71-1.77 (m, 1H), 1.59-1.62 (m, 2H), 1.45-1.55 (m, 1H), 1.25-1.30 (m, 3H)
107	*N*-(2-chloro-6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 561 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): 10.70 (s, 1H), 8.39 (s, 1H), 8.22 (m, 1H), 8.12 (d, 1H, *J*=8.7Hz), 7.76 (dd, 1H, *J*=8.7, 1.9Hz), 7.02 (m, 1H), 6.90 (m, 1H), 3.36-3.41 (m, 4H), 3.26-3.31 (m, 2H), 2.74 (s, 3H), 2.60-2.67 (m, 1H), 2.39-2.45 (m, 3H), 1.90-2.02 (m, 2H), 1.86 (s, 6H), 1.74-1.79 (m, 2H), 1.02 (t, 3H, *J*=7.2Hz)

108	*N*-(2-chloro-6-(octahydroisoquinolin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 546 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): 10.70 (s, 1H), 8.40 (s, 1H), 8.23 (m, 1H), 8.13 (d, 1H, *J*=8.7Hz), 7.78 (dd, 1H, *J*=8.7, 1.9Hz), 7.16 (s, 1H), 7.13 (s, 1H), 4.24 (d, 1H, *J*=12.4Hz), 4.04 (d, 1H, *J*=12.4Hz), 2.81-2.87 (m, 1H), 2.75 (s, 3H), 1.87 (s, 6H), 1.70-1.75 (m, 2H), 1.62-1.66 (m, 2H), 1.22-1.31 (m, 3H), 1.10-1.21 (m, 3H), 0.97-1.04 (m, 3H)

Example 109) Synthesis of *N*-(2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide

(a) Synthesis of 4-bromo-2,6-dichloropyridine 1-oxide

4-Bromo-2,6-dichloropyridine (5.0 g, 22.04 mmol) was dissolved in TFA (23.8 ml, 309.00 mmol) and H_2O_2 (4.8 ml, 55.10 mmol) was added at room temperature. The mixture was refluxed with stirring at 100°C for 14 hours, followed by cooling to room temperature and filtered. Filtrate was extracted with EtOAc. The organic extract was washed with 1N NaOH, dried with anhydrous Na_2SO_4, filtered and evaporated to obtain 4-bromo-2,6-dichloropyridine 1-oxide (2.7 g, 49%) as a yellow solid.

LC/MS ESI (+): 244 (M+1)

^{1}H-NMR(400MHz, $CDCl_3$): δ 7.61 (s, 2H)

(b) Synthesis of 4-bromo-2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridine 1-oxide

4-Bromo-2,6-dichloropyridine 1-oxide (112.0 mg, 0.46 mmol) was dissolved in DMF (4.0 ml) and 5-methylthiazol-2-ol (53.0 mg, 0.46 mmol), Cs_2CO_3 (300.0 mg, 0.92 mmol) were added at room temperature. The mixture was stirred at 40°C for 2 hours. The reaction mixture was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN: 0.1% formic acid in H_2O) to obtain 4-bromo-2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridine 1-oxide (50.0 mg, 33%) as a yellow solid.

LC/MS ESI (+): 321 (M+1)

^{1}H-NMR(400MHz, $CDCl_3$): δ 7.72 (d, 1H, *J*=2.8Hz), 7.67 (d, 1H, *J*=2.8Hz), 6.77-6.78 (m, 1H), 2.02 (d, 3H, *J*=1.6Hz)

(c) Synthesis of 2-((4-bromo-6-chloropyridin-2-yl)oxy)-5-methylthiazole

4-Bromo-2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridine 1-oxide (40.0 mg, 0.12 mmol) was dissolved in $CHCl_3$ (1.2 ml) and PCl_3 (33.0 μl, 0.37 mmol) was added thereto at 0 °C. The mixture was stirred at room temperature for 6 hours and extracted with EtOAc.

The organic extract was washed with 1N NaOH and brine, dried over anhydrous Na_2SO_4, filtered and evaporated to obtain 2-((4-bromo-6-chloropyridin-2-yl)oxy)-5-methylthiazole (35.0 mg, 92%) as an ivory solid.

LC/MS ESI (+): 305 (M+1)

^{1}H-NMR(400MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.40 (s, 1H), 7.37 (s, 1H), 2.21 (s, 3H)

(d) Synthesis of 2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-amine

2-((4-Bromo-6-chloropyridin-2-yl)oxy)-5-methylthiazole (30.0 mg, 0.10 mmol) was dissolved in DMSO (1.0 ml) and Cu_2O (16.9 mg, 0.12 mmol), sodium azide (12.8 mg, 0.20 mmol) were added at room temperature. The mixture was stirred at 100 °C for 1 hour and extracted with EtOAc. The organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under a reduced pressure. The residue was purified by reversed-phase column chromatography (C18-silica gel, 0.1% formic acid in CH_3CN: 0.1% formic acid in H_2O) to obtain 2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-amine (4.0 mg, 16%) as an off-white solid.

LC/MS ESI (+): 242 (M+1)

^{1}H-NMR(400MHz, $CDCl_3$): δ 7.48 (d, 1H, *J*=1.6Hz), 7.38 (d, 1H, *J*=1.2Hz), 6.42 (d, 1H, *J*=1.6Hz), 6.44 (brs, 2H), 2.18 (d, 3H, *J*=1.2Hz)

(e) Synthesis of N-(2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[b]thiophene-2-carboxamide

The synthesis procedure of Example 62-b was repeated except for using 2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-amine (4.0 mg, 0.02 mmol) to obtain N-(2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[b]thiophene-2-carboxamide (1.1 mg, 13%) as a white solid.

