

HETEROARYL-AMINE COMPOUNDS AND USE THEREOF AS HDAC6 INHIBITORS

FIELD OF INVENTION

- 5 [0001] The present invention relates to heteroaryl-amine compounds useful as Histone Deacetylase subtype 6 (HDAC6) inhibitors. In particular, the present invention relates to compounds for use in the treatment and/or the prevention of proliferative diseases such as cancers, neurodegenerative diseases, neuropathies or cardiovascular diseases.

10 BACKGROUND OF INVENTION

- [0002] Inhibition of the enzymes of the HDAC class, especially HDAC6 enzyme, plays a critical role in gene expression in humans. Thus, the development of potent HDAC inhibitors is of utmost clinical importance in severe medical conditions, including both major and rare diseases (**Seidel, C *et al.***: “Histone deacetylase 6 in health and disease.”
- 15 Epigenomics. 2015, Vol. 7, No. 1, pp. 103-18). HDAC6 inhibitors are expected to be useful for example in oncology, neurology, neuropsychiatry, neurodegeneration, inflammation (*e.g.*, neuroinflammation), nephropathy, neuropathy and pain. Significant examples of HDAC6 inhibitors with potential medical applications in the treatment of proliferative diseases are drugs of the hydroxamate class (hydroxamic acid and salts
- 20 thereof), which include vorinostat (or “SAHA”, trade name Zolinza®), Trichostatin A (TSA), belinostat (trade name Beleodaq®), panobinostat (Farydak®) or romidepsin (Istodax®).

- [0003] However, many HDAC6 inhibitors identified so far are not highly selective, so that they may cause significant side-effects. Poor pharmacokinetics and low
- 25 bioavailability also limit the potency of some HDAC6 inhibitors. Thus, most of the HDAC6 inhibitors have a poor developability profile, even for life-threatening applications in oncology. For example, high doses of non-selective HDAC inhibitors are responsible of fatigue and nausea. Side-effects may in particular be caused by the inhibition of class I HDACs. In addition, mutagenicity issues related to the hydroxamate

function in approved HDAC inhibitors has been reported (**Shen S. and Kozikowski A. P.** ChemMedChem 2016, No. 11, pp. 15-21). Other HDAC inhibitors, notably from the fluoromethyl oxadiazole class, have been reported to be mechanism-based inhibitors forming a quasi-irreversible binding intermediate (**Cellupica E. *et al.***: “Difluoromethyl-
5 1,3,4-oxadiazoles are slow-binding substrate analog inhibitors of histone deacetylase 6 with unprecedented isotype selectivity”, J. Biol. Chem. 2023, 299(1), 102800; **König B. *et al.***: “Difluoromethyl-1,3,4-oxadiazoles are selective, mechanism-based, and essentially irreversible inhibitors of histone deacetylase 6.”, ChemRxiv. Cambridge: Cambridge Open Engage; 2023).

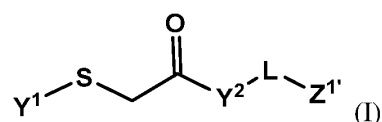
10 [0004] Therefore, there is an urgent need to develop highly selective HDAC6 inhibitors overcoming the limitations of some of the state-of-the-art HDCA6 inhibitors, such as hydroxamic acid-based HDCA6 inhibitors. Isoform-selective inhibitors over pan-HDAC are potentially advantageous both in terms of therapeutic efficacy and toxicity. In particular, selective inhibition of cytoplasmic HDAC6 may avoid toxicity resulting from
15 inhibition of other HDACs.

[0005] The Applicant surprisingly found out that amine compounds of formula (I) as described herein, which, for some of them, were originally prepared by the Applicant as synthetic intermediates, are actually highly selective HDAC6 inhibitors. The use of these heteroaryl-amine compounds may also represent significant improvements in terms of
20 bioavailability, side-effects, pharmacokinetics and/or water solubility over prior art drugs such as hydroxamates. The Applicant also surprisingly found the amine compounds of formula (I) were able to cross the blood-brain barrier, which makes them suitable candidates to treat neurodegenerative diseases with a central component such as amyotrophic lateral sclerosis (ALS).

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SUMMARY

[0006] This invention relates to a compound for use in the treatment and/or the prevention of an HDAC6-associated disease; wherein the compound is a compound of formula (I)



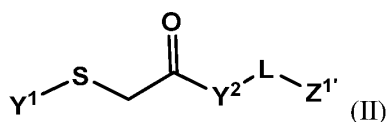
- 5 or a pharmaceutically acceptable salt and/or solvate thereof; wherein **Y¹**, **Y²**, **L** and **Z^{1'}** are as described in the claims or the detailed description.

[0007] According to one embodiment, the compound for use is selected from the compounds listed in **Table 2** herein, and pharmaceutically acceptable salts and/or solvates thereof.

- 10 [0008] This invention also relates to a pharmaceutical composition for use in the treatment and/or the prevention of an HDAC6-associated disease comprising a compound according to the invention and at least one pharmaceutically acceptable carrier.

- [0009] According to one embodiment, the HDAC6-associated disease is selected from inflammatory diseases, autoimmune diseases, proliferative diseases (such as cancers),
15 neurodegenerative diseases (including neuromuscular diseases), pains, neuropathies (including neuromuscular diseases), psychiatric diseases, neurodevelopmental disorders, sleep disorders and cardiovascular diseases, and metabolic or hormonal disorders.

[0010] This invention also relates to a compound of formula (II)



- 20 or a pharmaceutically acceptable salt and/or solvate thereof; wherein **Y¹**, **Y²**, **L** and **Z^{1'}** are as described in the claims or the detailed description.

[0011] According to one embodiment, the compound is selected from the compounds listed in **Table 1** herein, and pharmaceutically acceptable salts and/or solvates thereof.

[0012] This invention also relates to a process for manufacturing a compound according to the invention, wherein the process comprises the following steps: (i) reacting an amine-containing alkyl chain or heterocycloalkyl with a halo-heterocycle; then (ii) reacting a heterocycle or halo-heterocycle with first an acetylating reagent, and, where appropriate, subsequently a halogenating reagent, to form a halo-ketone; then (iii) reacting a halo-ketone with a thiol and, where appropriate, (iv) removal of at least one protective group.

[0013] This invention also relates to a compound selected from the compounds listed in **Table 3** herein, and pharmaceutically acceptable salts and/or solvates thereof.

10 DEFINITIONS

[0014] In the present invention, the following terms have the following meanings, unless indicated otherwise.

Chemical definitions

[0015] When referring to combination of groups, such as, for example, “alkylene-heteroaryl”, the point of attachment to the main structure is on the group cited on the left. Thus, the term “**alkylene-cyclyl**” and variants thereof (*e.g.*, “**alkylene-heteroaryl**”, “**alkylene-heterocycle**”, “**alkylene-cycloalkyl**”, “**alkylene-aryl**”, “**alkylene-heteroaryl**”, “**alkylene-heterocycle**” and “**alkylene-cycloalkyl**”) refers to a cyclyl group that is attached via an alkyl moiety to the main structure. In other words, the point of attachment is the alkylene group, and not the cyclyl group.

[0016] “**Alkene**” or “**alkenyl**” refers to a linear or branched hydrocarbon chain comprising at least one double bond and typically from 2 to 12 carbon atoms, preferably 3 to 6 carbon atoms. Non-limiting examples of alkenyl groups include ethynyl, 2propenyl, 2-butenyl, 3-butenyl, 2-pentenyl and its isomers, 2-hexenyl and its isomers and 2,4-pentadienyl.

[0017] “**Alkyl**” refers to a saturated linear or branched hydrocarbon chain, typically comprising from 1 to 12 carbon atoms, preferably from 1 to 6 carbon atoms, more preferably from 1 to 3 carbon atoms. In the present invention, alkyl groups may be

monovalent or polyvalent (*i.e.*, “**alkylene**” groups as defined herein are encompassed in “alkyl” definition) but alkyl groups are typically monovalent. Non-limiting examples of alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl and *t*-butyl, pentyl and its isomers (*e.g.*, *n*-pentyl, *iso*-pentyl), and hexyl and its isomers (*e.g.*, *n*-hexyl, *iso*-hexyl). Preferred alkyl groups include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *s*-butyl and *t*-butyl.

[0018] “**Alkylene**” refers to a divalent alkyl group. Non-limiting examples of alkylene groups include methylene, ethylene, *n*-propylene, *i*-propylene, divalent butyl, divalent pentyl and divalent hexyl. Preferred alkylene groups include methylene, ethylene, *n*-propylene, and *n*-butylene.

[0019] “**Alkyne**” or “**alkynyl**” refers to a linear or branched hydrocarbon chain comprising at least one triple bond and typically from 2 to 12 carbon atoms, preferably 3 to 6 carbon atoms. Non-limiting examples of alkynyl groups include ethynyl, 2-propynyl, 2-butylnyl, 3-butylnyl, 2-pentylnyl and its isomers, and 2-hexynyl and its isomers.

[0020] “**Amine**” refers to derivatives of ammonia (NH₃), wherein one or more hydrogen atoms have been replaced by a substituent such as, for example, alkyl or aryl.

[0021] “**Amino**” refers to the -NH₂ group.

[0022] “**Aryl**” refers to a cyclic, polyunsaturated, aromatic hydrocarbyl group comprising at least one aromatic ring. Aryl groups may have a single ring (*i.e.*, phenyl) or multiple aromatic rings fused together (*e.g.*, naphthyl) or linked covalently. Typically, aryl groups have from 5 to 12 carbon atoms, preferably from 6 to 10 carbon atoms. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocycloalkyl or heteroaryl) fused thereto. Aryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein, as long as at least one ring is aromatic. Non-limiting examples of aryl groups include phenyl, biphenyl, biphenylenyl, 5- or 6-tetralinyl, naphthalen-1- or -2-yl, 4-, 5-, 6 or 7-indenyl, 1- 2-, 3-, 4- or 5-acenaphthylenyl, 3-, 4- or 5-acenaphthenyl, 1- or 2-pentalenyl, 4- or 5-indanyl, 5-, 6-, 7- or 8-tetrahydronaphthyl, 1,2,3,4-tetrahydronaphthyl, 1,4-dihydronaphthyl, 1-, 2-, 3-, 4- or 5-pyrenyl. A preferred aryl group is phenyl.

[0023] “**Bicyclic**”, when referring to a cyclic group, means that the cyclic group consists of exactly two fused rings. In monovalent bicyclic groups, the notation “[**x**, **y**]” wherein **x** and **y** are integers is used herein to indicate that one cycle is **x**-membered and the other cycle is **y**-membered and that the point of attachment to the main structure is located on the **x**-membered cycle. “**Tricyclic**” and the like should be construed accordingly.

[0024] “**Cyano**” refers to the -CN group.

[0025] “**Cyclyl**” collectively refers to “cycloalkyl”, “heterocycloalkyl”, “aryl” and “heteroaryl” groups as defined herein.

[0026] “**Cycloalkyl**” refers to a cyclic monovalent alkyl, typically comprising from 3 to 11 carbon atoms, preferably from 4 to 9 carbon atoms, more preferably from 5 to 7 carbon atoms. This definition encompasses polycyclic cycloalkyls (*e.g.*, bicycles) and bridged cycloalkyl structures, including cycles bound together through one atom (“spiro”) or through two atoms.

[0027] “(**C_x**-**C_y**)” preceding the name of a group means that the group comprises from **x** to **y** carbon atoms, in accordance to common terminology in the chemistry field.

[0028] “**Difluoromethyl**” refers to the -CHF₂ group.

[0029] “**Halide**”, “**halo**” or “**halogen**” refers to a fluorine, chlorine, bromine or iodine atom, typically a chlorine or bromine atom.

[0030] “**Heteroalkyl**” refers to an alkyl group as defined hereinabove wherein one or more carbon atoms are replaced by a heteroatom selected from oxygen, nitrogen and sulfur. In heteroalkyl groups, the heteroatoms are bound along the alkyl chain only to carbon atoms, *i.e.*, each heteroatom is separated from any other heteroatom by at least one carbon atom. The nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. Heteroalkyl groups may further include one or more oxo (=O) groups. A heteroalkyl is bound to another group or molecule only through a carbon atom, *i.e.*, the binding atom is not selected among the heteroatoms included in the heteroalkyl group. When substituted by one or more other group(s), an heteroalkyl may be substituted either through a carbon atom or through a

heteroatom (*e.g.*, nitrogen), unless otherwise specified. Non-limiting examples of heteroalkyl include alkoxy, ethers and polyethers, secondary amines, tertiary amines and thioethers.

[0031] “**Heteroaryl**” refers to aromatic rings or aromatic ring systems comprising from 5 to 12 carbon atoms, preferably from 6 to 10 carbon atoms, having one or two rings which are fused together or linked covalently, wherein at least one ring is aromatic, and wherein one or more carbon atoms in one or more of these rings is replaced by oxygen, nitrogen and/or sulfur atoms. “Heteroaryl” may also be viewed as an “aryl” group as defined herein, wherein at least one carbon atom in the aryl group is replaced with a heteroatom and wherein the resulting molecule is chemically stable. The nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The aromatic ring may optionally include one to two additional rings (either cycloalkyl, heterocycloalkyl or aryl) fused thereto. Heteroaryl is also intended to include the partially hydrogenated derivatives of the carbocyclic systems enumerated herein, as long as at least one ring is aromatic. Non-limiting examples of heteroaryl groups include furanyl, thiophenyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, oxatriazolyl, thiatriazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, oxazinyl, dioxinyl, thiazinyl, triazinyl, imidazo[2,1-b][1,3] thiazolyl, thieno[3,2-b]furanyl, thieno[3,2-b]thiophenyl, thieno[2,3-d][1,3]thiazolyl, thieno[2,3-d]imidazolyl, tetrazolo[1,5-a]pyridinyl, indolyl, indolizinyl, isoindolyl, benzofuranyl, isobenzofuranyl, benzothiophenyl, isobenzothiophenyl, indazolyl, benzimidazolyl, 1,3-benzoxazolyl, 1,2-benzisoxazolyl, 2,1-benzisoxazolyl, 1,3-benzothiazolyl, 1,2-benzoisothiazolyl, 2,1-benzoisothiazolyl, benzotriazolyl, 1,2,3-benzoxadiazolyl, 2,1,3-benzoxadiazolyl, 1,2,3-benzothiadiazolyl, 2,1,3-benzothiadiazolyl, thienopyridinyl, purinyl, imidazo[1,2-a]pyridinyl, 6-oxo-pyridazin-1-(6H)-yl, 2-oxopyridin-1-(2H)-yl, 6-oxo-pyridazin-1-(6H)-yl, 2-oxopyridin-1-(2H)-yl, 1,3-benzodioxolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, and 6,7-dihydro-5H-pyrrolo[1,2-a]imidazolyl.

[0032] “**Heterocycloalkyl**” refers to a cyclic monovalent heteroalkyl, typically comprising from 2 to 7 carbon atoms, preferably from 3 to 6 carbon atoms, more preferably from 4 to 5 carbon atoms. This definition encompasses polycyclic heterocycloalkyls (*e.g.*, bicycles) and bridged heterocycloalkyl structures, including cycles bound together through one atom (“spiro”) or through two atoms. In one embodiment, the heterocycloalkyl is bound to another group or molecule through a carbon atom, *i.e.*, the binding atom is not selected among the heteroatoms included therein. In one embodiment, the heterocycloalkyl is bound to another group or molecule through one of the heteroatoms included therein. When substituted by one or more other group(s), an heterocycloalkyl may be substituted either through a carbon atom or through a heteroatom (*e.g.*, nitrogen), unless otherwise specified. Non-limiting examples of heterocycloalkyl include aziridine, pyrrolidine, piperidine, piperazine (also known as “hexahydropyrazine”), morpholine, thiomorpholine, azepane, azocane, octahydro-1*H*-isoindole, decahydroisoquinoline, tetrahydrofuran, tetrahydropyran, tetrahydroisoquinoline (*e.g.*, 1,2,3,4-tetrahydroisoquinoline), hexahydropyridazine, hexahydropyrimidine, decahydroquinoline, octahydropyrrolo[3,4-*c*]pyrrole, isoindoline, 1,2,3,4-tetrahydroquinoline and oxetane.

[0033] “**Hydroxy**” refers to the -OH group.

[0034] “**Ketone**” refers to a functional group with the connectivity C-(C=O)-C.

[0035] “**Oxo**” refers to the =O group, *i.e.*, one oxygen atom which is double-bonded, typically to a carbon atom.

[0036] “**Trifluoromethyl**” refers to the -CF₃ group.

General definitions

[0037] “**About**” is used herein to mean approximately, roughly, around, or in the region of. The term “about” preceding a figure means more or less 10 % of the value of the figure. When the term “about” is used in conjunction with a numerical range, it modifies

that range by extending the boundaries above and below the numerical values set forth by 10%.

[0038] “**Administration**”, or a variant thereof (*e.g.*, “**administering**”), means providing a therapeutic agent (*e.g.*, a compound of the invention) alone or as part of a
5 pharmaceutically acceptable composition, to the patient in whom/which the condition, symptom, or disease is to be treated and/or prevented.

[0039] “**Binding site**” or “**binding pocket**” refers to a specific arrangement of amino acids located on a protein (*e.g.*, on HDAC6) to which a compound (*e.g.*, the compounds of the present invention) bind. Binding sites often consist of a chemically-active surface
10 grouping of amino acids, and have specific 3-D structural characteristics as well as specific charge characteristics. Similarly to epitopes, binding sites can be linear or conformational, *i.e.*, they can involve sequences of amino acids which are not necessarily contiguous in the primary structure of the protein.

[0040] “**Comprise**” or a variant thereof (*e.g.*, “comprises”, “comprising”) is used herein
15 according to common patent application drafting terminology. Hence, “comprise” preceded by an object and followed by a constituent means that the presence of a constituent in the object is required (typically as a component of a composition), but without excluding the presence of any further constituent(s) in the object. Moreover, any occurrence herein of “comprise” or a variant thereof also encompasses narrower
20 expression “substantially consist of” or “consists essentially of”, further narrower expression “consist of” and any variants thereof (*e.g.*, “consists of”, “consisting of”).

[0041] “**HDAC**” or “**Histone Deacetylase**” refers to a class of enzymes that are able to remove acetyl groups ($\text{O}=\text{C}-\text{CH}_3$) from an ϵ -N-acetyl lysine amino acid on a histone, allowing the histones to wrap the DNA more tightly and condensate the chromatin. Gene
25 expression is regulated by histone acetylation and de-acetylation, and thus by HDAC activity. In the invention, HDAC is typically “HDAC6” as defined herein.

[0042] “**HDAC-associated disease**” or “**disease related to HDAC6 function**” or a variant thereof (*e.g.*, “**HDAC6-associated disease**”) refers to a disease that it due to, caused by, or characterized by, the dysregulation and in particular the increase of activity

of a least one HDAC enzyme in a subject, resulting in an abnormal acetylation profile of HDAC substrates (*e.g.*, histones, tubulin, Hsp90, cortactin). In the present application, **“HDAC-associated disease”** and **“disease related to HDAC6 function”** are synonyms and may be used interchangeably. Typically, HDAC-associated diseases are associated with, *inter alia*, altered epigenetic regulation of gene expression and/or cell motility. This definition encompasses diseases wherein reducing (inhibiting) normal HDAC activity treat and/or prevent the diseases. Typically, an HDAC-associated disease may be prevented and/or treated by means of HDAC inhibition. Non-limitative examples of HDAC-associated diseases include neuropathies, neurodegenerative diseases, proliferative diseases (*e.g.*, cancer), metabolic disorders, immune disorders and inflammatory diseases.

[0043] **“HDAC6”, “HDAC6 enzyme”** or **“Histone Deacetylase subtype 6”** refers to a HDAC enzyme that is encoded by the HDAC6 gene in humans.

[0044] **“HDAC6 gene”** refers to the gene coding for HDAC6 in humans. HDAC6 gene is also interchangeably referred to as KIAA0901 or JM21.

[0045] **“Human”** refers to a male or female subject at any stage of development, including neonate, infant, juvenile, adolescent and adult.

[0046] **“Patient”** refers to an animal, typically a warm-blooded animal, preferably a mammal (*e.g.*, mouse, rat, cat, guinea-pig, dog, monkey or human), more preferably a human, who/which is awaiting the receipt of, or is receiving medical care, or is/will be the object of a medical procedure. A patient may also be the subject of preventive care or procedure.

[0047] **“Pharmaceutically acceptable”** means that the ingredients of a composition are compatible with each other and not deleterious to the patient to which/whom it is administered.

[0048] **“Pharmaceutically acceptable carrier”** refers to an excipient that does not produce an adverse, allergic or other untoward reaction when administered to an animal, preferably a human. It includes any and all solvents, dispersion media, coatings,

antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by regulatory offices, such as, *e.g.*, FDA Office or EMA.

[0049] “**Prevent**”, “**preventing**” and “**prevention**” refer to delaying or precluding the onset of a condition and/or disease and/or any one of its attendant symptoms, barring a patient from acquiring a condition or disease, or reducing the risk for a patient of acquiring a condition and/or disease and/or any one of its attendant symptoms. The effect resulting from “preventing” a condition and/or disease is called “**prophylactic**”.

[0050] “**Prodrug**” refers to a pharmacologically acceptable derivative of a therapeutic agent (*e.g.*, a compound of the invention) whose *in vivo* biotransformation product is the therapeutic agent (active drug). Prodrugs are typically characterized by increased bioavailability and are readily metabolized *in vivo* into the active compounds. Non-limiting examples of prodrugs include amide prodrugs and carboxylic acid ester prodrugs, in particular alkyl esters, cycloalkyl esters and aryl esters.

[0051] “**Selected from**” is used herein according to common patent application drafting terminology, to introduce a list of elements among which an item is selected. Moreover, any occurrence herein of “selected from” also encompasses the expression “selected from the group comprising or consisting of” and any variants thereof (*e.g.*, “consists of”).

[0052] “**Solvate**” refers to molecular complex comprising a compound along with stoichiometric or sub-stoichiometric amounts of one or more molecules of one or more solvents, typically the solvent is a pharmaceutically acceptable solvent such as, for example, ethanol. The term “**hydrate**” refers to a solvate when the solvent is water (H₂O).

[0053] “**Therapeutic agent**”, “**active pharmaceutical ingredient**” and “**active ingredient**” refer to a compound for therapeutic use and relating to health. Especially, a therapeutic agent (*e.g.*, a compound of the invention) may be indicated for treating and/or preventing a disease, preferably an infectious disease. An active ingredient may also be indicated for improving the therapeutic activity of another therapeutic agent.

[0054] “**Therapeutically effective amount**” (in short “**effective amount**”) refers to the amount of a therapeutic agent (*e.g.*, a compound of the invention) that is sufficient to achieve the desired therapeutic or prophylactic effect in the patient to which/whom it is administered.

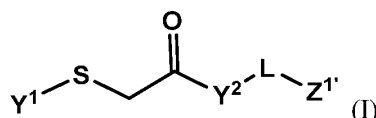
- 5 [0055] “**Treat**”, “**treating**” and “**treatment**” refer to alleviating, attenuating or abrogating a condition and/or disease and/or any one of its attendant symptoms, *e.g.*, an infectious disease.

DETAILED DESCRIPTION

10 Compounds

General formula

[0056] This invention relates to a compound of formula (I)



wherein **Y**¹, **Y**², **L** and **Z**^{1'} are as defined hereinafter in the detailed description.

- 15 [0057] In the compounds of formula (I) as described hereinafter in the detailed description, unless otherwise indicated, any **alkyl group** (which encompass alkylene group) **may be “optionally substituted”**, *i.e.*, each hydrogen atom bound to a carbon atom in the alkyl moiety can optionally be replaced by at least one low-molecular weight substituent such as, for example, a substituent selected from halogen, cyano, hydroxy,
- 20 oxo, amino, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl and -N-((C₁-C₆) alkyl)₂. Only substitutions wherein the resulting molecule is chemically stable are encompassed by this definition. Typically, the (C₁-C₆) alkyl group(s) present in the substituents are not themselves further substituted. Preferred substituted alkyls include alkyls substituted by one or more fluorine atom(s) and/or hydroxy such as, for example, trifluoromethyl.

[0058] In the compounds of formula (I) as described hereinafter in the detailed description, unless otherwise indicated, **any cyclyl group** (*i.e.*, cycloalkyl, heterocycloalkyl, aryl or heteroaryl group) **may be “optionally substituted”**, *i.e.*, each hydrogen atom bound to a carbon atom in the cyclyl moiety can optionally be replaced

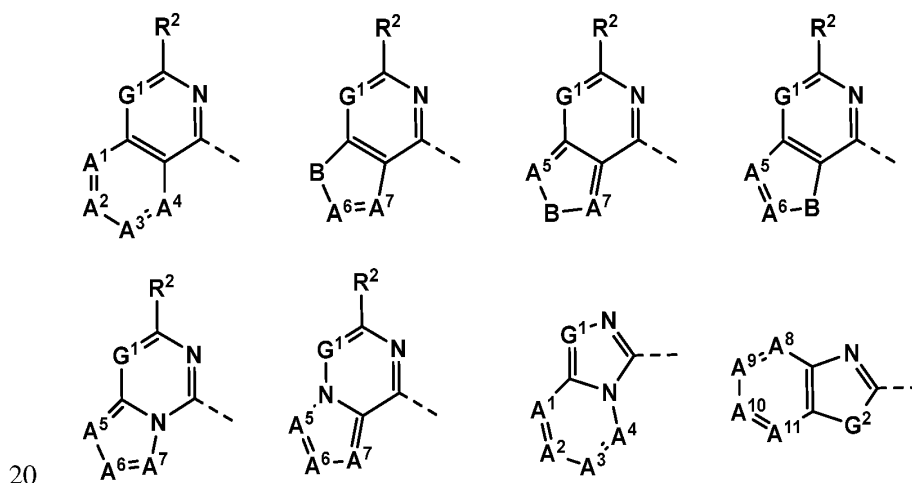
5 by at least one low-molecular weight substituent such as, for example, a group selected from halogen, cyano, hydroxy, oxo, amino, $-(C_1-C_6)$ alkyl, $-CH_2-O-(C_1-C_6)$ alkyl, $-CH_2-NH-(C_1-C_6)$ alkyl, $-CH_2-N-((C_1-C_6)$ alkyl) $_2$, $-O-(C_1-C_6)$ alkyl, $-NH-(C_1-C_6)$ alkyl and $-N-((C_1-C_6)$ alkyl) $_2$. Only substitutions wherein the resulting molecule is chemically stable are encompassed by this definition. Typically, the (C_1-C_6) alkyl group(s) present

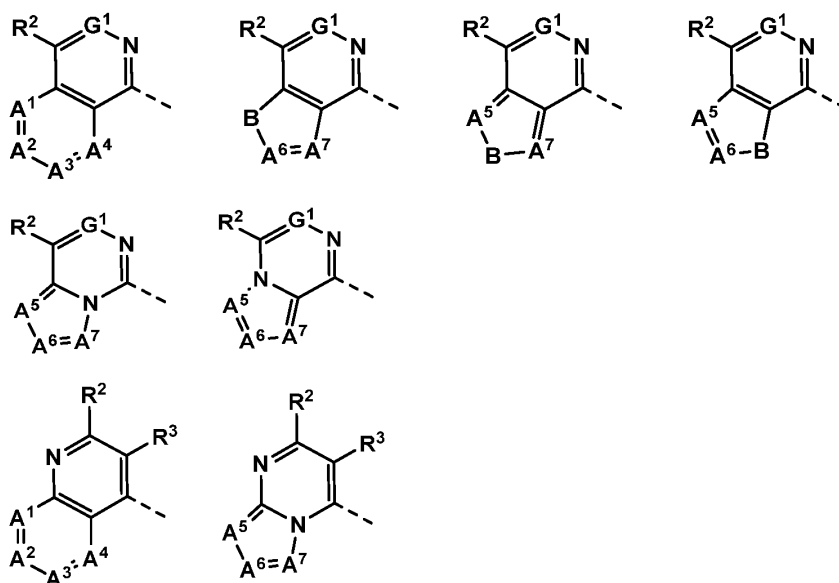
10 in the substituents are not themselves further substituted. Preferred substituted cyclyl groups include cyclyl substituted by substituted by one or more fluorine atom(s) and/or hydroxy such as, for example, difluorocyclopropyl.

[0059] In the formulae represented herein, the dotted line ---- represents the point of attachment of the depicted moiety to the main molecular structure.

15 *Y¹ definitions*

[0060] In formula (I) above, **Y¹** is a 9- or 10-membered bicyclic heteroaryl, preferably selected from the following group of formulae (**Y¹-I**) (also referred as “Scaffolds 1-16” or “Sc1-16”)

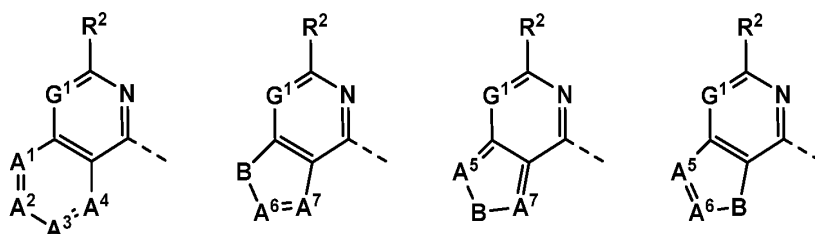


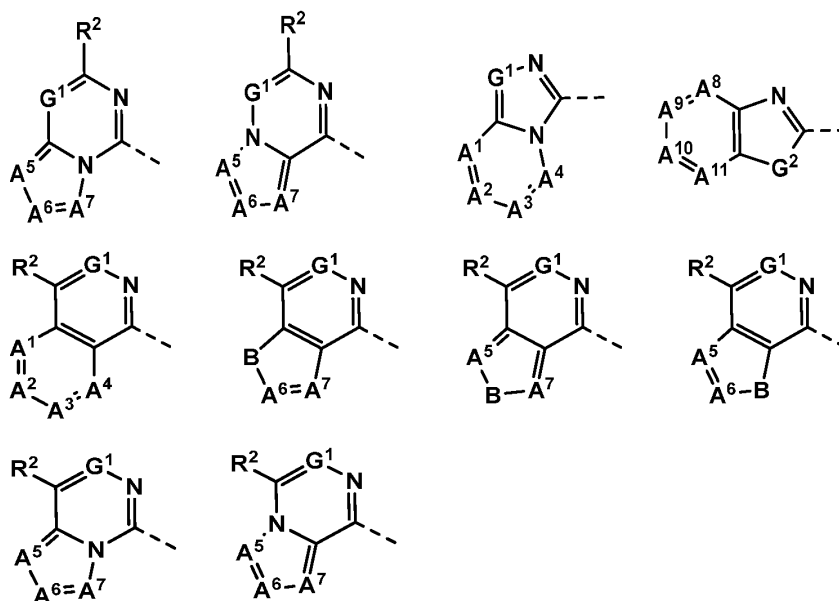


wherein

- 5 $A^1, A^2, A^3, A^4, A^5, A^6$ and A^7 are each independently selected from C- R^7 and N;
- A^8, A^9, A^{10} and A^{11} are each independently selected from C- R^7 and N, *provided that* at least one of A^8, A^9, A^{10} or A^{11} is N;
- G^1 is selected from C- R^3 and N; G^2 is selected from O and N- R^4 ; and
- B is selected from O, S and N- R^5 , *provided that* when A^5, A^6 and A^7 are C- R^7 , then
- 10 B is not S.

[0061] According to one preferred embodiment, Y^1 is a 9- or 10-membered bicyclic heteroaryl, preferably selected from the following group of formulae (Y^1 -Ia) (also referred as “Scaffolds 1-14” or “Sc1-14”)





wherein

- 5 **A**¹, **A**², **A**³, **A**⁴, **A**⁵, **A**⁶ and **A**⁷ are each independently selected from C-**R**⁷ and N;
- A**⁸, **A**⁹, **A**¹⁰ and **A**¹¹ are each independently selected from C-**R**⁷ and N, *provided that*
at least one of **A**⁸, **A**⁹, **A**¹⁰ or **A**¹¹ is N;
- G**¹ is selected from C-**R**³ and N; **G**² is selected from O and N-**R**⁴; and
- B** is selected from O, S and N-**R**⁵, *provided that* when **A**⁵, **A**⁶ and **A**⁷ are C-**R**⁷, then
- 10 **B** is not S.

- [0062] In **Y**¹ as defined herein, **R**² is selected from hydrogen, halogen, cyano, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -**OR**¹⁵, -(C₁-C₆) alkylene-**OR**¹⁵, -O-(C₂-C₆) alkylene-**OR**¹⁵, -**NR**¹⁶(C₂-C₆) alkylene-**OR**¹⁵,
15 -**NR**¹⁷**R**¹⁸, -(C₁-C₆) alkylene-**NR**¹⁷**R**¹⁸, -O-(C₂-C₆) alkylene-**NR**¹⁷**R**¹⁸, -**NR**¹⁶-(C₂-C₆) alkylene-**NR**¹⁷**R**¹⁸, -(C₁-C₆) alkylene-SO₂-**NR**¹⁷**R**¹⁸, -**NR**¹⁶-SO₂-**R**¹⁵, -(C₁-C₆) alkylene-**NR**¹⁶-SO₂-**R**¹⁵, -O-(C₂-C₆) alkylene-**NR**¹⁶-SO₂-**R**¹⁵, -**NR**¹⁶-(C₂-C₆) alkylene-**NR**¹⁷-SO₂-**R**¹⁵, -C(O)-**NR**¹⁷**R**¹⁸, -(C₁-C₆) alkylene-C(O)-**NR**¹⁷**R**¹⁸, -O-(C₁-C₆) alkylene-C(O)-**NR**¹⁷**R**¹⁸, -**NR**¹⁶-(C₁-C₆) alkylene-C(O)-**NR**¹⁷**R**¹⁸,
20 -**NR**¹⁶C(O)-**R**¹⁵, -(C₁-C₆) alkylene-**NR**¹⁶C(O)-**R**¹⁵, -O-(C₂-C₆) alkylene-**NR**¹⁶C(O)-**R**¹⁵,

-NR¹⁶-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -C(O)-R¹⁵, -C(O)OR¹⁵, -(C₁-C₆) alkylene-C(O)OR¹⁵, -O-(C₁-C₆) alkylene-C(O)OR¹⁵, and -NR¹⁶-(C₁-C₆) alkylene-C(O)OR¹⁵.

[0063] In Y¹ as defined herein, R³ is selected from hydrogen, halogen, cyano, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, 5 -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵, -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-SO₂-NR¹⁷R¹⁸, -NR¹⁶-SO₂-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷-SO₂-R¹⁵, -C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -O-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -C(O)-R¹⁵, -C(O)OR¹⁵, -(C₁-C₆) alkylene-C(O)OR¹⁵, -O-(C₁-C₆) alkylene-C(O)OR¹⁵, and -NR¹⁶-(C₁-C₆) alkylene-C(O)OR¹⁵.

[0064] In Y¹ as defined herein, R⁴ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -(C₁-C₆) alkylene-OR¹⁵, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-C(O)OR¹⁵, and -(C₁-C₆) alkylene-OC(O)-R¹⁵. 20

[0065] In Y¹ as defined herein, R⁵ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -(C₁-C₆) alkylene-OR¹⁵, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, 25 -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-C(O)OR¹⁵, and -(C₁-C₆) alkylene-OC(O)-R¹⁵.

[0066] In Y¹ as defined herein, R⁷ is selected from hydrogen, halogen, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl,

-OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵, -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶(C₂-C₆) alkylene-OR¹⁵,
 -NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸,
 -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -SO-R¹⁵, -SO₂-R¹⁵, -SO₂NR¹⁷R¹⁸, -(C₁-C₆) alkylene-
 SO₂-NR¹⁷R¹⁸, -NR¹⁶-SO₂-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -O-(C₂-C₆) alkylene-
 5 NR¹⁶-SO₂-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷-SO₂-R¹⁵, -C(O)-NR¹⁷R¹⁸,
 -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -O-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸,
 -NR¹⁶-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶C(O)-
 R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷C(O)-R¹⁵,
 -C(O)-R¹⁵, -C(O)-OR¹⁵, -(C₁-C₆) alkylene-C(O)-OR¹⁵, -O-(C₁-C₆) alkylene-C(O)-OR¹⁵,
 10 -NR¹⁶-(C₁-C₆) alkylene-C(O)-OR¹⁵, -OC(O)-R¹⁵, -(C₁-C₆) alkylene-OC(O)-R¹⁵,
 -O-(C₂-C₆) alkylene-OC(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-OC(O)-R¹⁵, and -NR¹⁶-C(O)-
 OR¹⁵.

[0067] Moreover, in **Y**¹ as defined herein, each of the -(C₁-C₆) alkyl or -(C₁-C₆) alkylene
 in **R**², **R**³, **R**⁴, **R**⁵ or **R**⁷ is optionally substituted with at least one group selected from
 15 halogen, cyano, hydroxy, oxo, amino, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and
 -N-((C₁-C₆) alkyl)₂; and each of the -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl
 or heteroaryl in **R**², **R**³, **R**⁴, **R**⁵ or **R**⁷ is optionally substituted with at least one group
 selected from halogen, cyano, hydroxy, oxo, amino, -(C₁-C₆) alkyl, -CH₂-O-(C₁-C₆) alkyl,
 -CH₂-NH-(C₁-C₆) alkyl, -CH₂-N-((C₁-C₆) alkyl)₂, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl,
 20 and -N-((C₁-C₆) alkyl)₂.

[0068] In **Y**¹ as defined herein, **R**¹⁵, **R**¹⁶, **R**¹⁷ and **R**¹⁸ are each independently selected
 from hydrogen, -(C₁-C₆) haloalkyl, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-
 C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-
 C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-
 25 C₆) alkylene-aryl; and/or two groups selected from **R**¹⁵, **R**¹⁶, **R**¹⁷ and **R**¹⁸ form together a
 cycle selected from -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, and heteroaryl.

[0069] Moreover, in **Y**¹ as defined herein, each of the -(C₁-C₆) alkyl or -(C₁-C₆) alkylene
 in **R**¹⁵, **R**¹⁶, **R**¹⁷ or **R**¹⁸ is optionally substituted with at least one group selected from
 halogen, cyano, hydroxy, oxo, amino, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and
 30 -N-((C₁-C₆) alkyl)₂; and each of the -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl

or heteroaryl in **R**¹⁵, **R**¹⁶, **R**¹⁷ or **R**¹⁸ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, amino, -(C₁-C₆) alkyl, -CH₂-O-(C₁-C₆) alkyl, -CH₂-NH-(C₁-C₆) alkyl, -CH₂-N-((C₁-C₆) alkyl)₂, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂.

5 [0070] According to one embodiment, in **Y**¹ as defined herein:

R² is selected from hydrogen, halogen, cyano, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵,
 10 -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶(C₂-C₆) alkylene-OR¹⁵, -NR¹⁷R¹⁸,
 -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, and
 -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸;

R³ is selected from hydrogen, halogen, cyano, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵,
 15 -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶(C₂-C₆) alkylene-OR¹⁵, -NR¹⁷R¹⁸,
 -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, and
 -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸;

R⁴ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, and -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl;

20 **R**⁵ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -(C₁-C₆) alkylene-OR¹⁵, and -(C₁-C₆) alkylene-NR¹⁷R¹⁸; and

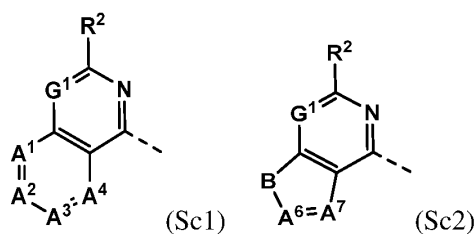
25 **R**⁷ is selected from hydrogen, halogen, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵, -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶(C₂-C₆) alkylene-OR¹⁵, -NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, and
 30 -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸;

wherein

each of the $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene, $-(C_3-C_7)$ cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl or heteroaryl in R^2 , R^3 , R^4 , R^5 or R^7 is optionally substituted as defined hereinabove; and

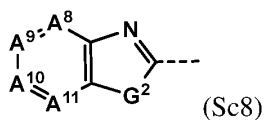
- 5 R^{15} , R^{16} , R^{17} and R^{18} are independently as defined hereinabove.

[0071] According to one preferred embodiment, Y^1 is a 9- or 10-membered bicyclic heteroaryl selected from the following formulae (Sc1) and (Sc2)



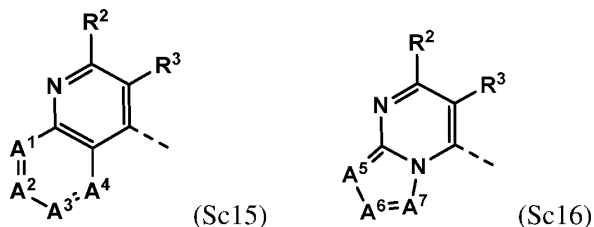
wherein A^1-A^4 , A^6 , A^7 , G^1 and R^2 are independently as defined hereinabove.

- 10 [0072] According to one preferred embodiment, Y^1 is a 9- or 10-membered bicyclic heteroaryl of the following formula (Sc8)



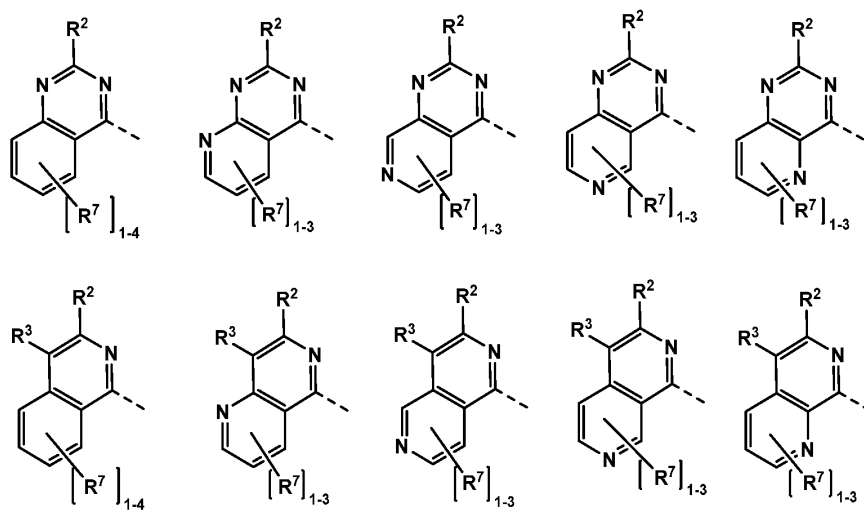
wherein A^8-A^{11} and G^2 are independently as defined hereinabove.

- [0073] According to one preferred embodiment, Y^1 is a 9- or 10-membered bicyclic heteroaryl selected from the following formulae (Sc15) and (Sc16)

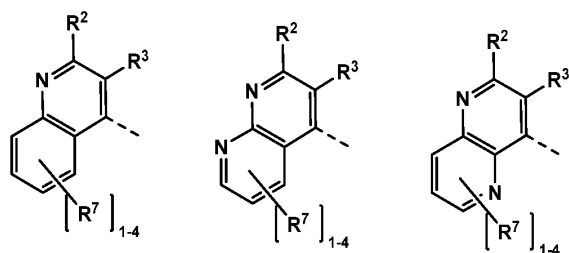


wherein A^1-A^4 , A^5-A^7 , R^2 and R^3 are independently as defined hereinabove.

[0074] In one embodiment, **Y**¹ is a 10-membered bicyclic [6,6] heteroaryl selected from the following group of formulae (**Y**¹-1)

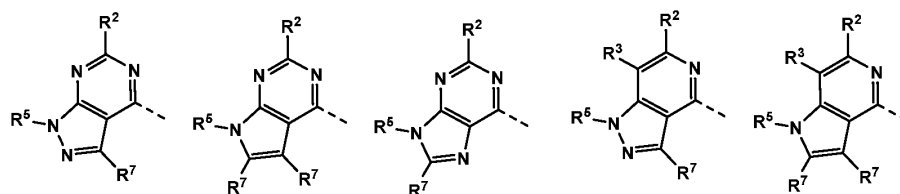


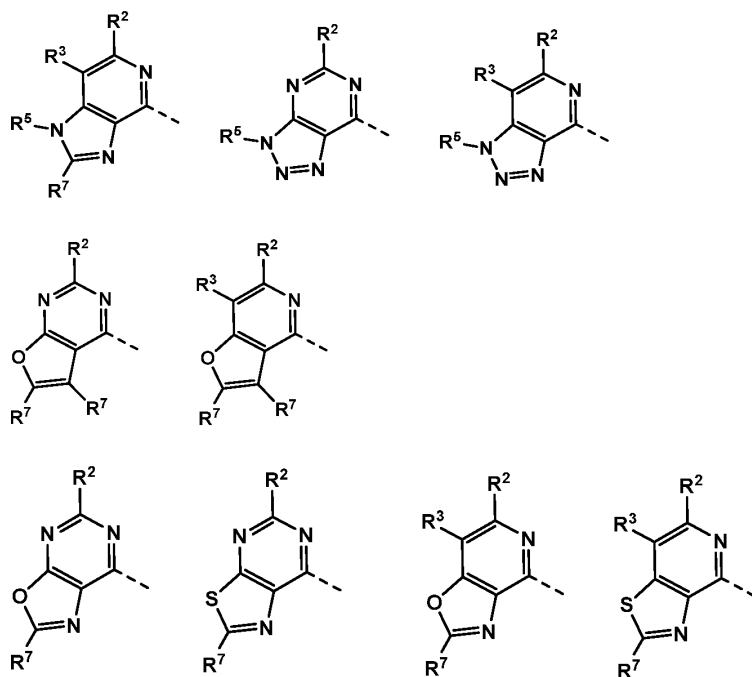
5 and the following group of formulae (**Y**¹-1a)



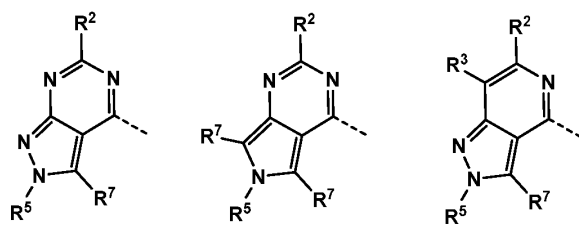
wherein **R**², **R**³ and **R**⁷ are independently as defined hereinabove.

[0075] In one embodiment, **Y**¹ is a 9-membered bicyclic [6,5] heteroaryl selected from the following group of formulae (**Y**¹-2)



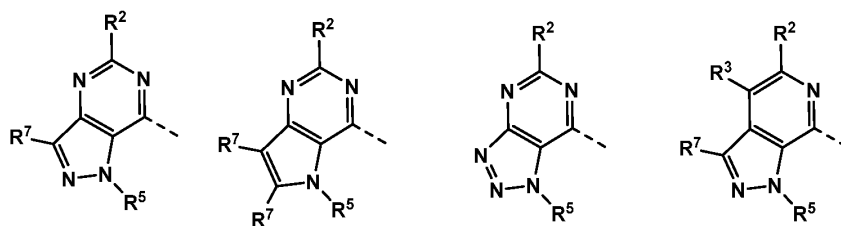


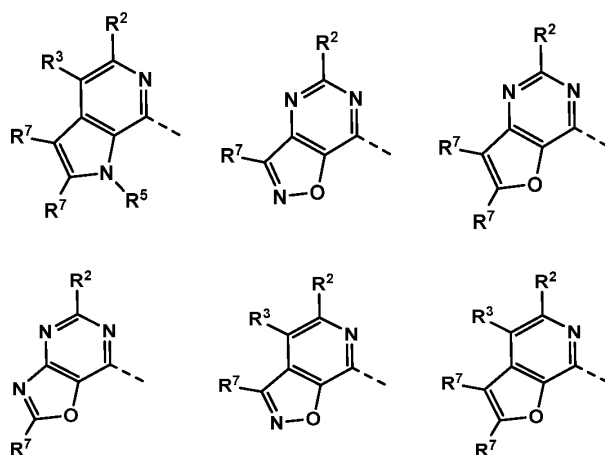
the following group of formulae (Y¹-3)



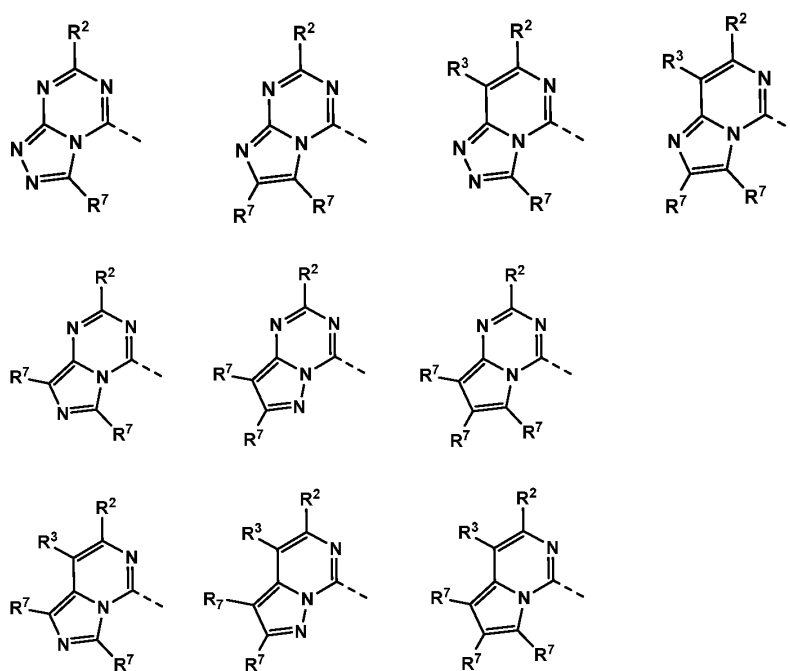
5

the following group of formulae (Y¹-4)



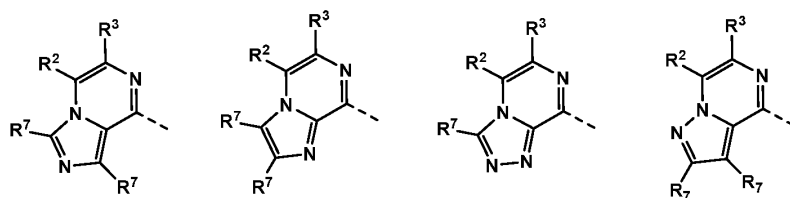


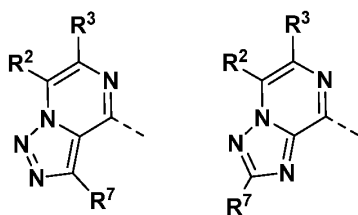
the following group of formulae (Y¹-5)



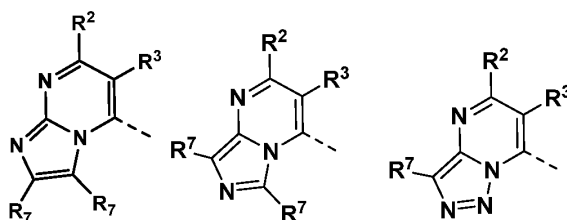
5

the following group of formulae (Y¹-6)





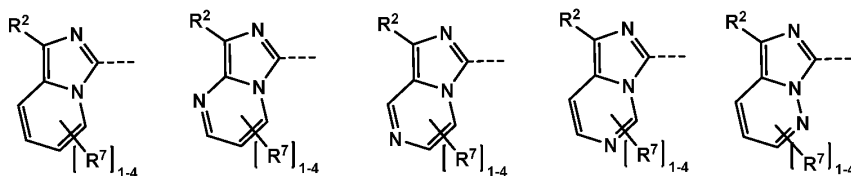
the following group of formulae (Y¹-6a)



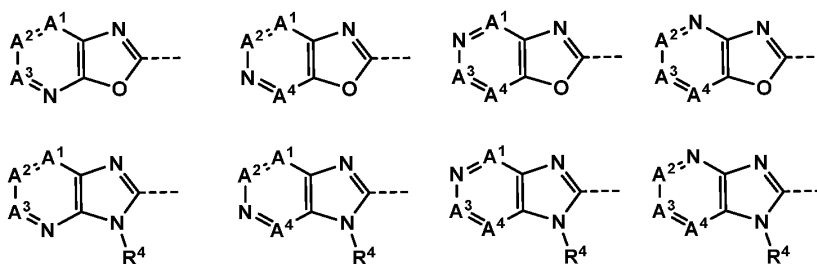
wherein **R**², **R**³, **R**⁵ and **R**⁷ are independently as defined hereinabove.

- 5 [0076] In one embodiment, **Y**¹ is a 9-membered bicyclic [5,6] heteroaryl selected from

the following group of formulae (Y¹-7)

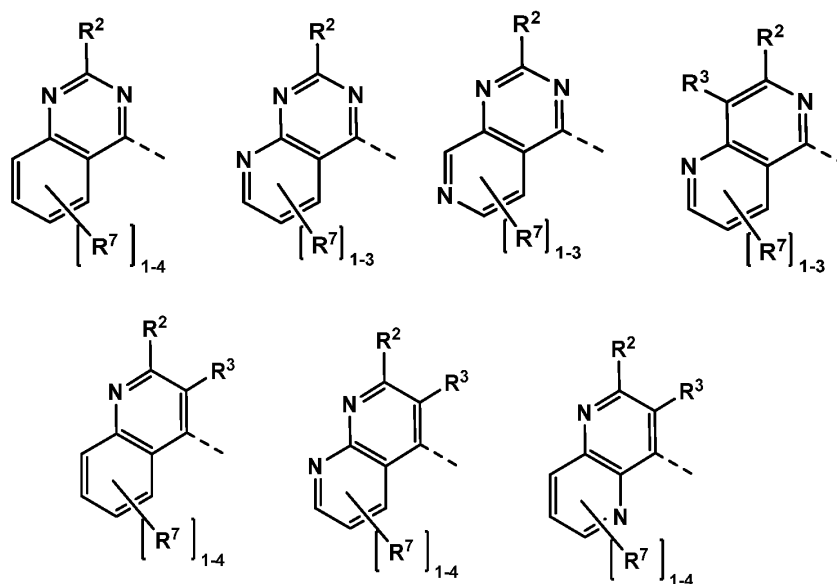


and the following group of formulae (Y¹-8)



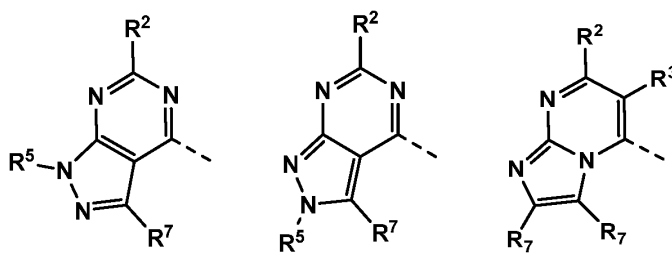
- 10 wherein **A**¹, **A**², **A**³, **A**⁴, **R**², **R**⁴ and **R**⁷ are independently as defined hereinabove.

[0077] In one preferred embodiment, **Y**¹ is a 10-membered bicyclic [6,6] heteroaryl of the following formula



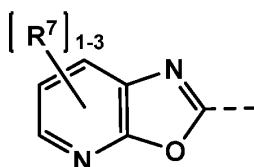
5 wherein **R**², **R**³ and **R**⁷ are independently as defined hereinabove.

[0078] In one preferred embodiment, **Y**¹ is a 9-membered bicyclic [6,5] heteroaryl of the following formula



wherein **R**², **R**³, **R**⁵ and **R**⁷ are independently as defined hereinabove.

[0079] In one preferred embodiment, **Y**¹ is a 9-membered bicyclic [6,5] heteroaryl of the following formula



wherein **R**² and **R**⁷ are independently as defined hereinabove.

- 5 [0080] In one further preferred embodiment, **Y**¹ is selected from 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 5-(trifluoromethyl)oxazolo[5,4-*b*]pyridin-2-yl, 2-(trifluoromethyl)quinazolin-4-yl, 1-(2-methoxyethyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 1-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 2-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4-yl, 2-(difluoromethyl)-6-methoxypyrido[2,3-*d*]pyrimidin-4-yl, 2-(trifluoromethyl)quinazolin-4-yl, and 6-methoxy-2-(trifluoromethyl)quinazolin-4-yl.

- [0081] In one further preferred embodiment, **Y**¹ is selected from 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 5-(trifluoromethyl)oxazolo[5,4-*b*]pyridin-2-yl, 2-(trifluoromethyl)quinazolin-4-yl, 1-(2-methoxyethyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 1-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 2-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4-yl, 2-(difluoromethyl)-6-methoxypyrido[2,3-*d*]pyrimidin-4-yl, 2-(trifluoromethyl)quinazolin-4-yl, 6-methoxy-2-(trifluoromethyl)quinazolin-4-yl, 6-methoxy-2-methylquinazolin-4-yl, 2-methylpyrido[2,3-*d*]pyrimidin-4-yl, 2-cyclopropyl-6-(trifluoromethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 6-methoxy-2-methylpyrido[2,3-*d*]pyrimidin-4-yl, 2-methyl-6-(trifluoromethyl)-2*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl, 6-methoxy-2-methyl-1,8-naphthyridin-4-yl, 7-(difluoromethyl)-1,6-naphthyridin-5-yl, 3-methoxy-7-methyl-1,6-naphthyridin-5-yl, 6-chloro-8-fluoro-2-methylquinazolin-4-yl, 2-methyl-6-(trifluoromethyl)quinazolin-4-yl, 6-ethoxy-2-methylquinazolin-4-yl, 6-chloro-7-fluoro-2-methylquinazolin-4-yl, 5-methoxy-2-methylquinazolin-4-yl, 6,7-dimethoxy-2-methylquinazolin-4-yl, 6,7-dimethoxyquinolin-4-yl, 3-chloro-7-methyl-1,6-naphthyridin-5-yl, 6-methoxyquinolin-4-yl, 6-methoxy-2-methylquinolin-4-yl, 6-chloro-

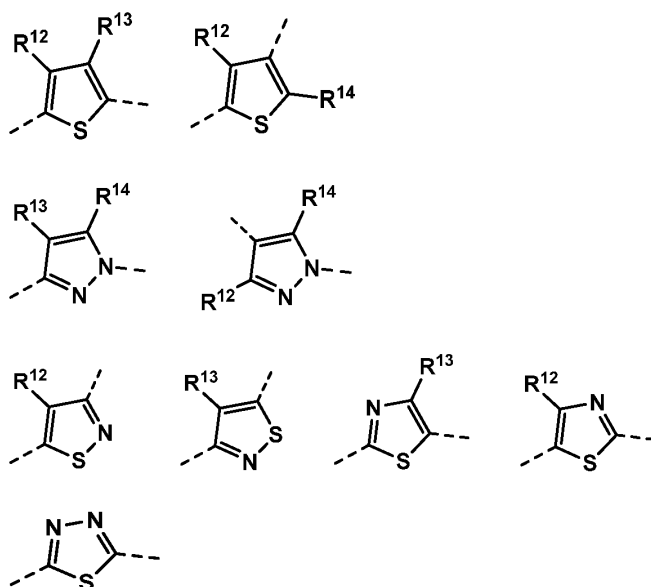
8-fluoro-2-methylquinazolin-4-yl, 6-chloroquinolin-4-yl, 7-methoxyquinolin-4-yl, 6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl, 7-(trifluoromethyl)imidazo[1,2-a]pyrimidin-5-yl, 7-methylimidazo[1,2-a]pyrimidin-5-yl, 2-methyl-1,8-naphthyridin-4-yl, 6-methoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl, 2-methyl-6-(trifluoromethyl)quinolin-4-yl, 6-methoxy-2-methyl-1,5-naphthyridin-4-yl, (6-methoxy-2-methyl-1,5-naphthyridin-4-yl, 2-methyl-6-(trifluoromethyl)-1,8-naphthyridin-4-yl, 5-fluoro-6-methoxy-2-methylquinazolin-4-yl, 6-(difluoromethoxy)-2-methylquinazolin-4-yl, 2-methyl-6-(trifluoromethoxy)quinazolin-4-yl, and 7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl.

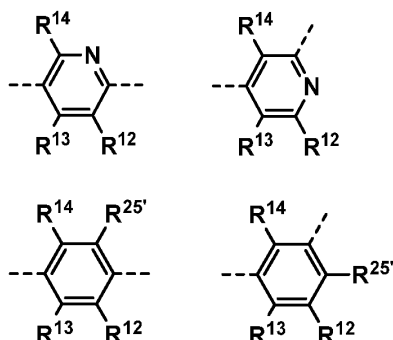
10 [0082] In one embodiment, Y^1 is *not* thieno[2,3-d]pyrimidin-4-yl.

[0083] In one embodiment, Y^1 is *not* 7H-pyrrolo[2,3-d]pyrimidinyl. In one embodiment, Y^1 is *not* 9H-purinyl.

Y^2 definitions

[0084] In formula (I) above, Y^2 is a 5- or 6-membered heteroaryl or 6-membered aryl,
15 preferably selected from the following group of formulae

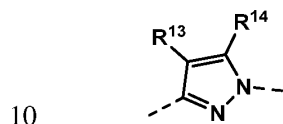




wherein $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ and $\mathbf{R}^{25'}$ are each independently selected from hydrogen, halogen, cyano, hydroxy, amino, $-(\text{C}_1\text{-C}_6)$ alkyl, $-(\text{C}_3\text{-C}_6)$ cycloalkyl,
 5 $-\text{CH}_2\text{-O}-(\text{C}_1\text{-C}_6)$ alkyl, $-\text{O}-(\text{C}_1\text{-C}_6)$ alkyl, and $-\text{N}-((\text{C}_1\text{-C}_6)$ alkyl) $_2$;

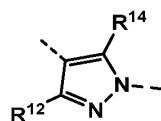
wherein each of the $-(\text{C}_1\text{-C}_6)$ alkyl in $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ or $\mathbf{R}^{25'}$ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, amino, $-\text{O}-(\text{C}_1\text{-C}_6)$ alkyl, and $-\text{N}-((\text{C}_1\text{-C}_6)$ alkyl) $_2$.

[0085] According to one embodiment, $\mathbf{Y}^2$ is *not* the following formula



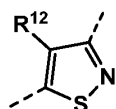
wherein $\mathbf{R}^{13}$ and $\mathbf{R}^{14}$ are each independently as defined hereinabove.

[0086] According to one embodiment, $\mathbf{Y}^2$ is *not* the following formula



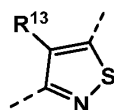
wherein $\mathbf{R}^{12}$ and $\mathbf{R}^{14}$ are each independently as defined hereinabove.

15 [0087] According to one embodiment, $\mathbf{Y}^2$ is *not* the following formulae



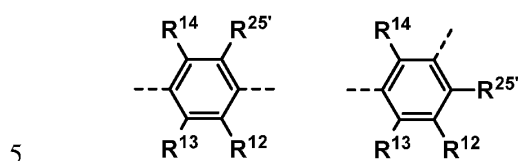
wherein $\mathbf{R}^{12}$ is as defined hereinabove.

[0088] According to one embodiment, $\mathbf{Y}^2$ is *not* the following formulae



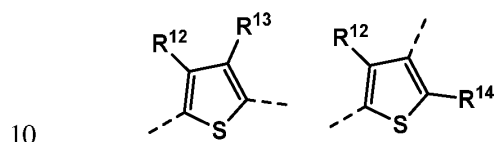
wherein $\mathbf{R}^{13}$ is as defined hereinabove.

[0089] According to one embodiment, $\mathbf{Y}^2$ is *not* selected from the following formulae



wherein $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ and $\mathbf{R}^{25'}$ are as defined hereinabove (*i.e.*, $\mathbf{Y}^2$ is *not* a 6-membered aryl).

[0090] According to one preferred embodiment, $\mathbf{Y}^2$ is selected from the following formulae



wherein $\mathbf{R}^{13}$ and $\mathbf{R}^{14}$ are each independently as defined hereinabove.

[0091] According to one embodiment, $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ and $\mathbf{R}^{25'}$ are each independently selected from hydrogen, halogen, cyano, hydroxy, $-(\text{C}_1\text{-C}_6)$ alkyl, $-(\text{C}_3\text{-C}_6)$ cycloalkyl, $-\text{CH}_2\text{-O}-(\text{C}_1\text{-C}_6)$ alkyl, and $-\text{O}-(\text{C}_1\text{-C}_6)$ alkyl; wherein each of the $-(\text{C}_1\text{-C}_6)$ alkyl in $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ or $\mathbf{R}^{25'}$ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, and $-\text{O}-(\text{C}_1\text{-C}_6)$ alkyl.

15

[0092] According to one embodiment, $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ or $\mathbf{R}^{25'}$ may optionally comprise at least one $(\text{C}_1\text{-C}_6)$ haloalkyl. In one embodiment, the $-(\text{C}_1\text{-C}_6)$ haloalkyl is trifluoromethyl (CF_3).

[0093] In one embodiment, $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ and $\mathbf{R}^{25'}$ are independently selected from hydrogen and (C₁-C₃) alkyl. In one preferred embodiment, $\mathbf{R}^{12}$, $\mathbf{R}^{13}$, $\mathbf{R}^{14}$ and $\mathbf{R}^{25'}$ are each hydrogen.

L definitions

5 [0094] In formula (I) above, - $\mathbf{L}$ is selected from $-(\mathbf{CR}^{10}\mathbf{R}^{11})_n$; wherein

n is an integer selected from 0, 1, 2, 3 and 4;

$\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are independently selected from hydrogen, halogen, hydroxy, amino, -(C₁-C₃) alkyl, -(C₁-C₂) haloalkyl, -(C₁-C₂) hydroxyalkyl, -(C₁-C₂) aminoalkyl, -O-(C₁-C₄) alkyl, -NH-(C₁-C₃) alkyl, and
10 -N-((C₁-C₃) alkyl)₂;

or $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ form together with the carbon atom to which they are bond a (C₃-C₆) cycloalkyl.

[0095] According to one embodiment, n is 0, 1, 2 or 3. In one embodiment, n is 0, 1, 2 or 3. In one particular embodiment, n is 0, 1 or 2. In one preferred embodiment, n is 0
15 or 1. In one preferred embodiment, n is 0. In one preferred embodiment, n is 1.

[0096] According to one embodiment, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are independently selected from hydrogen, halogen, hydroxy, -(C₁-C₃) alkyl, -(C₁-C₂) haloalkyl, -(C₁-C₂) hydroxyalkyl and -O-(C₁-C₄) alkyl; or $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ form together with the carbon atom to which they are bond a (C₃-C₆) cycloalkyl. In one embodiment, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are independently
20 selected from hydrogen, (C₁-C₃) alkyl and hydroxy. In one embodiment, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are independently selected from hydrogen and (C₁-C₃) alkyl. In one embodiment, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are independently selected from hydrogen and hydroxy. In one particular embodiment, $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$ are each hydrogen. In one preferred embodiment, $\mathbf{L}$ is -CH₂-. In one preferred embodiment, $\mathbf{L}$ is -CH(OH)-. In one preferred embodiment, $\mathbf{L}$ is
25 -CH(OH)CH₂-.

[0097] From the above definitions for $\mathbf{R}^{10}$ and $\mathbf{R}^{11}$, it results that $\mathbf{L}$ cannot include a carbonyl group, in particular, $\mathbf{L}$ cannot be -C(O)-, -CH₂C(O)- or -C(O)CH₂-.

***Z^{1'}* definitions**

[0098] In formula (I) above, **Z^{1'}** is selected from -NR^{23'}R^{24'} and a -(C₃-C₇) heterocycloalkyl comprising at least one nitrogen atom;

wherein

5 each nitrogen atom of the (C₃-C₇) heterocycloalkyl in **Z^{1'}** is optionally substituted with at least one group selected from -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl;

10 each carbon atom of the (C₃-C₇) heterocycloalkyl in **Z^{1'}** is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl;

wherein each of the -(C₁-C₆) alkyl, -(C₁-C₆) alkylene, -(C₃-C₇) cycloalkyl or -(C₃-C₇) heterocycloalkyl in **Z^{1'}** is optionally substituted with at least one halogen (*this definition applies to alkyl, alkylene, cycloalkyl or heterocycloalkyl present in the substituents of both nitrogen and carbon atom(s) of the heterocycloalkyl*); and

20 wherein each of the aryl or heteroaryl in **Z^{1'}** is optionally substituted with at least one group selected from halogen, CN, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl (*this definition applies to aryl or heteroaryl present in the substituents of both nitrogen and carbon atom(s) of the heterocycloalkyl*); and

R^{23'} and **R^{24'}** are each independently selected from hydrogen, -(C₁-C₆) alkyl, 25 -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-aryl;

wherein

each of the $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene, $-(C_3-C_7)$ cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl in $R^{23'}$ or $R^{24'}$ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, $-O-(C_1-C_6)$ alkyl, $-NH-(C_1-C_6)$ alkyl, and $-N-((C_1-C_6) \text{ alkyl})_2$; and

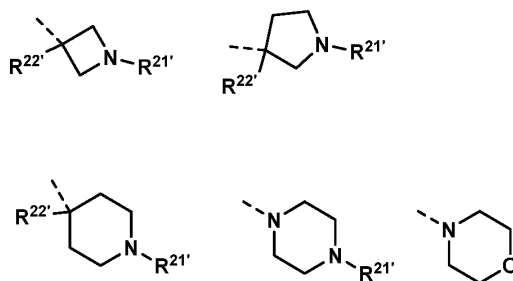
- 5 each of the aryl or heteroaryl in $R^{23'}$ or $R^{24'}$ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, $-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl, $-NH-(C_1-C_6)$ alkyl, and $-N-((C_1-C_6) \text{ alkyl})_2$.

[0099] According to one preferred embodiment, $Z^{1'}$ is as defined hereinabove, except that each nitrogen atom of the (C_3-C_7) heterocycloalkyl in $Z^{1'}$ is *not* substituted by $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl and each carbon atom of the (C_3-C_7) heterocycloalkyl in $Z^{1'}$ is *not* substituted by $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl.

[0100] According to one embodiment, $Z^{1'}$ may optionally comprise at least one $-(C_1-C_6)$ haloalkyl or $-(C_3-C_7)$ halocycloalkyl. In one embodiment, $Z^{1'}$ may optionally comprise at least one (C_1-C_6) haloalkyl. In one particular embodiment, the $-(C_1-C_6)$ haloalkyl is trifluoromethyl (CF_3).

[0101] According to one embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl comprising as intracyclic heteroatoms: one nitrogen atom, or two nitrogen atoms, or one nitrogen atom and one oxygen atom; wherein each nitrogen and carbon atom of the $-(C_3-C_7)$ heterocycloalkyl in $Z^{1'}$ is optionally substituted as defined hereinabove.

- 20 [0102] According to one embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl selected from the following formulae



wherein

$R^{21'}$ is selected from hydrogen, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, and $-(C_1-C_6)$ alkylene-O- (C_3-C_7) cycloalkyl;

- 5 $R^{22'}$ is selected from hydrogen, halogen, cyano, hydroxy, oxo, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene-O- (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, -O- (C_1-C_6) alkyl, and -O- (C_3-C_7) cycloalkyl; and

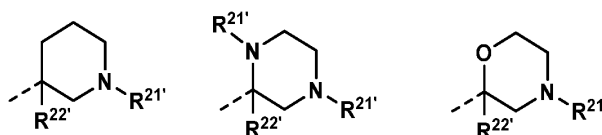
- 10 each carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl may optionally be substituted by at least one $R^{22''}$ group;

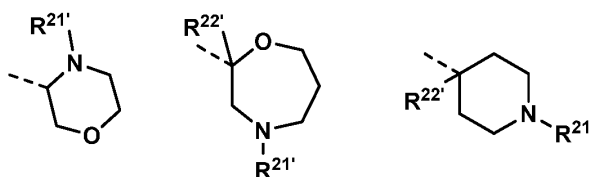
- wherein each $R^{22''}$ is independently selected from hydrogen, halogen, cyano, hydroxy, oxo, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene-O- (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, -O- (C_1-C_6) alkyl, and -O- (C_3-C_7) cycloalkyl;
- 15

- wherein each of the $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene $-(C_3-C_7)$ cycloalkyl or $-(C_3-C_7)$ heterocycloalkyl in $R^{21'}$, $R^{22'}$ or $R^{22''}$ is optionally substituted with at least one halogen; and
- 20

wherein each of the aryl or heteroaryl in $R^{21'}$, $R^{22'}$ or $R^{22''}$ is optionally substituted with at least one group selected from halogen, CN, $-(C_1-C_6)$ alkyl, -O- (C_1-C_6) alkyl, and O- (C_3-C_7) cycloalkyl.

- [0103] According to another embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl selected from the following formulae
- 25



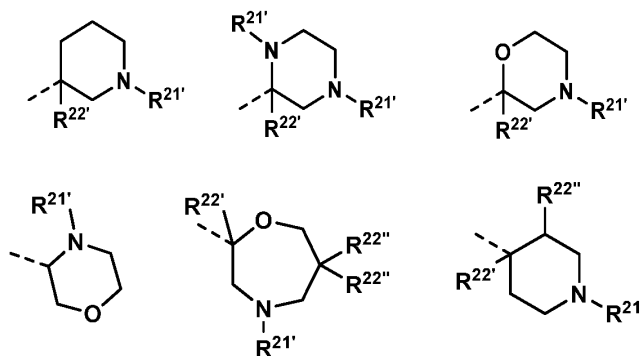


wherein

$R^{21'}$ and $R^{22'}$ are independently as defined hereinabove; and

- each carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl may optionally
 5 be substituted by at least one $R^{22''}$ group; wherein each $R^{22''}$ is independently as defined hereinabove.

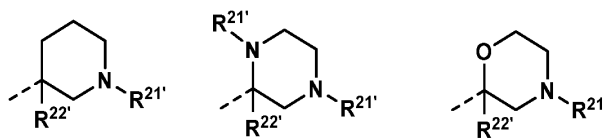
[0104] In another embodiment, Z^1 is a $-(C_3-C_7)$ heterocycloalkyl selected from the following formulae

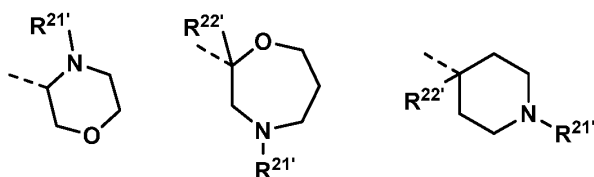


10

wherein $R^{21'}$ and $R^{22'}$ and each $R^{22''}$ are independently as defined hereinabove.

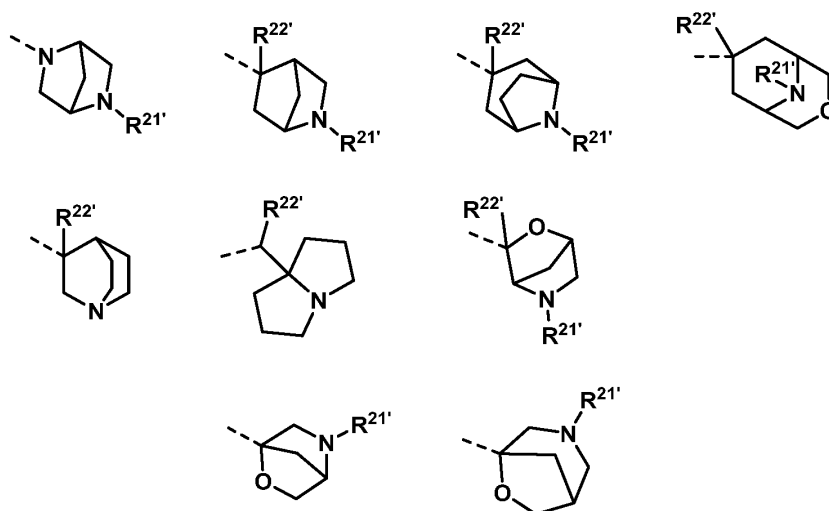
[0105] In another embodiment, Z^1 is a $-(C_3-C_7)$ heterocycloalkyl selected from the following formulae





wherein $R^{21'}$ and $R^{22'}$ are as defined hereinabove.

[0106] According to another embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl of the following formula



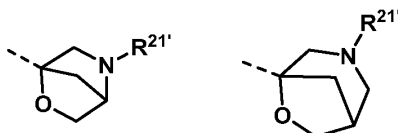
5

wherein

$R^{21'}$ is as defined hereinabove; and

each carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl may optionally
 10 be substituted by at least one $R^{22''}$ group; wherein each $R^{22''}$ is independently as defined hereinabove.

[0107] In another preferred embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl of the following formula



wherein

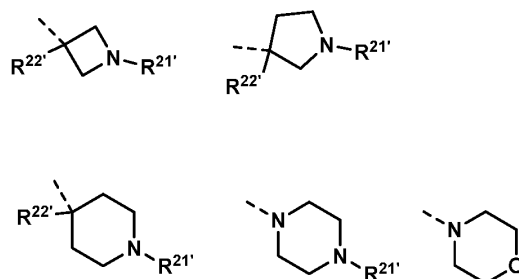
$R^{21'}$ is as defined hereinabove; and

each carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl may optionally be substituted by at least one $R^{22''}$ group; wherein each $R^{22''}$ is independently as defined hereinabove.

[0108] In one embodiment, only one carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl is substituted by at least one $R^{22''}$ group. In one embodiment, each carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl is either not substituted or substituted by only one $R^{22'}$ or $R^{22''}$ group.

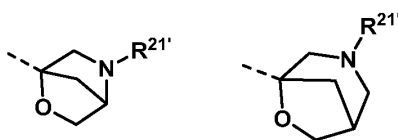
10 [0109] In one embodiment, no carbon atom in the cyclic moiety of the $-(C_3-C_7)$ heterocycloalkyl is substituted by at least one $R^{22''}$ group.

[0110] In one embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl selected from the following formulae



15 wherein $R^{21'}$ and $R^{22'}$ are independently as defined hereinabove.

[0111] In one embodiment, $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl of the following formula



wherein $R^{21'}$ is as defined hereinabove.

[0112] In one particular embodiment, $R^{21'}$ is selected from hydrogen, $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkyl substituted with at least one fluoro, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene-

(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, and -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl. In one preferred embodiment, **R**^{21'} is selected from hydrogen, -(C₁-C₃) alkyl, -(C₃-C₅) cycloalkyl, -(C₁-C₃) alkylene-(C₃-C₅) cycloalkyl, oxetanyl, and -(C₁-C₃) alkylene-O-(C₁-C₃) alkyl.

- 5 [0113] In one particular embodiment, **R**^{21'} is selected from hydrogen, -(C₁-C₆) alkyl and -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl. In one preferred embodiment, **R**^{21'} is selected from hydrogen, -(C₁-C₃) alkyl and -(C₁-C₃) alkylene-O-(C₁-C₃) alkyl.

- [0114] In one particular embodiment, **R**^{22'} is selected from hydrogen, halogen, -(C₁-C₆) alkyl, -(C₁-C₆) alkyl substituted with at least one fluoro, cyano, hydroxy and -O-(C₁-C₆) alkyl. In one preferred embodiment, **R**^{21'} is selected from hydrogen, fluoro, trifluoromethyl, cyano, hydroxy and -O-(C₁-C₃) alkyl.

[0115] In one particular embodiment, **R**^{22'} is selected from hydrogen, halogen, hydroxy and -O-(C₁-C₆) alkyl; preferably hydrogen, fluoro, hydroxy and -O-(C₁-C₃) alkyl.

- [0116] According to one preferred embodiment, **Z**^{1'} is selected from azetidiny, 1-methylazetidiny, 3-fluoroazetidiny, 3-hydroxyazetidiny, 3-methoxyazetidiny, 1-(2-methoxyethyl)azetidiny, pyrrolidiny, 3-fluoropyrrolidiny, 3-hydroxypyrrolidiny, 3-methoxypyrrolidiny, piperidiny, 4-hydroxypiperidiny, piperaziny, morpholinyl, aminoethyl, aminomethyl, and N-(methylamino)-methyl. In one preferred embodiment, **Z**^{1'} is selected from azetidin-3-yl, 1-methylazetidin-3-yl, 3-fluoroazetidin-3-yl, 3-hydroxyazetidin-3-yl, 3-methoxyazetidin-3-yl, 1-methylpiperidin-4-yl, 1-(2-methoxyethyl)azetidin-3-yl, pyrrolidin-3-yl, 3-fluoropyrrolidin-3-yl, 3-hydroxypyrrolidin-3-yl, 3-methoxypyrrolidin-3-yl, morpholinomethyl, 3-methoxy-1-methylpyrrolidin-3-yl, piperidin-4-yl, 4-hydroxypiperidin-4-yl, 4-cyano-1-methylpiperidin-4-yl, 3-hydroxy-1-methylpyrrolidin-3-yl, 4-methoxypiperidin-4-yl, 4-hydroxy-1-isopropylpiperidin-4-yl, 1-hydroxy-2-(methylamino)ethyl, 1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-methylpiperidin-4-yl, 4-hydroxy-1,3-dimethylpiperidin-4-yl, 1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-(2-methoxyethyl)piperidin-4-yl, 1-cyclobutyl-4-hydroxypiperidin-4-yl, thiophen-2-yl, 1-cyclopropyl-4-hydroxypiperidin-4-yl, piperazin-1-yl, 3-hydroxy-1-

methylpiperidin-4-yl, 4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl, 4-methoxy-1-methylpiperidin-4-yl, 3-hydroxy-1-methylpiperidin-3-yl, morpholin-4-yl, morpholin-2-yl, 4-methylmorpholin-2-yl, 4-methylmorpholin-3-yl, morpholin-3-yl, 2-aminoethyl, aminomethyl, and N-(methylamino)-methyl, 3-hydroxy-1-methylazetidin-3-yl, 5-(hydroxy(1-methylpiperidin-4-yl)methyl, 3-hydroxy-1-isopropylazetidin-3-yl, 6-oxa-3-azabicyclo[3.2.1]octan-5-yl, 3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl, 3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-3-yl, 6,6-difluoro-1,4-oxazepan-2-yl, 2-methylmorpholin-2-yl, 2-(trifluoromethyl)morpholin-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-isopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 7-hydroxy-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl, 5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl, 3-hydroxyquinuclidin-3-yl, 5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl, 1-hydroxy-2-morpholinoethyl, 5-(hydroxy(4-methylmorpholin-2-yl)methyl, 5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl, and 2-(dimethylamino)-1-hydroxyethyl.

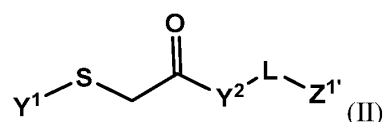
[0117] In one preferred embodiment, **Z¹** is selected from azetidiny, 1-methylazetidiny, 3-fluoroazetidiny, 3-hydroxyazetidiny, 3-methoxyazetidiny, 1-(2-methoxyethyl)azetidiny, pyrrolidiny, 3-fluoropyrrolidiny, 3-hydroxypyrrolidiny, 3-methoxypyrrolidiny, piperidiny, 4-hydroxypiperidiny, piperaziny, and morpholiny.

[0118] In one preferred embodiment, **Z¹** is selected from azetidin-3-yl, 1-methylazetidin-3-yl, 3-fluoroazetidin-3-yl, 3-hydroxyazetidin-3-yl, 3-methoxyazetidin-3-yl, 1-(2-methoxyethyl)azetidin-3-yl, pyrrolidin-3-yl, 3-fluoropyrrolidin-3-yl, 3-hydroxypyrrolidin-3-yl, 3-methoxypyrrolidin-3-yl, piperidin-4-yl, 4-hydroxypiperidin-4-yl, piperazin-1-yl, morpholin-4-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 6-oxa-3-azabicyclo[3.2.1]octan-5-yl, and 3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl.

[0119] In another preferred embodiment, **Z¹** is selected from aminoethyl, aminomethyl, and (methylamino)methyl.

Further general formulae

[0120] According to one embodiment, the compound of formula (I) is a compound of formula (II)



5 or a pharmaceutically acceptable salt and/or solvate thereof;

wherein

Y¹, **Y**² and **L** are independently as defined hereinabove under formula (I); and

Z^{1'} is a -(C₃-C₇) heterocycloalkyl comprising at least one nitrogen atom;

wherein

10 each nitrogen atom of the (C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one group selected from -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl;

15 each carbon atom of the (C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, 20 -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl;

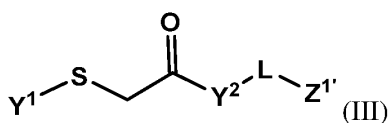
25 wherein each of the -(C₁-C₆) alkyl, -(C₁-C₆) alkylene -(C₃-C₇) cycloalkyl or -(C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one halogen (*this definition applies to alkyl, alkylene, cycloalkyl or heterocycloalkyl present in the substituents of both nitrogen and carbon atom(s) of the heterocycloalkyl*); and

wherein each of the aryl or heteroaryl in **Z**^{1'} is optionally substituted with at least one group selected from halogen, CN, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl (*this definition applies to aryl or heteroaryl present in the substituents of both nitrogen and carbon atom(s) of the heterocycloalkyl*); and

- 5 [0121] In other words, in the present application, a compound of formula (II) is a compound of formula (I), wherein **Z**^{1'} is a -(C₃-C₇) heterocycloalkyl comprising at least one nitrogen atom as defined hereinabove under formula (I).