LC/MS ESI (+): 522 (M+1)

^{1}H-NMR(400MHz, DMSO-d_6): δ 11.33 (brs, 1H), 8.49 (s, 2H), 8.24 (s, 1H), 8.12 (d, 1H, *J*=8.8Hz), 8.00 (d, 1H, *J*=1.2Hz), 7.77 (dd, 1H, *J*=8.8, 1.6Hz), 7.48 (d, 1H, *J*=1.2Hz), 2.74 (s, 3H), 2.22 (d, 3H, *J*=0.8Hz), 1.86 (s, 6H)

Compounds from **Example 110 and Example 121** were synthesized through the synthesis route of Example 109, data of these compounds are listed as follows.

[Table 8]

Ex.	Compound	Analysis data
110	*N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-5-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 505 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.18 (brs, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, *J*=8.7Hz), 7.78 (dd, 1H, *J*=8.7, 1.9Hz), 7.72 (d, 1H, *J*=1.4Hz),

		7.49 (d, 1H, *J*=1.4Hz), 7.45 (d, 1H, *J*=2.0Hz), 6.09 (d, 1H, *J*=2.0Hz), 3.65 (s, 3H), 2.74 (s, 3H), 1.86 (s, 6H)
111	*N*-(2-chloro-6-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 533 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.05 (brs, 1H), 8.40 (s, 1H), 8.25 (s, 1H), 8.13 (d, 1H, *J*=8.6Hz), 7.78 (d, 1H, *J*=8.6Hz), 7.67 (s, 1H), 7.22 (s, 1H), 3.69 (s, 3H), 2.74 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.86 (s, 6H)
112	*N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 505 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.08 (brs, 1H), 8.41 (s, 1H), 8.25 (d, 1H, *J*=1.6Hz), 8.13 (d, 1H, *J*=8.8Hz), 7.89 (s, 1H), 7.78 (dd, 1H, *J*=8.8, 2.0Hz), 7.66 (d, 1H, *J*=1.2Hz), 7.49 (s, 1H), 7.33 (d, 1H, *J*=0.8Hz) 3.86 (s, 3H), 2.75 (s, 3H), 1.86 (s, 6H)
113	*N*-(2-chloro-6-((3,5-dimethylisoxazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 520 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.15 (brs, 1H), 8.42 (s, 1H), 8.27 (s, 1H), 8.15 (d, 1H, *J*=8.7Hz), 7.80 (d, 1H, *J*=8.7Hz), 7.68 (s, 1H), 7.47 (s, 1H), 2.75 (s, 3H), 2.32 (s, 3H), 2.10 (s, 3H), 1.87 (s, 6H)
114	*N*-(2-chloro-6-((5-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 521 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.10 (brs, 1H), 8.42 (s, 1H), 8.26 (s, 1H), 8.13 (d, 1H, *J*=8.7Hz), 7.78 (d, 1H, *J*=8.7Hz), 7.69 (s, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 6.78 (s, 1H), 2.75 (s, 3H), 2.46 (s, 3H), 1.86 (s, 6H)
115	*N*-(2-chloro-6-((2-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 521 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.08 (brs, 1H), 8.41 (s, 1H), 8.26 (s, 1H), 8.14 (d, 1H, *J*=8.7Hz), 7.79 (d, 1H, *J*=8.7Hz), 7.65 (s, 1H), 7.40 (d, 1H, *J*=5.4Hz), 7.27 (s, 1H), 6.93 (d, 1H, *J*=5.4Hz), 2.75 (s, 3H), 2.24 (s, 3H), 1.86 (s, 6H)
116	*N*-(2-chloro-6-((4,5-dimethylisoxazol-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-	LC/MS ESI (+): 520 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.21 (brs, 1H), 8.43 (s, 1H), 8.27 (s,

	2-yl)benzo[*b*]thiophene-2-carboxamide	1H), 8.14 (d, 1H, *J*=8.7Hz), 7.80 (d, 1H, *J*=8.7Hz), 7.75 (s, 1H), 7.59 (s, 1H), 2.75 (s, 3H), 2.39 (s, 3H), 1.87 (s, 6H), 1.76 (s, 3H)
117	*N*-(2-chloro-6-((5-(trifluoromethyl)thiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 575 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.14 (brs, 1H), 8.41 (s, 1H), 8.27 (s, 1H), 8.14 (d, 1H, *J*=8.7Hz), 7.81 (m, 2H), 7.77 (s, 1H), 7.70 (s, 1H), 7.40 (s, 1H), 2.75 (s, 3H), 1.87 (s, 6H)
118	methyl 3-((6-chloro-4-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)pyridin-2-yl)oxy)isoxazole-5-carboxylate	LC/MS ESI (+): 550 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.20 (brs, 1H), 8.36 (s, 1H), 8.20 (s, 1H), 8.07 (d, 1H, *J*=9.2Hz), 7.71 (brs, 2H), 7.55 (s, 1H), 7.42 (s, 1H), 3.85 (s, 3H), 2.68 (s, 3H), 1.79 (s, 6H)
119	*N*-(2-chloro-6-((4-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 522 (M+1) ^{1}H-NMR(400MHz, DMSO-d_6): δ 11.63 (brs, 1H), 11.08 (brs, 1H), 8.43 (s, 1H), 8.27 (d, 1H, *J*=1.6Hz), 8.14 (d, 1H, *J*=8.8Hz), 7.85 (s, 1H), 7.77-7.80 (m, 2H), 2.76 (s, 3H), 2.44 (s, 3H), 1.87 (s, 6H)
120	*N*-(2-chloro-6-((5-methylthiophen-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 304 (M+1), 521 (M+3) ^{1}H-NMR (400MHz, $CDCl_3$): δ 11.16 (s, 1H), 8.41 (s, 1H), 8.25 (s, 1H), 8.12 (d, 1H, *J*=9.7Hz), 7.77 (d, 1H, *J*=8.2Hz), 7.71 (s, 1H), 7.42 (s, 1H), 6.64 (s, 2H), 2.74 (s, 3H), 2.41 (s, 3H), 1.85 (s, 6H)
121	*N*-(2-chloro-6-((2-chlorothiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide	LC/MS ESI (+): 540 (M+1) ^{1}H-NMR (400MHz, DMSO-d_6): δ 11.20 (brs, 1H), 8.42 (s, 1H), 8.27 (s, 1H), 8.13 (d, 1H, *J*=8.4Hz), 7.80 (d, 1H, *J*=9.6Hz), 7.69 (s, 1H), 7.59 (d, 1H, *J*=5.2Hz), 7.39 (s, 1H), 7.09 (d, 1H, *J*=6.0Hz), 2.74 (s, 3H), 1.86 (s, 6H)

Experimental Examples

Experiments were performed as shown below for the compounds prepared in Examples above.