[0122] In one preferred embodiment, the compound of formula (I), in particular the compound of formula (II), is *not* selected from 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-
 10 ((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one, and 2-((1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one.

[0123] According to one embodiment, the compound of formula (I) is a compound of formula (III)



- 15 or a pharmaceutically acceptable salt and/or solvate thereof;

wherein

Y¹, **Y**² and **L** are independently as defined hereinabove under formula (I); and

Z^{1'} is -**NR**^{23'}**R**^{24'}; wherein **R**^{23'} and **R**^{24'} are each independently selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -
 20 (C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-aryl;

wherein

each of the -(C₁-C₆) alkyl, -(C₁-C₆) alkylene, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl in **R**^{23'} or **R**^{24'} is optionally substituted with at least one group
 25 selected from halogen, cyano, hydroxy, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl and -N-((C₁-C₆) alkyl)₂; and

each of the aryl or heteroaryl in **R**^{23'} or **R**^{24'} is optionally substituted with at least one group selected from halogen, cyano, hydroxy, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl and -N-((C₁-C₆) alkyl)₂.

[0124] In other words, in the present application, a compound of formula (III) is a compound of formula (I), wherein **Z**^{1'} is -**NR**^{23'}**R**^{24'} as defined hereinabove under formula (I).

[0125] In one preferred embodiment, the compound of formula (I), in particular the compound of formula (III), is *not* selected from:

1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethanone hydrochloride
1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethanone
1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-cyclopropylquinazolin-4-yl)thio)ethanone
1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-ethylquinazolin-4-yl)thio)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((2,6-dimethyl-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-fluoro-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-fluoro-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-(difluoromethyl)-2-methyl-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-(trifluoromethyl)oxazolo[5,4-c]pyridin-2-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[4,5-b]pyridin-2-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((4-(trifluoromethyl)benzo[d]oxazol-2-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-cyclopropoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-((cyclopropylmethyl)amino)-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-morpholinoquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(piperidin-1-yl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(1,4-oxazepan-4-yl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-(3,3-difluoropyrrolidin-1-yl)-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(4-methylpiperazin-1-yl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-morpholino-2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(2-aminoethyl)thiophen-2-yl)-2-(quinazolin-4-ylthio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-ethoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
2-((6-methoxy-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-(trifluoromethyl)pyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylpyrido[3,2-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[3,2-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-8-(methylamino)-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((8-(dimethylamino)-2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-(dimethylamino)-2-methylpyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((8-methoxy-2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
2-((6-(2-oxa-5-azabicyclo[2.2.2]octan-5-yl)-2-methylquinazolin-4-yl)thio)-1-(5-(aminomethyl)thiophen-2-yl)ethan-1-one

1-(5-(aminomethyl)thiophen-2-yl)-2-((6-chloro-5-fluoro-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-ethoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-ethoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-chloro-8-fluoro-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(difluoromethyl)-6-methoxyquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((1-ethyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-ethyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((1-cyclopropyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(2-methoxyethyl)-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-((methylamino)methyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-(trifluoromethyl)oxazolo[4,5-b]pyridin-2-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-cyclopropyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3,5]triazin-4-yl)thio)ethan-1-one
2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((8-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-methyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3,5]triazin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-cyclopropyl-2-methylquinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)benzo[d]oxazol-2-yl)thio)ethan-1-one

1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethanone hydrochloride
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-cyclopropyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3,5]triazin-4-yl)thio)ethan-1-one hydrochloride
2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one hydrochloride
1-(5-(aminomethyl)thiophen-2-yl)-2-((8-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one hydrochloride
1-(5-(aminomethyl)thiophen-2-yl)-2-((7-methyl-2-(trifluoromethyl)pyrazolo[1,5-a][1,3,5]triazin-4-yl)thio)ethan-1-one hydrochloride
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-cyclopropyl-2-methylquinazolin-4-yl)thio)ethan-1-one hydrochloride
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)benzo[d]oxazol-2-yl)thio)ethan-1-one hydrochloride

[0126] The compounds listed hereinabove were named using ChemDraw® Professional 22.0 (PerkinElmer).

[0127] In one embodiment, the compound of formula (I), in particular the compound of formula (III), is *not* selected from:

(<i>rac</i>)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-cyclopropyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one
1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one

1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one
2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one

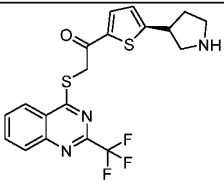
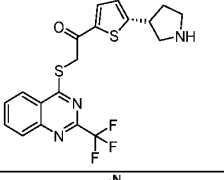
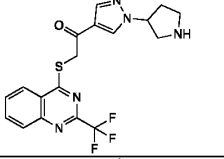
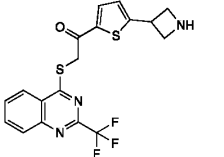
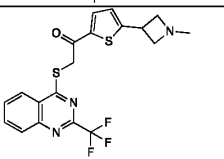
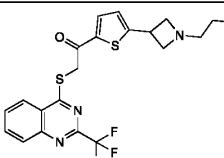
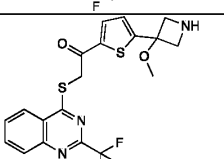
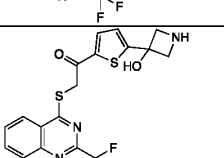
[0128] The compounds listed hereinabove were named using ChemDraw® Professional 22.0 (PerkinElmer).

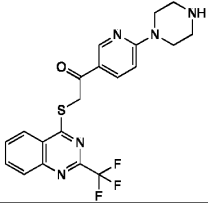
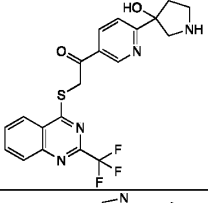
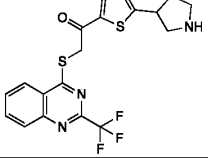
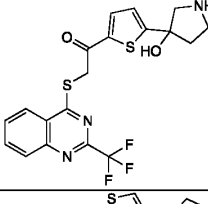
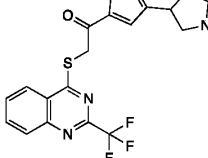
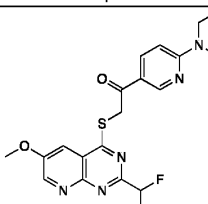
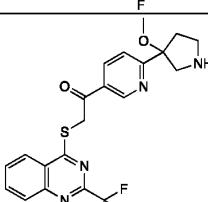
[0129] In one embodiment, the compound of formula (I), in particular the compound of formula (II), is *not* 1-morpholino-2-(5-(2-(thieno[2,3-d]pyrimidin-4-ylthio)acetyl)thiophen-2-yl)ethan-1-one.

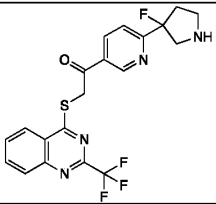
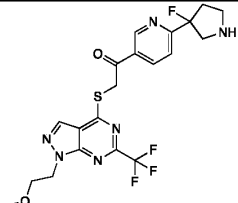
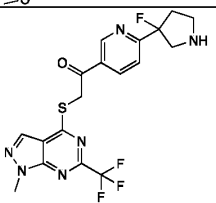
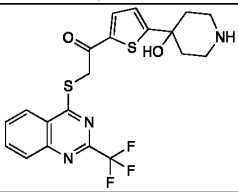
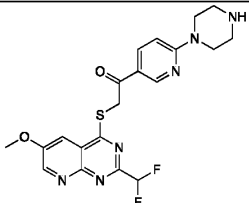
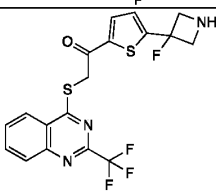
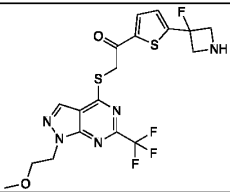
Specific compounds

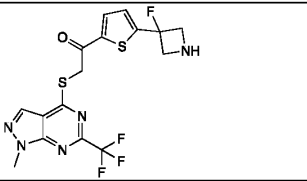
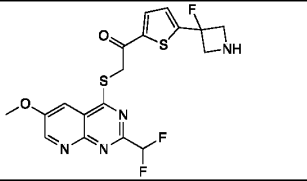
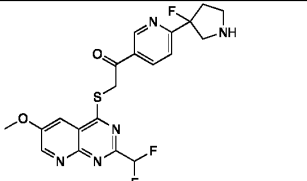
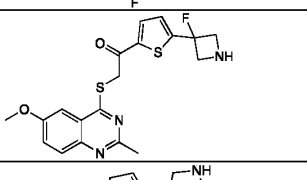
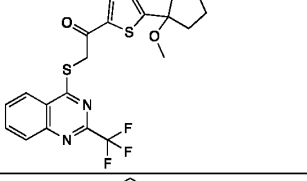
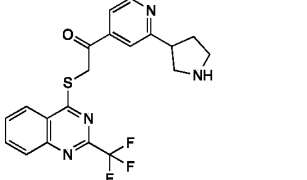
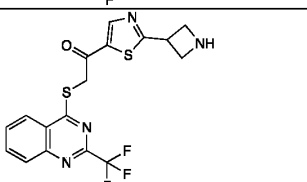
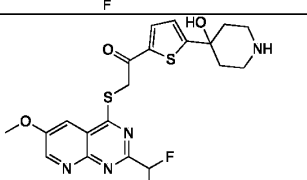
[0130] According to one embodiment, the compound of formula (I) is selected from the compounds of **Table 1** below.

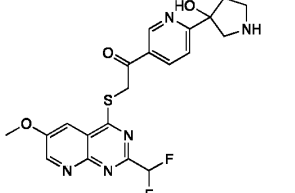
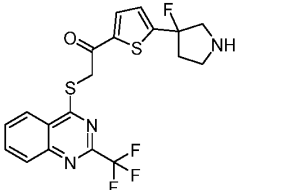
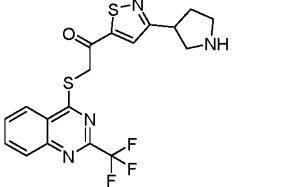
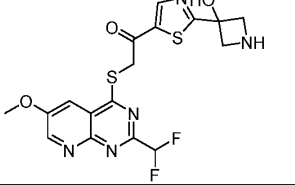
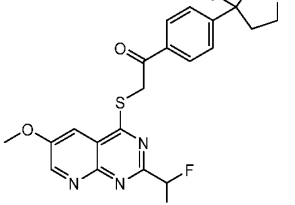
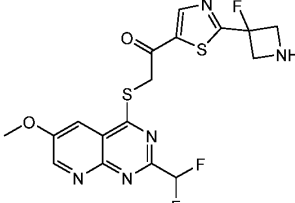
Cpd #	Structure	Name
2		1-(5-(piperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
3		1-(5-(morpholinomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
4		1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one
6		2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one

7 and 8		(R)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
		(S)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
9		1-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
10		1-(5-(azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
11		1-(5-(1-methylazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
12		1-(5-(1-(2-methoxyethyl)azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
13		1-(5-(3-methoxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
14		1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one

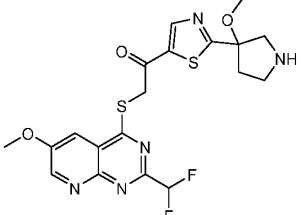
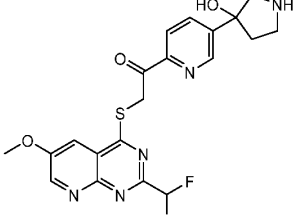
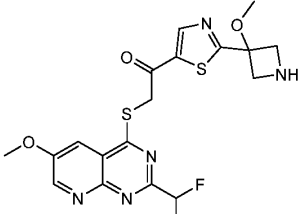
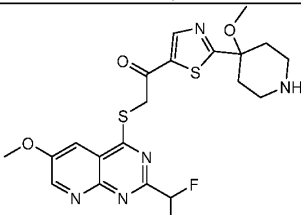
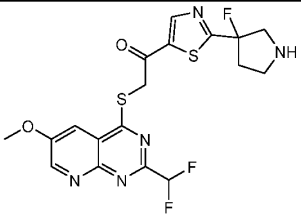
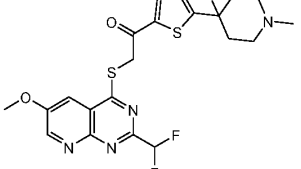
15		1-(6-(piperazin-1-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
16		1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
17		1-(2-(pyrrolidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
18		1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
19		1-(4-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
21		2-((2-(difluoromethyl)-6-methoxy)pyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-morpholinopyridin-3-yl)ethan-1-one
22		1-(6-(3-methoxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one

23		1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
24		1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
25		1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
26		1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
27		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(piperazin-1-yl)pyridin-3-yl)ethan-1-one
28		1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
29		1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one

30		1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
31		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)ethan-1-one
32		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)ethan-1-one
33		1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
34		1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
35		1-(2-(pyrrolidin-3-yl)pyridin-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
36		1-(2-(azetidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
37		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one

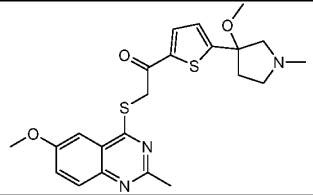
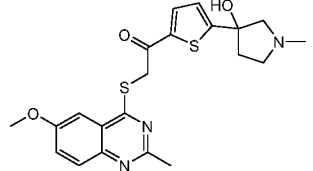
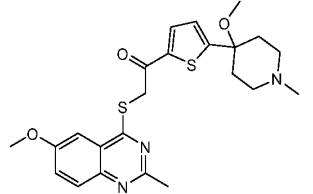
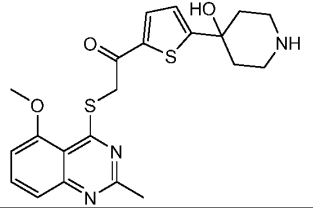
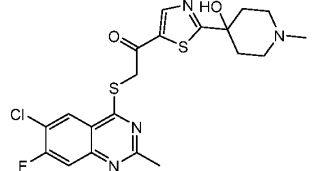
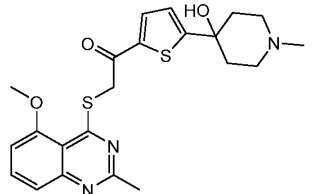
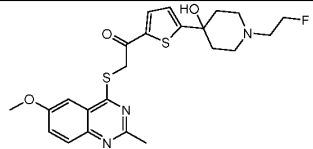
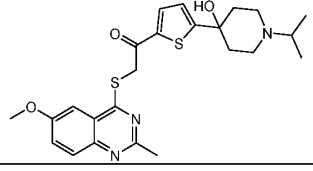
38		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)ethan-1-one
52		1-(5-(3-fluoropyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
53		1-(3-(pyrrolidin-3-yl)isothiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
54		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxyazetidin-3-yl)thiazol-5-yl)ethan-1-one
55		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(4-(3-hydroxypyrrolidin-3-yl)phenyl)ethan-1-one
56		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoroazetidin-3-yl)thiazol-5-yl)ethan-1-one

57		1-(4-(3-hydroxypyrrolidin-3-yl)phenyl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
58		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
59		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)ethan-1-one
60		2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
61		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
62		1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
63		2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one

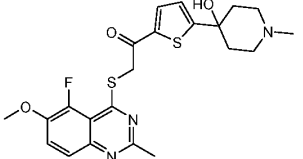
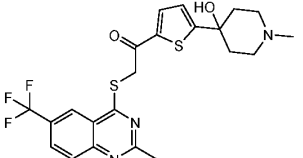
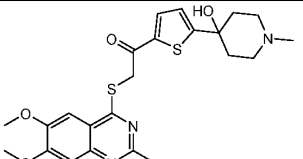
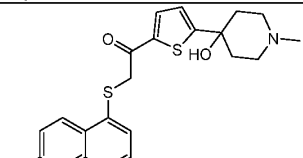
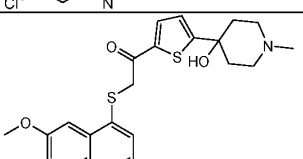
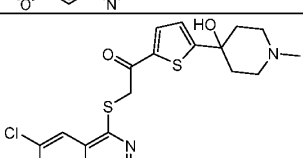
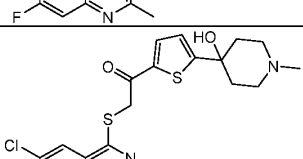
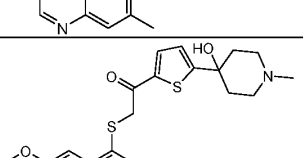
64		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-methoxypyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
65		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)pyridin-2-yl)ethan-1-one
66		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-methoxyazetidin-3-yl)thiazol-5-yl)ethan-1-one
67		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-methoxypiperidin-4-yl)thiazol-5-yl)ethan-1-one
68		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoropyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
69		2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one

70		1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
71		1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one
72		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
73		2-((6-chloro-8-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
74		1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
75		1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
76		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(piperidin-4-yl)thiophen-2-yl)ethan-1-one
77		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one

78		1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
79		1-(2-(3-hydroxy-1-methylpyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
80		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
81		1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
82		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
83		2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
84		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
85		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methoxypiperidin-4-yl)thiophen-2-yl)ethan-1-one

86		1-(5-(3-methoxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
87		1-(5-(3-hydroxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
88		1-(5-(4-methoxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
89		1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((5-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
90		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)ethan-1-one
91		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((5-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
92		1-(5-(1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
93		1-(5-(4-hydroxy-1-isopropylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

94		1-(5-(4-hydroxy-1-(2-methoxyethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
95		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
96		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
97		1-(5-(1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
98		1-(5-(1-(cyclopropyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
99		1-(5-(1-(cyclobutyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
100		1-(5-(4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
101		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-3-yl)thiophen-2-yl)ethan-1-one
102		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-3-yl)thiophen-2-yl)ethan-1-one

103		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
104		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
105		2-((6,7-dimethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
106		2-((7-chloroquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
107		2-((6,7-dimethoxyquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
108		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
109		2-((3-chloro-7-methyl-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
110		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one

111		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxyquinolin-4-yl)thio)ethan-1-one
112		1-(5-(hydroxy(1-methylpiperidin-4-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
113		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinolin-4-yl)thio)ethan-1-one
114		2-((6-chloro-8-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
115		2-((6-chloroquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
116		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methoxyquinolin-4-yl)thio)ethan-1-one
117		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methylimidazo[1,2-a]pyrimidin-5-yl)thio)ethan-1-one
118		2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one

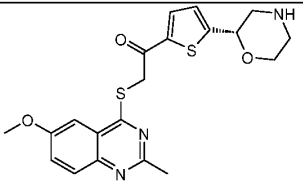
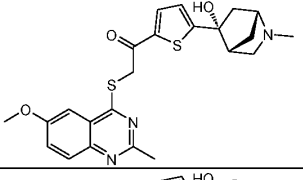
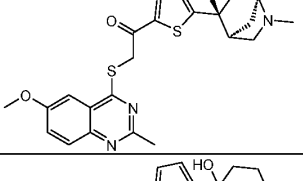
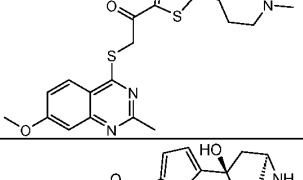
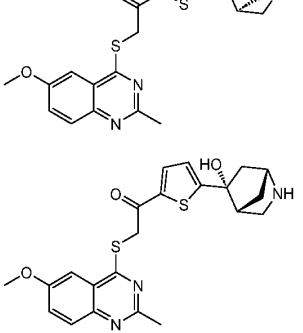
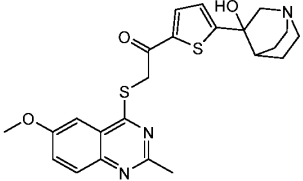
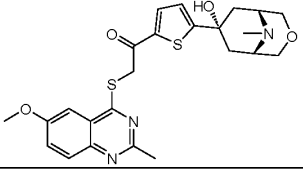
119		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
120		1-(5-(3-hydroxy-1-methylpiperidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
121		4-(5-(2-((6-methoxy-2-methylquinazolin-4-yl)thio)acetyl)thiophen-2-yl)-1-methylpiperidine-4-carbonitrile
122		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
123		1-(5-((3R,4S)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((3S,4R)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
124		1-(5-(4-hydroxy-1-(2,2,2-trifluoroethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
125		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethan-1-one

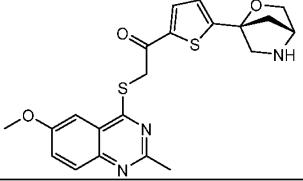
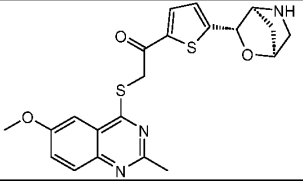
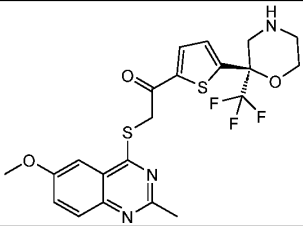
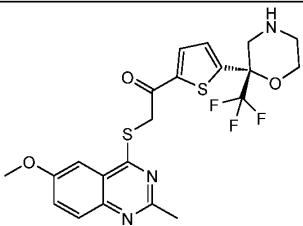
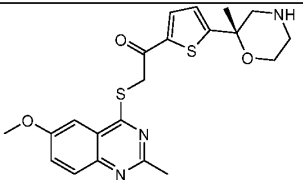
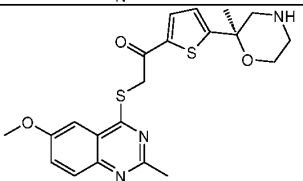
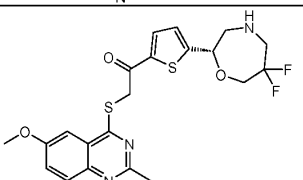
126 or 127		1-(5-((3R,4S)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
126 or 127		1-(5-((3S,4R)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
128		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
129		1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
130		1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
131		1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
133		1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one

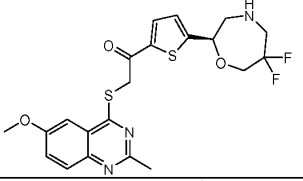
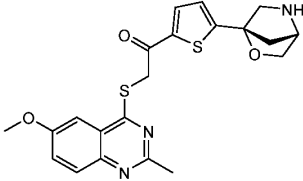
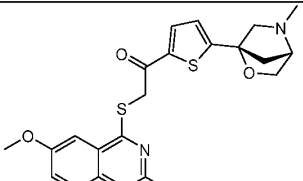
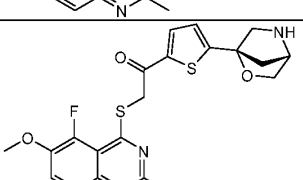
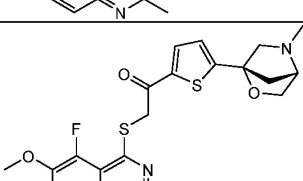
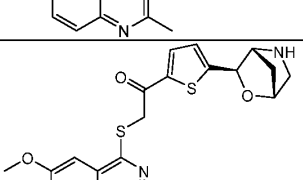
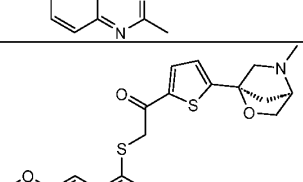
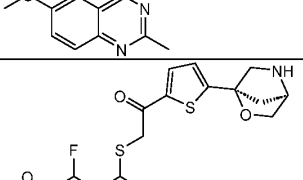
134		1-(2-(2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
135		1-(2-(5-isopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
136		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)ethan-1-one
137		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)ethan-1-one
138		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)ethan-1-one
139		1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
140		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-(trifluoromethyl)imidazo[1,2-a]pyrimidin-5-yl)thio)ethan-1-one

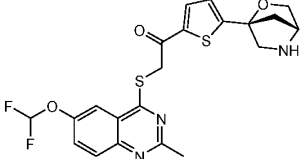
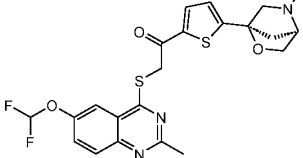
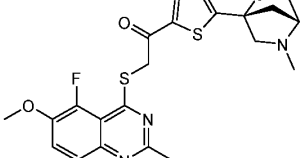
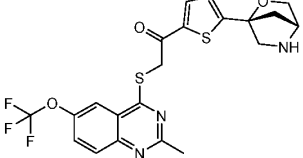
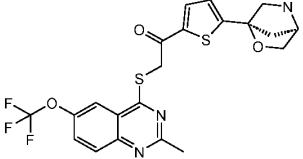
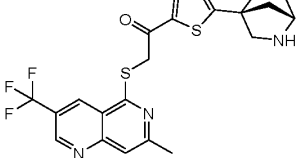
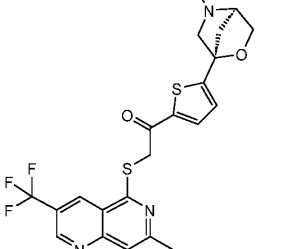
141		1-(5-(3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150		1-(5-((S)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150		1-(5-((R)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
144		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
145		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
147		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinolin-4-yl)thio)ethan-1-one
148		1-(5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150		1-(5-((R)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

142 or 143 or 149 or 150		1-(5-((S)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
151		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,5-naphthyridin-4-yl)thio)ethan-1-one
152		1-(5-(1-hydroxy-2-morpholinoethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
153		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
154		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-1,8-naphthyridin-4-yl)thio)ethan-1-one
155		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
156		2-((6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
157 or 158		(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one

157 or 158		(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
159 or 160		1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
159 or 160		1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
161		1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
162		1-(5-((1S,4S,5S)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((1R,4R,5R)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
163		1-(5-(3-hydroxyquinuclidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
164		1-(5-((1R,5S,7s)-7-hydroxy-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

165		1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
166		1-(5-((1S,3S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
167 or 168		(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethan-1-one
167 or 168		(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethan-1-one
169 or 170		(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
169 or 170		(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
171 or 172		(S)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

171 or 172		(R)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
173		1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
174		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
175		1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
176		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
177		1-(5-((1R,3R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
178		2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
179		1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

180		1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)ethan-1-one
181		2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
182		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
183		1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
184		1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
185		1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
186		1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one

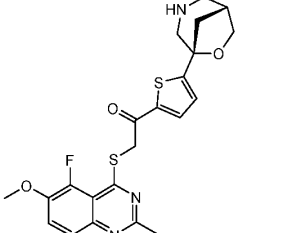
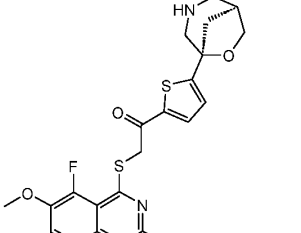
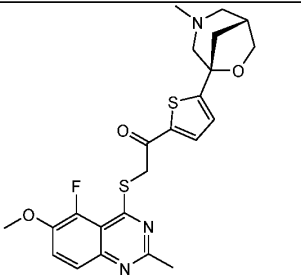
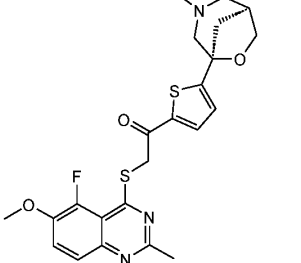
187 or 188		1-((5-((1R,5S)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
187 or 188		1-((5-((1S,5R)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
189 or 190		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-((5-((1R,5S)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one
189 or 190		2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-((5-((1S,5R)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one

Table 1

[0131] According to one preferred embodiment, the compound of formula (I) is selected from the compounds of **Table 1** herein and pharmaceutically acceptable salts and/or solvates thereof.

- 5 [0132] According to one embodiment, the compound of formula (I) is selected from the compounds of **Table 2** below.

<i>Cpd #</i>	<i>Structure</i>	<i>Name</i>
1		1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
5		2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
39		1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
40		1-(5-(aminomethyl)thiophen-2-yl)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
41		1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
42		2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethanone
43		1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethanone
44		1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one

45		1-(5-(aminomethyl)thiophen-2-yl)-2-((2-cyclopropyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
46		1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
47		2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one
48		1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
49		1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
50		1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one
51		2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one

Table 2

[0133] According to one preferred embodiment, the compound of formula (I) is selected from the compounds of **Table 2** herein and pharmaceutically acceptable salts and/or solvates thereof.

[0134] According to another embodiment, the compound of formula (I), in particular the compound of formula (II) or the compound of formula (III), is *not* selected from the compounds of **Table 2** herein.

- 5 [0135] According to one embodiment, the compound of formula (I) is selected from the compounds of **Table 3** below.

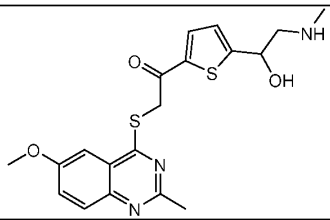
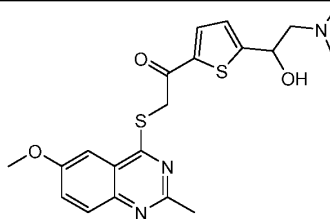
<i>Cpd #</i>	<i>Structure</i>	<i>Name</i>
132		1-(5-(1-hydroxy-2-(methylamino)ethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
146		1-(5-(2-(dimethylamino)-1-hydroxyethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

Table 3

[0136] According to one preferred embodiment, the compound of formula (I) is selected from the compounds of **Table 3** herein and pharmaceutically acceptable salts and/or solvates thereof.

- 10 [0137] According to another embodiment, the compound of formula (I), in particular the compound of formula (II) or the compound of formula (III), is *not* selected from the compounds of **Table 3** herein.

The compounds of **Table 1**, **Table 2** and **Table 3** were named using ChemDraw® Professional 22.0 (PerkinElmer).

15 **Alternative compounds**

[0138] All references herein to a compound of the invention (*e.g.*, a “compound of formula (I)”) include references to salts – preferably pharmaceutically acceptable salts, solvates, multi component complexes and liquid crystals thereof. All references herein to

a compound of the invention include references to polymorphs and crystal habits thereof. All references to a compound of the invention include references to pharmaceutically acceptable prodrugs thereof. All references to a compound of the invention include references to isotopically-labelled compounds, including deuterated compounds.

- 5 [0139] A compound of the invention (*e.g.*, a “compound of formula (I)”) and subformulae thereof may contain at least one asymmetric center(s) and thus may exist as different stereoisomeric forms. Accordingly, all references to a compound of the invention include references to all possible stereoisomers and includes not only the racemic compounds but the individual enantiomers and their non-racemic mixtures as well. When a compound is
10 desired as a single enantiomer, such single enantiomer may be obtained by stereospecific synthesis, by resolution of the final product or any convenient intermediate, or by chiral chromatographic methods as each are known in the art. Resolution of the final product, an intermediate, or a starting material may be carried out by any suitable method known in the art.
- 15 [0140] The compounds of the invention (*e.g.*, a “compound of formula (I)”) may be in the form of pharmaceutically acceptable salts. Pharmaceutically acceptable salts include the acid addition and base salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples include the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate,
20 cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate,
25 saccharate, stearate, succinate, tannate, tartrate, tosylate, trifluoroacetate and xinafoate salts. Suitable base salts are formed from bases which form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, 2-(diethylamino)ethanol, diolamine, ethanolamine, glycine, 4-(2-hydroxyethyl)-morpholine, lysine, magnesium, meglumine, morpholine, olamine, potassium, sodium,
30 tromethamine and zinc salts. Hemisalts of acids and bases may also be formed, for

example, hemisulphate and hemicalcium salts. When a compound contains an acidic group as well as a basic group the compound may also form internal salts, and such compounds are within the scope of the invention. When a compound contains a hydrogen-donating heteroatom (*e.g.*, NH), the invention also covers salts and/or isomers
5 formed by transfer of said hydrogen atom to a basic group or atom within the molecule. Pharmaceutically acceptable salts of compounds of the invention may be prepared by one or more of these methods: (i) by reacting the compound with the desired acid; (ii) by reacting the compound with the desired base; (iii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound or by ring-opening a suitable
10 cyclic precursor, *e.g.*, a lactone or lactam, using the desired acid; and/or (iv) by converting one salt of the compound to another by reaction with an appropriate acid or by means of a suitable ion exchange column. All these reactions are typically carried out in solution. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from
15 completely ionized to almost non-ionized.

Manufacturing process

[0141] This invention also relates to a process for manufacturing a compound of the invention as described herein. According to one embodiment, the process comprises the following steps (i-iv): (i) reacting an amine-containing alkyl chain or heterocycloalkyl
20 with a halo-heterocycle; then (ii) reacting a heterocycle or halo-heterocycle with first an acetylating reagent, and, where appropriate, subsequently a halogenating reagent, to form a halo-ketone; then (iii) reacting a halo-ketone with a thiol and, where appropriate, (iv) removal of at least one protective group.

Pharmaceutical compositions

25 [0142] This invention also relates to a pharmaceutical composition comprising a compound of the invention as described herein and at least one pharmaceutically acceptable carrier.

[0143] According to one embodiment, the pharmaceutical composition does not comprise any therapeutic agent other than the compound of the invention. According to another

embodiment, the pharmaceutical composition further comprises at least another therapeutic agent. In one embodiment, the at least another therapeutic agent is selected from therapeutic agent known in the art for treating inflammatory diseases, autoimmune diseases, proliferative diseases (such as cancers), neurodegenerative diseases, pains, neuropathies, psychiatric diseases, neurodevelopmental disorders, sleep disorders, cardiovascular diseases, addiction-related disorders, gastrointestinal diseases, pulmonary diseases, metabolic or hormonal disorders, immune disorders, age-related diseases, and/or idiopathic diseases.

[0144] The compound of the invention may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration.

Medical uses and methods of treatment

[0145] This invention also relates to a compound of the invention as described herein, or a pharmaceutical composition of the invention as described herein, for use as a medicament.

[0146] According to one particular embodiment, the compound or pharmaceutical composition of the invention is for use in the treatment and/or prevention of an HDAC6-associated disease as defined herein.

[0147] This invention also relates to a method of inhibiting an HDAC6 enzyme. According to one embodiment, the inhibition of an HDAC6 enzyme treats and/or prevents an HDAC6-associated disease. According to one embodiment, the method comprises a step of administering to a subject in need thereof a therapeutically effective amount of a compound of the invention as described herein, or of a pharmaceutical composition of the invention as described herein.

[0148] This invention also relates to a method for treating and/or preventing a HDAC6-associated disease comprising a step of administering to a subject in need thereof a therapeutically effective amount of a compound of the invention as described herein, or of a pharmaceutical composition of the invention as described herein. This invention also

relates to the use of a compound of the invention as described herein, or a pharmaceutical composition of the invention as described herein, in the manufacture of a medicament for the treatment and/or prevention of an HDAC6-associated disease. This invention also relates to the use of a compound of the invention as described herein, or a pharmaceutical
5 composition of the invention as described herein, in the treatment and/or prevention of an HDAC6-associated disease.

[0149] Advantageously, the compound of the invention shows a superior inhibitory activity against an HDAC enzyme (*e.g.*, class II HDAC enzyme, preferably HDAC6 enzyme) compared to state-of-the art compounds for treating and/or preventing an
10 HDAC-associated disease. Advantageously, the compound of the invention shows a low toxicity (*e.g.*, acute toxicity, chronic toxicity, genetic toxicity, hematotoxicity, reproductive toxicity, cardiotoxicity, carcinogenicity) against an HDAC enzyme (*e.g.*, class II HDAC enzyme, preferably HDAC6 enzyme) compared to state-of-the art compounds for treating and/or preventing an HDAC-associated disease. In particular, the
15 compound of the invention shows a low genetic toxicity.

[0150] According to one embodiment, the HDAC6-associated disease is selected from the group comprising or consisting of inflammatory diseases, autoimmune diseases, proliferative diseases (such as cancers), neurodegenerative diseases (including neuromuscular diseases), pains, neuropathies (including neuromuscular diseases),
20 psychiatric diseases, neurodevelopmental disorders, sleep disorders, cardiovascular diseases, addiction-related disorders, gastrointestinal diseases, pulmonary diseases, metabolic or hormonal disorders, immune disorders, age-related diseases, and idiopathic diseases. According to one embodiment, the HDAC6-associated disease is selected from the group comprising or consisting of inflammatory diseases, autoimmune diseases,
25 proliferative diseases (such as cancers), neurodegenerative diseases, pains, neuropathies, psychiatric diseases, neurodevelopmental disorders, sleep disorders and cardiovascular diseases. According to one embodiment, the HDAC6-associated disease is selected from the group comprising or consisting of proliferative diseases (such as cancers), neurodegenerative diseases, neuropathies and cardiovascular diseases.

Neurodegenerative diseases include neuromuscular diseases. Neuropathies include neuromuscular diseases.

[0151] A selection of references evidencing that inhibition of HDAC6 has the effect of treating and/or preventing a given class of diseases are listed as follows.

Diseases	References
Inflammatory diseases	Ran J and Zhou J.: "Targeted inhibition of histone deacetylase 6 in inflammatory diseases." Thorac. Cancer. 2019; 10(3):405-412. Lee JW et al.: "Histone Deacetylase 6 Inhibitor CKD-506 Inhibits NF-κB Signaling in Intestinal Epithelial Cells and Macrophages and Ameliorates Acute and Chronic Murine" Colitis. Inflamm. Bowel Dis. 2020; 26(6):852-862. Zhang Q et al. "Role of HDAC6 inhibition in sepsis-induced acute respiratory distress syndrome." Exp Ther Med. 2021; 21(5):422.
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Neurodegenerative diseases	Shen S and Kozikowski AP. "A patent review of histone deacetylase 6 inhibitors in neurodegenerative diseases (2014-2019)." <i>Expert Opin Ther Pat.</i> 2020;30(2):121-136. Li Y et al.: "Inhibition of Histone Deacetylase 6 (HDAC6) as a therapeutic strategy for Alzheimer's disease: A review (2010-2020)." <i>Eur J Med Chem.</i> 2021; 226:113874. Zhang K et al.: "Targeting autophagy using small-molecule compounds to improve potential therapy of Parkinson's disease." <i>Acta Pharm Sin B.</i> 2021; 11(10):3015-3034. Lemos M and Stefanova N. "Histone Deacetylase 6 and the Disease Mechanisms of alpha-Synucleinopathies." <i>Front Synaptic Neurosci.</i> 2020; 12:586453. Bae D et al.: "CKD-506: A novel HDAC6-selective inhibitor that exerts therapeutic effects in a rodent model of multiple sclerosis." <i>Sci Rep.</i> 2021; 11(1):14466. Guo W and Van Den Bosch L.: "Therapeutic potential of HDAC6 in amyotrophic lateral sclerosis." <i>Cell Stress.</i> 2017 Dec 19; 2(1):14-16
Pain	Sakloth F et al.: "HDAC6-selective inhibitors decrease nerve-injury and inflammation-associated mechanical hypersensitivity in mice." <i>Psychopharmacology (Berl).</i> 2020, 237(7):2139-2149.
Neuropathies	English K and Barton MC. "HDAC6: A Key Link Between Mitochondria and Development of Peripheral Neuropathy." <i>Front Mol Neurosci.</i> 2021; 14:684714. Prior R et al.: "HDAC6 as a potential therapeutic target for peripheral nerve disorders." <i>Expert Opin Ther Targets.</i> 2018;22(12):993-1007. Van Helleputte L et al.: "Inhibition of histone deacetylase 6 (HDAC6) protects against vincristine-induced peripheral neuropathies and inhibits tumor growth." <i>Neurobiol Dis.</i> 2018; 111:59-69.
Neuromuscular diseases	Rossaert E and Van Den Bosch L. "HDAC6 inhibitors: Translating genetic and molecular insights into a therapy for axonal CMT." <i>Brain Res.</i> 2020; 1733:146692. Osseni A, et al.: "Pharmacological inhibition of HDAC6 improves muscle phenotypes in dystrophin-deficient mice by downregulating TGF-β via Smad3 acetylation" <i>Nat Commun.</i> 2022; 13(1):7108.

Psychiatric diseases or Neurodevelopmental disorders	LoPresti P.: "HDAC6 in Diseases of Cognition and of Neurons." Cells. 2020;10(1):12. Kozikowski AP and al.: "Brain Penetrable Histone Deacetylase 6 Inhibitor SW-100 Ameliorates Memory and Learning Impairments in a Mouse Model of Fragile X Syndrome." ACS Chem Neurosci. 2019; 10(3):1679-1695.
Cardiovascular diseases	Patent application WO 2021/067859 A1 (2021-04-08) : Mandegar, M. A. et al. "5-Fluoronicotinamide Derivatives as HDAC6 Inhibitors for Treating Heart Diseases". Ranjbarvaziri, S. and al.: "(2023). HDAC6 inhibition to treat heart failure with preserved ejection fraction in mice". Nature Communications 2024; 15(1) Zhang, D., Hu, X., Henning, R. H., & Brundel, B. J. J. M. (2016). Keeping up the balance: Role of HDACs in cardiac proteostasis and therapeutic implications for atrial fibrillation. In Cardiovascular Research (Vol. 109, Issue 4, pp. 519–526). Oxford University Press. Zhang, D., Hu, X., Henning, R. H., & Brundel, B. J. J. M. (2016). Keeping up the balance: Role of HDACs in cardiac proteostasis and therapeutic implications for atrial fibrillation. In Cardiovascular Research (Vol. 109, Issue 4, pp. 519–526). Oxford University Press. Kishore, P., Collinet, A. C. T., & Brundel, B. J. J. M. (2023). Prevention of Atrial Fibrillation: Putting Proteostasis Derailment Back on Track. In Journal of Clinical Medicine (Vol. 12, Issue 13). Multidisciplinary Digital Publishing Institute (MDPI).
Immune disorders	Zhang L and al. "Diverse roles of HDAC6 in viral infection: Implications for antiviral therapy." Pharmacol Ther. 2016; 164:120-5.
Metabolic disorders	Guan, D., and al. "Central Inhibition of HDAC6 Re-Sensitizes Leptin Signaling during Obesity to Induce Profound Weight Loss." Cell Metabolism 36, no. 4 (April 2, 2024): 857-876.e10 Çakir I. and al. "Histone Deacetylase 6 Inhibition Restores Leptin Sensitivity and Reduces Obesity" Nat Metab. 2022 January ; 4(1): 44–59

[0152] According to one embodiment, the HDAC6-associated disease is an inflammatory disease such as, for example, acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, inflammatory bone disease, inflammatory pulmonary disease, inflammatory bowel disease, celiac disease, hepatitis, systemic inflammatory response

syndrome (SIRS), postoperative or posttraumatic inflammation, pneumonia, nephritis, meningitis, cystitis, pharyngolaryngitis, gastric mucosal injury, spondylitis, arthritis, dermatitis, chronic pneumonia, bronchitis, pulmonary infarction, silicosis, pulmonary sarcoidosis, diabetic nephropathy, uveitis, suppurative hidradenitis, cerebrospinal

5 meningitis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, and the like. In one embodiment, the inflammatory disease is selected from the group comprising or consisting of acute pancreatitis, chronic pancreatitis, asthma, adult respiratory distress syndrome, chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, inflammatory bone disease, inflammatory pulmonary disease, inflammatory

10 bowel disease, celiac disease, hepatitis, systemic inflammatory response syndrome (SIRS), postoperative or posttraumatic inflammation, pneumonia, nephritis, meningitis, cystitis, pharyngolaryngitis, gastric mucosal injury, spondylitis, arthritis, dermatitis, chronic pneumonia, bronchitis, pulmonary infarction, silicosis, pulmonary sarcoidosis, diabetic nephropathy, uveitis, suppurative hidradenitis, cerebrospinal meningitis,

15 inflammatory bowel disease, ulcerative colitis and Crohn's disease.