Experimental Example 1) Experiment on the inhibition of STAT3 and STAT1

activities *via* reporter gene assay

1-1) Experiment on the inhibition of STAT3 activity

A human prostate cancer cell line (LNCaP stable cell line; plasmid pSTAT3-TA-luc), which contains a stably operating STAT3 promoter, was cultured in RPMI1640 medium (Cat No. 11875, Life Technologies) containing 10% fetal bovine serum (FBS) (Cat No. SH30396, Thermo Scientific) and 150 μg/mL G-418 solution (Cat No. 04 727 894 001, Roche). The reporter gene assay using LNCaP stable cell line was performed in RPMI1640 medium containing 3% DCC-FBS without G-418 solution. LNCaP stable cells were plated in two (2) white 96-well plates with 30,000 cells/50 μL in each well. The cells were cultured at 37°C, under 5% CO_2 for 24 hours, and then treated with the compounds listed in Examples which were diluted in various concentrations. Subsequently, IL-6 was added to each well with a final concentration of 10 ng/mL. Upon completion of the treatment with the compounds and IL-6, the cells were cultured at 37°C, under 5% CO_2 for 24 hours. The plates were observed under microscope and drug precipitation and particular findings were investigated and recorded.

The luciferase assay and the cell viability assay were performed respectively with one of the two plates. For the luciferase assay, the liquid media in the 96-well plate was removed, and then, 20 μL of passive cell lysis buffer was added to each well. After shaking the plate for 30 minutes, luciferase activities of each well were measured in a PHERAstar™ microplate reader (BMG LABTECH) using a luciferase assay system (Cat No. E1501, Promega). For the cell viability assay, the 96-well plate was placed at room temperature for 30 minutes, added with 20 μL/well of CellTiter-Glo solution (Cat No. G7573, Promega), and shaken for 10 minutes in order to measure cytotoxicity caused by the compounds listed in Examples with a PHERAstar™ microplate reader (BMG LABTECH). Wells without 0.1% DMSO and stimulation were used as a negative control and wells with 0.1% DMSO and stimulation were used as a positive control.

1-2) Experiment on the inhibition of STAT1 activity

A human osteosarcoma cell line (U2OS stable cell line; pGL4-STAT1-TA-luc), which contains a stably operating STAT1 promoter, was cultured in McCoy 5'A medium (Cat No. 16600, Life Technologies) containing 10% FBS (Cat No. SH30396, Thermo Scientific) and 1000 μg /mL G418 solution (Cat No. 04 727 894 001, Roche). The reporter gene assay using U2OS stable cell line was performed in McCoy 5'A medium containing 10% FBS without G-418 solution. U2OS stable cells were plated in two (2) white 96-well plates with 25,000 cells/50 μL in each well. The cells were cultured at 37°C, under 5% CO_2 for 24 hours, and then treated with the compounds listed in Examples which were diluted in various concentrations. Subsequently, IFN-γ was added to each well with a final concentration of 50 ng/mL. Upon completion of the treatment with the compounds and IFN-γ, the cells were cultured at 37°C, under 5% CO_2 for 8 hours. The plates were observed under microscope and drug precipitation and particular findings were investigated and recorded.

The luciferase assay and the cell viability assay were performed respectively with one of two plates. For the luciferase assay, the liquid media in the 96-well plate was removed, and then, 20 μL of passive cell lysis buffer was added to each well. After shaking the plate for 30 minutes, luciferase activities of each well were measured in a PHERAstar™ microplate reader (BMG LABTECH) using a luciferase assay system (Cat No. E1501, Promega). For the cell viability assay, the 96-well plate was placed at room temperature for 30 minutes, added with 20 μL/well of CellTiter-Glo solution (Cat No. G7573, Promega), and shaken for 10 minutes in order to measure cytotoxicity caused by the compounds listed in Examples with a PHERAstar™ microplate reader (BMG LABTECH). Wells without 0.1% DMSO and stimulation were used as a negative control and wells with 0.1% DMSO and stimulation were used as a positive control.

The results of evaluation on the inhibitory effect of the compounds listed in the Examples on the dimerization of STAT3 and STAT1 obtained *via* the STAT3 and STAT1 reporter gene assays are shown in Table 9 below.

[Table 9]

Ex.	IC_{50} (μM) pSTAT3	IC_{50} (μM) pSTAT1	Ex.	IC_{50} (μM) pSTAT3	IC_{50} (μM) pSTAT1
1	0.0076	>50	**2**	0.008	>50
3	0.0098	>50	**4**	0.0091	>50
5	0.028	>50	**6**	0.019	>50
7	0.0088	>50	**8**	0.061	>50
9	0.00065	>50	**10**	0.018	>50
11	0.0021	>50	**12**	0.0020	>50
13	0.01	>50	**14**	0.0083	>50
15	0.0057	>50	**16**	0.0057	>50
17	0.045	>50	**18**	0.031	>50
19	0.029	>50	**20**	0.067	>50
21	0.11	>50	**22**	0.015	>50
23	0.084	>50	**24**	0.90	>50
25	0.034	>50	**26**	0.065	>50
27	0.075	>50	**28**	0.0085	>50
29	0.0041	>50	**30**	0.0013	>50
31	0.0025	>50	**32**	0.010	>50
33	0.054	>50	**34**	8.7	>50
35	0.1	>50	**36**	0.064	42.1

37	0.015	>50	**38**	0.018	>50
39	0.0089	>50	**40**	0.21	>50
41	0.16	>50	**42**	1.25	>50
43	0.023	>50	**44**	0.019	>50
45	0.078	>50	**46**	0.054	>50
47	0.022	>50	**48**	0.014	>50
49	0.019	>50	**50**	0.078	>50
51	0.022	>50	**52**	0.025	>50
53	0.033	>50	**54**	0.014	>50
55	0.0022	>50	**56**	3.3	>50
57	0.027	>50	**58**	0.86	>50
59	0.31	>50	**60**	0.12	>50
61	0.08	>50	**62**	0.020	>50
63	0.034	>50	**64**	0.021	>50
65	0.079	>50	**66**	0.18	>50
67	0.0084	>50	**68**	0.011	>50
69	0.010	>50	**70**	0.024	>50
71	0.011	>50	**72**	0.01	>50
73	0.13	>50	**74**	0.12	>50
75	0.24	>50	**76**	0.39	3.1
77	0.10	>50	**78**	0.050	>50
79	0.041	>50	**80**	0.04	>50
81	0.0050	>50	**82**	0.0058	>50
83	0.0082	>50	**84**	0.0065	>50
85	0.11	>50	**86**	0.089	>50
87	0.0097	>50	**88**	>10	>50
89	0.14	>50	**90**	0.011	>50
91	0.0051	>50	**92**	5.5	9.6
93	0.072	>50	**94**	5.2	13.3
95	0.028	35.7	**96**	0.19	>50
97	0.025	>50	**98**	0.031	>50
99	0.11	>50	**100**	0.07	>50
101	0.0093	>50	**102**	2.1	14.5
103	0.18	>50	**104**	1.4	8.7
105	0.049	>50	**106**	0.43	8.5
107	>10	33.5	**108**	0.085	>50
109	0.46	>50	**110**	0.53	44.8
111	1.3	>50	**112**	0.32	18.9

113	0.18	>50	**114**	0.063	>50
115	0.019	>50	**116**	0.20	>50
117	0.028	>50	**118**	6.0	8.6
119	2.8	12.8	**120**	0.078	39.6
121	0.027	>50			

As shown in Table 9, the compounds according to the present invention exhibited excellent inhibitory effects against the activity of STAT3 protein but showed almost no inhibitory effect against the activity of STAT1 protein.

Experimental Example 2) Cell growth inhibition assay

The inhibitory effects of the compounds of the present invention against the growth of cancer cells were evaluated as shown below. The cancer cell lines including prostate cancer cell lines (LNCaP, DU-145), stomach cancer cell line (NCI-N87), and breast cancer cell lines (MDA-MB-468) were cultured under the protocol provided by each supplier. A medium supplemented with 10 ng/mL of IL-6 was used for LNCaP, a prostate cancer cell line, when treated with a drug. Each type of cells to be used in experiments was sub-cultured in a 96-well plate by counting the exact number of cells using Tali™ Image-based Cytometer (Life Technologies). In a 96-well plate, DU-145 was employed with 3,000 cells/well; NCI-N87 was employed with 5,000 cells/well; and LNCaP and MDA-MB-468 were employed with 10,000 cells/well. The cells were treated with the compounds listed in Examples which were diluted in various concentrations. Upon completion of the compounds treatment, LNCaP, DU-145, NCI-N87 cells were cultured at 37°C under 5% CO_2 for 96 hours, and MDA-MB-468 cells were cultured at 37°C in air for 96 hours. Subsequently, the cells were observed under microscope and drug precipitation and particular findings were investigated and recorded. And then, the 96-well plate was placed at room temperature for 30 minutes, added with 20 µL/well of CellTiter-Glo solution (Cat No. G7573, Promega) and shaken for 10 minutes, followed by being subjected to the measurement using PHERAstar™ microplate reader (BMG LABTECH) according to the supplier's general luminometer protocol. Wells where only culture liquid added without cell plating were used as a negative control, whereas wells where culture liquid containing 0.1% DMSO instead of the compounds listed in Examples were used as a positive control.

The results of the inhibitory effects of the compounds prepared in Examples against the growth of cancer cells are shown in Tables 10 to 13 below.

[Table 10]

Ex.	IC_{50} (μM) LNCap	Ex.	IC_{50} (μM) LNCap	Ex.	IC_{50} (μM) LNCap	Ex.	IC_{50} (μM) LNCap
16	0.0022	17	0.080	18	0.056	19	0.043
21	0.040	22	0.024	23	0.80	24	>1.1
25	0.072	27	0.029	33	0.030	34	>1.1
37	0.01	38	0.0083	41	0.12	42	>1.1
43	0.032	44	0.039	45	0.53	46	0.11
47	0.02	48	0.01	49	0.019	51	0.031
52	0.022	53	0.037	54	0.029	56	>1.1
58	0.24	63	0.046	64	0.013	66	0.26
67	0.047	88	>1.1	89	0.24	92	>1.1
93	0.26	94	>1.1'	95	0.023	97	0.028
98	0.031	99	0.14	100	0.14		

[Table 11]