[0153] According to one embodiment, the HDAC6-associated disease is an autoimmune disease, such as, for example, arthritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease (*e.g.*, Crohn's disease or ulcerative colitis), Sjogren's syndrome, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, discoid lupus erythematosus,

20 Castleman's disease, ankylopoietic spondylarthritis, polymyositis, dermatomyositis (DM), polyarteritis nodosa (PN), mixed connective tissue disease (MCTD), scleroderma, lupus erythematosus profundus, chronic thyroiditis, Graves' disease, autoimmune gastritis, type I diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, pemphigus, chronic active hepatitis, myasthenia

25 gravis, graft versus host disease, dermatitis, radiodermatitis, primary biliary cirrhosis, and the like. In one embodiment, the autoimmune disease is selected from the group comprising or consisting of arthritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease (*e.g.*, Crohn's disease or ulcerative colitis), Sjogren's syndrome, multiple sclerosis, systemic lupus erythematosus, lupus nephritis, discoid lupus erythematosus,

30 Castleman's disease, ankylopoietic spondylarthritis, polymyositis, dermatomyositis (DM), polyarteritis nodosa (PN), mixed connective tissue disease (MCTD), scleroderma,

lupus erythematosus profundus, chronic thyroiditis, Graves' disease, autoimmune gastritis, type I diabetes, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, atopic dermatitis, pemphigus, chronic active hepatitis, myasthenia gravis, graft versus host disease, dermatitis, radiodermatitis and primary biliary cirrhosis.

- 5 [0154] According to one embodiment, the HDAC6-associated disease is a proliferative disease, *e.g.*, cancer, such as, for example, malignant tumor, angiogenesis glaucoma, infantile hemangioma, multiple myeloma, chronic sarcoma, metastasis melanoma, Kaposi's sarcoma, vascular proliferation, cachexia, metastasis of the breast cancer, colorectal cancer (*e.g.*, familial colorectal cancer, hereditary nonpolyposis colorectal
- 10 cancer or gastrointestinal stromal tumor), lung cancer (*e.g.*, non-small cell lung cancer, small cell lung cancer or malignant mesothelioma), mesothelioma, pancreatic cancer (*e.g.*, pancreatic duct cancer), gastric cancer (*e.g.*, papillary adenocarcinoma, mucinous adenocarcinoma or adenosquamous carcinoma), breast cancer (*e.g.*, invasive ductal carcinoma, ductal carcinoma in situ or inflammatory breast cancer), ovarian cancer (*e.g.*,
- 15 ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor or ovarian low malignant potential tumor), prostate cancer (*e.g.*, hormone-dependent prostate cancer or non-hormone dependent prostate cancer), liver cancer (*e.g.*, primary liver cancer or extrahepatic bile duct cancer), thyroid cancer (*e.g.*, medullary thyroid carcinoma), kidney cancer (*e.g.*, renal cell carcinoma, transitional cell carcinoma in
- 20 kidney or transitional cell carcinoma in urinary duct), uterine cancer, brain tumor (*e.g.*, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma or anaplastic astrocytoma), melanoma, sarcoma, urinary bladder cancer, hematologic cancer and the like including multiple myeloma, hypophyseal adenoma, glioma, acoustic neurinoma, retinoblastoma, pharyngeal cancer, laryngeal cancer, cancer of the tongue, thymoma,
- 25 esophagus cancer, duodenal cancer, colorectal cancer, rectal cancer, hepatoma, pancreatic endocrine tumor, bile duct cancer, gallbladder cancer, penile cancer, urinary duct cancer, testis tumor, vulvar cancer, cervix cancer, endometrial cancer, uterus sarcoma, chorionic disease, vaginal cancer, skin cancer, fungoid mycosis, basal cell tumor, soft tissue sarcoma, malignant lymphoma, Hodgkin's disease, myelodysplastic syndrome, adult T
- 30 cell leukemia, chronic bone marrow proliferative disease, pancreatic endocrine, tumor fibrous histiocyoma, leiomyosarcoma, rhabdomyosarcoma, cancer of unknown primary,

leukemia (such as acute leukemia (*e.g.*, acute lymphatic leukemia or acute myelocytic leukemia), chronic leukemia (*e.g.*, chronic lymphatic leukemia or chronic myelocytic leukemia)), myelodysplastic syndrome, uterine sarcoma (*e.g.*, mixed mesodermal tumor, uterine leiomyosarcoma or endometrial stromal tumor), myelofibrosis, and the like. In

5 one embodiment, the proliferative disease, *e.g.*, cancer is selected from the group comprising or consisting of malignant tumor, angiogenesis glaucoma, infantile hemangioma, multiple myeloma, chronic sarcoma, metastasis melanoma, Kaposi's sarcoma, vascular proliferation, cachexia, metastasis of the breast cancer, colorectal cancer (*e.g.*, familial colorectal cancer, hereditary nonpolyposis colorectal cancer or

10 gastrointestinal stromal tumor), lung cancer (*e.g.*, non-small cell lung cancer, small cell lung cancer or malignant mesothelioma), mesothelioma, pancreatic cancer (*e.g.*, pancreatic duct cancer), gastric cancer (*e.g.*, papillary adenocarcinoma, mucinous adenocarcinoma or adenosquamous carcinoma), breast cancer (*e.g.*, invasive ductal carcinoma, ductal carcinoma in situ or inflammatory breast cancer), ovarian cancer

15 (*e.g.*, ovarian epithelial carcinoma, extragonadal germ cell tumor, ovarian germ cell tumor or ovarian low malignant potential tumor), prostate cancer (*e.g.*, hormone-dependent prostate cancer or non-hormone dependent prostate cancer), liver cancer (*e.g.*, primary liver cancer or extrahepatic bile duct cancer), thyroid cancer (*e.g.*, medullary thyroid carcinoma), kidney cancer (*e.g.*, renal cell carcinoma, transitional

20 cell carcinoma in kidney or transitional cell carcinoma in urinary duct), uterine cancer, brain tumor (*e.g.*, pineal astrocytoma, pilocytic astrocytoma, diffuse astrocytoma or anaplastic astrocytoma), melanoma, sarcoma, urinary bladder cancer, hematologic cancer and the like including multiple myeloma, hypophyseal adenoma, glioma, acoustic neurinoma, retinoblastoma, pharyngeal cancer, laryngeal cancer, cancer of the tongue,

25 thymoma, esophagus cancer, duodenal cancer, colorectal cancer, rectal cancer, hepatoma, pancreatic endocrine tumor, bile duct cancer, gallbladder cancer, penile cancer, urinary duct cancer, testis tumor, vulvar cancer, cervix cancer, endometrial cancer, uterus sarcoma, chorionic disease, vaginal cancer, skin cancer, fungoid mycosis, basal cell tumor, soft tissue sarcoma, malignant lymphoma, Hodgkin's disease, myelodysplastic

30 syndrome, adult T cell leukemia, chronic bone marrow proliferative disease, pancreatic endocrine, tumor fibrous histiocytooma, leiomyosarcoma, rhabdomyosarcoma, cancer of unknown primary, leukemia (such as acute leukemia (*e.g.*, acute lymphatic leukemia or

acute myelocytic leukemia), chronic leukemia (*e.g.*, chronic lymphatic leukemia or chronic myelocytic leukemia)), myelodysplastic syndrome, uterine sarcoma (*e.g.*, mixed mesodermal tumor, uterine leiomyosarcoma or endometrial stromal tumor) and myelofibrosis. In one particular embodiment, the proliferative disease is cancer. In one
5 embodiment, the cancer is selected from the group comprising or consisting of malignant melanoma, multiple myeloma, leukemia, lymphoma, breast cancer and Hodgkin's disease.

[0155] According to one embodiment, the HDAC6-associated disease is a neurodegenerative disease, such as, for example, Alzheimer's disease, dementia of
10 Alzheimer type, Alzheimer-type senile dementia, Parkinson's disease, muscular dystrophy, Parkinson's disease associated with dementia, senile dementia, age-related cognition memory disorders, Huntington's disease, multi-infarct dementia, frontotemporal lobar degeneration, frontotemporal dementia, Pick's disease, Parkinson's type dementia, Niemann-Pick syndrome, Down's disease, vascular dementia,
15 postencephalitic parkinsonism, Lewy body dementia, Rubinstein-Taybi syndrome, HIV dementia, amyotrophic lateral sclerosis (ALS), motor neurogenesis disease (MND), Creutzfeldt, and the like. In one embodiment, the neurodegenerative disease is selected from the group comprising or consisting of Alzheimer's disease, dementia of Alzheimer type, Alzheimer-type senile dementia, Parkinson's disease, muscular dystrophy,
20 Parkinson's disease associated with dementia, senile dementia, age-related cognition memory disorders, Huntington's disease, multi-infarct dementia, frontotemporal lobar degeneration, frontotemporal dementia, Pick's disease, Parkinson's type dementia, Niemann-Pick syndrome, Down's disease, vascular dementia, postencephalitic parkinsonism, Lewy body dementia, Rubinstein-Taybi syndrome, HIV dementia,
25 amyotrophic lateral sclerosis (ALS), motor neurogenesis disease (MND) and Creutzfeldt. In one particular embodiment, the neurodegenerative disease is selected from the group comprising or consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, frontotemporal dementia, Pick's disease, Niemann-Pick syndrome, Down's disease, Lewy body dementia, HIV dementia, amyotrophic lateral sclerosis (ALS), and
30 multiple sclerosis.

[0156] According to one embodiment, the HDAC6-associated disease is a pain (including central or peripheral pain), such as, for example, pain, cancer pain, acute pain caused by inflammation, pain associated with chronic inflammation, postoperative pain (*e.g.*, incision pain, deep pain, visceral pain or chronic pain after operation), muscular pain
5 (*e.g.*, muscular pain associated with chronic pain disease or stiff shoulder), arthralgia, toothache, temporomandibular joint pain, headache (*e.g.*, migraine, catatonic headache, headache associated with fever or headache associated with hypertension), visceral pain (*e.g.*, cardiac pain, angina pain, abdominal pain, renal pain, urinary tract pain or bladder pain), obstetric and gynecologic pain (*e.g.*, mittelschmerz, dysmenorrhea, labor pain),
10 neuropathic pain (*e.g.*, hernia of intervertebral disk, nerve root pain, neuralgia after herpes zoster, trigeminal neuralgia or lumbago), migraine, stress headache, catatonic headache, muscular spasm, irritable bowel syndrome, and the like. In one embodiment, the pain is selected from the group comprising or consisting of pain, cancer pain, acute pain caused by inflammation, pain associated with chronic inflammation, postoperative pain (*e.g.*,
15 incision pain, deep pain, visceral pain or chronic pain after operation), muscular pain (*e.g.*, muscular pain associated with chronic pain disease or stiff shoulder), arthralgia, toothache, temporomandibular joint pain, headache (*e.g.*, migraine, catatonic headache, headache associated with fever or headache associated with hypertension), visceral pain (*e.g.*, cardiac pain, angina pain, abdominal pain, renal pain, urinary tract pain or bladder
20 pain), obstetric and gynecologic pain (*e.g.*, mittelschmerz, dysmenorrhea, or labor pain), neuropathic pain (*e.g.*, hernia of intervertebral disk, nerve root pain, neuralgia after herpes zoster, trigeminal neuralgia or lumbago), migraine, stress headache, catatonic headache, muscular spasm and irritable bowel syndrome.

[0157] According to one embodiment, the HDAC6-associated disease is a neuropathy
25 (including central or peripheral neuropathy), such as, for example, demyelinating diseases and neuropathy (*e.g.*, multiple sclerosis, Guillain-Barre syndrome, Fisher syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathy or familial amyloidotic polyneuropathy), peripheral neuropathy (CIPN)
30 derived from anticancer drugs and neurological symptoms associated therewith (*e.g.*, chemotherapy-induced neuropathic pain (CINP)), diabetic neuropathy, autonomic

ataxia, injury-related neuropathy (*e.g.*, traumatic brain injury or cerebral apoplexy), and the like. Anticancer drugs susceptible to cause neuropathy include taxanes (*e.g.*, paclitaxel (Taxol)), vinca alkaloids (*e.g.*, vincristine), platinum-based agents (*e.g.*, cisplatin, carboplatin or oxaliplatin), or other molecularly targeted drugs (*e.g.*, bortezomib). In one embodiment, the neuropathy is selected from the group comprising or consisting of demyelinating diseases and neuropathy (*e.g.*, multiple sclerosis, Guillain-Barre syndrome, Fisher syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathy or familial amyloidotic polyneuropathy), peripheral neuropathy (CIPN) derived from anticancer drugs and neurological symptoms associated therewith (*e.g.*, chemotherapy-induced neuropathic pain (CINP)), diabetic neuropathy, autonomic ataxia and injury-related neuropathy (*e.g.*, traumatic brain injury or cerebral apoplexy).

[0158] In one particular embodiment, the neuropathy is selected from the group comprising or consisting of Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathy, familial amyloidotic polyneuropathy, chemotherapy-induced peripheral neuropathy (CIPN) using chemotherapeutic anticancer agents, diabetic peripheral neuropathy (DPN), neuralgia, pain and neuropathic pain.

[0159] According to one embodiment, the HDAC6-associated disease is a psychiatric disease, such as, for example, depression, major depression, bipolar depression, psychotic major depression, refractory major depression, treatment-resistant depression, depression symptom, postpartum depression, bipolar disorder, schizophrenia (*e.g.*, positive symptom, negative symptom or cognitive symptom), cognitive dysfunction associated with schizophrenia, stress disorder, mania, anxiety, generalized anxiety disorder, anxiety syndrome, panic disorder, social anxiety disorder, obsessive disorder, post-traumatic stress syndrome, post-traumatic stress disorder, dysthymic disorder, emotional disorder (*e.g.*, seasonal affective disorder), phobia, social phobia, neurosis, chronic fatigue syndrome, epilepsy, cyclothymia, addiction, neurotic anorexia, eating disorder, anorexia

nervosa, hyperorexia or other eating disorder, pharmacophilia, pharmacophobia, pharmacomania, and the like. In one embodiment, the psychiatric disease is selected from the group comprising or consisting of depression, major depression, bipolar depression, psychotic major depression, refractory major depression, treatment-resistant depression, depression symptom, postpartum depression, bipolar disorder, schizophrenia (e.g., positive symptom, negative symptom or cognitive symptom), cognitive dysfunction associated with schizophrenia, stress disorder, mania, anxiety, generalized anxiety disorder, anxiety syndrome, panic disorder, social anxiety disorder, obsessive disorder, post-traumatic stress syndrome, post-traumatic stress disorder, dysthymic disorder, emotional disorder (e.g., seasonal affective disorder), phobia, social phobia, neurosis, chronic fatigue syndrome, epilepsy, cyclothymia, addiction, neurotic anorexia, eating disorder, anorexia nervosa, hyperorexia or other eating disorder, pharmacophilia, pharmacophobia, and pharmacomania.

[0160] According to one embodiment, the HDAC6-associated disease is a neurodevelopmental disorder, such as, for example, Tourette syndrome, autism, autistic spectrum syndrome, fragile X syndrome, Rett syndrome, attention deficit hyperactivity disorder (ADHD), and the like. In one embodiment, the neurodevelopmental disorder is selected from the group comprising or consisting of Tourette syndrome, autism, autistic spectrum syndrome, fragile X syndrome, Rett syndrome, and attention deficit hyperactivity disorder (ADHD).

[0161] According to one embodiment, the HDAC6-associated disease is a sleep disorder, such as, for example, intrinsic sleep disorders (e.g., psychophysiological insomnia), extrinsic sleep disorder, circadian rhythm disorders (e.g., time zone change syndrome (jet lag), shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome or non-24-hour sleep-wake), parasomnia, sleep disorders associated with internal medical or psychiatric disorder (e.g., chronic obstructive pulmonary diseases, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, schizophrenia, depression or anxiety neurosis), stress, insomnia, insomniac neurosis, sleep apnea syndrome, and the like. In one embodiment, the sleep disorder is selected from the group comprising or consisting of

intrinsic sleep disorders (*e.g.*, psychophysiological insomnia), extrinsic sleep disorder, circadian rhythm disorders (*e.g.*, time zone change syndrome (jet lag), shift work sleep disorder, irregular sleep-wake pattern, delayed sleep phase syndrome, advanced sleep phase syndrome or non-24-hour sleep-wake), parasomnia, sleep disorders associated with
5 internal medical or psychiatric disorder (*e.g.*, chronic obstructive pulmonary diseases, Alzheimer's disease, Parkinson's disease, cerebrovascular dementia, schizophrenia, depression or anxiety neurosis), stress, insomnia, insomnia, insomniac neurosis and sleep apnea syndrome.

[0162] According to one embodiment, the HDAC6-associated disease is a cardiovascular
10 disease, such as, for example, chronic heart failure or acute heart failure, acute decompensated heart failure, ischemic heart disease, cardiomyopathy, myocarditis, valvular disease, hypertension, cardiac disease, tachycardia, congestive cardiac failure, and the like. In one embodiment, the cardiovascular disease is selected from the group comprising or consisting of chronic heart failure or acute heart failure, acute
15 decompensated heart failure, ischemic heart disease, cardiomyopathy, myocarditis, valvular disease, hypertension, cardiac disease, tachycardia and congestive cardiac failure. In one particular embodiment, the heart-related disease is selected from the group comprising or consisting of heart failure, cardiomyopathy and myocarditis.

[0163] According to one embodiment, the HDAC6-associated disease is an
20 addiction-related disorder, such as, for example, alcohol dependence, alcohol abuse, alcoholic amnesia, alcohol paranoia, alcohol preference, alcohol withdrawal, alcoholic insanity, alcohol poisoning, alcoholic jealousy, alcoholic mania, alcohol-dependent psychiatric disorder, alcoholic insanity, drug withdrawal, and the like. In one
25 embodiment, the addiction related disorder is selected from the group comprising or consisting of alcohol dependence, alcohol abuse, alcoholic amnesia, alcohol paranoia, alcohol preference, alcohol withdrawal, alcoholic insanity, alcohol poisoning, alcoholic jealousy, alcoholic mania, alcohol-dependent psychiatric disorder, alcoholic insanity and drug withdrawal.

[0164] According to one embodiment, the HDAC6-associated disease is a
30 gastrointestinal disease, such as, for example, peptic ulcer, stress gastrointestinal disorder,

stress vomiting, peptic ulcer, diarrhea, constipation or postoperative ileus, and the like. In one embodiment, the gastrointestinal disease is selected from the group comprising or consisting of peptic ulcer, stress gastrointestinal disorder, stress vomiting, peptic ulcer, diarrhea, constipation ileus and postoperative ileus.

- 5 [0165] According to one embodiment, the HDAC6-associated disease is a pulmonary disease, such as, for example, hyperventilation, bronchial asthma, apnea, and the like. In one embodiment, the pulmonary disease is selected from the group comprising or consisting of hyperventilation, bronchial asthma and apnea.

- [0166] According to one embodiment, the HDAC6-associated disease is a metabolic or
10 hormonal disorder, such as, for example, obesity, diabetes, acromegaly, infertility, metabolic syndrome, and the like. In one embodiment, the metabolic or hormonal disorder is selected from the group comprising or consisting of obesity, diabetes, acromegaly, infertility and metabolic syndrome.

- [0167] According to one embodiment, the HDAC6-associated disease is an immune
15 disorder, such as, for example, allergic disease, immunodeficiency syndrome caused by HIV infection, immunodeficiency syndrome caused by stress, and the like. In one embodiment, the immune disorder is selected from the group comprising or consisting of immunodeficiency syndrome caused by HIV infection and immunodeficiency syndrome caused by stress.

- 20 [0168] According to one embodiment, the HDAC6-associated disease is an age-related disease, such as, for example, alopecia, glaucoma, impotence, climacteric disorder, incontinence, osteoporosis, and the like. In one embodiment, the age-related disease is selected from the group comprising or consisting of alopecia, glaucoma, impotence, climacteric disorder, incontinence and osteoporosis.

- 25 [0169] According to one embodiment, the HDAC6 associated disease is an idiopathic disease, such as, for example, Meniere's disease, sudden infant death syndrome, and the like. In one embodiment, the idiopathic disease is Meniere's disease or sudden infant death syndrome.

[0170] The compound or pharmaceutical composition of the invention may be administered by oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous, intracerebroventricular (ICV), intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration. In the treatment and/or prevention of an infectious disease an appropriate dosage level may be from about 0.01 to 500 mg per kg patient body weight per day (mg/kg/day), which can be administered in single or multiple doses. Typically, the dosage level will be from about 0.1 to about 250 mg/kg/day, preferably from about 0.5 to about 100 mg/kg/day, more preferably from about 2.5 to about 20 mg/kg/day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular diseases and the host undergoing therapy.

[0171] Advantageously, the compound of the invention is selective over at least one HDAC other than HDAC6, preferably over at least one class II HDAC other than HDAC6, more preferably over any class II HDAC other than HDAC6, furthermore preferably over HDAC other than HDAC6. Particularly advantageously, the compound of the invention is selective over HDAC1. Particularly advantageously, the compound of the invention is selective over HDAC10. Selectivity is strongly associated with the avoidance of side-effects of HDAC inhibitors.

Kit

[0172] This invention also relates to a kit comprising a compound of the invention as described herein, or a pharmaceutical composition of the invention as described herein, and means to administer the compound or pharmaceutical composition.

[0173] Means for administering a compound or a pharmaceutical composition are well-known in the art and may be identified by a person skilled in the art depending of the desired administration route.

5 EXAMPLES

[0174] The present invention is further illustrated by the following examples.

Example 1: Synthesis of the compounds

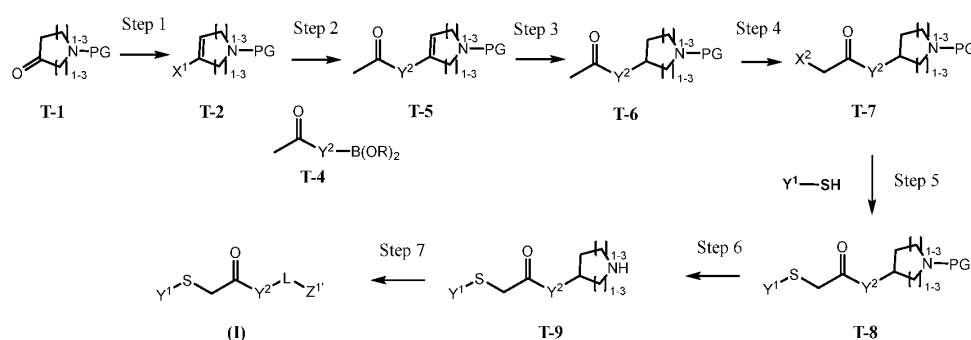
[0175] The compounds of formula (I) **(1)-(190)** represented on **Table 1, Table 2** and/or **Table 3** hereinabove were prepared as described hereinafter.

10 *General synthetic methods*

[0176] The compounds according to the invention, in particular the compounds according to the formula (I), may be prepared by methods known to the person skilled in the art of organic synthesis or by using the following synthesis schemes. In all of the schemes described below it is understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with the general principles of organic chemistry. Protecting groups are manipulated according to standard methods (T.W. Green and P.G.M. Wuts, *Protecting Groups in Organic Synthesis*, 1991, John Wiley & Sons, Inc.). These groups are then removed at a convenient stage of the synthesis using methods that are readily apparent to those skilled in the art. Many of the heterocyclic compounds of formula (I) where **Y¹** or **Y²** is a heteroaryl may be prepared using synthetic routes well known in the art (A.R. Katritzky and C. W. Rees, 1984, *Comprehensive Heterocyclic Chemistry*, Pergamon Press).

[0177] The synthesis of the HDAC6 inhibitors disclosed in the present invention have been prepared using the following synthetic schemes. Specific conditions for carrying out these reactions are provided in the detailed examples. The synthetic schemes described below show exemplified approaches to compounds of the present invention, but these routes should not be taken as the only possible synthetic routes to compounds of the present invention.

[0178] Compounds of formula (I) in which **L** is a direct bond, and **Z^{1'}** represents a cyclic amine such as, for example, pyrrolidine, and **Y¹** and **Y²** are as defined above, may be obtained also according to **Scheme 1** (Method 1) below:

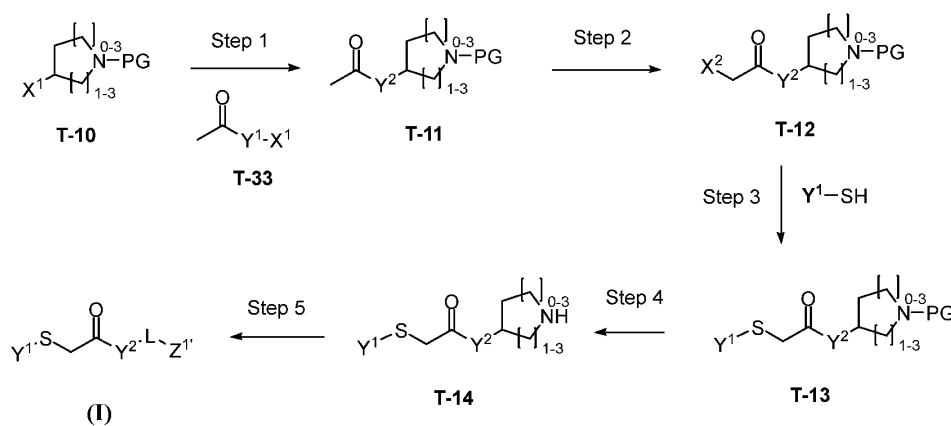


Scheme 1 / Method 1

[0179] Protected cyclic amines **T-1** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature. Compound **T-1** can be reacted with phenyltriflimide, *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-trifluoromethylsulfonyl) methanesulfonamide or trifluoromethanesulfonic anhydride in the presence of a suitable base (*e.g.*, LiHMDS) and solvent (*e.g.*, THF) at the appropriate temperature to provide the triflate enol ether **T-2** in which **X¹** is an OSO₂CF₃ group (*Step 1*). A Suzuki cross coupling-type reaction of triflate **T-2** with a boronic acid or boronic ester of Formula **T-4** in the presence of a catalyst (*e.g.*, Pd(dppf)Cl₂), a base (*e.g.*, Cs₂CO₃), in a solvent (*e.g.*, DMF) at the appropriate temperature may provide intermediate ketone **T-5** (*Step 2*). Boronic acid or boronic ester of Formula **T-4** may be commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature. The double-bond of the cyclic amine intermediate **T-5** can then be reduced upon hydrogenation using H₂ in the presence of a catalyst (*e.g.*, Pd/C or Pd(OH)₂) in a solvent (*e.g.*, MeOH) to provide the corresponding saturated amine intermediate **T-6** (*Step 3*). Ketone **T-6** can be engaged into a halogenation reaction, using for example NBS or phenyltrimethylammonium tribromide in a solvent (*e.g.*, DCM or THF) at the appropriate temperature to provide halo-ketone **T-7**, in which **X²** is a halogen such as, for example, bromide (*Step 4*). Halo-ketone **T-7** can then be reacted with thiol hetero-aryl derivatives

of Formula **Y¹-SH** in the presence of a base (*e.g.*, MeONa or K₂CO₃) in a solvent (*e.g.*, DMF or ACN) at the appropriate temperature to provide heteroaryl intermediate **T-8** (*Step* 5). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by methods known to the person skilled in the art. The protected amine **T-8** can be deprotected in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or aqueous HCl solution, to provide the corresponding amine **T-9** (*Step* 6). Some amines **T-9** can be treated as compounds of formula (I), while other amines **T-9** can be further alkylated with an appropriate alkylating agent (*Step* 7) such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide N-alkylated amines of formula (I).

[0180] Compounds of formula (I) in which **L** is a direct bond, and **Z¹** represents a cyclic amine such as, for example, azetidine, and **Y¹** and **Y²** are as defined above, may also be obtained according to **Scheme 2** (Method 2) below:



Scheme 2 / Method 2

[0181] Halides **T-10** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature. Intermediate **T-11** can be prepared by reacting intermediate **T-10** with a suitable metalating agent such as, for instance zinc metal with catalytic I₂, and reacting the

5 resulting organometal with a suitable acylated (hetero)aromatic halide **T-33** such as, for instance, 2-bromo-5-acetylthiophene, in presence of a suitable catalyst such as, for example, Pd₂(dba)₃/S-Phos, in a suitable solvent such as, for example, toluene, at a suitable temperature such as, for example 15 °C. Compounds **T-33** are commercially available or may be prepared by methods known to the person skilled in the art. The acetyl

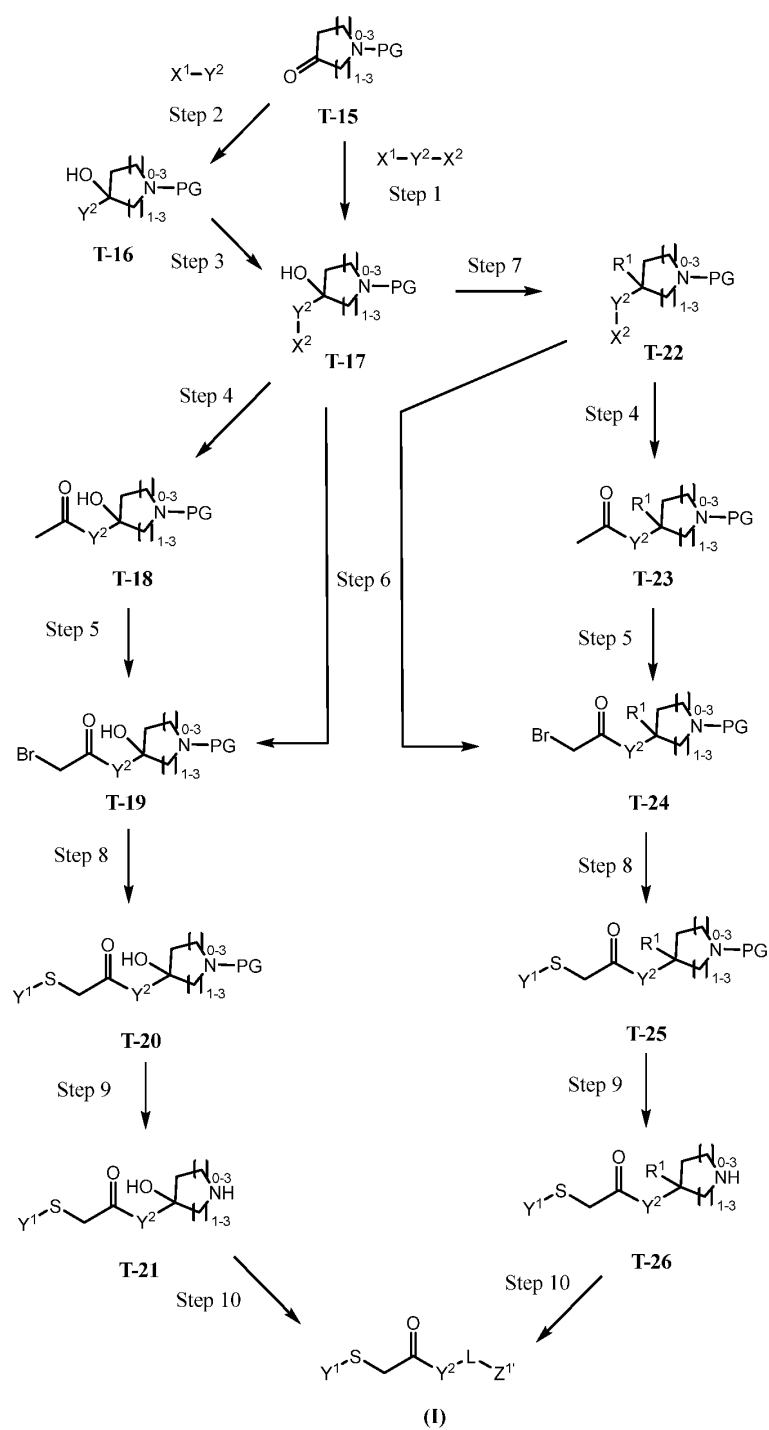
10 group of intermediate **T-11** can be halogenated with a proper halogenating agent such as, for example, tetrabutylammonium tribromide, in a suitable solvent such as, for example, DCM/MeOH, at a suitable temperature such as, for example, 20 °C, providing halo-ketone **T-12** (*Step 2*). The halo of intermediate **T-12** can be substituted by a suitable thiol of Formula **Y¹-SH**, in presence of a suitable base (*e.g.*, MeONa or K₂CO₃) in a solvent

15 (*e.g.*, DMF or ACN) at the appropriate temperature to provide heteroaryl intermediate **T-13** (*Step 3*). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be

20 prepared by methods known to the person skilled in the art. The protected amine **T-13** can be deprotected in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or aqueous HCl solution, to provide the corresponding amine **T-14** (*Step 4*). Some amines **T-14** can be treated as compounds of formula (I), while other amines **T-14**

25 can be further alkylated with an appropriate alkylating agent (*Step 5*) such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide N-alkylated amines of formula (I).

[0182] Compounds of formula (I) in which **L** is a direct bond, and **Z¹** represents a cyclic amine such as, for example, azetidine or pyrrolidine or piperidine, and **Y¹** and **Y²** are as defined above, may be obtained also according to **Scheme 3** (Method 3) below:



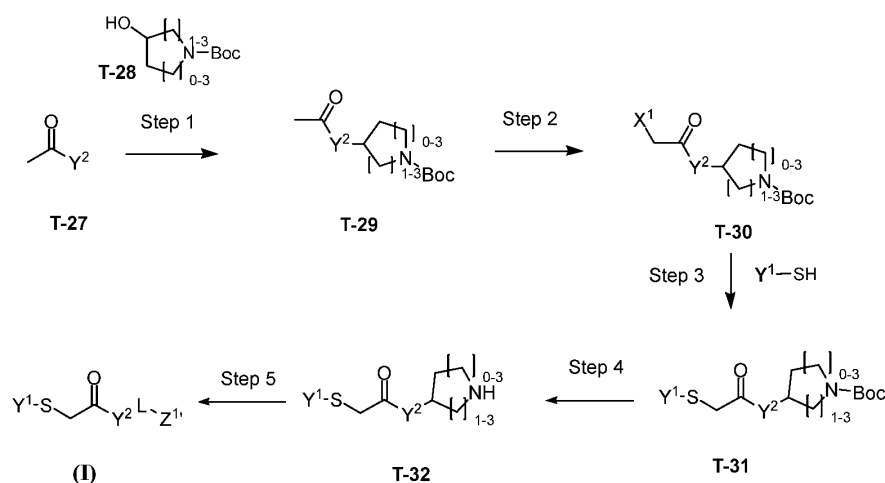
Scheme 3 / Method 3

[0183] Protected cyclic amines **T-15** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature. The keto function in compound **T-15** can be converted to intermediate of formula **T-17** by reaction with bis-halogenated (hetero)aryl groups, after conversion of the most reactive halogen of the latter into an organometal with a suitable metalating reagent such as, for instance, n-butyllithium in a suitable solvent such as, for instance, THF, at a suitable temperature such as, for instance, -78 °C (*Step 1*). Alternatively, compound **T-15** can be converted to an intermediate of formula **T-16** by reaction with mono-halogenated (hetero)aryl groups, after conversion of the halogen of the latter into an organometal with a suitable metalating reagent such as, for instance, n-butyllithium in a suitable solvent such as, for instance, THF, at a suitable temperature such as, for instance, -78 °C (*Step 2*). Intermediate **T-16** can in a next step be halogenated with a suitable halogenating reagent such as, for instance, N-bromosuccinimide with a catalyst such as, for instance N,N-dimethylaminopyridine, in a suitable solvent such as, for instance, acetonitrile, at a suitable temperature such as, for example, room temperature to provide intermediate **T-17** (*Step 3*). Intermediate **T-17** can be acetylated with a suitable acylating reagent such as, for example, ethoxyvinyltributyltin, in presence of a suitable catalyst such as, for example, Pd(PPh₃)₄, in a suitable solvent such as, for example, toluene, at a suitable temperature such as, for instance, 120 °C, and an ensuing work up with a suitable enol ether deprotection agent such as, for example 0.5 M aq. HCl, at a suitable temperature such as, for example, room temperature, to provide intermediate **T-18** (*Step 4*). The acetyl group of intermediate **T-18** can be halogenated with a suitable reagent such as, for example, tetrabutylammonium tribromide (TBATB) or trimethylphenylammonium tribromide or CuBr₂, in a suitable solvent such as, for example, DCM/MeOH or EtOAc/CHCl₃, at a suitable temperature such as, for instance room temperature or 85 °C, to provide intermediate **T-19** (*Step 5*). Alternatively, intermediate **T-19** can be obtained by reacting **T-18** with a suitable 1-alkoxyvinylating reagent such as, for example, ethoxyvinyltributyltin, in presence of a suitable catalyst such as, for example, Pd(PPh₃)₂Cl₂, in a suitable solvent such as, for example, 1,4-dioxane, at a suitable temperature such as, for instance, 90 °C, and engaging the resulting enol ether in a subsequent halogenation reaction with a suitable halogenating reagent such as, for example, N-bromosuccinimide, in a suitable solvent such as, for example,

THF/water, at a suitable temperature such as, for example, room temperature (*Step 6*). The halogen in intermediate **T-19** can be further reacted with a suitable thiol of formula **Y¹-SH** in presence of a suitable base such as, for instance NaOMe or K₂CO₃, in a suitable solvent such as, for example, DMF or ACN, at a suitable temperature such as, for example, room temperature or 50 °C, to provide intermediate **T-20** (*Step 8*). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by methods known to the person skilled in the art. The protected amine **T-20** can be deprotected in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or aqueous HCl solution, to provide the corresponding amine **T-21** (*Step 9*). Some amines **T-21** can be treated as compounds of formula (I), while other amines **T-21** can be further alkylated with an appropriate alkylating agent (*Step 10*) such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide N-alkylated amines of formula (I).

[0184] Intermediates of formula **T-17** may also be converted to intermediates of formula **T-22** in which **R¹** is a fluoro (F) atom by treatment with a suitable deoxofluorinating agent such as, for example, diethylaminosulfur trifluoride (DAST), in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for instance, 0 °C (*Step 7*). Alternatively, intermediates of formula **T-17** may also be converted to intermediates of formula **T-22** in which **R¹** is a methoxy (OMe) group by treatment with a suitable methylating agent such as, for example, methyl iodide, in presence of a suitable base such as, for example, sodium hydride, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for instance, room temperature. Intermediates of formula **T-22** in which **R¹** is a fluoro (F) atom or methoxy (OMe) group may be further carried on to compounds of formula (I) using Steps 4, 5, 6, 8, 9 and 10 as described hereinabove.

[0185] Compounds of formula (I) in which Y^2 represents a heterocycle N-linked to an amine-containing heterocycloalkyl such as, for example, pyrazole, and Y^1 is as defined above, may also be obtained also according to **Scheme 4** (Method 4).



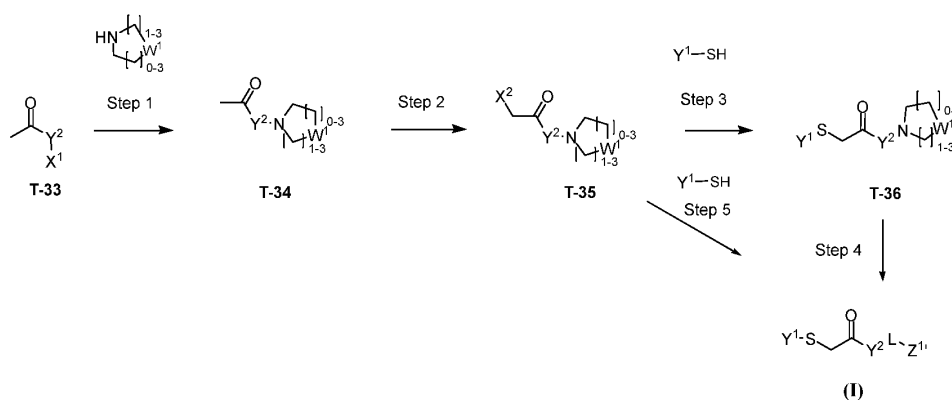
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Scheme 4 / Method 4

[0186] Protected cyclic amines **T-28**, and 1-ethanone substituted NH-containing heteroaromatic cycles **T-27** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature. The NH function of **T-27** can be N-alkylated to an intermediate of formula **T-28** with a hydroxy-substituted N-protected cyclic amine such as, for example, tert-butyl 3-hydroxypyrrolidine-1-carboxylate, using a suitable reagent such as, for example, diisopropylazodicarboxylate (DIAD) and triphenylphosphine, in a suitable solvent such as, for example, tetrahydrofuran, at a suitable temperature such as, for 20 °C (*Step 1*). The acetyl group of intermediate **T-29** can be further halogenated with a suitable reagent such as, for example, tetrabutylammonium tribromide (TBATB) or trimethylphenylammonium tribromide or CuBr_2 , in a suitable solvent such as, for example, DCM/MeOH or EtOAc/ CHCl_3 , at a suitable temperature such as, for instance room temperature or 85 °C, to provide intermediate **T-30** (*Step 2*). The halogen X^1 in intermediate **T-30** can be further reacted with a suitable thiol of formula Y^1-SH in presence of a suitable base such as, for instance NaOMe or K_2CO_3 , in a suitable solvent such as, for example, DMF or ACN, at a suitable temperature such as, for example, room

temperature or 50 °C, to provide intermediate **T-31** (Step 3). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by methods known to the person skilled in the art. The protected amine **T-31** can be deprotected in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or aqueous HCl solution, to provide the corresponding amine **T-32** (Step 4). Some amines **T-32** can be treated as compounds of formula (I), while other amines **T-32** can be further alkylated with an appropriate alkylating agent (Step 5) such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide N-alkylated amines of formula (I).