Ex.	IC_{50} (μM) DU-145	Ex.	IC_{50} (μM) DU-145	Ex.	IC_{50} (μM) DU-145	Ex.	IC_{50} (μM) DU-145
16	0.0018	17	0.039	18	0.023	19	0.022
21	0.017	22	0.014	23	0.04	24	>1.1
25	0.066	27	0.024	33	0.023	34	>1.1
37	0.0071	38	0.0053	41	0.063	42	>1.1
43	0.011	44	0.019	45	0.037	46	0.07
47	0.016	48	0.008	49	0.013	51	0.0082
52	0.015	53	0.02	54	0.0059	56	>1.1
58	0.11	63	0.032	64	0.0057	66	0.17
67	0.0053	88	>1.1	89	0.11	92	>1.1
93	0.1	94	>1.1	95	0.013	97	0.016
98	0.0066	99	0.046	100	0.026		

[Table 12]

Ex.	IC_{50} (μM) NCI-N87	Ex.	IC_{50} (μM) NCI-N87	Ex.	IC_{50} (μM) NCI-N87	Ex.	IC_{50} (μM) NCI-N87
9	0.02	10	0.01	11	0.011	12	0.025
13	0.028	14	0.010	15	0.0093	31	0.24
32	0.076	36	0.25	39	0.031	57	0.2
62	0.034	64	0.034	67	0.021	68	0.03
69	0.015	70	0.057	71	0.020	72	0.021
73	0.45	74	0.61	77	0.052	78	0.2

79	0.043	**80**	0.069	**81**	0.033	**82**	0.035
83	0.020	**84**	0.020	**86**	0.15	**96**	1.5
101	0.068	**103**	1.3	**104**	1.7	**105**	0.087
106	1.8	**107**	5.5	**108**	0.13	**109**	1.7
110	1.2	**111**	2.4	**112**	1	**113**	0.27
114	0.13	**115**	0.14	**116**	0.91	**117**	0.037
119	7.8	**120**	0.12	**121**	0.15		

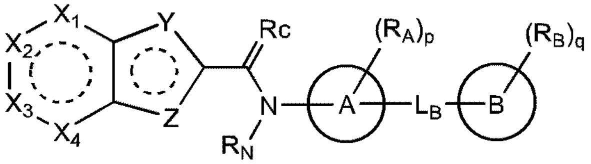
[Table 13]

Ex.	**IC_{50} (μM) MDA-MB-468**	**Ex.**	**IC_{50} (μM) MDA-MB-468**	**Ex.**	**IC_{50} (μM) MDA-MB-468**	**Ex.**	**IC_{50} (μM) MDA-MB-468**
64	0.0065	71	0.0056	**72**	0.0040	**79**	0.0074
80	0.0084	**81**	0.0038	**82**	0.0041	**83**	0.0052
84	0.0026	**86**	0.024	**109**	0.068	**115**	0.021
116	0.062	**117**	0.0053	**119**	>0.1	**120**	0.026
121	0.027						

As shown in Tables 10 to 13, the compounds according to the present invention exhibited excellent inhibitory effects against the growth of various kinds of cancer cells.

WHAT IS CLAIMED IS:

1. A compound of formula (I), a pharmaceutically acceptable salt or a stereoisomer thereof:

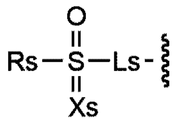


(I)

wherein

one of X_1, X_2, X_3 and X_4 is -C(-Rx)=, and the others are each independently -C(-Rx')= or -N=;

one of Y and Z is -S- or -NH-, and the other is -CH= or -N=;

Rx is  ;

Xs is =O or =NH;

Ls is -C(-Rs')(-Rs'')-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl or 5- to 10-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

Rs' and Rs'' are each independently hydrogen, halogen, C_{1-6}alkyl, carbamoyl-C_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl or diC_{1-6}alkylamino-C_{1-6}alkyl, or Rs' and Rs'' are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen, halogen, nitro, amino, C_{1-6}alkoxy, haloC_{1-6}alkoxy, or C_{1-6}alkylsulfonyl;

A and B are each independently a monocyclic- or bicyclic-saturated or unsaturated C_{3-10}carbocycle or 5- to 12-membered heterocycle;

Rc is =O, =NH, =N(-C_{1-6}alkyl), or =N(-OH);

R_N is hydrogen or C_{1-6}alkyl, or R_N is linked to R_A to form a chain;

L_B is -[C(-R_L)(-R_L')]$_m$-, -[C(-R_L)(-R_L')]$_n$-O-, -O-, -NH-, -N(C_{1-6}alkyl)-, -S(=O)$_2$-, -C(=O)-, or -C(=CH_2)-, wherein m is an integer of 0 to 3, n is an integer of 1 to 3, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form a chain;

R_A is hydrogen, halogen, cyano, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkylcarbonyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{1-6}alkylamino, diC_{1-6}alkylamino, C_{1-6}alkylthio, C_{1-6}alkylaminocarbonyl, diC_{1-6}alkylaminocarbonyl, C_{2-8}alkynyl, C_{1-6}alkoxycarbonylamino-C_{1-6}alkoxy, aminoC_{1-6}alkoxy or 3- to 6-membered heterocyclyl, or R_A is linked to R_N to form a chain;

R_B is hydrogen, halogen, hydroxy, cyano, nitro, amino, oxo, aminosulfonyl, sulfonylamido, C_{1-}

Date Reçue/Date Received 2023-04-14

$_6$alkylamino, C_{1-6}alkyl, haloC_{1-6}alkyl, cyanoC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, cyanoC_{1-6}alkoxy, C_{3-8}cyclcoalkyloxy, C_{2-8}alkenyl, C_{2-8}alkenyloxy, C_{2-8}alkynyl, C_{2-8}alkynyloxy, C_{1-6}alkylamino-C_{1-6}alkoxy, diC_{1-6}alkylamino-C_{1-6}alkoxy, C_{1-6}alkoxycarbonyl, carbamoyl, carbamoyl-C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylsulfinyl, C_{1-6}alkylsulfonyl, 5- to 10-membered heterocyclyl, 5- to 10-membered heterocyclyl-C_{1-6}alkyl, 5- to 10-membered heterocyclyl-C_{1-6}alkoxy, or 5- to 10-membered heterocyclyl-oxy;

p is an integer of 0 to 4, and, when p is 2 or higher, R_A moieties are the same as or different from each other;

q is an integer of 0 to 4, and, when q is 2 or higher, R_B moieties are the same as or different from each other; and

each of said chains is independently a saturated or unsaturated C_{2-10} hydrocarbon chain not containing or containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy; and

each of said heterocycle and heterocyclyl moieties independently contains at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$-.

2. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 1, wherein

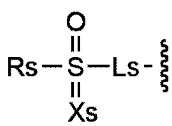
one of X_2 and X_3 is -C(-Rx)=, and the other is -C(-Rx')= or -N=;

X_1 and X_4 are each independently -C(-Rx')= or -N=;

one of Y and Z is -S- or -NH-, and the other is -CH=; and

Rx and Rx' are the same as defined in claim 1.

3. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 2, wherein

Rx is 

;

Xs is =O or =NH;

Ls is -C(-Rs')(-Rs")-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl or 5- to 6-membered heterocyclyl, or Rs is linked to Rs' to form a chain;

Rs' and Rs" are each independently hydrogen, halogen or C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, or Rs' is linked to Rs to form a chain;

Rx' is each independently hydrogen or halogen; and

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each of said chains is independently a saturated or unsaturated C_{2-7} hydrocarbon chain not containing or containing at least one heteroatom selected from the group consisting of O, N and S.

4. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 3, wherein

A is benzene or a 5- to 10-membered heteroaryl containing 1 to 3 nitrogen atoms;

B is a monocyclic- or bicyclic-saturated or unsaturated C_{6-10}carbocycle or 5- to 10-membered heterocycle;

L_B is -[C(-R_L)(-R_L')]$_m$-, -O-, -NH-, or -N(C_{1-6}alkyl)-, wherein m is 0 or 1, R_L and R_L' are each independently hydrogen, hydroxy, halogen or C_{1-6}alkyl, or R_L and R_L' are linked together to form C_{2-5}alkylene;

R_A is halogen, C_{1-6}alkoxycarbonylamino-C_{1-6}alkoxy, aminoC_{1-6}alkoxy, or 3- to 6-membered heterocyclyl;

R_B is halogen, C_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkyloxy, C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, C_{1-6}alkoxycarbonyl, C_{3-10}carbocyclyl-oxy, or 3- to 10-membered heterocyclyl-C_{1-3}alkoxy; and

each of said heteroaryl, heterocycle and heterocyclyl moieties independently contains 1 to 3 heteroatoms selected from the group consisting of O, N and S.

5. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 1, wherein

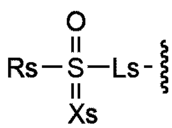
X_1 and X_4 are -CH=;

X_2 is -C(-Rx)=;

X_3 is -N= or -C(-Rx')-;

Y is -C=;

Z is -S-;

Rx is 

;

Ls is -C(-CH_3)(-CH_3)-;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylcarbonylC_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl, or a 5- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of O, N and S;

Rx' is hydrogen, halogen, nitro, amino, C_{1-6}alkoxy, haloC_{1-6}alkoxy, or C_{1-6}alkylsulfonyl;

Rc is =O; and

R_N is hydrogen.

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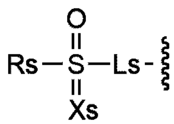
6. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 1, wherein

X_1, X_3 and X_4 are -CH=;

X_2 is -C(-Rx)=;

Y is -C=;

Z is -S-;

Rx is  ;

Ls is -C(-Rs')(-Rs")-;

Xs is =O or =NH;

Rs is C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy-C_{1-6}alkyl, C_{1-6}alkylcarbonyl-C_{1-6}alkyl, C_{2-7}alkenyl, amino, aminoC_{1-6}alkyl, or a 5- to 10-membered heterocyclyl containing 1 to 3 heteroatoms selected from the group consisting of O, N and S;

Rs' and Rs" are each independently hydrogen, halogen, C_{1-6}alkyl, carbamoylC_{1-6}alkyl, C_{1-6}alkylamino-C_{1-6}alkyl or diC_{1-6}alkylamino-C_{1-6}alkyl, or Rs' and Rs" are linked together to form a chain, wherein the chain is a saturated or unsaturated C_{2-10} hydrocarbon chain not containing or containing at least one heterogroup selected from the group consisting of -O-, -NH-, -N=, -S-, -S(=O)- and -S(=O)$_2$- in the chain, and unsubstituted or substituted with at least one selected from the group consisting of halogen, C_{1-6}alkyl and C_{1-6}alkoxy;

Rc is =O; and

R_N is hydrogen.

7. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 1, wherein

X_1, X_3 and X_4 are -CH=;

X_2 is -C(-Rx)=;

Y is -C=;

Z is -S-;

Rx is the same as defined in claim 1;

Rc is =O; and

R_N is hydrogen.

8. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim

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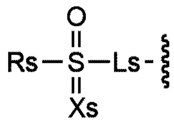
1, wherein

X_1, X_2 and X_4 are -CH=;

X_3 is -C(-Rx)=;

Y is -C=;

Z is -S- or -NH-;

Rx is  ;

Xs is =O;

Ls is -C(-CH_3)(-CH_3)-;

Rs is methyl;

Rc is =O; and

R_N is hydrogen.