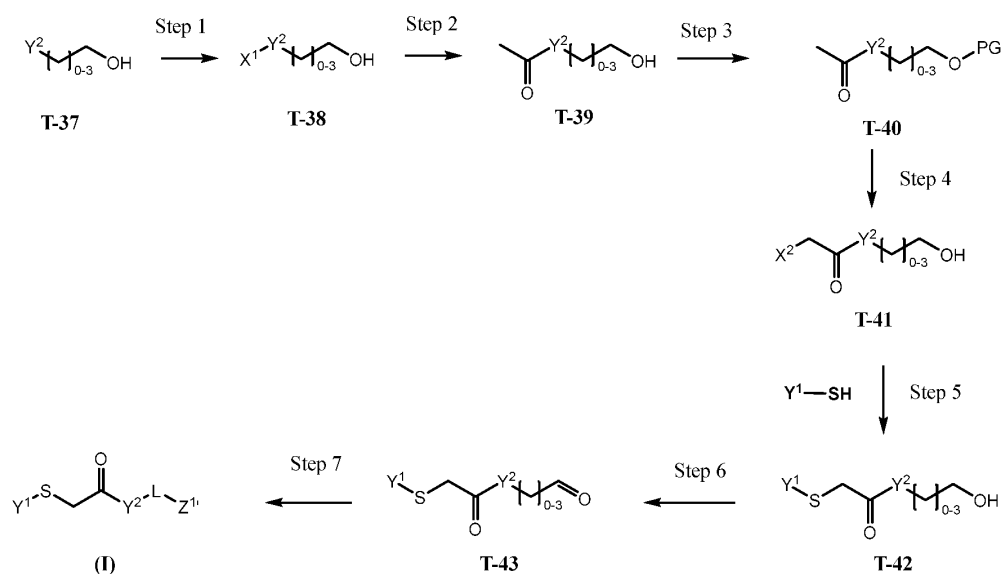
[0187] Compounds of formula (I) in which **L** is a direct bond, **Z¹** represents an amine linked to **Y²**, of which **W¹** is a (substituted) carbon, (substituted) nitrogen or O, and **Y¹** and **Y²** are as defined above, may also be obtained also according to **Scheme 5** (Method 5) below:



[0188] Intermediates **T-33**, in which **X¹** is a suitable halogen such as, for example, bromo, and **Y²** is a heteroaryl such as, for example, thiazole, can be obtained commercially or prepared via art known conditions. The halo **X¹** on intermediate **T-33** can be substituted with a suitable amine such as, for example, tert-butyl piperazine-1-carboxylate, in
5 presence of a suitable base such as, for example, K₂CO₃, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 85 °C, to provide intermediate **T-34** (*Step 1*). The acetyl group of intermediate **T-34** can be further halogenated with a suitable reagent such as, for example, tetrabutylammonium tribromide (TBATB) or trimethylphenylammonium tribromide or CuBr₂, in a suitable solvent such
10 as, for example, DCM/MeOH or EtOAc/CHCl₃, at a suitable temperature such as, for instance room temperature or 85 °C, to provide intermediate **T-35** (*Step 2*). The halogen **X²** in intermediate **T-35** can be further reacted with a suitable thiol of formula **Y¹-SH** in presence of a suitable base such as, for instance NaOMe or K₂CO₃, in a suitable solvent such as, for example, DMF or ACN, at a suitable temperature such as, for example, room
15 temperature or 50 °C, to provide intermediate **T-36** (*Step 3*). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by
20 methods known to the person skilled in the art. Intermediates of formula **T-36** in which **W¹** is a protected amine can be N-deprotected to compounds of formula (I) in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or aqueous HCl solution, to provide the corresponding amine (*Step 4*). A skilled person will understand
25 that compounds of formula (I) containing a free amine (NH) can be further alkylated with an appropriate alkylating agent such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide N-alkylated amines of formula (I).
30 Intermediates in which **W¹** is a (substituted) carbon (C) or oxygen (O) atom can be reacted with a suitable thiol of formula **Y¹-SH** in presence of a suitable base such as, for instance NaOMe or K₂CO₃, in a suitable solvent such as, for example, DMF or ACN, at a suitable

temperature such as, for example, room temperature or 50 °C, to immediately provide compounds of formula (I) (*Step 5*).

- [0189] Compounds of formula (I) in which **L** is an alkylene, and **Z^{1'}** represents an amine which is N-linked to **L**, and **Y¹** and **Y²** are as defined above, may also be obtained also according to **Scheme 6** (Method 6) below:



Scheme 6 / Method 6

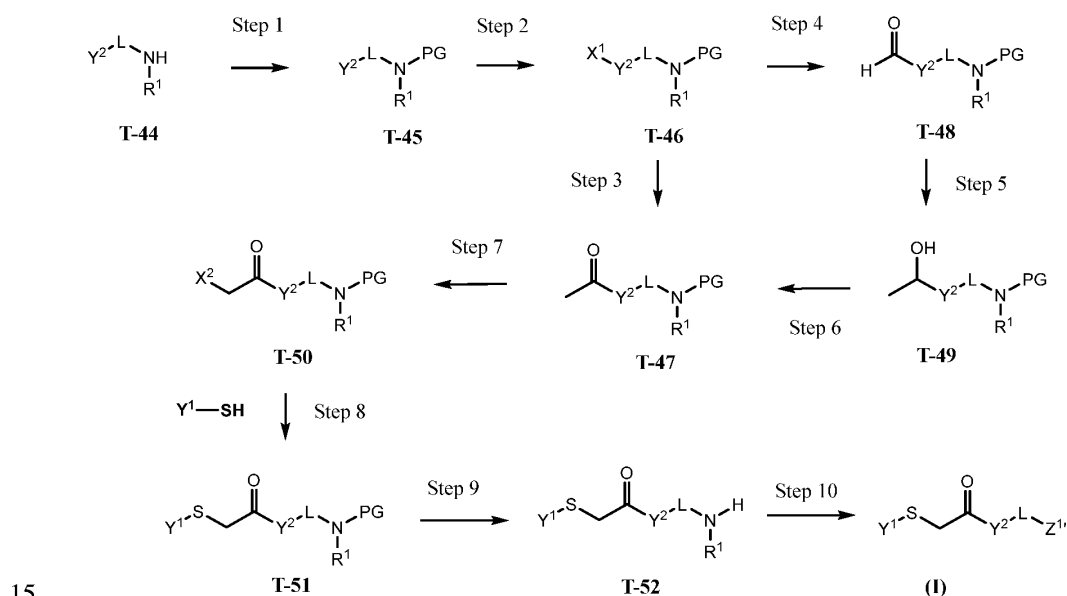
- [0190] Alcohols **T-37** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature.
- Intermediate **T-38**, in which **X¹** is a halogen such as, for example, bromide, can be obtained by halogenation of **T-37** with a suitable halogenating reagent such as, for example, N-iodosuccinimide (NIS) with para-toluenesulfonic acid catalysis, in a suitable solvent such as, for example, ethanol, at a suitable temperature such as, for example, 25 °C (*Step 1*). The halogen of intermediate **T-38** can be acetylated with a suitable acylating reagent such as, for example, ethoxyvinyltributyltin, in presence of a suitable catalyst such as, for example, $\text{Pd(PPh}_3\text{)}_4$, in a suitable solvent such as, for example, toluene, at a suitable temperature such as, for instance, 120 °C, and an ensuing work up with a suitable enol ether deprotection agent such as, for example 0.5 M aq. HCl, at a suitable temperature such as, for example, room temperature, to provide intermediate **T-39** (*Step*

2). The alcohol of intermediate **T-39** can be protected with a suitable protective group (PG) such as, for example, tert-butyl diphenylsilyl (TBDPS), by treatment with a suitable silylating reagent such as, for example, TBDPS-Cl, in presence of a suitable base such as, for example, imidazole and catalytic DMAP, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 15 °C, to provide intermediate **T-40** (Step 3). The acetyl group of intermediate **T-40** can be halogenated with a suitable reagent such as, for example, tetrabutylammonium tribromide (TBATB) or trimethylphenylammonium tribromide or CuBr₂, in a suitable solvent such as, for example, DCM/MeOH or EtOAc/CHCl₃, at a suitable temperature such as, for instance room temperature or 85 °C, to provide intermediate **T-41**, in which **X²** is a halogen such as, for example, bromide (Step 4). A skilled person will understand a silyl protective group might be removed during Step 4, while other protective groups might require an additional deprotection step following art known conditions. The halogen in intermediate **T-41** can be further reacted with a suitable thiol of formula **Y¹-SH** in presence of a suitable base such as, for instance NaOMe or K₂CO₃, in a suitable solvent such as, for example, DMF or ACN, at a suitable temperature such as, for example, room temperature or 50 °C, to provide intermediate **T-42** (Step 5). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by methods known to the person skilled in the art. The alcohol of **T-42** can be oxidized to the corresponding aldehyde **T-43** by a suitable oxidant such as, for example, Dess-Martin periodinane (DMP), in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 25 °C. Intermediates **T-43** can be engaged in a reductive amination reaction to provide compounds of formula (I) by reaction with a suitable amine such as, for example, morpholine, in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 25 °C. A skilled person will understand that if **Z¹** in compounds of formula (I) carries a protected amine, this amine can be deprotected in acidic, neutral or basic media depending on the choice of the protecting group, for example in acidic media to remove of a Boc-protecting group using formic acid or

aqueous HCl solution, to provide the corresponding free amine (NH), which presents another compound of formula (I). Alternatively, such free amine can be further alkylated with an appropriate alkylating agent such as, for example, formaldehyde or 2-methoxyethanal in presence of a suitable reductant such as, for example, sodium triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example 0 °C to room temperature, to provide other N-alkylated amines of formula (I).

[0191] A skilled person will understand that while the Schemes 1-6 above depict monocyclic amines, it is equally possible to engage polycyclic amines in the same type of reactions to prepare compounds of formula (I) in which **Z¹** is a polycyclic amine such as, for example, a bicycle, spirocycle or bridged cycle.

[0192] Compounds of formula (I) in which **Z¹** represents a non-cyclic amine of formula -NR^{23'}R^{24'}, and **Y¹** and **Y²** are as defined above, may be obtained according to **Scheme 7** (Method 7) below:



Scheme 7 / Method 7

[0193] Amines **T-44** are commercially available or may be synthesized by a person skilled in the art of organic chemistry using multiple ways described in the literature.

Intermediates **T-45**, in which PG is a suitable protective group such as, for example, Boc, may be prepared by protecting the amine group of **T-44** (*Step 1*) by, for example using Boc₂O in the presence of a base (*e.g.*, Et₃N or NaHCO₃) and in a solvent (*e.g.* DCM or THF) at the appropriate temperature. Protected amine intermediate **T-45** can be engaged

5 into a halogenation step to provide a **T-46** in which **X¹** is a halo such as, for instance, bromo (Br) using, for example NBS or Br₂ in a solvent (*e.g.*, DCM) at the appropriate temperature (*Step 2*). Halide **T-46** can next be transformed into the corresponding ketone **T-47** in a single or multiple step-sequence, for example: (*Option 1*) a 2-step sequence such as (i) metal-catalyzed cross coupling sequence using tributyl(1-ethoxyvinyl)tin, in

10 the presence of a catalyst/ligand system (*e.g.*, Pd(PPh₃)₄, a base (*e.g.*, *t*-BuOK), in a solvent (*e.g.*, dioxane)), at the appropriate temperature to provide the enol ether intermediate, which is then transformed into the desired ketone **T-47** using acidic media such as aqueous HCl or formic acid at the appropriate temperature (*Step 3*); or (*Option 2*) in a 3-step sequence such as (i) a metal-halide exchange, using for example *n*-BuLi, under

15 inert atmosphere like nitrogen atmosphere, at controlled temperature like -78 °C, in a non protic solvent like dry THF, followed by the introduction of dimethylformaldehyde, or equivalent reagent, to provide the corresponding aldehyde intermediate **T-48** (*Step 4*). Intermediate **T-48** can be treated with a methylating agent such as, for instance, MeMgBr, in a non-protic solvent (*e.g.*, THF) at the appropriate temperature to provide the resulting

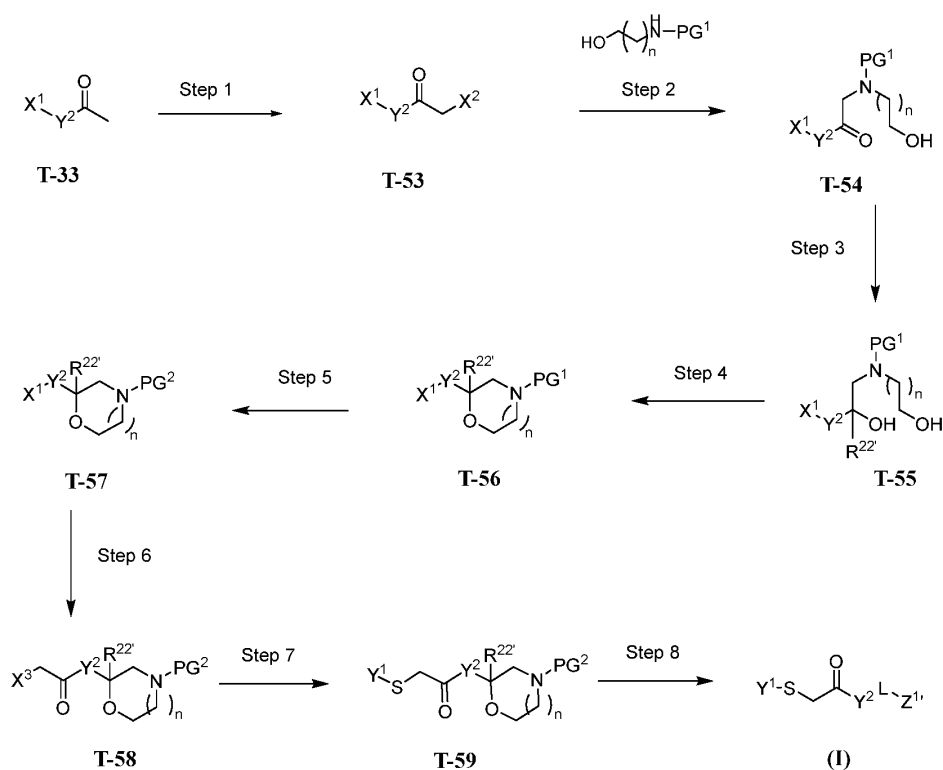
20 alcohol **T-49** (*Step 5*). Alcohol **T-49** can be transformed into the corresponding ketone **T-47** by the use of an oxidizing agent for example DMP or PCC in a solvent (*e.g.*, DCM) at the appropriate temperature (*Step 6*). Ketone **T-47** can be further engaged into a halogenation reaction, using for example NBS or phenyltrimethylammonium tribromide in a solvent (*e.g.*, DCM or THF) at the appropriate temperature to provide halo-ketone **T-**

25 **50**, in which **X²** is a suitable halogen such as, for example, bromide (*Step 7*). Halo-ketone **T-50** is then reacted with thiol hetero-aryl derivatives of Formula **Y¹-SH** in the presence of a base (*e.g.*, MeONa or K₂CO₃) in a solvent (*e.g.*, DMF or ACN) at the appropriate temperature to provide heteroaryl intermediate **T-51** (*Step 8*). Heteroaryl **Y¹-SH** are commercially available or may be prepared by methods known to the person skilled in

30 the art, for example from the corresponding heteroaryl **Y¹-OH** derivatives using Lawesson's reagent or P₂S₅ reagent in a solvent (*e.g.*, toluene) at the appropriate temperature. Heteroaryl **Y¹-OH** are commercially available or may be prepared by

methods known to the person skilled in the art. The protected amine **T-51** can then be deprotected in acidic or basic media depending of the choice of the protecting group, for example in acidic media such as, for example, formic acid or aqueous HCl, to remove of a Boc-protecting group, or upon hydrogenolysis using H₂ in the presence a of catalyst
5 (*e.g.*, Pd(OH)₂) in a protic solvent (*e.g.*, MeOH) to remove a benzyl-type protecting group such as, for example, Cbz, to finally provide the corresponding amine intermediate **T-52** (*Step 9*). Amine **T-52** can directly be considered a compound of formula (I), or can be further alkylated with a suitable alkylating reagent such as, for example, formaldehyde, in presence of a suitable reducing agent such as, for example, sodium
10 triacetoxyborohydride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as for example, 0-25 °C, to provide compounds of formula (I) in which the amine carries an alkyl group. A skilled person will understand that the alkylation of the amine in compounds of formula (I) can also occur at an earlier stage of the synthesis, for instance when a primary amine is Boc-protected, by alkylating the NH-Boc function
15 with a suitable alkylating reagent such as, for example, methyl iodide, in presence of a suitable base such as, for example sodium hydride, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 0 °C.

[0194] Compounds of formula (I) in which **L** is a direct bond and in which **Z¹** represents a substituted morpholine or homomorpholine, and **Y¹** and **Y²** are as defined above, may
20 be obtained also according to **Scheme 8** (Method 8) below:



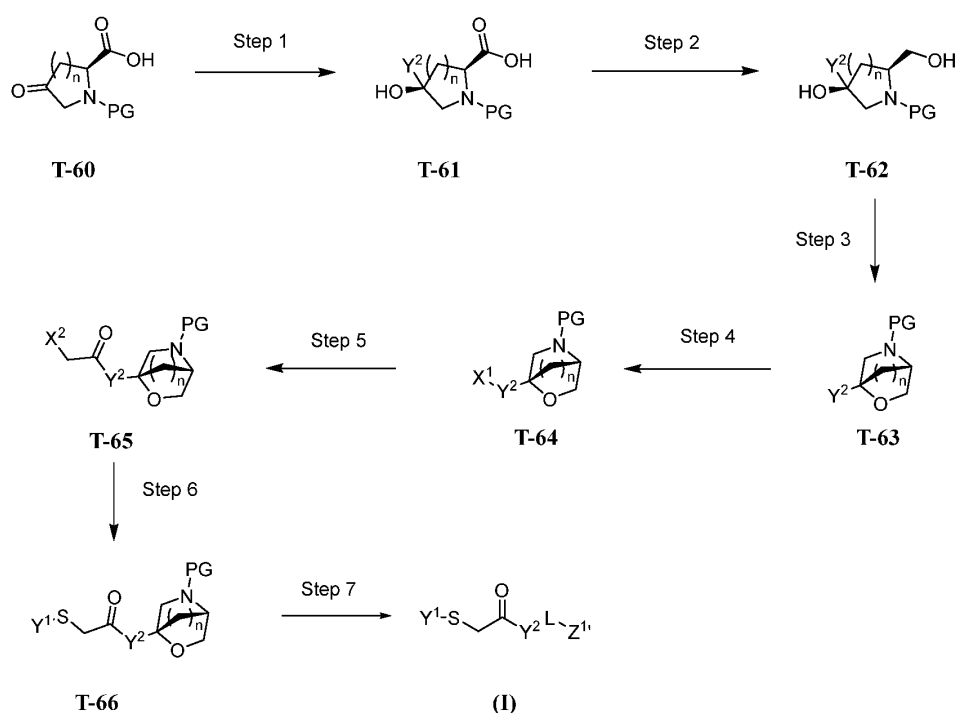
Scheme 8 / Method 8

[0195] Intermediates **T-33**, in which X^1 is a suitable halogen such as, for example, bromo, and Y^2 represents a heteroaryl such as, for example, thiophene, can be obtained commercially or prepared via art known conditions. The acetyl group of intermediate **T-33** can be halogenated with a suitable reagent such as, for example, tetrabutylammonium tribromide (TBATB) or trimethylphenylammonium tribromide or $CuBr_2$, in a suitable solvent such as, for example, DCM/MeOH or EtOAc/ $CHCl_3$, at a suitable temperature such as, for instance room temperature or 85 °C, to provide intermediate **T-53** in which X^2 is a halide such as, for example, bromide (*Step 1*). Intermediate **T-54** can be obtained by reacting intermediate **T-53** with a suitable amino alcohol of formula $HOCH_2(CH_2)_nNH-PG^1$, in which n is 1 or 2, and in which PG^1 is a suitable protective group such as, for example, benzyl, in presence of a suitable base such as, for example K_2CO_3 , in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C. Intermediate **T-55** in which $R^{22'}$ is a hydrogen can be obtained by

reacting intermediate **T-54** with a suitable reducing agent such as, for example, NaBH₄, in a suitable solvent such as, for example, MeOH, at a suitable temperature such as, for example, 25 °C (*Step 3*). A skilled person will understand that alternatively nucleophiles such as, for example, MeMgBr or TMS-CF₃/TBAF can be reacted with the ketone of **T-54** yielding tertiary alcohols **T-55** in which **R^{22'}** is, for example, a methyl or a CF₃ group, and a skilled person will also understand that this may require protection of the primary OH group with a suitable protective group such as, for example, TBDMS. Intermediate **T-56** can be obtained from intermediate **T-55** using suitable intramolecular ether formation conditions such as, for example, HBr in acetic acid (used as solvent), at a suitable temperature such as, for example, 25 °C (*Step 4*). Intermediate **T-57**, in which PG² is a suitable alternative protective group to PG¹, such as, for example, Boc, can be obtained by first removing the protective group PG¹ using a suitable deprotecting method such as, for example in case PG¹ is a benzyl group, 1-chloroethyl chloroformate, in a suitable solvent such as, for example, DME, followed by treatment with MeOH, and subsequent re-protection of the resulting amine with a suitable reagent such as, for example, Boc₂O, in presence of a suitable base such as, for example, triethylamine, a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 25 °C (*Step 5*). Intermediate **T-57** can be converted to **T-58**, in which **X³** is a halogen such as, for example, bromo, via a suitable haloacetylation method such as, for example, metal-catalyzed cross coupling sequence using tributyl(1-ethoxyvinyl)tin, in the presence of a catalyst/ligand system (*e.g.*, Pd(PPh₃)₄, a base (*e.g.*, *t*-BuOK), in a solvent (*e.g.*, dioxane)), at the appropriate temperature to provide the enol ether intermediate, which can in turn be transformed into haloketone **T-58** using a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, THF/water, at a suitable temperature such as, for example, room temperature (*Step 6*). Halo-ketone **T-58** can be reacted with heteroaryl thiol derivatives of formula **Y¹-SH** in the presence of a base (*e.g.*, MeONa or K₂CO₃) in a solvent (*e.g.*, DMF or ACN) at the appropriate temperature to provide intermediate **T-59** (*Step 7*). Intermediate thiols **Y¹-SH** can be prepared as described hereinbefore. Compounds of formula (**I**) in which **Z^{1'}** is a N-unsubstituted morpholine or homomorpholine can be obtained by reacting intermediate **T-59** with a suitable protective group removing reagent such as, for example, HCl/EtOAc (used as solvent), at a suitable temperature such as, for example, 25 °C (*Step 8*).

Compounds of formula (I) in which the morpholine or homomorpholine is N-alkylated can be obtained by subsequent reaction of the deprotected amine with a suitable alkylating reagent such as, for example, formaldehyde, in presence of a suitable reducing agent such as, for example, $\text{NaBH}(\text{OAc})_3$, in a suitable solvent such as, for example, AcOH/DCM ,
 5 at a suitable temperature such as, for example, 25°C . A skilled person will understand that racemic compounds of formula (I) can be further subjected to chiral separation such as, for example, chiral SFC to provide enantiopure compounds of formula (I).

[0196] Compounds of formula (I) in which **L** is a direct bond and in which **Z^{1'}** represents a bridged substituted morpholine or homomorpholine and **Y¹** and **Y²** are as defined above
 10 may be obtained also according to **Scheme 9** (Method 9) below:



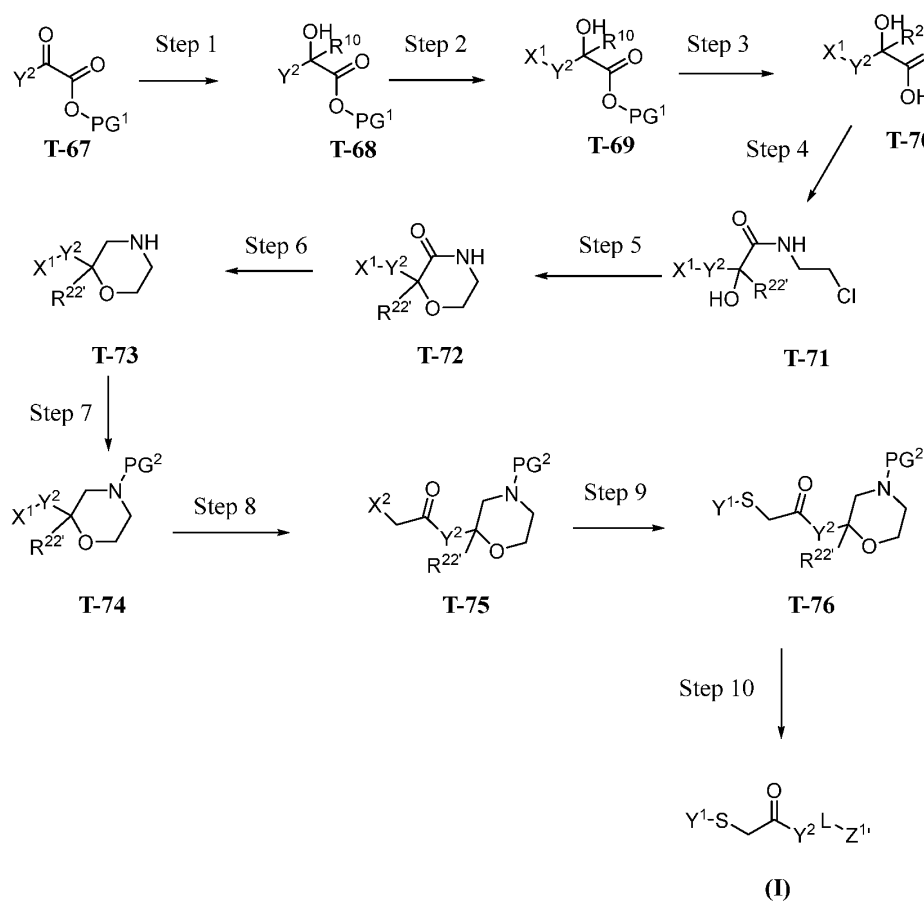
Scheme 9 / Method 9

[0197] Keto-acid intermediates **T-60**, in which PG is a suitable protective group such as, for example, Boc, and *n* is 1 or 2, can be obtained commercially or prepared via art known
 15 conditions. Intermediate **T-61** can be obtained by reacting intermediate **T-60** with a

suitable organometal such as, for example, thiophen-2-ylmagnesium bromide, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, 0 °C (*Step 1*). Intermediate **T-62** can be obtained by reacting intermediate **T-61** with a suitable acid reducing reagent such as, for example, BH₃.THF, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, 0-70 °C (*Step 2*). Intermediate **T-63** can be obtained by reacting intermediate **T-62** under suitable intramolecular ether formation conditions such as, for example, PPh₃/DIAD, in a suitable solvent such as, for example, toluene, at a suitable temperature such as, for example, 25 °C (*Step 3*). Intermediate **T-64**, in which X¹ is a halogen such as, for example, bromide, can be obtained by reacting intermediate **T-63** with a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C (*Step 4*). Intermediate **T-64** can be converted to halo ketone **T-65** in which X² is a halide such as, for example, bromide, via a suitable haloacetylation method such as, for example, metal-catalyzed cross coupling sequence using tributyl(1-ethoxyvinyl)tin, in the presence of a catalyst/ligand system (*e.g.*, Pd(PPh₃)₄, a base (*e.g.*, *t*-BuOK), in a solvent (*e.g.*, dioxane)), at the appropriate temperature to provide the enol ether intermediate, which can in turn be transformed into halo ketone **T-65** using a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, THF/water, at a suitable temperature such as, for example, room temperature (*Step 5*). Halo ketone **T-65** can be reacted with heteroaryl thiol derivatives of formula Y¹-SH in the presence of a base (*e.g.*, MeONa or K₂CO₃) in a solvent (*e.g.*, DMF or ACN) at the appropriate temperature to provide intermediate **T-66** (*Step 6*). Intermediate thiols Y¹-SH can be prepared as described hereinbefore. Compounds of formula (I) in which Z¹ is a N-unsubstituted bridged morpholine or homomorpholine can be obtained by reacting intermediate **T-66** with a suitable protective group removing reagent such as, for example, HCl/EtOAc (used as solvent), at a suitable temperature such as, for example, 25 °C (*Step 7*). Compounds of formula (I) in which the bridged morpholine or homomorpholine is N-alkylated can be obtained by subsequent reaction of the deprotected amine with a suitable alkylating reagent such as, for example, formaldehyde, in presence of a suitable reducing agent such as, for example, NaBH(OAc)₃, in a suitable solvent such as, for example, AcOH/DCM, at a suitable temperature such as, for example, 25 °C. A skilled person will understand that other N-

protected cyclic amines containing both a ketone and an acid, such as, for example, 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate can similarly be converted to compounds of formula (I). A skilled person will also understand that starting from the opposite enantiomer of **T-60** will provide a compound of formula (I) with opposite stereochemistry, hence the stereochemistry of the acid group in a starting material such as **T-60** will determine the stereochemistry in the compound of formula (I).

[0198] Compounds of formula (I) in which **L** is a direct bond and in which **Z¹** represents a substituted morpholine or homomorpholine, and **Y¹** and **Y²** are as defined above, may be obtained also according to **Scheme 10** (Method 10) below:



10

Scheme 10 / Method 10

[0199] Alpha-keto esters **T-67** in which PG¹ is a suitable acid protective group such as, for example, methyl, are commercially available or may be synthesized by a person

skilled in the art of organic chemistry using multiple ways described in the literature. Intermediates **T-68** in which **R^{22'}** is as defined above may be prepared by reacting **T-67** with an organometallic nucleophile such as, for example, methylmagnesium bromide, in a solvent (e.g., THF) at a suitable temperature such as, for example -40 °C (*Step 1*).

5 Intermediates **T-68** may also be prepared by reacting **T-67** with other ketone-reactive nucleophiles such as, for example, trifluoromethyltrimethylsilane in presence of a suitable anionic initiator such as, for example, tetrabutylammonium fluoride, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 0°C to room temperature. Intermediate **T-69** in which **X¹** is a halide such as, for example bromide, can

10 be prepared by reacting intermediate **T-68** with a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C (*Step 2*). Intermediates **T-70** may be prepared by reacting **T-69** with a suitable base such as, for example, KOH, in a suitable solvent such as, for example, EtOH/water, at a suitable temperature such as, for example, 25 °C (*Step*

15 3). Intermediates **T-71** may be prepared by reacting **T-70** with 2-chloroethylamine using a suitable amide coupling reagent such as, for example, HATU, in presence of a suitable base such as, for example, DIPEA, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 0-25 °C (*Step 4*). Intermediates **T-72** may be obtained by reacting **T-71** with a suitable base such as, for example, tBuOK, in a suitable

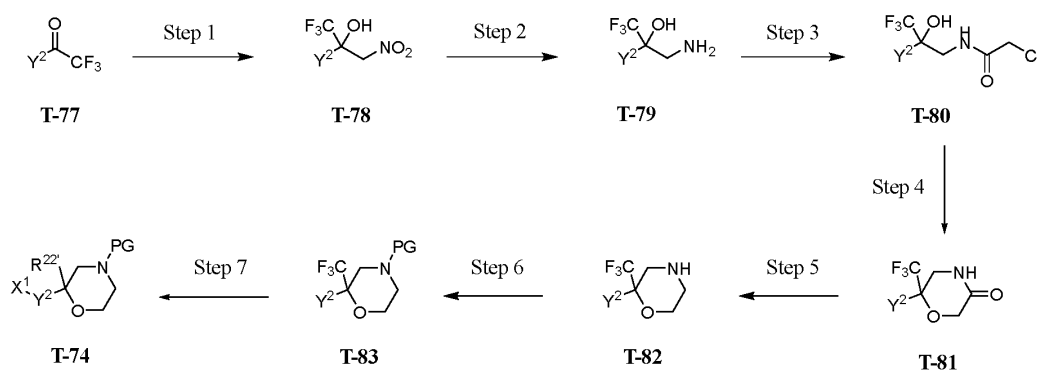
20 solvent such as, for example, THF, at a suitable temperature such as, for example, 0-80 °C (*Step 5*). Intermediates **T-73** may be obtained by reacting **T-72** with a suitable reducing agent such as, for example, BH₃.THF, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, -60 to 25 °C (*Step 6*). Intermediate **T-74**, in which PG² is a suitable protective group such as, for example, Boc, may be

25 obtained by reacting **T-73** with a suitable protecting reagent such as, for example, Boc₂O, in presence of a suitable base such as, for example, K₂CO₃, in a suitable solvent such as, for example, THF/water, at a suitable temperature such as, for example, 25 °C (*Step 7*). Intermediate **T-74** can be converted to haloketone **T-75** in which **X²** is a halide such as, for example, bromide, via a suitable haloacetylation method such as, for example, metal-

30 catalyzed cross coupling sequence using tributyl(1-ethoxyvinyl)tin, in the presence of a catalyst/ligand system (e.g., Pd(PPh₃)₄, a base (e.g., *t*-BuOK), in a solvent (e.g., dioxane)), at the appropriate temperature to provide the enol ether intermediate, which

can in turn be transformed into **T-75** in which X^2 is a halide such as, for example, bromide, using a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, THF/water, at a suitable temperature such as, for example, 25 °C (Step 5). Halo-ketone **T-75** can be reacted with heteroaryl thiol derivatives of formula Y^1 -SH in the presence of a base (*e.g.*, MeONa or K_2CO_3) in a solvent (*e.g.*, DMF or ACN) at the appropriate temperature to provide intermediate **T-76** (Step 9). Intermediate thiols Y^1 -SH can be prepared as described hereinbefore. Compounds of formula (I) in which Z^1 is a morpholine can be obtained by reacting intermediate **T-76** with a suitable protective group removing reagent such as, for example, HCl/EtOAc (used as solvent), at a suitable temperature such as, for example, 25 °C (Step 10). Compounds of formula (I) in which the morpholine is N-alkylated can be obtained by subsequent reaction of the deprotected amine with a suitable alkylating reagent such as, for example, formaldehyde, in presence of a suitable reducing agent such as, for example, $NaBH(OAc)_3$, in a suitable solvent such as, for example, AcOH/DCM, at a suitable temperature such as, for example, 25 °C. A skilled person will understand that racemic compounds of formula (I) can be further subjected to chiral separation such as, for example, chiral SFC to provide enantiopure compounds of formula (I).

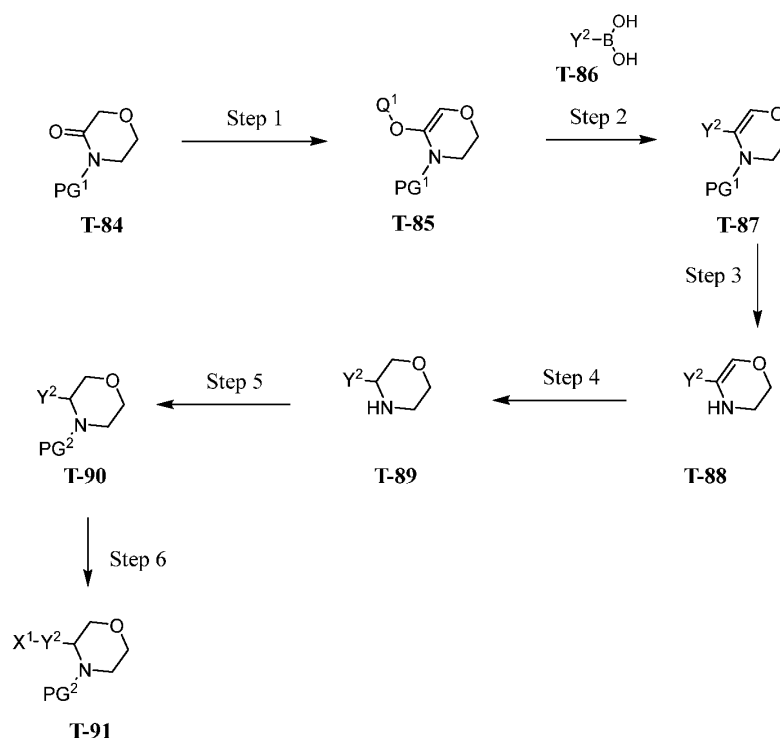
[0200] Intermediates **T-74** in which Y^2 is as described above, X^1 is a halo such as, for example, bromide, PG is a protective group, and $R^{22'}$ is a CF_3 group may be obtained also according to **Scheme 11** (Method 11) below:



Scheme 11 / Method 11

[0201] Intermediates **T-77** are commercially available or can be made using art known conditions. Intermediates **T-78** can be prepared by reacting **T-77** with a suitable reagent such as, for example, nitromethane, in presence of a suitable base such as, for example, K₂CO₃, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 25 °C (*Step 1*). Intermediates **T-79** can be obtained by reacting **T-78** with a suitable reducing agent such as, for example, hydrogen gas, in presence of a suitable catalyst such as, for example Pd/C, in a suitable solvent such as, for example, EtOH, at a suitable temperature such as, for example, 25 °C (*Step 2*). Intermediates **T-80** can be obtained by reacting **T-79** with chloroacetyl chloride, in presence of a suitable base such as, for example, triethylamine, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 0 °C (*Step 3*). Intermediate **T-81** can be obtained by reacting **T-80** with a suitable base such as, for example, NaH, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, 0 °C (*Step 4*). Intermediate **T-82** can be obtained by reducing intermediate **T-81** with a suitable reagent such as, for example, LiAlH₄, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, 0-70 °C (*Step 5*). Intermediate **T-83**, in which PG is a suitable protective group such as, for example, Boc, can be prepared by reacting intermediate **T-82** with a suitable protecting reagent such as, for example, Boc₂O, in presence of a suitable base such as, for example, triethylamine, in a suitable solvent such as, for example, MeOH, at a suitable temperature such as, for example, 25 °C (*Step 6*). Intermediate **T-74** in which **R^{22'}** is a CF₃ group can be prepared by reacting intermediate **T-83** with a suitable halogenating reagent such as, for example, NBS, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C (*Step 7*). A skilled person will understand that intermediate **T-74** in which **R^{22'}** is a CF₃ group can be progressed to compounds of formula (**I**) in a similar manner as described in **Scheme 10** hereinabove.

[0202] Intermediates **T-91** in which **Y²** is as described above, **X¹** is a halo such as, for example, bromide, PG is a protective group, and **R^{22'}** is a CF₃ group may be obtained according to **Scheme 12** (Method 12) below:

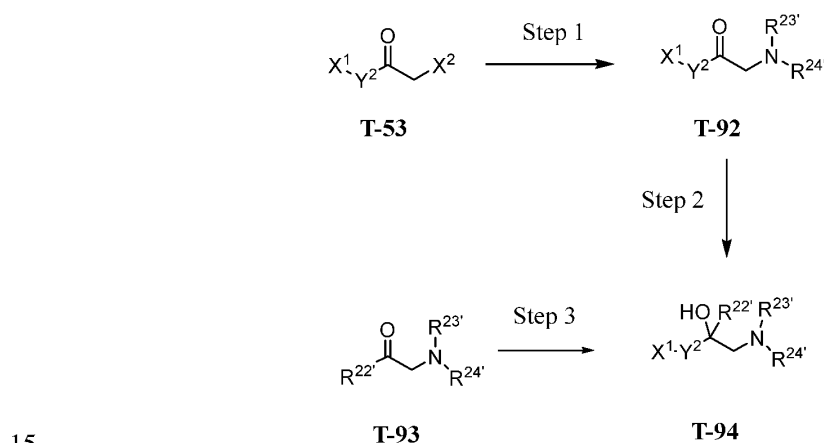


Scheme 12 / Method 12

- [0203] Intermediates **T-84** in which PG^1 is a suitable protective group such as, for example, Boc, are commercially available or can be prepared using art known conditions.
- 5 Intermediates **T-85**, in which Q^1 is an activating group such as, for example, diphenyl phosphonate or triflate, can be prepared by reacting **T-84** with a suitable activating reagent such as, for example, diphenyl phosphorochloridate, in the presence of a suitable base such as, for example, LiHMDS, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, -30 to $25\text{ }^\circ\text{C}$ (*Step 1*). Intermediate **T-87** can
- 10 be prepared by reacting **T-85** with a suitable boronate **T-86** of formula $\text{Y}^2\text{-B(OH)}_2$, in presence of a suitable catalyst such as, for example, $\text{Pd}(\text{tBu}_3\text{P})_2$, in presence of a suitable base such as, for example, K_3PO_4 , in a suitable solvent such as, for example, ACN/water, at a suitable temperature such as, for example, $65\text{ }^\circ\text{C}$ (*Step 2*). Intermediate **T-88** prepared by reacting **T-87** with a suitable deprotecting agent such as, for example, 2 M HCl in
- 15 dioxane, at a suitable temperature such as, for example, 0 - $25\text{ }^\circ\text{C}$ (*Step 3*). Intermediate **T-89** can be prepared by reacting **T-88** with a suitable reducing agent such as, for example,

NaBH₃CN, in a suitable solvent such as, for example, AcOH/MeOH, at a suitable temperature such as, for example, 25 °C (*Step 4*). Intermediate **T-90**, in which PG² is a suitable protective group such as, for example, Boc, can be prepared by reacting **T-89** with a suitable protecting agent such as, for example, Boc₂O, in presence of a suitable base such as, for example, DIPEA, in a suitable solvent such as, for example, DCM, at a suitable temperature such as, for example, 25 °C. Intermediate **T-91** in which **X¹** is a suitable halogen such as, for example, bromide, can be prepared by reacting **T-90** with a suitable halogenating agent such as, for example, NBS, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C. A skilled person will understand that intermediate **T-91** can be progressed to compounds of formula (I) in a similar manner as described for intermediate **T-74** in **Scheme 10** hereinabove.

[0204] Intermediates **T-94** in which **Y²** is as described above, **X¹** is a halide such as, for example, bromide, and **R^{22'}**, **R^{23'}** and **R^{24'}** are as defined hereinabove may be obtained also according to **Scheme 13** (Method 13) below:

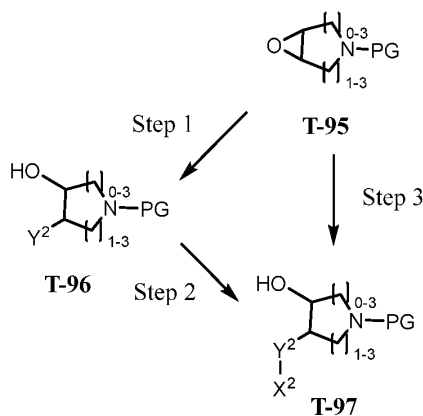


Scheme 13 / Method 13

[0205] Intermediate **T-92** can be prepared by reacting **T-53** with a suitable amine **R^{23'}R^{24'}NH**, in presence of a suitable base such as, for example K₂CO₃, in a suitable solvent such as, for example, CH₃CN, at a suitable temperature such as, for example, 25 °C (*Step 1*). Intermediate **T-94** in which **R^{22'}** is hydrogen can be prepared by reducing the ketone of **T-92** with a suitable reducing agent such as, for example, NaBH₄, in a suitable solvent such as, for example, EtOH, at a suitable temperature such as, for example 0-25

°C (*Step 2*). Intermediate **T-94** in which **R^{22'}** is an alkyl or aryl group can be prepared by reacting the ketone of **T-92** with a suitable organometal such as, for example, methylmagnesium bromide, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example -78 to 25 °C (*Step 2, alternative*). Intermediate **T-94** can alternatively be prepared by reacting **T-93** with a suitable organometal such as, for example, (5-bromothiophen-2-yl)lithium prepared in situ from 2,5-dibromothiophene/*n*-BuLi, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, -78 to 25 °C (*Step 3*). A skilled person will understand that intermediate **T-94** can be progressed to compounds of formula (I) in a similar manner as described for intermediate **T-74** in **Scheme 10** hereinabove. A skilled person will also understand that other amine-containing aldehydes or ketones than intermediate **T-93** can similarly provide compounds of formula (I).