9. The compound, pharmaceutically acceptable salt or stereoisomer thereof according to claim 1, wherein the compound is selected from the group consisting of:

1) *N*-(3-chloro-5-(2-(3-ethoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

2) *N*-(3-chloro-5-(2-(3-propoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

3) *N*-(3-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

4) *N*-(3-bromo-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

5) *N*-(3-chloro-5-(2-(3-(1,1,2,2-tetrafluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

6) *N*-(3-methoxy-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

7) *N*-(3-chloro-5-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

8) *N*-(3-chloro-5-(2-(3-(2-morpholinoethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

9) *N*-(3-bromo-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

10) *N*-(3-(2-(3-(but-2-yn-1-yloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-

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5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

11) *N*-(3-chloro-5-(2-(3-isobutoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

12) *N*-(3-chloro-5-(2-(3-(2,2,2-trifluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

13) *N*-(3-chloro-5-(2-(3-(2,2-difluoroethoxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

14) *N*-(3-(2-(3-(allyloxy)-5-(trifluoromethoxy)phenyl)propan-2-yl)-5-chlorophenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

15) *N*-(3-chloro-5-(2-(3-cyclopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

16) *N*-(3-chloro-5-(2-(3-isopropoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

17) *N*-(3-chloro-5-(2-(4-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

18) *N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

19) *N*-(3-chloro-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

20) *N*-(3-bromo-5-(2-(4-fluorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

21) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

22) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

23) 6-chloro-*N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

24) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

25) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(fluoro(methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

26) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

27) *N*-(3-chloro-5-(2-(5-chlorothiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

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28) *N*-(3-chloro-5-(2-(5-isopropylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

29) *N*-(3-chloro-5-(2-(5-methoxythiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

30) *N*-(3-chloro-5-(2-(2-methoxythiophen-3-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

31) *N*-(3-chloro-5-(2-(1-methyl-1*H*-pyrrol-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

32) *N*-(3-chloro-5-(2-(4-methylthiophen-2-yl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

33) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(1-(methylsulfonyl)cyclopropyl)benzo[*b*]thiophene-2-carboxamide;

34) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

35) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide;

36) *N*-(3-chloro-5-(2-(4-chlorophenyl)propan-2-yl)phenyl)-5-((S-methylsulfonimidoyl)methyl)benzo[*b*]thiophene-2-carboxamide;

37) *N*-(3-chloro-5-(4-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

38) *N*-(3-chloro-5-(4-(trifluoromethyl)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

39) *N*-(3-bromo-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

40) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)-1*H*-indole-2-carboxamide;

41) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

42) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(((trifluoromethyl)sulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

43) *N*-(3-chloro-5-(4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

44) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-fluoro-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

45) 6-chloro-*N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-

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yl)benzo[*b*]thiophene-2-carboxamide;

46) *N*-(3-(4-chlorophenoxy)-5-methoxyphenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

47) *N*-(3-chloro-5-(3-chloro-5-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

48) *N*-(3-chloro-5-(3-(trifluoromethoxy)phenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

49) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

50) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)thieno[2,3-*c*]pyridine-2-carboxamide;

51) *N*-(3-chloro-5-(3-chloro-4-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

52) *N*-(3-chloro-5-(3,4-difluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

53) *N*-(3-chloro-5-(3-fluoro-5-methoxyphenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

54) *N*-(3-chloro-5-(4-chloro-3-fluorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

55) *N*-(3-chloro-5-(2-(3-chloro-5-methoxyphenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

56) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(4-(methylsulfonyl)tetrahydro-2*H*-pyran-4-yl)benzo[*b*]thiophene-2-carboxamide;

57) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-((2-methoxyethyl)sulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

58) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-6-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

59) *N*-(3-(azetidin-1-yl)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

60) *N*-(3-chloro-5-((6-chloropyridin-3-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

61) *N*-(3-chloro-5-((5-chloropyridin-2-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

62) *N*-(2-chloro-6-(3,5-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

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63) *N*-(6-chloro-4-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

64) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

65) *N*-(2-chloro-6-((6-chloropyridin-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

66) *N*-(4-chloro-6-(4-chlorophenoxy)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

67) *N*-(2-chloro-6-(4-(trifluoromethyl)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

68) *N*-(2-chloro-6-(4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

69) *N*-(2-bromo-6-(4-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

70) *N*-(2-chloro-6-(3-chloro-5-methoxyphenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

71) *N*-(2-chloro-6-(3-chloro-4-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

72) *N*-(2-chloro-6-(4-chloro-3-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

73) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-dioxidotetrahydrothiophen-2-yl)benzo[*b*]thiophene-2-carboxamide;

74) *N*-(2-chloro-6-(4-chlorophenoxy)pyridin-4-yl)-5-(1,1-dioxidotetrahydro-2*H*-thiopyran-2-yl)benzo[*b*]thiophene-2-carboxamide;

75) *N*-(2-chloro-6-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

76) *N*-(6-chloro-2-(4-chlorophenoxy)pyrimidin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

77) *N*-(2-(4-chlorophenoxy)-6-fluoropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

78) *N*-(2-(bicyclo[2.2.1]hept-5-en-2-yloxy)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

79) *N*-(2-chloro-6-(3,4-difluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

80) *N*-(2-chloro-6-(3-chlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-

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yl)benzo[*b*]thiophene-2-carboxamide;

81) *N*-(2-chloro-6-(3-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

82) *N*-(2-chloro-6-(3,4-dichlorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

83) *N*-(2-chloro-6-(4-chloro-2-fluorophenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

84) *N*-(2-chloro-6-(4-(trifluoromethoxy)phenoxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

85) *N*-(2-chloro-6-((5-chloropyridin-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

86) *N*-(2-chloro-6-((4-chlorobenzyl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

87) *N*-(3-chloro-5-(2-(3-(prop-1-yn-1-yl)-5-(trifluoromethoxy)phenyl)propan-2-yl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

88) *N*-(1-(*tert*-butyl)-3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

89) *N*-(3-(2-(4-chlorophenyl)propan-2-yl)-1*H*-pyrazol-5-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

90) *N*-(2-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

91) *N*-(4-chloro-6-(2-(3-methoxy-5-(trifluoromethoxy)phenyl)propan-2-yl)pyridin-2-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

92) *N*-(3-chloro-5-((2,2,6,6-tetramethylpiperidin-4-yl)oxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

93) *tert*-butyl (2-(3-(4-chlorophenoxy)-5-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)phenoxy)ethyl)carbamate;

94) *N*-(3-(2-aminoethoxy)-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

95) *N*-(5-chloro-2',4'-difluoro-[1,1'-biphenyl]-3-yl)-5-((methylsulfonyl)methyl)benzo[*b*]thiophene-2-carboxamide;

96) (8-chloro-6-(4-chlorophenoxy)-2,3-dihydro-4*H*-benzo[*b*][1,4]oxazin-4-yl)(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophen-2-yl)methanone;

97) *N*-(3-chloro-5-(1-(4-chlorophenyl)cyclopropyl)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

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98) *N*-(3-chloro-5-((2,4-difluorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

99) *N*-(3-chloro-5-((4-chlorophenyl)(methyl)amino)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

100) *N*-(2-chloro-6-((4-chlorophenyl)(methyl)amino)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

101) *N*-(2-chloro-6-((4-chlorocyclohex-3-en-1-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

102) *N*-(2-chloro-6-((octahydroindolizin-7-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

103) *N*-(3-chloro-5-(4-chlorophenoxy)phenyl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboximidamide 2,2,2-trifluoroacetate;

104) *N*-(2-chloro-6-(hexahydropyrrolo[1,2-*a*]pyrazin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

105) *N*-(2-(4-(*tert*-butyl)piperidin-1-yl)-6-chloropyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

106) *N*-(2-chloro-6-(octahydro-2*H*-pyrido[1,2-*a*]pyrazin-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

107) *N*-(2-chloro-6-(7-ethyl-2,7-diazaspiro[4.4]nonan-2-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

108) *N*-(2-chloro-6-(octahydroisoquinolin-2(1*H*)-yl)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

109) *N*-(2-chloro-6-((5-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

110) *N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-5-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

111) *N*-(2-chloro-6-((1,3,5-trimethyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

112) *N*-(2-chloro-6-((1-methyl-1*H*-pyrazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

113) *N*-(2-chloro-6-((3,5-dimethylisoxazol-4-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

114) *N*-(2-chloro-6-((5-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

115) *N*-(2-chloro-6-((2-methylthiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-

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2-yl)benzo[*b*]thiophene-2-carboxamide;

116) *N*-(2-chloro-6-((4,5-dimethylisoxazol-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

117) *N*-(2-chloro-6-((5-(trifluoromethyl)thiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

118) methyl 3-((6-chloro-4-(5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamido)pyridin-2-yl)oxy)isoxazole-5-carboxylate;

119) *N*-(2-chloro-6-((4-methylthiazol-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide;

120) *N*-(2-chloro-6-((5-methylthiophen-2-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide; and

121) *N*-(2-chloro-6-((2-chlorothiophen-3-yl)oxy)pyridin-4-yl)-5-(2-(methylsulfonyl)propan-2-yl)benzo[*b*]thiophene-2-carboxamide.

10. A pharmaceutical composition comprising the compound, pharmaceutically acceptable salt or stereoisomer thereof as defined in any one of claims 1 to 9 and a non-toxic pharmaceutically acceptable additive.

11. The pharmaceutical composition according to claim 10 for use in preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

12. The pharmaceutical composition according to claim 10 for use in preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

13. A use of the compound, pharmaceutically acceptable salt or stereoisomer thereof as defined

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in any one of claims 1 to 9 for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

14. A use of the compound, pharmaceutically acceptable salt or stereoisomer thereof as defined in any one of claims 1 to 9 for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

15. The compound, pharmaceutically acceptable salt or stereoisomer thereof as defined in any one of claims 1 to 9 for use in preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of solid cancers, hematological or blood cancers, radio- or chemo-resistant cancers, metastatic cancers, inflammatory diseases, immunological diseases, diabetes, macular degeneration, human papillomavirus infection and tuberculosis.

16. A use of the compound, pharmaceutically acceptable salt or stereoisomer thereof as defined in any one of claims 1 to 9 for the manufacture of a medicament for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

17. A use of the compound, pharmaceutically acceptable salt or a stereoisomer thereof as defined in any one of claims 1 to 9 for preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer,

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thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

18. The compound, pharmaceutically acceptable salt or stereoisomer thereof as defined in any one of claims 1 to 9 for use in preventing or treating diseases associated with the activation of STAT3 protein, wherein the diseases associated with the activation of STAT3 protein are selected from the group consisting of breast cancer, lung cancer, stomach cancer, prostate cancer, uterine cancer, ovarian cancer, kidney cancer, pancreatic cancer, liver cancer, colon cancer, skin cancer, head and neck cancer, thyroid cancer, osteosarcoma, acute or chronic leukemia, multiple myeloma, B- or T-cell lymphoma, non-Hodgkin's lymphoma, auto-immune diseases comprising rheumatoid arthritis, psoriasis, hepatitis, inflammatory bowel disease, Crohn's disease, diabetes, macular degeneration, human papillomavirus infection, and tuberculosis.

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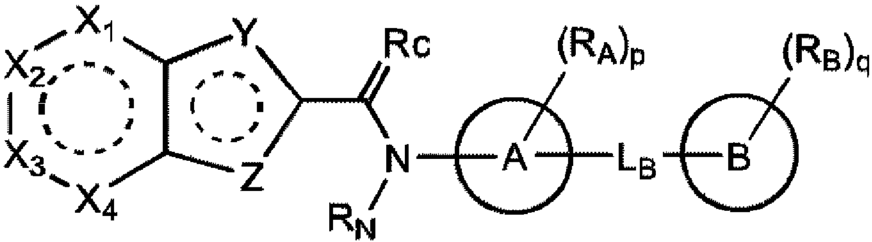

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