[0206] Intermediates **T-97** in which **Y²** is as defined above, **X¹** is a halide such as, for example, bromide, and PG is a protective group may be obtained according to **Scheme 14** (Method 14):



Scheme 14 / Method 14

[0207] Intermediates **T-95** in which PG is a suitable protective group such as, for example, Boc, are commercially available or can be prepared using art known conditions. Intermediate **T-96** can be prepared by reacting **T-95** with a suitable organometal such as, for example, thiophen-2-ylmagnesium bromide, in presence of a suitable catalyst such as, for example, copper(I) iodide, in a suitable solvent such as, for example THF, at a suitable

temperature such as, for example, -30 to 25 °C (*Step 1*). Intermediate **T-97**, in which **X¹** is a halogen such as, for example, bromide, can be prepared by reacting **T-96** with a suitable halogenating agent such as, for example, NBS, in a suitable solvent such as, for example, DMF, at a suitable temperature such as, for example, 25 °C (*Step 2*).

5 Intermediate **T-97** can alternatively be prepared by reacting **T-95** with a suitable organometal such as, for example, (5-bromothiophen-2-yl)lithium prepared in situ from 2,5-dibromothiophene/*n*-BuLi, in a suitable solvent such as, for example, THF, at a suitable temperature such as, for example, -78 to 25 °C (*Step 3*). A skilled person will understand that intermediate **T-97** can be progressed to compounds of formula (I) in a

10 similar manner as described for intermediate **T-74** in **Scheme 10** hereinabove. A skilled person will also understand that when **T-94** is chiral, the resulting compounds of formula (I) will also have well-defined chirality.

Synthesis of the compounds – Experimental results

[0208] Several methods for preparing the compounds of this invention are illustrated in

15 the following Examples. Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. Specifically, the following abbreviations may be used in the examples and throughout the specification.

Abbreviations

[0209] Abbreviations are used as follows.

Abbreviation	Name	Abbreviation	Name
aq.	aqueous	M	molar
AMC	7-amino-4-methylcoumarin	Me	methyl
1-BuOH	1-butanol	MeOH	methanol
ACN	acetonitrile	MeONa	sodium methoxide
AIBN	azobisisobutyronitrile	mg	milligram
BRET	Bioluminescence Resonance Energy Transfer	MHz	megahertz
BSA	Bovine Serum Albumin	μw	microwave
(Boc)₂O	di-tert-butyl dicarbonate	N₂	nitrogen
cHex	cyclohexane	NaH	sodium hydride

Cpd	compound	Na₂CO₃	sodium carbonate
d	days	NaHCO₃	sodium bicarbonate
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NaOH	sodium hydroxide
DAST	diethylaminosulfur trifluoride	Na₂SO₄	sodium sulfate
DCM	dichloromethane	MTBE	Methyl tert-butyl ether
DEAD	diethyl azodicarboxylate	NBS	N-bromosuccinimide
DIAD	diisopropyl azodicarboxylate	NMP	N-methylpyrrolidone
DIBAL-H	diisobutylaluminium hydride	NMR	nuclear magnetic resonance
DIPEA or DIEA	N,N-diethylisopropyl amine	PBS	Phosphate-buffered saline
DMAP	4-dimethylaminopyridine	P₂S₅	Phosphorus pentasulfide
DMF	N,N-dimethylformamide	PCC	Pyridinium chlorochromate
DMSO	dimethyl sulfoxide	PE	Petroleum ether
DPPA	diphenylphosphoryl azide	PK	pharmacokinetics
DPPP	<u>1,3-bis(diphenylphosphino)propane</u>	Pd/C	Palladium on charcoal
DTT	dithiothreitol	PdCl₂(dppf)	[1,1'-Bis(diphenylphosphino)-ferrocene]dichloropalladium (II)
EDCI	1-ethyl-3-(3-dimethylamino-propyl)carbodiimide	Pd(PPh₃)₄	Tetrakis(triphenylphosphine) palladium
EA	Ethyl acetate	PE	Petroleum ether
EDTA	ethylenediaminetetraacetic acid	Pd(OH)₂	Palladium hydroxide
Et₂O	diethyl ether	PTSA	para-toluenesulfonic acid
EtOAc	ethyl acetate	QC	Quality control
eq. or equiv.	equivalents	quant.	quantitative
FA	Formic Acid	R_f or R_t	retention factor or retention time
g	gram	RP	Reversed Phase
GST	Glutathione-S-transferase	rt or RT	room temperature

h	hours	SAHA	suberoylanilide hydroxamic acid
H	proton	Sat.	saturated
HCl	hydrochloric acid	SFC	Supercritical fluid chromatography
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium	SiO₂	silica
HDAC	histone deacetylase	SOCl₂	thionyl chloride
HMDS	bis(trimethylsilyl)amide	TBAF	Tetrabutylammonium fluoride
HOBt	1-hydroxy-benzotriazole	TBATB	Tetrabutylammonium tribromide
Hz	Hertz	TBDPS	tert-Butyldiphenylsilyl
IPA	iso-propanol	TBS	tert-Butyldimethylsilyl
J	scalar ¹ H- ¹ H coupling constant	TEA	triethylamine
K₂CO₃	potassium carbonate	TFA	Trifluoroacetic acid
KOH	potassium hydroxide	THF	Tetrahydrofuran
LCMS or LC-MS	liquid chromatography – mass spectrometry	TLC	thin layer chromatography
LLOQ	Lowest level of quantification	TMSCF₃	Trifluoromethyltrimethylsilane
LiHMDS	lithium bis(trimethylsilyl)amide	TSA	Trichostatin A
MSA	Methane sulfonic acid	RockPhos Pd G3	[(2-Di- <i>tert</i> -butylphosphino-3-methoxy-6-methyl-2',4',6'-triisopropyl-1,1'-biphenyl)-2-(2-aminobiphenyl)]palladium(II) methanesulfonate
		TfOH	Trifluoromethylsulfonic acid

Analytical methods

- [0210] **LCMS (Method 1)**: LC-MS were recorded on an Agilent 1200-G6140. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the
- 5 Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to

obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. An ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the [M+H⁺] (protonated molecule) or [M-H⁺] (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used. The gradient conditions used are described below:

Method name:	0_95AB_7min-220-254						
Instrument:	Agilent 1200 & 6140						
Column:	Waters, Xbridge C18 30*2.1mm,3.5um						
Column temperature:	40 °C						
Mobile phase A(MPA)	H ₂ O+0.04 % (v/v) TFA						
Mobile phase B(MPB)	ACN+0.02 % (v/v) TFA						
Flow rate:	1.0 mL/min						
Gradient Ratio:	Time(min)	0.00	5.80	6.60	6.61	6.80	7.00
	MPA (%)	100	5	0	100	100	100
	MPB (%)	0	95	100	0	0	0
Detection:	220 nm&254nm						
MS Mode:	Positive						
MS Range:	100-1000						

[0211] **LCMS (Method 2):** LC-MS were recorded on an Agilent 1200-G6140. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. An ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the [M+H⁺] (protonated molecule) or [M-H⁺] (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained

with experimental uncertainties that are commonly associated with the method used. The gradient conditions used are described below:

Method name:	0_95CD_7min-220-254						
Instrument:	Agilent 1200 & 6140						
Column:	Waters, Xbridge C18 30*2.1mm,3.5um						
Column temperature:	40 °C						
Mobile phase A(MPA)	H2O+0.05 % (v/v) NH3H2O						
Mobile phase B(MPB)	ACN						
Flow rate:	1.0 mL/min						
Gradient Ratio:	Time(min)	0.00	5.80	6.60	6.61	6.80	7.00
	MPA (%)	100	5	0	100	100	100
	MPB (%)	0	95	100	0	0	0
Detection:	220 nm&254nm						
MS Mode:	Positive						
MS Range:	100-1000						

[0212] **LCMS (method 3):** Liquid chromatography-mass spectroscopy (LCMS) spectra were recorded on a Waters Acquity I class UPLC system. The gradient conditions used are described below:

Column	Method 3: Kinetex EVO C18 (2.1 x 50 mm, 1.7 μm)					
Column temperature	40 °C					
Mobile phase A (MPA)	0.01% FA in water					
Mobile phase B (MPB)	0.01% FA in ACN					
Flow rate:	0.8 mL/min					
Gradient Ratio:	Time (min)	0.01	0.2	1.5	3	
	A (%)	90	90	10	10	
	B (%)	10	10	90	90	
Detection:	220 nm and 254 nm					
MS Mode:	Positive and negative					
MS Range:	100-1000					

[0213] **LCMS (method 4):** Liquid chromatography-mass spectroscopy (LCMS) spectra were recorded on a Waters Acquity I class UPLC system. The gradient conditions used are described below:

Column	Method 3: Kinetex EVO C18 (2.1 x 50 mm, 1.7 μ m)
Column temperature	40 °C
Mobile phase A (MPA)	0.01% FA in water

Mobile phase B (MPB)	0.01% FA in ACN				
Flow rate:	0.4 mL/min				
Gradient Ratio:	Time (min)	0.01	0.5	4	7
	A (%)	90	90	10	10
	B (%)	10	10	90	90
Detection:	220 nm and 254 nm				
MS Mode:	Positive and negative				
MS Range:	100-1000				

[0214] **LCMS (method 5):** Liquid chromatography-mass spectroscopy (LCMS) spectra were recorded on a Waters Acquity I class UPLC system. The gradient conditions used are described below:

Column	Interchim Acquity BEH C18 (2.1 x 100 mm, 1.7 µm)				
Column temperature	ambient temperature				
Mobile phase A (MPA)	0.01% FA in water				
Mobile phase B (MPB)	0.01% FA in ACN				
Flow rate:	0.4 mL/min				
Gradient Ratio:	Time (min)	0.01	0.5	4	7
	A (%)	90	90	10	10
	B (%)	10	10	90	90
Detection:	220 nm and 254 nm				
MS Mode:	Positive				
MS Range:	100-1000				

- 5 [0215] **LCMS (method 6):** Liquid chromatography-mass spectroscopy (LCMS) spectra were recorded on a Waters Acquity I class UPLC system. The gradient conditions used are described below:

Column	ZORBAX Eclipse Plus C18 (2.1 x 100 mm, 1.8 µm)				
Column temperature	ambient temperature				
Mobile phase A (MPA)	0.01% FA in water				
Mobile phase B (MPB)	0.01% FA in ACN				
Flow rate:	0.4 mL/min				
Gradient Ratio:	Time (min)	0.01	0.5	4	7
	A (%)	90	90	10	10
	B (%)	10	10	90	90
Detection:	220 nm and 254 nm				
MS Mode:	Positive				

MS Range:	100-1000
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[0216] **LCMS (Method 7):** LC-MS spectra were recorded on a Waters Acquity I class UPLC system using the following system [solvent A: acetonitrile, solvent B: 0.1% formic in water or solvent A: acetonitrile, solvent B: 0.1% ammonia in water or solvent A: acetonitrile, solvent B: 0.1% TFA in water. Formic acid and ammonia or TFA was used as HPLC grade. All the separations were performed at ambient temperatures. Reverse phase HPLC was performed on a Waters HPLC system using following solvent system [solvent A: acetonitrile, solvent B: 0.1% NH₃ in water] or [solvent A: acetonitrile, solvent B: 0.1% TFA in water]. Ammonia was used as HPLC grade. All the separations were performed at ambient temperatures. For analytical RP-HPLC analysis [Interchim: Acquity BEH C18 (2.1 x 100 mm, 1.7 μ m)], the flow rate was 0.4 mL.min⁻¹; injection volume: 10 μ L, detection wavelengths: 220 nm and 254 nm. The following gradient was used: 0.01 min 90 % B, over 8 min to 10 % B, 4 min 10 % B.

[0217] **LCMS (Method 8):** LC-MS were recorded on an Agilent 1200 & 6120B. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the [M+H⁺] (protonated molecule) or [M-H⁺] (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used.

[0218] The gradient conditions used are described below:

Column:	Xbridge C18 2.1 * 50 mm, 5 μ m
Column temperature:	40 °C
Mobile phase A (MPA)	H ₂ O+10 mM NH ₄ HCO ₃
Mobile phase B (MPB)	Acetonitrile

Flow rate:	0.8 mL/min						
Gradient Ratio:	Time(min)	0.00	0.40	3.40	3.85	3.86	4.50
	MPA(%)	95	95	5	5	95	95
	MPB(%)	5	5	95	95	5	5
Detection:	220 nm						
MS Mode:	Positive						
MS Range:	100-1000						

- [0219] **LCMS (Method 9):** LC-MS were recorded on a Shimadzu LC-20AD&MS 2020. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. An ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the $[M+H^+]$ (protonated molecule) or $[M-H^+]$ (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used. The gradient conditions used are described below:

Column:	Xbridge C18 2.1*50mm,5 μ m					
Column temperature:	40 °C					
Mobile phase A (MPA)	H ₂ O+10mM NH ₄ HCO ₃					
Mobile phase B (MPB)	Acetonitrile					
Flow rate:	1.5 mL/min					
Gradient Ratio:	Time(min)	0.01	0.70	1.16	1.50	
	MPA(%)	95	5	5	95	
	MPB(%)	5	95	95	5	
Detection:	220 nm & 254 nm					
MS Mode:	Positive					
MS Range:	100-1000					

- 15 [0220] **LCMS (Method 10):** LC-MS were recorded on a Shimadzu LC-20AD&MS 2020. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric

pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. An ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the [M+H⁺] (protonated molecule) or [M-H⁺] (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained with experimental uncertainties that are commonly associated with the method used. The gradient conditions used are described below:

Column:	Xbridge C18 2.1*50mm,5µm					
Column temperature:	40 °C					
Mobile phase A (MPA)	H ₂ O+10mM NH ₄ HCO ₃					
Mobile phase B (MPB)	Acetonitrile					
Flow rate:	1.0 mL/min					
Gradient Ratio:	Time(min)	0.01	3.00	3.50	3.51	4.30
	MPA(%)	95	5	5	95	95
	MPB(%)	5	95	95	5	5
Detection:	220 nm & 254 nm					
MS Mode:	Positive					
MS Range:	100-1000					

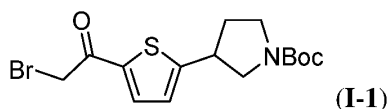
[0221] **LCMS (Method 11):** LC-MS were recorded on an Agilent Agilent 1260 & 6125B. The High-Performance Liquid Chromatography (HPLC) measurement was performed using a LC pump, a diode-array or a UV detector. Flow from the column was brought to the Mass Spectrometer (MS) which was configured with an atmospheric pressure ion source. It is within the knowledge of the skilled person to set the tune parameters in order to obtain ions allowing the identification of the compound's nominal monoisotopic molecular weight (MW) and/or exact mass monoisotopic molecular weight. Data acquisition was performed with appropriate software. An ES MS detector was used, acquiring in positive or negative ionization modes. Compounds can be described by their molecular ion corresponding to the [M+H⁺] (protonated molecule) or [M-H⁺] (deprotonated molecule). For molecules with multiple isotopic patterns (Br, Cl), the reported value is the one obtained for the lowest isotope mass. All results were obtained

with experimental uncertainties that are commonly associated with the method used. The gradient conditions used are described below:

Column:	Luna-C18(2) 2.0*50mm, 5um						
Column temperature:	40 °C						
Mobile phase A(MPA)	H ₂ O+0.04 % (v/v) TFA						
Mobile phase B(MPB)	ACN+0.02 % (v/v) TFA						
Flow rate:	1.0 mL/min						
Gradient Ratio:	Time(min)	0.00	0.40	3.00	4.00	4.01	4.50
	MPA (%)	95	95	5	5	95	95
	MPB (%)	5	5	95	95	5	5
Detection:	220 nm&254nm						
MS Mode:	Positive						
MS Range:	100-1000						

Preparation of synthetic intermediates

5 [0222] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (I-1):**



[0223] **Synthesis of tert-butyl 3-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1H-pyrrole-1-carboxylate (I-1-1)** To a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (1 g, 5.398 mmol) in dry THF (10 mL) cooled to -78°C was added dropwise LiHMDS (1.0 M soln. in THF) (6.0 mL, 5.934 mmol), and the resulting mixture was stirred for 60 min. N-(5-chloropyridin-2-yl)-1,1,1-trifluoro-N-(trifluoromethylsulfonyl)methanesulfonamide in THF (2.33 g, 5.934 mmol) was added to the solution and stirred for 30 min at the same temperature. Next, the reaction mixture was warmed to rt, quenched with sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (2 x 50 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel (60-120 mesh) eluting with 10% EtOAc in hexane to afford compound **I-1-1** (0.63 g, 37 % yield) as gummy liquid.

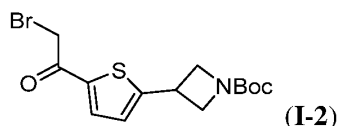
[0224] **Synthesis of tert-butyl 3-(5-acetylthiophen-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (I-1-2)** To a stirred solution of (5-acetylthiophen-2-yl) boronic acid (1.6 g,

9.463 mmol) and tert-butyl 3-(((trifluoromethyl)sulfonyl)oxy)-2,5-dihydro-1H-pyrrole-1-carboxylate **2** (3 g, 9.463 mmol) in dioxane:H₂O (30 mL, 3:1), K₂CO₃ (3.9 g, 28.389 mmol) and Pd(dppf)Cl₂ (1.0 g, 0.9463 mmol) was added. The reaction was purged with N₂ for 15 min, then heated to 100 °C for 16 h. Next, the mixture was quenched with sat. aq. NaHCO₃ (20 mL), and then extracted with EtOAc (2 x 50 mL). The organic layer was separated, dried over Na₂SO₄, and the solvent evaporated under reduced pressure. The residue was purified by column chromatography using a silica gel (60-120 mesh, eluent: 50% EtOAc in hexane) to afford the title compound **I-1-2** (2.7 g, 75% yield) as a gummy liquid.

- 10 [0225] **Synthesis of tert-butyl 3-(5-acetylthiophen-2-yl)pyrrolidine-1-carboxylate (I-1-3)** To a stirred solution of tert-butyl 3-(5-acetylthiophen-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate **I-1-2** (2 g, 6.825 mmol) in MeOH (20 mL) was added 10% Pd-C (2.0 g), then H₂ gas was inserted for 5 h at 60 psi. The reaction mixture was filtered through a celite bed in vacuo. The solvent was evaporated under reduced pressure and the residue
- 15 purified by column chromatography over silica gel (60-120 mesh, eluent: 50% EtOAc in hexane) to afford the title compound **I-1-3** (1.5 g, 74% yield) as yellow liquid.

- [0226] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (I-1)** To a solution of compound **I-1-3** (0.2 g, 0.680 mmol) in dry THF (5 mL) tetrabutylammonium tribromide (0.8 g, 1.360 mmol) added then stirred at room
- 20 temperature for 16 h. The reaction mixture was concentrated to get crude compound, which was purified by Combi-flash reversed phase chromatography to afford **I-1** (0.07 g, 27% yield) as a white solid. ¹H NMR [400 MHz, DMSO-*d*₆]: 7.95 (d, *J* = 3.6 Hz, 1H), 7.15 (d, *J* = 4 Hz, 1H), 4.78 (s, 2H), 3.73-3.69 (m, 2H), 3.40-3.23 (m, 4H), 2.33-2.29 (m, 1H), 1.40 (s, 9H).

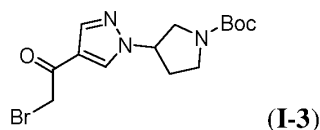
- 25 [0227] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)azetidine-1-carboxylate (I-2):**



[0228] **Synthesis of tert-butyl 3-(5-acetylthiophen-2-yl)azetidine-1-carboxylate (I-2-1)** Zn (4.78 g, 73.1 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (35.0 mL) was added via syringe followed by a catalytic amount of I₂ (928 mg, 3.66 mmol, 737 µL). A color change of the DMF was observed from colorless to yellow and back. Tert-butyl 3-iodoazetidine-1-carboxylate (8.97 g, 31.7 mmol) was added immediately followed by a catalytic amount of I₂ (928 mg, 3.66 mmol, 737 µL). The solution was stirred at 15 °C and gave a noticeable exotherm. When the solution was cooled to 25 °C, SPhos (500 mg, 1.22 mmol, 0.05 eq), Pd₂(dba)₃ (447 mg, 488 µmol) and 1-(5-bromo-2-thienyl)ethanone (5.00 g, 24.4 mmol) were added to the flask and stir at 15 °C for 12 h under positive pressure of nitrogen. The reaction mixture was diluted with water (60.0 mL) and extracted with DCM (30.0 mL x 2). The combined organic layers were washed with water (20.0 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1) to give compound **I-2-1** (3.50 g, 51.0% yield) as a brown oil.

[0229] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)azetidine-1-carboxylate (I-2)** To a solution of compound **I-2-1** (3.00 g, 10.7 mmol) in DCM (18.0 mL) and MeOH (45.0 mL) was added TBATB (5.40 g, 11.2 mmol) and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by addition of H₂O (10.0 mL) at 25 °C, and then extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 0/1) to give compound **I-2** (1.1 g, 28.6% yield) as a yellow oil.

[0230] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (I-3):**

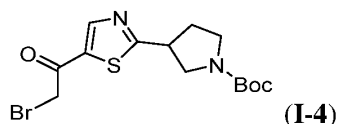


[0231] **Synthesis of tert-butyl 3-(4-acetyl-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (I-3-1)** To a solution of 1-(1H-pyrazol-4-yl)ethan-1-one (5.00 g, 45.4 mmol) and tert-

butyl 3-hydroxypyrrolidine-1-carboxylate (8.50 g, 45.4 mmol) in THF (35.0 mL) was added DIAD (13.8 g, 68.1 mmol, 13.2 mL) and PPh₃ (17.8 g, 68.1 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was quenched by addition of H₂O (50.0 mL) at 25 °C, and then extracted with EtOAc (25.0 mL x 3). The combined organic layers were washed with brine (50.0 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep-HPLC (neutral condition) to give compound **I-3-1** (5.40 g, 42.6% yield) as a white solid.

[0232] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)-1H-pyrazol-1-yl)pyrrolidine-1-carboxylate (I-3)** To a solution of compound **I-3-1** (2.00 g, 7.16 mmol) in MeOH (20.0 mL) and DCM (3.00 mL) was added TBATB (3.62 g, 7.52 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was diluted with DCM (50.0 mL) and washed with water (50.0 mL x 2). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-3** (500 mg, 19.5% yield) as a colorless oil.

[0233] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)pyrrolidine-1-carboxylate (I-4):**



[0234] **Synthesis of tert-butyl 3-carbamothioylpyrrolidine-1-carboxylate (I-4-1)** To a solution of tert-butyl 3-carbamoylpyrrolidine-1-carboxylate (4.60 g, 21.5 mmol) in toluene (46.0 mL) was added Lawesson's reagent (4.34 g, 10.7 mmol). The mixture was stirred at 80 °C for 16 h. The suspension was filtered through a pad of celite and washed with EtOAc (100 mL). The combined filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-4-1** (1.30 g, 26.2% yield) as a white solid.

[0235] **Synthesis of tert-butyl 3-(5-formylthiazol-2-yl)pyrrolidine-1-carboxylate (I-4-2)** To a solution of compound **I-4-1** (1.00 g, 4.34 mmol) in AcOH (10.0 mL) was added NaOAc (534 mg, 6.51 mmol) and 2-bromomalonaldehyde (721 mg, 4.78 mmol). The

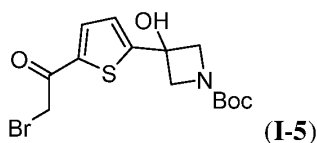
mixture was stirred at 100 °C for 0.3 h. The reaction was added H₂O (3.00 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 0/1, compound **I-4-2** R_f = 0.5) to give compound **I-4-2** (0.70 g, 57.1% yield) as a yellow oil.

[0236] **Synthesis of tert-butyl 3-(5-(1-hydroxyethyl)thiazol-2-yl)pyrrolidine-1-carboxylate (I-4-3)** To a solution of compound **I-4-2** (160 mg, 567 µmol) in THF (2.00 mL) was added MeMgBr (135 mg, 1.13 mmol) at -20 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (2.00 mL) and extracted with EtOAc (10.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a compound **I-4-3** (140 mg 82.8% yield) as a white solid.

[0237] **Synthesis of tert-butyl 3-(5-acetylthiazol-2-yl)pyrrolidine-1-carboxylate (I-4-4)** To a solution of compound **I-4-3** (120 mg, 402 µmol) in DCM (1.50 mL) was added Dess-Martin reagent (256 mg, 603 µmol, 187 µL) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 3/1) to give compound **I-4-4** (108 mg, 90.6% yield) as a colorless oil.

[0238] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)pyrrolidine-1-carboxylate (I-4)** To a solution of compound **I-4-4** (68.0 mg, 229 µmol) in THF (1.00 mL) was added pyridinium tribromide (129 mg, 344 µmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was diluted with H₂O (2.00 mL) and extracted with EtOAc (2.00 mL x 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuum to give compound **I-4** (100 mg, 44.1% yield, 38.0% purity) as a yellow solid.

[0239] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxyazetidine-1-carboxylate (I-5):**



[0240] **Synthesis of tert-butyl 3-hydroxy-3-(thiophen-2-yl)azetidine-1-carboxylate (I-5-1)** To a solution of 2-bromothiophene (95.0 g, 582 mmol, 56.4 mL) in THF (950 mL) was added n-BuLi (2.50 M, 233 mL) in one portion at -60 °C under N₂. The mixture was stirred at -60 °C for 1 h, then added tert-butyl 3-oxoazetidine-1-carboxylate (109 g, 640 mmol). The mixture was stirred at -60 °C for 2 h. The reaction mixture was poured into ice-water (1.50 L) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give compound **I-5-1** (160 g, 49.4% yield, 92.6% purity) as a white solid.

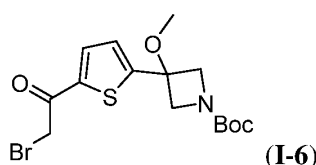
10 [0241] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)-3-hydroxyazetidine-1-carboxylate (I-5-2)** To a solution of compound **I-5-1** (114 g, 734 mmol), DMAP (4.49 g, 36.7 mmol) and NBS (156 g, 881 mmol) in ACN (798 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The reaction mixture was poured into water (500 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried with anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give compound **I-5-2** (117 g, 42.9% yield) as a yellow solid.

[0242] **Synthesis of tert-butyl 3-(5-acetylthiophen-2-yl)-3-hydroxyazetidine-1-carboxylate (I-5-3)** To a solution of compound **I-5-2** (10.0 g, 29.9 mmol), 1-(vinylloxy)butane (7.49 g, 74.8 mmol, 9.62 mL), Pd(OAc)₂ (806 mg, 3.59 mmol), DPPP (2.96 g, 7.18 mmol) and Na₂CO₃ (7.93 g, 74.8 mmol) in MeOH (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 70 °C for 12 h under N₂ atmosphere. The reaction mixture was acidified with aqueous HCl (1 M) until pH = 4 was reached and extracted with EtOAc (30.0 mL x 3). The organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 1/1) to give compound **I-5-3** (7.30 g, 82.0% yield) as a white solid.

[0243] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxyazetidine-1-carboxylate (I-5)** To a solution of compound **I-5-3** (6.27 g, 21.0 mmol), TBATB (10.6 g, 22.1 mmol) in MeOH (94.0 mL) and DCM (37.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 2

h under N₂ atmosphere. The reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 1/1) to give compound **I-5** (1.93 g, 21.8% yield, 90.0% purity) as a white solid.

5 [0244] Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-methoxyazetidine-1-carboxylate (I-6):

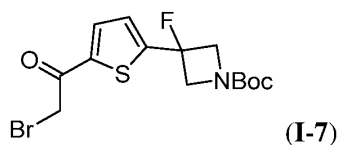


[0245] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)-3-methoxyazetidine-1-carboxylate (I-6-1)** To a solution of compound **I-5-2** (10.0 g, 29.9 mmol) in THF (70.0 mL) was added NaH (1.44 g, 35.9 mmol, 60.0% purity) at 0 °C. After addition, the mixture was stirred at this temperature for 0.5 h, and then MeI (16.9 g, 119 mmol, 7.45 mL) was added at 0 °C. The resulting mixture was stirred at 20 °C for 3.5 h. The reaction mixture was quenched by addition NH₄Cl (100 mL) at 25 °C and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 2/1) to give compound **I-6-1** (8.40 g, 80.6% yield) as a white solid.

[0246] **Synthesis of tert-butyl 3-(5-acetylthiophen-2-yl)-3-methoxyazetidine-1-carboxylate (I-6-2)** To a solution of compound **I-6-1** (8.30 g, 23.8 mmol) in MeOH (58.0 mL) was added 1-(vinylloxy)butane (5.97 g, 59.5 mmol, 7.66 mL), Pd(OAc)₂ (642 mg, 2.86 mmol), Na₂CO₃ (6.32 g, 59.5 mmol) and DPPP (2.36 g, 5.72 mmol). The mixture was stirred at 70 °C for 12 h under N₂ atmosphere. The reaction mixture was quenched by addition HCl (100 mL) at 20 °C, and then extracted with CHCl₃/isopropanol (20.0 mL x 6). The combined organic layers were washed with brine (30.0 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give compound **I-6-2** (0.800 g, 10.7% yield) as a yellow solid.

[0247] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-methoxyazetidine-1-carboxylate (I-6)** To a solution of compound **I-6-2** (200 mg, 642 μ mol) in DCM (1.20 mL) and MeOH (3.00 mL) was added TBATB (325 mg, 674 μ mol) and the mixture was stirred at 25 °C for 16 h. The reaction mixture was diluted with H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-6** (97.8 mg, 39.0% yield) as a yellow oil.

[0248] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-fluoroazetidine-1-carboxylate (I-7):**

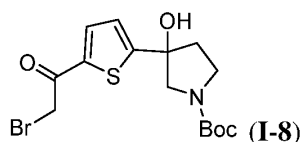


[0249] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)-3-fluoroazetidine-1-carboxylate (I-7-1)** To a solution of compound **I-5-1** (15.0 g, 44.9 mmol) in DCM (150 mL) was added DAST (10.9 g, 67.3 mmol, 8.89 mL) at -78 °C under N₂ atmosphere. The mixture was stirred at -78 °C for 12 h. The reaction mixture was quenched by addition aqueous NaHCO₃ (200 mL) at -60 °C, diluted with H₂O 100 mL and extracted with DCM (100 mL x 3). The combined organic layers were washed with aqueous NaHCO₃ (200 mL x 2), dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give compound **I-7-1** (29.0 g, 86.5% yield, 90.0% purity) as yellow oil.

[0250] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiophen-2-yl)-3-fluoroazetidine-1-carboxylate (I-7-2)** To a solution of compound **I-7-1** (10.0 g, 29.7 mmol) and tributyl(1-ethoxyvinyl)stannane (18.8 g, 52.1 mmol, 17.6 mL) in dioxane (100 mL) was added TEA (6.02 g, 59.5 mmol, 8.28 mL) and Pd(PPh₃)₂Cl₂ (2.09 g, 2.97 mmol) under N₂ atmosphere. The mixture was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (200 mL) at 25 °C and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (300 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuum to give compound **I-7-2** (20.0 g, crude) as a brown oil.

[0251] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-fluoroazetidine-1-carboxylate (I-7)** To a solution of compound **I-7-2** (20.0 g, 24.4 mmol) in THF (100 mL) and H₂O (50.0 mL) was added NBS (4.35 g, 24.4 mmol). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was quenched by addition H₂O (200 mL) at 25 °C and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 4/1) to give compound **I-7** (6.00 g, 57.8% yield, 89.0% purity) as a yellow oil.

10 [0252] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-8):**



[0253] **Synthesis of tert-butyl 3-hydroxy-3-(thiophen-2-yl)pyrrolidine-1-carboxylate (I-8-1)** To a solution of 2-bromothiophene (90.0 g, 552 mmol) in THF (900 mL) was added n-BuLi (2.50 M, 243 mL) at -60 °C dropwise under N₂ atmosphere. The mixture was stirred at -60 °C for 1 h, then added a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (112 g, 607 mmol) in THF (62.5 mL) dropwise at -60 °C. The mixture was stirred at -60 °C for 2 h. The residue was poured into sat. aq NH₄Cl (1 L) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with brine (500 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 1/1) to give compound **I-8-1** (45.0 g, 29.1% yield, 96.1% purity) as a white solid.

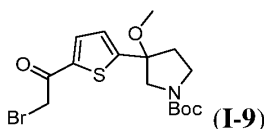
[0254] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-8-2)** To a solution of compound **I-8-1** (45.0 g, 167 mmol) in DMF (315 mL) was added NBS (32.7 g, 184 mmol) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (700 mL) and extracted with EtOAc (300 mL x 3). The combined organic layers were washed with H₂O (100 mL x 5), dried over

anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-8-2** (61.9 g, 97.9% yield) as a light yellow solid.

[0255] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiophen-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-8-3)** To a solution of compound **I-8-2** (3.00 g, 8.61 mmol) in dioxane (30.0 mL) was added tributyl(1-ethoxyvinyl)stannane (4.67 g, 12.9 mmol), TEA (1.74 g, 17.2 mmol) and Pd(PPh₃)₂Cl₂ (604 mg, 861 μmol) under N₂. The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched by H₂O (20.0 mL) and was extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-8-3** (7.50 g, 64.1% yield, 25.0% purity) as a brown solid.

[0256] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-8)** To a solution of compound **I-8-3** (4.00 g, 2.95 mmol) in THF (30.0 mL) and H₂O (10.0 mL) was added NBS (472 mg, 2.65 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched by H₂O (20.0 mL) and was extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-8** (720 mg, 62.6% yield) as a yellow solid.

[0257] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-9):**



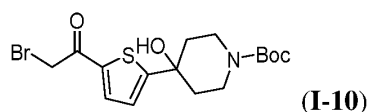
[0258] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-9-1)** To a solution of compound **I-8-1** (1.00 g, 2.87 mmol) in THF (10.0 mL) was added NaH (230 mg, 5.74 mmol, 60.0% purity). The mixture was stirred at 0 °C for 1 h under N₂. Then the mixture was added MeI (1.63 g, 11.5 mmol) and stirred at 20 °C for 2 h. The reaction mixture was diluted with H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over MgSO₄, filtered and

concentrated in vacuum to give compound **I-9-1** (550 mg, 1.52 mmol, 52.9% yield) was obtained as a yellow oil.

[0259] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiophen-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-9-2)** To a solution of compound **I-9-1** (300 mg, 828 μ mol) in dioxane (3.00 mL) was added tributyl(1-ethoxyvinyl)stannane (570 mg, 1.58 mmol), TEA (168 mg, 1.66 mmol) and Pd(PPh₃)₂Cl₂ (58.1 mg, 82.8 μ mol) under N₂. The mixture was stirred at 80 °C for 2 h. The reaction was quenched by H₂O (10.0 mL) and extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-9-2** (760 mg, 64.9% yield, 25.0% purity) as a black solid.

[0260] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-9)** To a solution of compound **I-9-2** (300 mg, 848 μ mol) in THF (2.20 mL) and H₂O (0.800 mL) was added NBS (136 mg, 764 μ mol). The mixture was stirred at 25 °C for 1.5 h. The reaction was quenched by H₂O (10.0 mL) and extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-9** (220 mg, 64.1% yield) as a yellow solid.

[0261] **Synthesis of tert-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)-4-hydroxypiperidine-1-carboxylate (I-10):**



[0262] **Synthesis of tert-butyl 4-hydroxy-4-(thiophen-2-yl)piperidine-1-carboxylate (I-10-1)** To a solution of 2-bromothiophene (16.0 g, 98.1 mmol) in THF (160 mL) was added n-BuLi (2.50 M, 43.2 mL) at -60 °C dropwise and the mixture was stirred at -60 °C for 1 h, and then was added to a solution of tert-butyl 4-oxopiperidine-1-carboxylate (21.5 g, 108 mmol) in THF (96.0 mL) dropwise at -60 °C. The mixture was stirred at -60 °C for 2 h. The residue was poured into sat. aq. NH₄Cl (300 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine

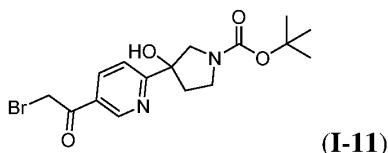
(200 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 0/1) to give compound **I-10-1** (15.8 g, 53.7% yield, 94.6% purity) as a white solid.

- 5 [0263] **Synthesis of tert-butyl 4-(5-bromothiophen-2-yl)-4-hydroxypiperidine-1-carboxylate (I-10-2)** To a solution of compound **I-10-1** (5.00 g, 17.6 mmol) in DMF (35.0 mL) was added NBS (3.45 g, 19.4 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with EtOAc (50.0 mL x 3). The combined organic layers were washed with sat NaCl (50.0 mL x 2), dried over
10 Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-10-2** (6.00 g, 75.1% yield, 79.1% purity) as a brown solid.

- [0264] **Synthesis of tert-butyl 4-(5-(1-ethoxyvinyl)thiophen-2-yl)-4-hydroxypiperidine-1-carboxylate (I-10-3)** To a solution of compound **I-10-2** (3.00 g,
15 8.28 mmol) in dioxane (30.0 mL) was added tributyl(1-ethoxyvinyl)stannane (5.98 g, 16.6 mmol, 5.59 mL), TEA (1.68 g, 16.6 mmol, 2.30 mL) and Pd(PPh₃)₂Cl₂ (581 mg, 828 μmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted with H₂O (60 mL) and extracted with EtOAc (50.0 mL x 3), dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-10-3** (9.30 g, crude) was
20 obtained as a black oil.

- [0265] **Synthesis of tert-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)-4-hydroxypiperidine-1-carboxylate (I-10)** To a solution of compound **I-10-3** (8.20 g, 23.2 mmol) in THF (80.0 mL) and H₂O (40.0 mL) was added NBS (4.13 g, 23.2 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (100
25 mL) and extracted with EtOAc (40.0 mL x 3). The combined organic layers were washed with sat NaCl (50.0 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 2/1) to give compound **I-10** (1.34 g, 40.1% yield, 93.3% purity) as a yellow solid.

[0266] Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-11):

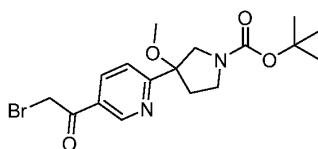


- [0267] **Synthesis of tert-butyl 3-(5-bromopyridin-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-11-1)** To a solution of 2, 5-dibromopyridine (105 g, 443 mmol) in toluene (1200 mL) was added n-BuLi (1.60 M, 305 mL, 1.10 *eq*) dropwise at -70 °C under N₂. The mixture was stirred at -70 °C for 1 h under N₂. To the mixture was added a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (90.3 g, 487 mmol, 1.10 *eq*) in toluene (300 mL) dropwise at -70 °C and stirred at -70 °C for 1 h under N₂. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (750 mL) dropwise at 0 °C under N₂ and extracted with EtOAc (750 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 2/1) to give **I-11-1** (30.1 g, 19.8% yield) as a yellow solid.
- [0268] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)pyridin-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-11-2)** To a solution of **I-11-1** (4.00 g, 11.7 mmol) and tributyl(1-ethoxyvinyl)stannane (7.76 g, 21.5 mmol, 7.26 mL) in dioxane (40.0 mL) was added TEA (2.36 g, 23.3 mmol, 3.24 mL) and Pd(PPh₃)₂Cl₂ (818 mg, 1.17 mmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction mixture was quenched by addition of H₂O (80.0 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **I-11-2** (10.3 g, crude) as a brown oil.

- [0269] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-11)** To a solution of compound **I-11-2** (10.3 g, 30.8 mmol) in THF (100 mL) and H₂O (70.0 mL) was added NBS (3.84 g, 21.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H₂O (100 mL) and extracted with DCM (100 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by

column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-11** (3.07 g, 35.0% yield, 50.0% purity) as a yellow oil.

[0270] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-12):**



5

(I-12)

[0271] **Synthesis of tert-butyl 3-(5-bromopyridin-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-12-1)** To a solution of compound **I-11-1** (3.00 g, 8.74 mmol) in THF (30.0 mL) was added NaH (454 mg, 11.4 mmol, 60.0% purity) at 0 °C under N₂. The mixture was stirred at 0 °C for 1 h. The mixture was added MeI (4.96 g, 35.0 mmol, 2.18 mL) and stirred at 25 °C for 2 h. The reaction mixture was quenched by H₂O (50.0 mL) at 0 °C under N₂ and extracted with EtOAc (70.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-12-1** (3.26 g, 93.8% yield, 89.8% purity) as a yellow oil.

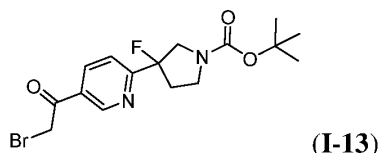
[0272] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)pyridin-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-12-2)** To a solution of compound **I-12-1** (3.26 g, 9.13 mmol) and tributyl(1-ethoxyvinyl)stannane (5.66 g, 15.7 mmol, 5.29 mL) in dioxane (33.0 mL) was added TEA (1.85 g, 18.3 mmol, 2.54 mL) and Pd(PPh₃)₂Cl₂ (641 mg, 913 μmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction mixture was quenched by H₂O (60.0 mL) at 25 °C, and then extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-12-2** (8.30 g, crude) as a brown oil.

[0273] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-12)** To a solution of compound **I-12-2** (5.00 g, 14.4 mmol) in THF (50.0 mL) and H₂O (35.0 mL) was added NBS (1.79 g, 10.0 mmol) at 0 °C. The reaction mixture was diluted with H₂O (50.0 mL) and extracted with DCM (70.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂,

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petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-12** (803 mg, 36.5% yield, 85.9% purity) as a yellow oil.

[0274] Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-13):



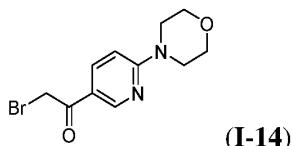
[0275] **Synthesis of tert-butyl 3-(5-bromopyridin-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-13-1)** To a solution of compound **I-11-1** (15.0 g, 43.7 mmol) in DCM (600 mL) was added DAST (9.16 g, 56.8 mmol, 7.51 mL) at -70 °C under N₂. The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 9/1) to give compound **I-13-1** (10.2 g, 64.4% yield, 95.3% purity) as a yellow solid.

[0276] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)pyridin-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-13-2)** To a solution of compound **I-13-1** (10.2 g, 29.6 mmol) and tributyl(1-ethoxyvinyl)stannane (18.6 g, 51.5 mmol, 17.4 mL) in dioxane (102 mL) was added TEA (5.98 g, 59.1 mmol, 8.23 mL) and Pd(PPh₃)₂Cl₂ (2.07 g, 2.95 mmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction mixture was quenched by addition of H₂O (200 mL) at 25 °C, and then extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-13-2** (28.8 g, crude) as a brown oil.

[0277] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)pyridin-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-13)** To a solution of compound **I-13-2** (28.8 g, 85.6 mmol) in THF (300 mL) and H₂O (210 mL) was added NBS (10.7 g, 59.9 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was diluted with H₂O (300 mL) at 25 °C, and then extracted with DCM (300 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give

compound **I-13** (5.12 g, 35.6% yield, 75.0% purity) as a yellow solid.

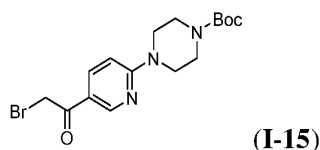
[0278] **Synthesis of 2-bromo-1-(6-morpholinopyridin-3-yl)ethan-1-one (I-14):**



[0279] **Synthesis of 1-(6-morpholino-3-pyridyl)ethanone (I-14-1)** To a solution of morpholine (2.40 g, 27.5 mmol, 2.42 mL) and 1-(6-bromo-3-pyridyl)ethanone (5.00 g, 25.0 mmol) in DMF (70.0 mL) was added K₂CO₃ (10.4 g, 75.0 mmol). The mixture was stirred at 80 °C for 16 h. The residue was diluted with H₂O (300 mL) and extracted with DCM (300 mL x 2). The combined organic layers were washed with sat. aq. NaHCO₃ solution (300 mL x 2), dried over MgSO₄, filtered and concentrated in vacuum to give compound **I-14-1** (5.16 g, 97.1% yield, 97.0% purity) as white solid.

[0280] **Synthesis of 2-bromo-1-(6-morpholinopyridin-3-yl)ethan-1-one (I-14)** To a solution of compound **I-14-1** (4.50 g, 21.8 mmol) in MeOH (45.0 mL) and CHCl₃ (45.0 mL) was added CuBr₂ (4.87 g, 21.8 mmol) under N₂. The mixture was stirred at 85 °C for 12 h. The reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 50/1 to 8/1) to give compound **I-14** (1.80 g, 10.9% yield, 37.7% purity) as a white solid.

[0281] **Synthesis of tert-butyl 4-[5-(2-bromoacetyl)-2-pyridyl]piperazine-1-carboxylate (I-15):**

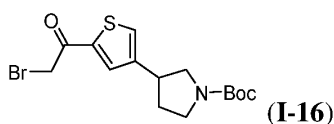


[0282] **Synthesis of tert-butyl 4-(5-acetyl-2-pyridyl)piperazine-1-carboxylate (I-15-1)** To a solution of 1-(6-bromo-3-pyridyl)ethanone (5.00 g, 25.0 mmol) in DMSO (200 mL) was added K₂CO₃ (6.91g, 50.0 mmol) and tert-butyl piperazine-1-carboxylate (6.98 g, 37.5 mmol). The mixture was stirred at 90 °C for 16 h. The reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (200 mL x 2). The combined organic layers

were washed with sat NaCl (200 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 2/1) to give compound **I-15-1** (5.52 g, 72.3% yield, 100% purity) as a white solid.

- 5 [0283] **Synthesis of tert-butyl 4-[5-(2-bromoacetyl)-2-pyridyl]piperazine-1-carboxylate (I-15)** To a solution of compound **I-15-1** (1.50 g, 4.91 mmol) in MeOH (15.0 mL) and CHCl₃ (15.0 mL) was added CuBr₂ (1.10 g, 4.91 mmol) under N₂. The mixture was stirred at 85 °C for 12 h. The reaction mixture was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ THF = 50/1 to 8/1) to give compound **I-15** (1.00 g, 21.8% yield, 41.1% purity) as a white solid.

[0284] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-3-yl)pyrrolidine-1-carboxylate (I-16):**



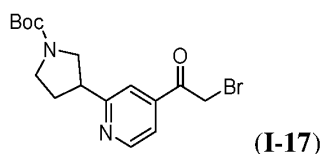
- 15 [0285] **Synthesis of tert-butyl 3-(5-acetylthiophen-3-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (I-16-1)** To a solution of 1-(4-bromo-2-thienyl)ethanone (5.00 g, 24.4 mmol) in dioxane (50.0 mL) and H₂O (10.0 mL) was added tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate (8.64 g, 29.3 mmol), K₂CO₃ (10.1 g, 73.2 mmol) and Pd(PPh₃)₄ (1.41 g, 1.22 mmol) under N₂. The mixture was stirred at 100 °C for 16 h. The reaction mixture was diluted with H₂O (50.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 4/1) to give compound **I-16-1** (7.00 g, 97.8% yield, 93.3% purity) as a yellow solid.

- 25 [0286] **Synthesis of tert-butyl 3-(5-acetylthiophen-3-yl)pyrrolidine-1-carboxylate (I-16-2)** To a solution of compound **I-16-1** (6.90 g, 23.5 mmol) in MeOH (400 mL) was added Pd/C (7.51 g, 7.06 mmol, 10.0% purity). The mixture was stirred at 25 °C for 16 h under H₂ (50 psi). The mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate

= 50/1 to 4/1) to give compound **I-16-2** (5.90 g, 84.9% yield, 91.2% purity) as a colorless oil.

[0287] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-3-yl)pyrrolidine-1-carboxylate (I-16)** To a solution of compound **I-16-2** (1.00 g, 3.39 mmol) in DCM (5.00 mL) and MeOH (2.00 mL) was added TBATB (1.71 g, 3.55 mmol). The mixture was stirred at 20 °C for 4 h. The reaction mixture was diluted with H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over MgSO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 4/1) to give compound **I-16** (1.20 g, 2.24 mmol, 66.3% yield, 70.0% purity) as a yellow solid.

[0288] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)pyridin-2-yl)pyrrolidine-1-carboxylate (I-17):**



[0289] **Synthesis of tert-butyl 3-(4-acetylpyridin-2-yl)-2,5-dihydro-1H-pyrrole-1-carboxylate (I-17-1)** To a solution of 1-(2-bromo-4-pyridyl)ethanone (5.00 g, 25.0 mmol), tert-butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,5-dihydropyrrole-1-carboxylate (8.85 g, 30.0 mmol), K₂CO₃ (10.4 g, 75.0 mmol), Pd(PPh₃)₄ (1.44 g, 1.25 mmol) in dioxane (50.0 mL) and H₂O (10.0 mL) was degassed and purged with N₂ for 3 times. The mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The reaction mixture was diluted with H₂O (200 mL) and extracted with EtOAc (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 5/1) to give compound **I-17-1** (6.50 g, 70.3% yield) as a yellow solid.

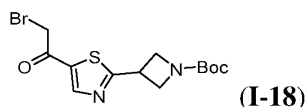
[0290] **Synthesis of tert-butyl 3-(4-(1-hydroxyethyl)pyridin-2-yl)pyrrolidine-1-carboxylate (I-17-2)** To a solution of compound **I-17-1** (1.00 g, 3.47 mmol) in MeOH (10.0 mL) was added Pd/C (1.08 g, 1.02 mmol, 10.0% purity). The mixture was stirred at 25 °C for 16 h under H₂ (20 Psi). The reaction mixture was filtered and concentrated in

vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 1/1) to give compound **I-17-2** (420 mg, 40.0% yield) as a yellow oil.

[0291] **Synthesis of tert-butyl 3-(4-acetylpyridin-2-yl)pyrrolidine-1-carboxylate (I-17-3)** To a solution of compound **I-17-2** (400 mg, 1.37 mmol) in DCM (10.0 mL) was added Dess-Martin reagent (870 mg, 2.05 mmol) at 0 °C for 10 min. The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 1/1) to give compound to give compound **I-17-3** (300 mg, 75.5% yield) as a yellow solid.

[0292] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)pyridin-2-yl)pyrrolidine-1-carboxylate (I-17)** To a solution of compound **I-17-3** (100 mg, 258 μmol) in THF (1.00 mL) was added pyridinium tribromide (146 mg, 387 μmol). The mixture was stirred at 50 °C for 16 h. The reaction mixture was quenched by H₂O (3.00 mL) and extracted with EtOAc (10.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 3/1) to give compound to give compound **I-17** (100 mg, 44.1% yield, 38.0% purity) as a yellow solid.

20 [0293] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)azetidine-1-carboxylate (I-18):**



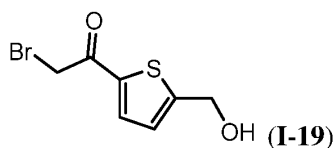
[0294] **Synthesis of tert-butyl 3-(5-bromothiazol-2-yl)azetidine-1-carboxylate (I-18-1)** To a solution of Zn (4.62 g, 70.6 mmol) in DMF (50.0 mL) was added TMSCl (0.200 mL) and 1,2-dibromoethane (0.200 mL). Then the mixture was added to a solution of tert-butyl 3-iodoazetidine-1-carboxylate (5.00 g, 17.7 mmol) in DMF (10.0 mL) and stirred at 25 °C for 0.5 h under N₂ atmosphere. To a solution of 2,5-dibromothiazole (5.00 g, 20.6 mmol) in DMF (50.0 mL) was added Pd(PPh₃)₄ (1.19 g, 1.03 mmol) and above

solution under N₂. The mixture was stirred at 65 °C for 16 h under N₂. The reaction mixture was quenched by H₂O (200 mL) and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with sat NaCl (50 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 4/1) to give compound **I-18-1** (2.40 g, 23.5% yield, 64.4% purity) as a yellow oil.

[0295] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiazol-2-yl)azetidine-1-carboxylate (I-18-2)** To a solution of compound **I-18-1** (2.40 g, 7.52 mmol) in dioxane (24.0 mL) was added tributyl(1-ethoxyvinyl)stannane (5.43 g, 15.0 mmol, 5.08 mL), TEA (1.52 g, 15.0 mmol, 2.09 mL) and Pd(PPh₃)₂Cl₂ (528 mg, 752 μmol) under N₂ atmosphere. The mixture was stirred at 90 °C under N₂ atmosphere for 16 h. The reaction mixture was added H₂O (60.0 mL) and extracted with EtOAc (50.0 mL x 3), dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-18-2** (7.80 g, crude) was obtained as a black oil.

[0296] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)azetidine-1-carboxylate (I-18)** To a solution of compound **I-18-2** (6.80 g, 21.9 mmol) in THF (78.0 mL) and H₂O (39.0 mL) was added NBS (3.90 g, 21.9 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was added H₂O (50.0 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with sat NaCl (50 mL x 2), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 3/1) to give compound **I-18** (1.40 g, 15.4% yield, 86.8% purity) as a brown solid.

[0297] **Synthesis of 2-bromo-1-(5-(hydroxymethyl)thiophen-2-yl)ethan-1-one (I-19):**



[0298] **Synthesis of (5-iodothiophen-2-yl)methanol (I-19-1)** A mixture of thiophen-2-ylmethanol (25.0 g, 219 mmol, 20.7 mL), NIS (54.2 g, 241 mmol), PTSA (3.77 g, 21.9 mmol) in EtOH (175 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 6 h under N₂ atmosphere. The reaction mixture was

concentrated under reduced pressure to remove EtOH. The residue was diluted with EtOAc (50.0 mL) and washed with H₂O (50.0 mL x 3), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 0/1) to give compound **I-19-1** (44.0 g, 83.7% yield) as a yellow oil.

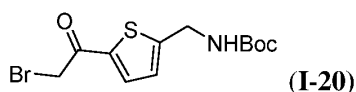
[0299] **Synthesis of 1-(5-(hydroxymethyl)thiophen-2-yl)ethan-1-one (I-19-2)** To a solution of compound **I-19-1** (20.0 g, 83.3 mmol) in toluene (140 mL) was added dropwise tributyl (1-ethoxyvinyl)stannane (36.1 g, 99.9 mmol, 33.7 mL) at 25 °C, palladium tetrakis(triphenylphosphine) (9.63 g, 8.33 mmol) was added at 25 °C. The resulting mixture was stirred at 110 °C for 16 h. Saturated potassium fluoride solution was added to the reaction mixture and stirred for 30 min at 15 °C. The organic layer was separated and concentrated under reduced pressure to get the crude compound. HCl (0.5 M, 100 mL) was added to the crude reaction mixture and stirred for 30 min and solid Na₂CO₃ was added until pH~7. The reaction mixture diluted with water (100 mL) extracted with thyl acetate (80.0 mL x 2). The organic layer was separated, dried over Na₂SO₄, concentrated under reduced pressure to get crude compound. The residue was purified by prep-TLC (SiO₂, petroleum ether/ethyl acetate = 0/1) to give compound **I-19-2** (4.40 g, 33.8% yield) as a brown solid.

[0300] **Synthesis of 1-(5-(((tert-butyldiphenylsilyl)oxy)methyl)thiophen-2-yl)ethan-1-one (I-19-3)** To a solution of compound **I-19-2** (4.20 g, 26.9 mmol) and imidazole (3.66 g, 53.8 mmol) and DMAP (164 mg, 1.34 mmol) in DCM (25.0 mL) was added TBDPSCI (8.87 g, 32.2 mmol, 8.29 mL). The mixture was stirred at 15 °C for 12 h. The reaction mixture was quenched by addition H₂O (30.0 mL) at 25°C, extracted with EtOAc (30.0 mL x 3) dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 0/1) to give compound **I-19-3** (8.60 g, 67.3% yield, 83.1% purity) as a yellow oil.

[0301] **Synthesis of 2-bromo-1-(5-(hydroxymethyl)thiophen-2-yl)ethan-1-one (I-19-4)** A mixture of compound **I-19-3** (3.00 g, 7.60 mmol), TBAB (3.85 g, 7.98 mmol) in DCM (18.0 mL) and MeOH (45.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 0 °C for 1 h under N₂ atmosphere. The resulting mixture was stirred at 25 °C for 4 h. The reaction mixture was quenched by addition H₂O (100 mL) at

25 °C, and then extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 0/1) to give compound **I-19** (800 mg, 44.7% yield) as a brown oil.

5 [0302] **Synthesis of tert-butyl ((5-(2-bromoacetyl)thiophen-2-yl)methyl)carbamate (I-20)**



[0303] **Synthesis of tert-butyl (thiophen-2-ylmethyl)carbamate (I-20-1)** To a solution mixture of thiophen-2-ylmethanamine (50.0 g, 441.770 mmol) in THF (500 mL) was added NaHCO₃ (37.1 g, 485.947 mmol) and (Boc)₂O (111.5 mL, 441.770 mmol) slowly. The resulting mixture was stirred at rt for 4 h. The reaction mixture was diluted with 30% EtOAc in hexane and passed through silica gel to afford compound **(I-20-1)** (100 g, quantitative) as a white gummy solid.

[0304] **Synthesis of tert-butyl ((5-bromothiophen-2-yl)methyl)carbamate (I-20-2)** To a solution mixture of compound **I-20-1** (50 g, 234.741 mmol) in DMF (500.0 mL) was added NBS (45.9 g, 258.2 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt. Cold water was added to reaction mixture and it was extracted with EtOAc (2x 500 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh) and compound was eluted using 10% EtOAc in hexane to afford compound **(I-20-2)** (60.5 g, Yield: 87%) as a brown gummy liquid.

[0305] **Synthesis of tert-butyl ((5-formylthiophen-2-yl)methyl)carbamate (I-20-3)** To a solution mixture of compound **I-20-2** (30.0 g, 102.739 mmol) in dry THF (600.0 mL) was added n-BuLi (1.6 M in hexane) (321 mL, 513.7 mmol) at -78°C and stirring for 30 min at same temperature. DMF (39 mL, 513.7 mmol) was added dropwise at -78 °C and stirring was continued for 2 h. After completion of reaction, the reaction mixture was quenched with sat. aq. NH₄Cl solution (200 mL) and extracted with EtOAc (2x 500 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh)

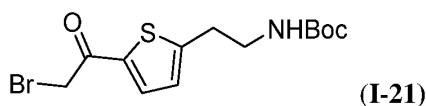
and compound was eluted using 12% EtOAc in hexane to afford compound **I-20-3** (12.0 g, Yield: 49%) as a brown gummy liquid. ¹H NMR [400 MHz, CDCl₃]: 9.83 (s, 1H), 7.63 (d, *J* = 3.6 Hz, 1H), 7.05 (d, *J* = 3.6 Hz, 1H), 5.0 (s, 1H) 4.52 (d, *J* = 6 Hz, 2H) 1.41 (s, 9H).

- 5 [0306] **Synthesis of tert-butyl ((5-(1-hydroxyethyl)thiophen-2-yl)methyl)carbamate (I-20-4)** To a solution of compound **I-20-3** (18.5 g, 76.7 mmol) in dry THF (400.0 mL) was added methyl magnesium bromide (1.0 M in THF) (767 mL, 767.0 mmol) at 0 °C, after which it was stirred for 2 h at rt. The reaction mixture was quenched with sat. aq. NH₄Cl solution (500 mL) and washed with EtOAc (2x 500 mL). The combined organic
10 layers were dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh) and compound was eluted using 20% EtOAc in hexane to afford compound **I-20-4** (13.0 g, Yield: 66%) as a brown gummy liquid. ¹H NMR [400 MHz, DMSO-*d*₆]: 8.13 (s, 1H), 7.43 (s, 1H), 7.00 (s, 1H), 4.85 (d, *J* = 5.6 Hz, 2H), 4.19 (d, *J* = 2.0 Hz, 1H) 1.38-1.23 (m, 12H).

- 15 [0307] **Synthesis of tert-butyl ((5-acetylthiophen-2-yl)methyl)carbamate (I-20-5)** To a solution mixture of compound **I-20-4** (6.5 g, 25.26 mmol) in DCM (65.0 mL) was added PCC (13.6 g, 63.15 mmol) at rt. The reaction mixture was stirred for 2 h at rt. After completion of reaction, the mixture was filtered in vacuo and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh)
20 and the compound was eluted using 20% EtOAc in hexane to afford compound **I-20-5** (4.9 g, Yield: 75%) as a brown gummy liquid.

- [0308] **Synthesis of tert-butyl ((5-(2-bromoacetyl)thiophen-2-yl)methyl)carbamate (I-20)** To a solution mixture of **I-20-5** (4.8 g, 18.8 mmol) in THF (50 mL) was added phenyltrimethylammonium tribromide (4.95 g, 13.1 mmol) at 0 °C. The reaction mixture
25 was stirred for 16 h at rt. After completion of reaction, mixture was filtered through a celite bed and concentrated in vacuo. The crude compound was purified using combi-flash C-18 purification to afford compound **I-20** (1.5 g, Yield: 24%) as pale brown solid. ¹H NMR [400 MHz, DMSO-*d*₆]: 7.91 (d, *J* = 4 Hz, 1H), 7.65 (t, *J* = 6 Hz, 1H), 7.06 (d, *J* = 3.6 Hz, 1H), 4.77(s, 2H), 4.31(d, *J* = 6 Hz, 2H), 1.39 (s, 9H).

[0309] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)ethyl)carbamate (I-21)**



[0310] **Synthesis of tert-butyl (2-(thiophen-2-yl)ethyl)carbamate (I-21-1)** To a stirred solution of 2-(thiophen-2-yl)ethan-1-amine (20.0 g, 157.22 mmol) in dichloromethane (200 mL) cooled to 0 °C was added (Boc)₂O (41.1 g, 188.66 mmol) followed by Et₃N (24.6 g, 243.10 mmol). The resulting mixture was stirred for 16 h at rt, after which it was concentrated under reduced pressure. The crude residue was diluted with water (100 mL), extracted with DCM (2 x 100 mL), and the combined organic layers
10 dried over Na₂SO₄, and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh) eluting with 10% EtOAc in hexane, and the pure fractions were evaporated to afford compound **I-21-1** (28 g, Yield: 74%) as a brown gummy liquid.

[0311] **Synthesis of tert-butyl (2-(5-bromothiophen-2-yl)ethyl)carbamate (I-21-2)**
15 To a solution of compound **I-21-1** (28 g, 123.172 mmol) in DMF (400 mL) cooled to 0 °C was added portion wise NBS (21.9 g, 123.172 mmol). The mixture was then stirred for 2 h at rt before it was poured into a mixture of ice/water (100 mL) and EtOAc (200 mL). The organic layer was separated, washed with brine solution (100 mL), dried over Na₂SO₄ and then concentrated under reduced pressure. The crude compound was purified
20 by column chromatography over silica gel (100-200 mesh) compound was eluted using 10% EtOAc in hexane to afford compound **I-21-2** (37.08 g, Yield: 98%) as an off-white solid.

[0312] **Synthesis of tert-butyl (2-(5-formylthiophen-2-yl)ethyl)carbamate (I-21-3)**
To a solution of compound **I-21-2** (20.0 g, 65.312 mmol) in dry THF (200 mL) cooled to
25 -78°C was added dropwise n-BuLi (1.6 M solution in hexanes) (204.0 mL, 326.563 mmol) and the resulting mixture was stirred for 15 min, after which dry DMF (35.9 g, 491.80 mmol) was added and stirring was continued for 30 min at same temperature. After completion of reaction, the reaction mixture was quenched with sat. aq. NH₄Cl solution (150 mL) and extracted with EtOAc (2 x 200 mL). The organic layer was

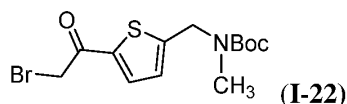
separated, dried over Na₂SO₄, and concentrated under reduced pressure. The crude compound was purified by column chromatography over silica gel (100-200 mesh) compound was eluted using 15% EtOAc in hexane to afford compound **I-21-3** (10.0 g, Yield: 57%) as gummy liquid.

- 5 [0313] **Synthesis of tert-butyl (2-(5-(1-hydroxyethyl)thiophen-2-yl)ethyl)carbamate (I-21-4)** To a solution of compound **I-21-3** (18.0 g, 70.496 mmol) in dry THF (180 mL) cooled to 0°C was added dropwise of methyl magnesium bromide (1.0 M solution in THF) (705.0 mL, 70.496 mmol), after which it was slowly warmed to rt and stirred for 2 h. The reaction mixture was diluted with ice water (100 mL) and extracted with EtOAc
10 (2 x 300 mL). The organic layer was separated, dried over Na₂SO₄, and concentrated reduced pressure. The crude compound was purified by column chromatography over silica gel (100-200 mesh) compound was eluted using 20% EtOAc in hexane to afford compound **I-21-4** (15.0 g, Yield: 78%) as gummy solid.

- [0314] **Synthesis of tert-butyl (2-(5-(2-acetylthiophen-2-yl)ethyl)carbamate (I-21-5)** To a solution of compound **I-21-4** (10 g, 36.849 mmol) in dry DCM (100 mL) cooled to 0°C was added Dess–Martin periodinane (46.8 g, 110.547 mmol) after which it was slowly warmed to rt and stirred for 16 h. The reaction mixture was filtered through a celite pad and washed with dichloromethane before the solvent was evaporated under reduced pressure. The crude compound was purified by column chromatography over silica gel
20 (100-200 mesh) eluting with 15% EtOAc in hexane to afford compound **I-21-5** (7.1 g, Yield: 72 %) as gummy solid.

- [0315] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)ethyl)carbamate (I-21)** To a solution of compound **I-21-5** (7.0 g, 25.987 mmol) in dry THF (70.0 mL) was added trimethylphenylammonium tribromide (7.8 g, 20.789 mmol), and mixture was then
25 stirred at room temperature for 16 h. The solvent was then evaporated, and the crude was purified by Combi-flash reversed phase chromatography to afford **I-21** (2.05 g, Yield: 23%) as an off-white solid.

[0316] Synthesis of tert-butyl ((5-(2-bromoacetyl)thiophen-2-yl)methyl)(methyl)carbamate (I-22)



[0317] **Synthesis of tert-butyl ((5-bromothiophen-2-yl)methyl)(methyl)carbamate (I-22-1)** To a solution mixture of tert-butyl ((5-bromothiophen-2-yl)methyl)carbamate (**I-20-2**) (40 g, 137.0 mmol) in DMF (400.0 mL) was added NaH (6.56 g, 273.0 mmol) followed by methyl iodide (12.8 mL, 205.5 mmol) at 0°C. The reaction mixture was stirred for 3 h at rt. The reaction mixture was quenched with ice water (150 mL) and extracted with EtOAc (2 x 500 mL) and dried over Na₂SO₄, concentrated in vacuo gave crude 43 g of compound **I-22-1**, which was taken to the next step without further purification.

[0318] **Synthesis of tert-butyl ((5-formylthiophen-2-yl)methyl)(methyl)carbamate (I-22-2)** To a solution mixture of compound (**I-22-1**) (22.0 g, 71.89 mmol) in dry THF (400.0 mL) and added n-BuLi (1.6 M in hexane) (224 mL, 359.47 mmol) at -78 °C and stirring for 30 min at -78 °C. After DMF (27.9 mL, 359.47 mmol) was added at -78 °C and stirring for 2 h, reaction mixture was quenched with sat. aq. NH₄Cl solution (200.0 mL) and extracted with EtOAc (2 x 500 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh) eluting with 12% EtOAc in hexane to afford compound **I-22-2** (6.5 g, Yield: 35%) as gummy liquid, used without further purification.

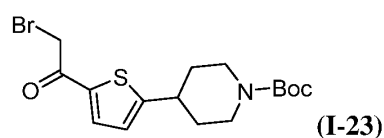
[0319] **Synthesis of tert-butyl ((5-(1-hydroxyethyl)thiophen-2-yl)methyl)(methyl)carbamate (I-22-3)** To a solution mixture of compound **I-22-2** (13.0 g, 50.9 mmol) in dry THF (250.0 mL) was added methyl magnesium bromide (1.0M in THF) (509 mL, 509.0 mmol) at 0 °C and stirred the reaction for 2 h at rt. The reaction mixture was quenched with sat. aq. NH₄Cl solution (500 mL) and washed with EtOAc (2x 500 mL). The combined organic layers were dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel

(100-200 mesh) eluting with 20% EtOAc in hexane to afford compound **I-22-3** (10 g, Yield: 72%) as gummy liquid, used without further purification.

[0320] **Synthesis of tert-butyl ((5-acetylthiophen-2-yl)methyl)(methyl)carbamate (I-22-4)** To a solution mixture of compound **I-22-3** (10.0 g, 36.9 mmol) in DCM (100.0 mL) was added PCC (19.8 g, 92.2 mmol) at rt. The reaction mixture was stirred for 2 h at rt. The reaction mixture after which it was filtered and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (100-200 mesh) compound was eluted using 20% EtOAc in hexane to afford compound **I-22-4** (7.6 g, Yield: 77%) as gummy liquid, which was used without further purification.

[0321] **Synthesis of tert-butyl ((5-(2-bromoacetyl)thiophen-2-yl)methyl)(methyl)carbamate (I-22)** To a solution mixture of compound **I-22-4** (4.3 g, 15.9 mmol) in THF (50 mL) and added phenyltrimethylammonium tribromide (4.20 g, 11.1 mmol) at 0 °C. The reaction mixture was stirred for 16 h at rt. The reaction mixture was filtered through a celite bed and concentrated in vacuo. The crude compound was purified using combi-flash reverse phase purification (using an ACN and 0.001% TFA in Water) to afford compound **I-22** (1.5 g, Yield: 27%) as pale brown solid.

[0322] **Synthesis of tert-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)piperidine-1-carboxylate (I-23)**



[0323] **Synthesis of tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (I-23-1)** A solution of *tert*-butyl 4-oxopiperidine-1-carboxylate (1 g, 5.405 mmol) in dry THF (10 mL) was cooled to -78 °C, after which was added dropwise LiHMDS (1.0 M in THF, 6.0 mL, 5.934 mmol). The mixture was stirred for 60 min, then *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*-(trifluoromethylsulfonyl)methanesulfonamide in THF (2.33 g, 5.934 mmol) was added. The reaction mixture was stirred for 30 min at the same temperature, after which it was slowly warmed to rt. The reaction mixture was quenched with sat. aq. NaHCO₃ (10 mL) and then extracted with EtOAc (2x50 mL). The organic layer was separated, dried over

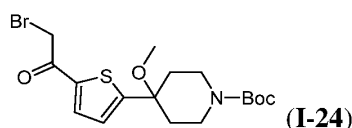
Na₂SO₄, and evaporated under reduced pressure. The residue was purified by column chromatography using a silica gel (60-120 mesh, 10% ethyl acetate in hexanes) to afford title compound **I-23-1** (0.63 g, 37 % yield) as gummy liquid.

[0324] **Synthesis of *tert*-butyl 4-(5-acetylthiophen-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (I-23-2)** To a stirred solution of (5-acetylthiophen-2-yl) boronic acid **I-23-1** (268 mg, 1.557 mmol) and *tert*-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-5,6-dihydropyridine-1(2H)-carboxylate (500 mg, 1.557 mmol) in 1,4-dioxane:H₂O (10:2 mL), K₂CO₃ (652 mg, 4.731 mmol) and Pd(PPh₃)₄ (182 mg, 0.155 mmol) was added under N₂. The mixture was stirred for 15 min, and then heated to 90 °C for 16 h. The reaction mixture was quenched with sat. aq. NaHCO₃ (20 mL), and then extracted with EtOAc (2x50 mL). The organic later was separated, dried over Na₂SO₄, and evaporated under reduced pressure to get crude compound. The residue was purified by column chromatography using a silica gel (60-120 mesh, 20% ethyl acetate in hexane) to afford title compound **I-23-2** (201 mg, 44% yield) as gummy liquid.

[0325] **Synthesis of *tert*-butyl 4-(5-acetylthiophen-2-yl)piperidine-1-carboxylate (I-23-3)** To a stirred solution of *tert*-butyl 4-(5-acetylthiophen-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate **I-23-2** (1.5 g, 4.885 mmol) in MeOH (15 mL) was added 10% Pd-C (1.5 g) then inserted H₂ gas for 5 h at 60 psi. The reaction mixture was filtered in vacuo. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography using a silica gel (60-120 mesh, 50% ethyl acetate in hexane) to afford title compound **I-23-3** (852 mg, 66 % yield) as yellow liquid.

[0326] **Synthesis of *tert*-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)piperidine-1-carboxylate (I-23):** To a solution of *tert*-butyl 4-(5-acetylthiophen-2-yl) piperidine-1-carboxylate **I-23-3** (500 mg, 1.618 mmol) in dry THF (5 mL) tetrabutylammonium tribromide (3 g, 6.261 mmol) was added, stirring was continued at room temperature for 16 h. The reaction mixture was concentrated providing title compound **I-23** (310 mg, 49% yield). The crude was directly used for the next step.

[0327] **Synthesis of *tert*-butyl 4-[5-(2-bromoacetyl)-2-thienyl]-4-methoxy-piperidine-1-carboxylate (I-24):**



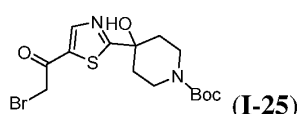
[0328] **Synthesis of tert-butyl 4-(5-bromo-2-thienyl)-4-methoxy-piperidine-1-carboxylate (I-24-1)** To a solution of **I-10-2** (11 g, 30.36 mmol) in THF (100 mL) was added NaH (1.46 g, 36.44 mmol, 16.56 μ L, 60% purity) at 0 °C. After addition, the mixture was stirred at this temperature for 20 min, and then MeI (17.24 g, 121.45 mmol, 7.56 mL) in THF (5 mL) was added dropwise at 0°C. The resulting mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition H₂O 100 mL at 0 °C, and extracted with EtOAc 300 mL (100 mL * 3). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-24-1** (7 g, 18.60 mmol, 61.26% yield) as a yellow oil.

[0329] **Synthesis of tert-butyl 4-[5-(1-ethoxyvinyl)-2-thienyl]-4-methoxy-piperidine-1-carboxylate (I-24-2)** A mixture of **I-24-1** (10 g, 26.57 mmol), TEA (5.38 g, 53.15 mmol, 7.40 mL), Pd(PPh₃)₂Cl₂ (932.61 mg, 1.33 mmol,) and tributyl(1-ethoxyvinyl)stannane (16.52 g, 45.74 mmol, 15.45 mL) in dioxane (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 85 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched with saturated KF (100 mL) and was extracted with EtOAc 100 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **I-24-2** (11 g, 23.95 mmol, 90.11% yield, 80% purity) was obtained as a black oil.

[0330] **Synthesis of tert-butyl 4-[5-(2-bromoacetyl)-2-thienyl]-4-methoxy-piperidine-1-carboxylate (I-24)** To a solution of **I-24-2** (430 mg, 1.17 mmol, 1.0 eq) in THF (3 mL) and H₂O (1 mL) was added NBS (187.43 mg, 1.05 mmol, 0.9 eq). The mixture was stirred at 25°C for 2 h. The reaction mixture was quenched with H₂O (10 mL) and was extracted with EtOAc 10 mL. The combined organic layers are dried over

Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60 % THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-24** (500 mg, 956.15 µmol, 81.72% yield, 80% purity) was obtained as a yellow solid.

- 5 [0331] **2-(difluoromethyl)-6-methoxy-pyrido[2,3-d]pyrimidin-4-yl)sulfanyl-1-[2-(4-hydroxy-4-piperidyl)thiazol-5-yl]ethanone (I-25):**



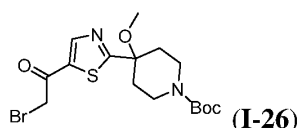
- [0332] **Synthesis of tert-butyl 4-(5-bromothiazol-2-yl)-4-hydroxy-piperidine-1-carboxylate (I-25-1)** To a solution of tert-butyl 4-hydroxy-4-thiazol-2-yl-piperidine-1-carboxylate (12.0 g, 42.2 mmol) in MeCN (120 mL) was added NBS (9.01 g, 50.6 mmol).
 10 The mixture was stirred at 25 °C for 16 h. The reaction was quenched with H₂O 30 mL and extracted with EtOAc 90 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~17%
 15 EtOAc/Petroleum ether gradient @ 100 mL/min) to give compound **I-25-1** (9.3 g, 25.60 mmol, 60.67% yield) as a yellow oil.

- [0333] **Synthesis of tert-butyl 4-[5-(1-ethoxyvinyl)thiazol-2-yl]-4-hydroxy-piperidine-1-carboxylate (I-25-2)** To a solution of **I-25-1** (1.00 g, 2.75 mmol) in dioxane (10 mL) was added tributyl(1-ethoxyvinyl)stannane (1.49 g, 4.13 mmol, 1.39 mL),
 20 Pd(PPh₃)₂Cl₂ (193 mg, 275 µmol) and TEA (557 mg, 5.51 mmol, 766 µL) under N₂. The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with H₂O (20 mL) and was extracted with EtOAc 30 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give compound **I-25-2** (2.30 g, 1.82 mmol, 66.0 %
 yield, 28.0 % purity) as a brown oil.

- 25 [0334] **Synthesis of 2-[2-(difluoromethyl)-6-methoxy-pyrido[2,3-d]pyrimidin-4-yl)sulfanyl-1-[2-(4-hydroxy-4-piperidyl)thiazol-5-yl]ethanone (I-25)** To a solution of **I-25-2** (2.30 g, 6.49 mmol) in THF (20 mL) and H₂O (5 mL) was added NBS (1.27 g,

7.14 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H₂O (20 mL) and was extracted with EtOAc 30 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/Petroleum ether gradient @ 40 mL/min) to give compound **I-25** (694 mg, 1.71 mmol, 26.4 % yield) as a yellow solid.

[0335] **Synthesis of tert-butyl 4-[5-(2-bromoacetyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxylate(I-26):**



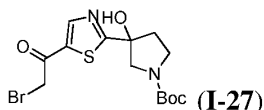
[0336] **Synthesis of tert-butyl 4-(5-bromothiazol-2-yl)-4-methoxy-piperidine-1-carboxylate (I-26-1)** To a solution of tert-butyl 4-(5-bromothiazol-2-yl)-4-hydroxy-piperidine-1-carboxylate (1.50 g, 4.13 mmol) in THF (15 mL) was added NaH (198 mg, 4.95 mmol, 60.0 % purity) at 0 °C under N₂. The mixture was stirred at 0 °C for 2 h. Then the mixture was added MeI (2.34 g, 16.5 mmol) and was stirred at 25 °C for 1 h. The reaction mixture was quenched with H₂O (10 mL) and was extracted with EtOAc 30 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~12% EtOAc/Petroleum ether gradient @ 40 mL/min) to give compound **I-26-1** (1.10 g, 2.92 mmol, 70.6 % yield) as a colorless oil.

[0337] **Synthesis of tert-butyl 4-[5-(1-ethoxyvinyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxylate (I-26-2)** To a solution of **I-26-1** (1.10 g, 2.92 mmol) in dioxane (10 mL) was added tributyl(1-ethoxyvinyl)stannane (1.58 g, 4.37 mmol), Pd(PPh₃)₂Cl₂ (205 mg, 292 μmol) and TEA (590 mg, 5.83 mmol) under N₂. The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with H₂O (20 mL) and was extracted with EtOAc 30 mL. The combined organic layers are dried over Na₂SO₄,

filtered and concentrated to give compound **I-26-2** (2.70 g, 2.20 mmol, 75.4 % yield, 30.0 % purity) was obtained as a brown solid.

[0338] **Synthesis of tert-butyl 4-[5-(2-bromoacetyl)thiazol-2-yl]-4-methoxy-piperidine-1-carboxylate (I-26)** To a solution of **I-26-2** (2.70 g, 3.30 mmol) in THF (20 mL) and H₂O (7 mL) was added NBS (587 mg, 3.30 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H₂O (20 mL) and was extracted with EtOAc 30 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~30% EtOAc/Petroleum ether gradient @ 40 mL/min) give compound **I-26** (320 mg, 789 µmol, 23.9 % yield) was obtained as a yellow solid.

[0339] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-27):**



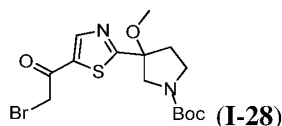
[0340] **Synthesis of tert-butyl 3-hydroxy-3-(thiazol-2-yl)pyrrolidine-1-carboxylate (I-27-1)** To a solution of 2-bromothiazole (54 g, 329 mmol) in THF (500 mL) was added dropwise n-BuLi (2.5 M, 145 mL) at -78 °C. After addition, the mixture was stirred at this temperature for 0.5 hr, and then tert-butyl 3-oxopyrrolidine-1-carboxylate (67.1 g, 362 mmol) in THF (300 mL) was added dropwise at -78 °C. The resulting mixture was stirred at 25 °C for 2.5 h. TLC indicated 2-bromothiazole was consumed completely and one new spot formed. The reaction mixture was quenched by addition saturated NH₄Cl aqueous solution 500 mL at 0 °C, and then diluted with H₂O 1000 mL and extracted with EtOAc 2000 mL (1000 mL * 2). The combined organic layers were washed with brine 1000 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give compound **I-27-1** (45.5 g, 46.1% yield) as a yellow oil.

[0341] **Synthesis of tert-butyl 3-(5-bromothiazol-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-27-2)** To a solution of **I-27-1** (45.3 g, 168 mmol) in DMF (220 mL) was added NBS (35.8 g, 201 mmol). The mixture was stirred at 25 °C for 16 h. The reaction mixture was partitioned between H₂O 800 mL and EtOAc 1500 mL. The organic phase
5 was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give Compound **I-27-2** (29 g, 49.6% yield) as a brown oil.

[0342] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiazol-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-27-3)** A mixture of **I-27-2** (1.5 g, 4.30 mmol), tributyl(1-ethoxyvinyl)stannane (3.10 g, 8.59 mmol), TEA (1.30 g, 12.9 mmol) and Pd(PPh₃)₂Cl₂ (151 mg, 215 µmol) in dioxane (15 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 100 mL at 25
15 °C, and then diluted with H₂O 50 mL and extracted with EtOAc 200 mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-27-3** (2.4 g, crude) as a brown oil.

[0343] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-hydroxypyrrolidine-1-carboxylate (I-27)** To a solution of **I-27-3** (1.3 g, 3.82 mmol) in THF (13 mL) and H₂O (6 mL) was added dropwise NBS (680 mg, 3.82 mmol) at 0 °C. After addition, the mixture was stirred at this temperature for 0.5 h. The resulting mixture was stirred at 25 °C for 1.5 h. The reaction mixture was partitioned between EtOAc 20 mL and H₂O 20 mL. The organic phase was separated, washed with brine 100 mL (50 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give
20 Compound **I-27** (3.5 g, crude) as a yellow oil.

[0344] Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-28):

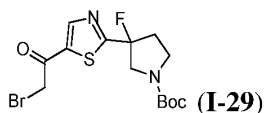


[0345] **Synthesis of tert-butyl 3-(5-bromothiazol-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-28-1)** To a solution of **I-27-2** (6.6 g, 18.9 mmol) in THF (60 mL) was added NaH (1.13 g, 28.35 mmol, 60% purity) under N₂ atmosphere at 0 °C. After addition, the mixture was stirred at this temperature for 0.5 h, and then CH₃I (10.7 g, 75.6 mmol) was added at 0 °C. The resulting mixture was stirred at 25 °C for 3.5 h. The reaction mixture was quenched by addition saturated NH₄Cl aqueous solution 50 mL at 0 °C, and then diluted with H₂O 100 mL and extracted with EtOAc 200 mL (100 mL x 2). The combined organic layers were washed with brine 100 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-28-1** (6.4 g, 91.4% yield) as a yellow oil.

[0346] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiazol-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-28-2)** A mixture of **I-28-1** (4 g, 11.0 mmol), tributyl(1-ethoxyvinyl)stannane (7.95 g, 22.0 mmol), TEA (3.34 g, 33.0 mmol) and Pd(PPh₃)₂Cl₂ (386 mg, 551 μmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 100 mL at 25 °C, and then diluted with H₂O 100 mL and extracted with EtOAc 200 mL (100 mL x 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give compound **I-28-2** (2.9 g, 67.1% yield) was obtained as a yellow oil.

[0347] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-methoxypyrrolidine-1-carboxylate (I-28)** To a solution of **I-28-2** (1.78 g, 5.02 mmol) in THF (20 mL) and H₂O (10 mL) was added NBS (894 mg, 5.02 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was partitioned between EtOAc 50 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL x 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-28** (1.38 g, 67.0% yield) as a yellow oil.

10 [0348] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-29):**



[0349] **Synthesis of tert-butyl 3-(5-bromothiazol-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-29-1)** To a solution of **I-27-2** (8 g, 22.91 mmol) in DCM (80 mL) was added DAST (4.06 g, 25.2 mmol) at -78 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by addition H₂O 50 mL at 0 °C, and then diluted with H₂O 100 mL and extracted with DCM 200 mL (100 mL * 2). The combined organic layers were washed with brine 100 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give Compound **I-29-1** (6.5 g, 76.0% yield, 94.1% purity) as a brown solid.

[0350] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiazol-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-29-2)** A mixture of **I-29-1** (4 g, 11.4 mmol), tributyl(1-ethoxyvinyl)stannane (8.9 g, 24.6 mmol), TEA (3.46 g, 34.2 mmol) and Pd(PPh₃)₂Cl₂ (400 mg, 569 μmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 100 mL at 25 °C, and

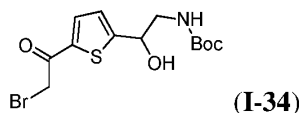
then diluted with H₂O 50 mL and extracted with EtOAc 200 mL (100 mL * 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 50 mL/min) to give
 5 Compound **I-29-2** (3.99 g, 94.3% yield, 92.2% purity) as a yellow oil.

[0351] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-fluoropyrrolidine-1-carboxylate (I-29)** To a solution of **I-29-2** (2 g, 5.84 mmol, 1 eq) in THF (20 mL) and H₂O (10 mL) was added NBS (1.04 g, 5.84 mmol, 1 eq). The mixture was stirred at 0 °C for 2h. TLC indicated **I-29-2** was consumed completely and one new
 10 spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between EtOAc 60 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~15% Ethyl
 15 acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-29** (1.6 g, 67.0 % yield, 96.1% purity) as a yellow solid.

[0352] The compounds **I-30** to **I-33** below have been prepared using the same experimental conditions as described for **I-27** to **I-29**.

Cpd number	Structure	Name
I-30		tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-hydroxyazetidine-1-carboxylate
I-31		tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-methoxyazetidine-1-carboxylate
I-32		tert-butyl 3-(5-(2-bromoacetyl)thiazol-2-yl)-3-fluoroazetidine-1-carboxylate
I-33		tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-fluoropyrrolidine-1-carboxylate

[0353] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)-2-hydroxyethyl)carbamate (I-34):**



[0354] **Synthesis of tert-butyl (2-(5-bromothiophen-2-yl)-2-hydroxyethyl)carbamate (I-34-1)** To a solution of 2,5-dibromothiophene (12 g, 49.6 mmol) in THF (100 mL) was added dropwise n-BuLi (2.5 M, 19.8 mL) at -78 °C. After addition, the mixture was stirred at this temperature for 0.5 h, and then tert-butyl N-(2-oxoethyl)carbamate (8.69 g, 54.6 mmol) in THF (100 mL) was added dropwise at -78 °C. The resulting mixture was stirred at 25 °C for 2.5 h. The reaction mixture was quenched by addition saturated NH₄Cl aqueous solution 500 mL at 0 °C, and then diluted with H₂O 1000 mL and extracted with EtOAc 2000 mL (1000 mL * 2). The combined organic layers were washed with brine 1000 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-34-1** (4.5 g, 28.2% yield) as a yellow solid.

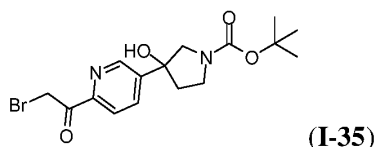
[0355] **Synthesis of tert-butyl (2-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-hydroxyethyl)carbamate (I-34-2)** A mixture of **I-34-1** (4 g, 12.4 mmol), tributyl(1-ethoxyvinyl)stannane (9.15 g, 25.3 mmol), Pd(PPh₃)₂Cl₂ (871 mg, 1.24 mmol) and TEA (3.77 g, 37.2 mmol) in dioxane (40 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 100 mL at 25 °C, and then diluted with H₂O 100 mL and extracted with EtOAc 400 mL (200 mL * 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-34-2** (13 g, crude) was obtained as a black oil.

[0356] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)-2-hydroxyethyl)carbamate (I-34)** To a solution of **I-34-2** (3.89 g, 12.4 mmol) in THF (40 mL) and H₂O (20 mL) was added NBS (2.21 g, 12.4 mmol). The mixture was stirred at

0 °C for 1h. TLC indicated **I-34-2** was consumed completely and two new spots formed. The reaction mixture was partitioned between EtOAc 80 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was
5 purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~35% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-34** (5 g, 34.3% yield, 31% purity) was obtained as a yellow solid.

[0357] Synthesis of 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxy-1-methylpyrrolidin-2-one (I-35):

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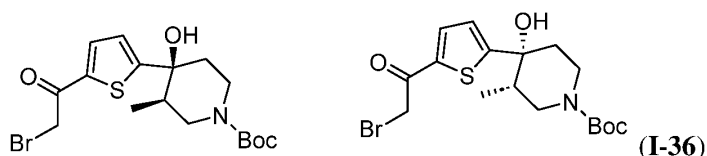
[0358] **Synthesis of tert-butyl 3-(6-bromo-3-pyridyl)-3-hydroxy-pyrrolidine-1-carboxylate (I-35-1)** To a solution of 2-bromo-5-iodo-pyridine (4.00 g, 14.09 mmol) in THF (60 mL) was added n-BuLi (2.5 M, 6.20 mL) at -78 °C under N₂. The mixture was stirred at -78°C for 1 h under N₂. Then tert-butyl 3-oxopyrrolidine-1-carboxylate (2.87
15 g, 15.50 mmol) in THF (60 mL) was added dropwise at -78 °C. The mixture was stirred at 25°C for 16 h. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.46) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched by addition H₂O 80 mL at 0 °C, and extracted with EtOAc 80 mL (50 mL * 3). The combined organic layers were dried over MgSO₄, filtered and
20 concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-35-1** (2.23 g, 6.50 mmol, 46.11% yield) as a yellow solid.

[0359] **Synthesis of tert-butyl 3-[6-(1-ethoxyvinyl)-3-pyridyl]-3-hydroxy-pyrrolidine-1-carboxylate (I-35-2)** A mixture of **I-35-1** (0.30 g, 874.09 μmol), tributyl(1-ethoxyvinyl)stannane (631.35 mg, 1.75 mmol, 590.60 μL), TEA (176.90 mg, 1.75 mmol, 243.32 μL), Pd(PPh₃)₂Cl₂ (61.35 mg, 87.41 μmol,) in dioxane (15 mL) was
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degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched with saturated KF (10 mL) and was extracted with EtOAc 30 mL (10 mL*3). The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **I-35-2** (800 mg, 717.68 μmol, 82.11% yield, 30.00% purity) was obtained as a black oil.

[0360] **Synthesis of tert-butyl 3-[6-(2-bromoacetyl)-3-pyridyl]-3-hydroxy-pyrrolidine-1-carboxylate (I-35)** To a solution of **I-35-2** (400.00 mg, 1.20 mmol) in THF (3 mL) and H₂O (1 mL) was added NBS (212.89 mg, 1.20 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with H₂O (10 mL) and extracted with EtOAc 10 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-35** (200 mg, 519.14 μmol, 43.40% yield) was obtained as a yellow solid.

15 [0361] **Synthesis of tert-butyl (3R,4S)-4-(5-(2-bromoacetyl)thiophen-2-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(5-(2-bromoacetyl)thiophen-2-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate mixture (I-36):**



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[0362] **Synthesis of tert-butyl 4-hydroxy-3-methyl-4-(2-thienyl)piperidine-1-carboxylate (I-36-1)** To a solution of 2-bromothiophene (10 g, 61.34 mmol) in THF (100 mL) was added n-BuLi (2.5 M, 26.99 mL) at -78 °C under N₂. The mixture was stirred at -78 °C for 1 h under N₂. Tert-butyl 3-methyl-4-oxo-piperidine-1-carboxylate (15.70 g, 73.60 mmol) was added into the mixture at -78 °C and stirred at -78 °C for 1 h under N₂. Then the mixture was stirred at 25 °C for 16 h. TLC (petroleum ether/ethyl acetate = 3/1,

R_f = 0.64) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched by addition H₂O 100 mL at 0 °C, extracted with EtOAc 100 mL. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-36-1** (17 g, 57.16 mmol, 93.19% yield) as a colourless oil.

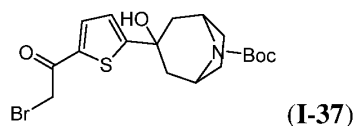
[0363] **Synthesis of tert-butyl 4-(5-bromo-2-thienyl)-4-hydroxy-3-methyl-piperidine-1-carboxylate (I-36-2)** To a solution of **I-36-1** (5.5 g, 18.49 mmol) in DMF (30 mL) was added NBS (3.62 g, 20.34 mmol). The mixture was stirred at 25 °C for 2 h. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.64) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched by addition H₂O 100 mL at 0 °C, and extracted with EtOAc 300 mL (100 mL * 3). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~40% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-36-2** (6 g, 15.94 mmol, 86.22% yield) as a yellow oil.

[0364] **Synthesis of tert-butyl 4-[5-(1-ethoxyvinyl)-2-thienyl]-4-hydroxy-3-methyl-piperidine-1-carboxylate (I-36-3)** A mixture of **I-36-2** (6 g, 15.94 mmol), TEA (3.23 g, 31.89 mmol), tributyl(1-ethoxyvinyl)stannane (11.510 g, 31.87 mmol, 10.77 mL) and Pd(PPh₃)₂Cl₂ (223.83 mg, 318.89 µmol) in dioxane (60 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 85 °C for 16 h under N₂ atmosphere. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.68) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched with saturated KF (100 mL) and extracted with EtOAc 100 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **I-36-3** (6 g, 11.43 mmol, 71.68% yield, 70% purity) was obtained as a black oil.

[0365] **Synthesis of tert-butyl (3R,4S)-4-(5-(2-bromoacetyl)thiophen-2-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(5-(2-**

bromoacetyl)thiophen-2-yl)-4-hydroxy-3-methylpiperidine-1-carboxylate mixture (I-36) To a solution of **I-36-3** (6 g, 11.43 mmol) in THF (40 mL) and H₂O (20 mL) was added NBS (4.07 g, 22.86 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H₂O (80 mL) and was extracted with EtOAc 80 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~60 % THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-36** (5 g, 8.13 mmol, 71.11% yield, 68% purity) was obtained as a yellow solid.

10 [0366] Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (I-37)



[0367] **Synthesis of tert-butyl 3-hydroxy-3-(2-thienyl)-8-azabicyclo[3.2.1]octane-8-carboxylate (I-37-1)** To a solution of 2-bromothiophene (2 g, 12.27 mmol) in THF (50 mL) was added n-BuLi (2.5 M, 5.40 mL) at -78 °C under N₂. The mixture was stirred at -78 °C for 1 h under N₂. Tert-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (3.32 g, 14.72 mmol) was added dropwise at -78 °C and stirred at -78 °C for 1 h N₂. Then the mixture was stirred at 25 °C for 16 h. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.64) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched by addition H₂O 80 mL at 0 °C, and extracted with EtOAc 80 mL. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-37-1** (2.4 g, 7.76 mmol, 63.23% yield) as a yellow solid.

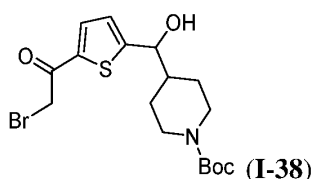
[0368] **Synthesis of tert-butyl 3-(5-bromo-2-thienyl)-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (I-37-2)** To a solution of **I-37-1** (4.7 g, 15.19 mmol) in DMF (40 mL) was added NBS (3.51 g, 19.75 mmol). The mixture was stirred at 25 °C for 1 h. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.64) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched by addition H₂O 100 mL at 0 °C, and extracted with EtOAc 300 mL (100 mL * 3). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~40% THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-37-2** (4.3 g, 11.07 mmol, 72.90% yield) as a yellow solid

[0369] **Synthesis of tert-butyl 3-[5-(1-ethoxyvinyl)-2-thienyl]-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (I-37-3)** A mixture of **I-37-2** (4.3 g, 11.07 mmol), tributyl(1-ethoxyvinyl)stannane (10.150 g, 28.10 mmol), TEA (2.24 g, 22.15 mmol) and Pd(PPh₃)₂Cl₂ (155.45 mg, 221.47 µmol) in dioxane (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 85 °C for 16 h under N₂ atmosphere. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.64) showed the compound starting material was consumed and one new spot was formed. The reaction mixture was quenched with saturated KF (60 mL) and was extracted with EtOAc 60 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **I-37-3** (6 g, 6.32 mmol, 57.11% yield, 40% purity) was obtained as a black oil.

[0370] **Synthesis of tert-butyl 3-[5-(2-bromoacetyl)-2-thienyl]-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (I-37)** To a solution of **I-37-3** (4 g, 10.54 mmol) in THF (30 mL) and H₂O (15 mL) was added NBS (3.75 g, 21.08 mmol). The mixture was stirred at 0-25 °C for 2 h. The reaction mixture was quenched with H₂O (80 mL) and was extracted with EtOAc 80 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~60 %

THF/Petroleum ether gradient @ 60 mL/min) to give compound **I-37** (2.3 g, 5.34 mmol, 50.71% yield) was obtained as a yellow oil.

[0371] Synthesis of tert-butyl 4-((5-(2-bromoacetyl)thiophen-2-yl)(hydroxy)methyl)piperidine-1-carboxylate (**I-38**):



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[0372] **Synthesis of tert-butyl 4-(hydroxy(thiophen-2-yl)methyl)piperidine-1-carboxylate (**I-38-1**)** To a solution of 2-bromothiophene (5 g, 30.67 mmol, 2.97 mL) in THF (150 mL) was added n-BuLi (2.5 M, 13.49 mL) in one portion at -70 °C under N₂. The mixture was stirred at -70 °C for 1 h, then tert-butyl 4-formylpiperidine-1-carboxylate (7.19 g, 33.73 mmol) was added. The mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into ice-water (100 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-38-1** (4.6 g, 15.47 mmol, 50.43% yield) as a white solid.

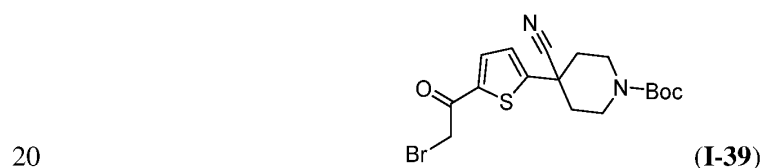
15 [0373] **Synthesis of tert-butyl 4-((5-bromothiophen-2-yl)(hydroxy)methyl)piperidine-1-carboxylate (**I-38-2**)** To a solution of compound **I-38-1** (4.5 g, 15.13 mmol) and NBS (2.96 g, 16.64 mmol) in DMF (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 2 h under N₂ atmosphere. The reaction mixture was poured into water (50 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-38-2** (4.6 g, 12.22 mmol) as a yellow solid.

25 [0374] **Synthesis of tert-butyl 4-((5-(1-ethoxyvinyl)thiophen-2-yl)(hydroxy)methyl)piperidine-1-carboxylate tert-butyl 4-((5-(1-ethoxyvinyl)thiophen-2-yl)(hydroxy)methyl)piperidine-1-carboxylate (**I-38-3**)** To a solution of compound **I-38-2** (3 g, 7.97 mmol) and tributyl(1-ethoxyvinyl)stannane (5.76

g, 15.94 mmol, 5.39 mL) in dioxane (20 mL) was added TEA (2.42 g, 23.92 mmol, 3.33 mL) and Pd(PPh₃)₂Cl₂ (559.56 mg, 797.22 μmol) under N₂ atmosphere. The mixture was stirred at 90 °C for 12h under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (100 mL) at 25 °C and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine (100 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-38-3** (6.1 g, crude) as a brown oil.

[0375] **Synthesis of tert-butyl 4-((5-(2-bromoacetyl)thiophen-2-yl)(hydroxymethyl)piperidine-1-carboxylate (I-38)** To a solution of compound **I-38-3** (3 g, 8.16 mmol) in THF (20 mL) and H₂O (5.0 mL) was added NBS (1.45 g, 8.16 mmol). The mixture was stirred at 0 °C for 0.5 h. TLC indicated compound **I-38-3** was consumed completely and many new spots were formed. The reaction mixture was quenched by addition H₂O (20 mL) at 25°C and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 4/1) to give compound **I-38** (1.7 g, crude) as a yellow oil.

[0376] **Synthesis of tert-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)-4-cyanopiperidine-1-carboxylate (I-39):**



[0377] **Synthesis of tert-butyl 4-cyano-4-(thiophen-2-yl)piperidine-1-carboxylate (I-39-1)** To a solution of 2-(thiophen-2-yl)acetonitrile (10 g, 81.19 mmol, 8.65 mL) in DMF (100 mL) was added dropwise NaNH₂ (9.50 g, 243.56 mmol) at 0 °C under N₂ atmosphere. The mixture was stirred at 0 °C for 1 h. Then a solution of tert-butyl N,N-bis(2-chloroethyl)carbamate (35.38 g, 146.13 mmol) in DMF (50 mL) was added dropwise at 0 °C. The mixture was stirred at 25 °C for 12 h. The residue was poured into sat. NH₄Cl (10 mL) and extracted with EtOAc (100 mL* 3). The combined organic layers

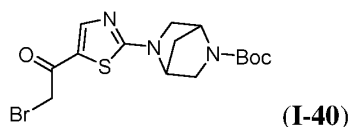
were washed with brine (300 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 2/1) to give compound **I-39-1** (11 g, 37.62 mmol) as a red solid.

- 5 [0378] **Synthesis of tert-butyl 4-(5-bromothiophen-2-yl)-4-cyanopiperidine-1-carboxylate (I-39-2)** To a solution of compound **I-39-1** (3 g, 10.26 mmol) in DMF (30 mL) was added NBS (2.19 g, 12.31 mmol), the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (70 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with H₂O (100 mL), dried over anhydrous
10 Na₂SO₄, filtered and concentrated in vacuum to give compound **I-39-2** (2.6 g, 7.00 mmol, 68.25% yield) as light yellow solid.

- [0379] **Synthesis of tert-butyl 4-cyano-4-(5-(1-ethoxyvinyl)thiophen-2-yl)piperidine-1-carboxylate (I-39-3)** To a solution of compound **I-39-2** (2.5 g, 6.73 mmol) in dioxane (30 mL) was added tributyl(1-ethoxyvinyl)stannane (4.86 g, 13.47
15 mmol, 4.55 mL), TEA (2.04 g, 20.20 mmol) and Pd(PPh₃)₂Cl₂ (472.60 mg, 673.32 μmol) under N₂. The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by H₂O (20 mL) and was extracted with EtOAc (30 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-39-3** (5.3 g, crude) as a brown oil.

- 20 [0380] **Synthesis of tert-butyl 4-(5-(2-bromoacetyl)thiophen-2-yl)-4-cyanopiperidine-1-carboxylate (I-39)** To a solution of compound **I-39-3** (2 g, 5.52 mmol) in THF (30 mL) and H₂O (10 mL) was added NBS (1.18 g, 6.62 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by H₂O (20 mL) and was extracted with EtOAc (30 mL). The combined organic layer was dried over
25 Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-39** (2.3 g, crude) as a yellow oil.

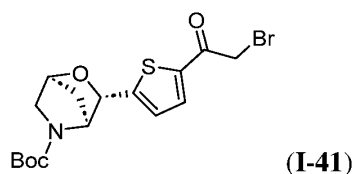
[0381] Synthesis of tert-butyl 5-(5-(2-bromoacetyl)thiazol-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (I-40):



- [0382] **Synthesis of tert-butyl 5-(5-bromothiazol-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (I-40-1)** To a solution of 2,5-dibromothiazole (9 g, 37.05 mmol) in DMF (100 mL) was added tert-butyl 2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (8.81g, 44.46 mmol), K₂CO₃ (15.36 g, 111.15 mmol). The mixture was stirred at 85 °C for 2 h. TLC showed starting material was consumed completely, and one new spot was formed. The residue was poured into sat. NH₄Cl (30 mL) and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 2/1) to give compound **I-40-1** (8 g, 22.21 mmol, 59.94% yield) as a white solid.
- [0383] **Synthesis of tert-butyl 5-(5-(1-ethoxyvinyl)thiazol-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (I-40-2)** To a solution of compound **I-40-1** (8 g, 22.21 mmol) and tributyl(1-ethoxyvinyl)stannane (16.04 g, 44.41 mmol, 15.00 mL) in dioxane (200 mL) was added TEA (6.74 g, 66.62 mmol, 9.27 mL) and Pd(PPh₃)₂Cl₂ (1.56 g, 2.22 mmol) under N₂ atmosphere. The mixture was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (100 mL) at 25 °C and extracted with EtOAc (150 mL * 3). The combined organic layers were washed with brine (100 mL * 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-40-2** (15.4 g, crude) as a brown oil.
- [0384] **Synthesis of tert-butyl 5-(5-(2-bromoacetyl)thiazol-2-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (I-40)** To a solution of compound **I-40-2** (6 g, 17.07 mmol) in THF (60 mL) and H₂O (30.0 mL) was added NBS (6.08 g, 34.14

mmol). The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was quenched by addition H₂O (100 mL) at 25 °C and extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (50 mL * 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=10/1 to 4/1) to give compound **I-40** (8.2 g, crude) as a yellow oil.

[0385] Synthesis of tert-butyl (1S,3S,4S)-3-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (**I-41**):



- [0386] **Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-(thiophene-2-carbonyl)pyrrolidine-1-carboxylate (**I-41-1**)** To a solution of tert-butyl (1S,4S)-3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (10 g, 50.20 mmol) in THF (200 mL) was added dropwise thiophen-2-ylmagnesium bromide (1 M, 50.20 mL) at -70 °C under N₂. The mixture was stirred at 25 °C for 2 h under N₂. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (50 mL) dropwise at 0 °C under N₂ and extracted with EtOAc (150 mL * 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 2/1) to give **I-41-1** (4.8 g, 16.14 mmol, 32.15% yield) as a white solid.
- [0387] **Synthesis of tert-butyl (2S,4S)-4-hydroxy-2-((S)-hydroxy(thiophen-2-yl)methyl)pyrrolidine-1-carboxylate (**I-41-2**)** To a solution of **I-41-1** (100 mg, 336.28 μmol) in MeOH (10.0 mL) was added NaBH₄ (25.44 mg, 672.56 μmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition of H₂O (2.0 mL) and extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **I-41-2** (68 mg, 227.13 μmol) as white oil

[0388] **Synthesis of tert-butyl (1S,3S,4S)-3-(thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-41-3)** To a solution of compound **I-41-2** (3.00 g, 10.02 mmol) in toluene (30 mL) added 2-(tributyl-phosphanylidene)acetonitrile (4.84 g, 20.04 mmol) at 25 °C. The mixture was stirred at 100 °C for 1 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM (10 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-41-3** (2.5 g, 8.89 mmol, 88.67% yield) as a yellow oil.

10 [0389] **Synthesis of tert-butyl (1S,3S,4S)-3-(5-bromothiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-41-4)** To a solution of compound **I-41-3** (1.6 g, 5.69 mmol) in DMF (30 mL) was added NBS (1.21 g, 6.82 mmol) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (70 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H₂O (100 mL * 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-41-4** (1.9 g, 5.27 mmol, 92.74% yield) as a light yellow solid.

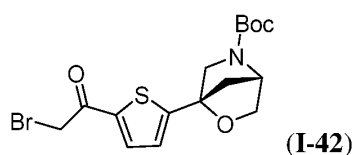
[0390] **Synthesis of tert-butyl (1S,3S,4S)-3-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-41-5)** To a solution of compound **I-41-4** (2 g, 5.55 mmol) in dioxane (30.0 mL) was added tributyl(1-ethoxyvinyl)stannane (8.02 g, 22.21 mmol, 7.50 mL), TEA (1.69 g, 16.65 mmol, 2.32 mL) and Pd(PPh₃)₂Cl₂ (389.65 mg, 555.15 μmol) under N₂. The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by H₂O (20.0 mL) and was extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-41-5** (4.8 g, crude) as a brown oil.

25 [0391] **Synthesis of tert-butyl (1S,3S,4S)-3-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-41)** To a solution of compound **I-41-5** (1.95 g, 5.55 mmol) in THF (30.0 mL) and H₂O (10.0 mL) was added NBS (988.07 mg, 5.55 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by H₂O (20.0 mL), extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue

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was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-41** (2.5 g, crude) as a yellow oil.

[0392] **Synthesis of tert-butyl (1S,4S)-1-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-42):**



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[0393] **Synthesis of (2S,4S)-1-(tert-butoxycarbonyl)-4-hydroxy-4-(thiophen-2-yl)pyrrolidine-2-carboxylic acid (I-42-1)** To a solution of (S)-1-(tert-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid (10 g, 43.62 mmol) in THF (200 mL) was added dropwise thiophen-2-ylmagnesium bromide (1 M, 52.35 mL) at -70 °C under N₂. The mixture was stirred at 25 °C for 2 h under N₂. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (50 mL) dropwise at 0 °C under N₂ and extracted with EtOAc (250 mL x 2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 2/1) to give **I-42-1** (9.5 g, 30.32 mmol, 69.49% yield) as a white solid.

[0394] **Synthesis of tert-butyl (2S,4S)-4-hydroxy-2-(hydroxymethyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (I-42-2)** To a solution of **I-42-1** (5 g, 15.96 mmol) in THF (10.0 mL) was added BH₃.THF (1 M, 15.96 mL). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition of MeOH (20.0 mL) and extracted with EtOAc (200 mL* 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **I-42-2** (3 g, 10.02 mmol, 62.80% yield) as white oil

[0395] **Synthesis of tert-butyl (1S,4S)-1-(thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-42-3)** To a solution of compound **I-42-2** (3.0 g, 1.00 mmol) in toluene (30 mL) added 2-(tributyl-phosphanylidene)acetonitrile (4.8 g,

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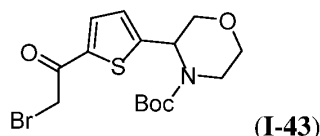
20.04 mmol) at 25 °C. The mixture was stirred at 100 °C for 1 h. The reaction mixture was diluted with H₂O (10 mL) and extracted with DCM (10 mL * 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-42-3** (2.5 g, 8.89 mmol, 95.00% yield) as a yellow oil.

[0396] **Synthesis of tert-butyl (1S,4S)-1-(5-bromothiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-42-4)** To a solution of compound **I-42-3** (2.5 g, 8.89 mmol) in DMF (30 mL) was added NBS (2.06 g, 11.55 mmol) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (70 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with H₂O (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-42-4** (2.8 g, 7.77 mmol, 87.47% yield) as a light yellow solid.

[0397] **Synthesis of tert-butyl (1S,4S)-1-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-42-5)** To a solution of compound **I-42-4** (2.8 g, 7.77 mmol) in dioxane (30 mL) was added tributyl(1-ethoxyvinyl)stannane (5.61 g, 15.54 mmol, 5.25 mL), TEA (2.36 g, 23.32 mmol, 3.25 mL) and Pd(PPh₃)₂Cl₂ (818.27 mg, 1.17 mmol) under N₂. The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by H₂O (20.0 mL) and was extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-42-5** (4.4 g, crude) as a brown oil.

[0398] **Synthesis of tert-butyl (1S,4S)-1-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-42)** To a solution of compound **I-42-5** (2.73 g, 7.77 mmol) in THF (30 mL) and H₂O (10 mL) was added NBS (2.77 g, 15.54 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by H₂O (20.0 mL) and was extracted with EtOAc (30.0 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-42** (3.1 g, crude) as a yellow oil.

[0399] **Synthesis of tert-butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)morpholine-4-carboxylate (I-43):**



[0400] **Synthesis of tert-butyl 5-((diphenoxyphosphoryl)oxy)-2H-1,4-oxazine-4(3H)-carboxylate (I-43-1)** Tert-butyl 3-oxomorpholine-4-carboxylate (20 g, 99.4 mmol) was dissolved in THF (200 mL). The mixture was cooled to -30 °C and LiHMDS (1 M, 109 mL) was added dropwise. The resulting mixture was stirred for 1 h, then [chloro(phenoxy)phosphoryl]oxybenzene (28.0 g, 104 mmol) was added dropwise. The resulting mixture was allowed to warm slowly to 43 °C for 6 h. The reaction mixture was poured into saturated ammonium chloride solution (1000 mL) and diluted with EtOAc (1000 mL). The organic phase was separated and washed with sat NaHCO₃ (500 mL), then brine (500 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~12% THF/Petroleum ether gradient @ 80 mL/min) to give Compound **I-43-1** (26.6 g, 61.8% yield) as a yellow oil.

[0401] **Synthesis of tert-butyl 5-(thiophen-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate (I-43-2)** A mixture of **I-43-1** (24 g, 55.4 mmol), 2-thienylboronic acid (11.3 g, 88.6 mmol), Na₂CO₃ (2 M, 360 mL) and Pd(PPh₃)₂Cl₂ (3.89 g, 5.54 mmol) in THF (720 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 60 °C for 16 h under N₂ atmosphere. The reaction mixture was partitioned between EtOAc 800 mL and brine 600 mL. The organic phase was separated, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~3% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give Compound **I-43-2** (14.5 g, 97.9% yield) as a red oil.

[0402] **Synthesis of 5-(thiophen-2-yl)-3,4-dihydro-2H-1,4-oxazine (I-43-3)** To a solution of **I-43-2** (13.5 g, 50.5 mmol) in DCM (60 mL) was added HCl/dioxane (2 M,

252 mL). The mixture was stirred at 25 °C for 6 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The reaction mixture was poured into Saturated NaHCO₃ solution (pH>7), extracted with EtOAc 900 mL (300 mL * 3). The organic phase was separated, washed with brine 1200 mL (600 mL * 2), dried over
5 MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-43-3** (7.8 g, 92.4% yield) as a white solid.

[0403] **Synthesis of 3-(thiophen-2-yl)morpholine (I-43-4)** To a solution of **I-43-3** (6 g, 35.9 mmol) in MeOH (15 mL) was added NaBH₃CN (4.51 g, 71.8 mmol) and AcOH (6.46 g, 108 mmol). The mixture was stirred at 25 °C for 6 h. The reaction mixture was
10 partitioned between EtOAc 60 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-43-4** (10 g, crude) as a brown oil.

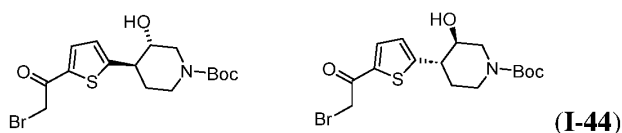
[0404] **Synthesis of tert-butyl 3-(thiophen-2-yl)morpholine-4-carboxylate (I-43-5)** To a solution of **I-43-4** (10 g, 59.1 mmol) in THF (100 mL) was added DIEA (15.3 g, 118 mmol) and Boc₂O (25.79 g, 118.17 mmol, 27.15 mL). The mixture was stirred at 25
15 °C for 16 h. TLC indicated **I-43-4** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~6%
20 THF/Petroleum ether gradient @ 80 mL/min) to give **I-43-5** (10 g, 61.3% yield, 97.6% purity) was obtained as a colourless oil.

[0405] **Synthesis of tert-butyl 3-(5-bromothiophen-2-yl)morpholine-4-carboxylate (I-43-6)** To a solution of **I-43-5** (10 g, 37.13 mmol) in DMF (100 mL) was added NBS (6.61 g, 37.1 mmol). The mixture was stirred at 25 °C for 6 h. The reaction mixture was
25 partitioned between EtOAc 600 mL and H₂O 600 mL. The organic phase was separated, washed with brine 600 mL (300 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~5%
THF/Petroleum ether gradient @ 80 mL/min) to give Compound **I-43-6** (11 g, 85.1%
30 yield) as a yellow oil.

[0406] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiophen-2-yl)morpholine-4-carboxylate (I-43-7)** A mixture of **I-43-6** (10 g, 28.7 mmol), tributyl(1-ethoxyvinyl)stannane (20.7 g, 57.4 mmol) and Pd(PPh₃)₂Cl₂ (1.01 g, 1.44 mmol) TEA (8.72 g, 86.1 mmol) in dioxane (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 1000 mL at 25 °C, and then diluted with H₂O 1000 mL and extracted with EtOAc 2000 mL (1000 mL * 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-43-7** (20 g, crude) was obtained as a brown oil.

[0407] **Synthesis of tert-butyl 3-(5-(1-ethoxyvinyl)thiophen-2-yl)morpholine-4-carboxylate (I-43)** To a solution of **I-43-7** (9.7 g, 28.6 mmol) in THF (90 mL) and H₂O (90 mL) was added NBS (5.09 g, 28.6 mmol). The mixture was stirred at 0 °C for 1h. TLC indicated **I-43-7** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between EtOAc 600 mL and H₂O 600 mL. The organic phase was separated, washed with brine 800 mL (400 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give Compound **I-43** (6 g, 30.1% yield, 56% purity) as a yellow solid.

[0408] **Synthesis of tert-butyl (3S,4R)-4-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypiperidine-1-carboxylate mixture (I-44):**



[0409] **Synthesis of tert-butyl 3-hydroxy-4-(thiophen-2-yl)piperidine-1-carboxylate (I-44-1)** To a solution of bromo(2-thienyl)magnesium (1 M, 301) in THF (300 mL) was added dropwise CuI (4.78 g, 25.09 mmol, 0.1 eq) at 0 °C. After addition, and then tert-

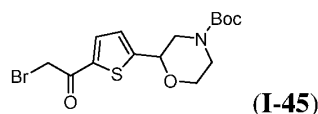
butyl 7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (50 g, 251 mmol) in THF (150 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition saturated NH₄Cl aqueous solution 100 mL at 0 °C, and then diluted with H₂O 800 mL and extracted with EtOAc 1000 mL (500 mL * 2). The combined organic layers were washed with brine 500 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 80 mL/min), which was further separated by prep-HPLC (NH₃H₂O condition) to give Compound **I-44-1** (9 g, 12.7% yield) was obtained as a yellow oil.

[0410] **Synthesis of tert-butyl 4-(5-bromothiophen-2-yl)-3-hydroxypiperidine-1-carboxylate (I-44-2)** To a solution of **I-44-1** (7.8 g, 27.5 mmol) in DMF (60 mL) was added NBS (4.90 g, 27.5 mmol). The mixture was stirred at 0 °C for 2 h. TLC indicated **I-44-1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between EtOAc 600 mL and H₂O 600 mL. The organic phase was separated, washed with brine 1200 mL (600 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~20% THF/Petroleum ether gradient @ 60 mL/min) to give Compound **I-44-2** (8.3 g, 83.2% yield) as a yellow solid.

[0411] **Synthesis of tert-butyl 4-(5-(1-ethoxyvinyl)thiophen-2-yl)-3-hydroxypiperidine-1-carboxylate (I-44-3)** A mixture of **I-44-2** (8.3 g, 22.9 mmol), tributyl(1-ethoxyvinyl)stannane (17 g, 47.0 mmol), Pd(PPh₃)₂Cl₂ (1.61 g, 2.29 mmol) and TEA (6.95 g, 68.7 mmol) in dioxane (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 6 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 500 mL at 25 °C, and then diluted with H₂O 600 mL and extracted with EtOAc 800 mL (400 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-44-3** (30 g, crude) was obtained as a brown oil.

[0412] **Synthesis of tert-butyl (3S,4R)-4-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypiperidine-1-carboxylate and tert-butyl (3S,4R)-4-(5-(2-bromoacetyl)thiophen-2-yl)-3-hydroxypiperidine-1-carboxylate mixture (I-44)** To a solution of **I-44-3** (8.1 g, 22.9 mmol) in THF (100 mL) and H₂O (50 mL) was added NBS (4.08 g, 22.9 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was partitioned between EtOAc 80 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~25% THF/Petroleum ether gradient @ 60 mL/min) to give Compound **I-44** (5 g, 32.3% yield, 59.8% purity) as a yellow solid.

[0413] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)morpholine-4-carboxylate (I-45):**



[0414] **Synthesis of 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (I-45-1)** To a solution of 1-(5-bromo-2-thienyl)ethanone (50.0 g, 244 mmol) in EtOAc (250 mL) and CHCl₃ (269 mL) was added CuBr₂ (136 g, 607 mmol). The mixture was stirred at 90 °C for 16 h. After cooling, the mixture was concentrated in vacuum to give a residue. The residue was dissolved in EtOAc (1000 mL), filtered through a Celite pad. The combined organic layer was washed with aq. NaHCO₃ (500 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, DCM/MeOH = 100/1 to 8/1) to give compound **I-45-1** (42.1 g, 148 mmol, 60.8% yield) as a brown solid.

[0415] **Synthesis of 2-(benzyl(2-hydroxyethyl)amino)-1-(5-bromothiophen-2-yl)ethan-1-one (I-45-2)** To a solution of compound **I-45-1** (41.4 g, 146 mmol) and 2-(benzylamino)ethanol (33.1 g, 219 mmol, 31.0 mL) in DMF (420 mL) was added K₂CO₃ (60.4 g, 437 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was added water (800 mL) and extracted with EtOAc (1000 mL * 3). The combined organic

layer was dried with Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 6/1) to give compound **I-45-2** (37.3 g, 104 mmol, 71.3% yield, 98.8% purity) as a brown oil.

- 5 [0416] **Synthesis of 2-(benzyl(2-hydroxyethyl)amino)-1-(5-bromothiophen-2-yl)ethan-1-ol (I-45-3)** To a solution of compound **I-45-2** (37.3 g, 104 mmol,) in MeOH (380 mL) was added NaBH₄ (4.41 g, 117 mmol,) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was quenched by water (500 mL) at 0 °C under N₂ and extracted with EtOAc (800 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-45-3** (34.8 g, 87.4 mmol, 84.1% yield, 89.6% purity) as a brown oil.

- [0417] **Synthesis of 4-benzyl-2-(5-bromothiophen-2-yl)morpholine (I-45-4)** A solution of compound **I-45-3** (34.8 g, 97.6 mmol,) in HBr (207 g, 845 mmol, 139 mL, 33.0% purity) was stirred at 25 °C for 2 h. The mixture was quenched by water (400 mL) at 0 °C under N₂ and extracted with EtOAc (600 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1) to give compound **I-45-4** (26.9 g, 74.7 mmol, 76.5% yield, 94.0% purity) as a brown oil.

- [0418] **Synthesis of 2-chloroethyl 2-(5-bromothiophen-2-yl)morpholine-4-carboxylate (I-45-5)** To a solution of compound **I-45-4** (15.0 g, 44.3 mmol) in DCM (150 mL) was added 2-chloroethyl chloroformate (9.00 g, 63.0 mmol, 6.50 mL). The mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF= 100/1 to 7/1) to give compound **I-45-5** (10.8 g, 27.7 mmol, 62.4% yield, 90.8% purity) as a brown oil.

[0419] **Synthesis of 2-(5-bromothiophen-2-yl)morpholine (I-45-6)** To a solution of compound **I-45-5** (10.0 g, 25.6 mmol) in dioxane (50.0 mL) was added a solution of NaOH (1.54 g, 38.4 mmol) in H₂O (50 mL). The mixture was stirred at 110 °C for 3 h. The reaction mixture was added water (100 mL) and extracted with DCM (200 mL * 3).

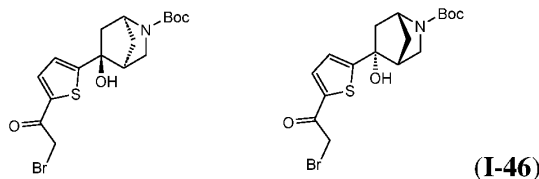
The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **I-45-6** (8.83 g, 17.4 mmol, 67.9% yield, 48.8% purity) as a brown oil.

- [0420] **Synthesis of tert-butyl 2-(5-bromothiophen-2-yl)morpholine-4-carboxylate (I-45-7)** To a solution of compound **I-45-6** (8.63 g, 17.0 mmol) in DCM (86 mL) was added Boc₂O (5.56 g, 25.5 mmol, 5.85 mL) and TEA (5.16 g, 51.0 mmol, 7.09 mL). The mixture was stirred at 25 °C for 2 h. The mixture was added water (150 mL) and extracted with EtOAc (200 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 7/1) to give compound **I-45-7** (3.65 g, 9.61 mmol, 56.61% yield, 91.73% purity) as a brown oil.

- [0421] **Synthesis of tert-butyl 2-(5-(1-ethoxyvinyl)thiophen-2-yl)morpholine-4-carboxylate (I-45-8)** To a solution of compound **I-45-7** (3.65 g, 9.61 mmol) and tributyl(1-ethoxyvinyl)stannane (6.18 g, 17.1 mmol, 5.78 mL) in dioxane (37.0 mL) was added TEA (1.95 g, 19.2 mmol, 2.68 mL) and Pd(PPh₃)₂Cl₂ (675 mg, 961 μmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction was quenched by aq. KF (60 mL) and extracted with EtOAc (100 mL * 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-45-8** (10.2 g, crude) as a brown oil.

- [0422] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)morpholine-4-carboxylate (I-45)** To a solution of compound **I-45-8** (10.2 g, 30.1 mmol) in THF (100 mL) and H₂O (50 mL) was added NBS (2.00 g, 11.2 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was added water (60 mL) and extracted with EtOAc (100 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 4/1) to give compound **I-45** (2.90 g, 5.48 mmol, 18.2% yield, 73.7% purity) as a yellow solid.

[0423] Synthesis of tert-butyl (1S,4S,5S)-5-(5-(2-bromoacetyl)thiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate and tert-butyl (1R,4R,5R)-5-(5-(2-bromoacetyl)thiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate mixture (I-46):



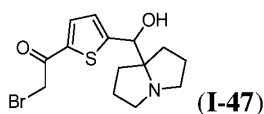
[0424] **Synthesis of tert-butyl 5-hydroxy-5-(thiophen-2-yl)-2-azabicyclo[2.2.1]heptane-2-carboxylate (I-46-1)** To a solution of 2-bromothiophene (5.00 g, 30.7 mmol, 2.97 mL) in Tol. (50 mL) was added n-BuLi (2.50 M, 17.2 mL) at -70 °C under N₂. The mixture was stirred at -70 °C for 1 h under N₂. A solution of tert-butyl 5-oxo-2-azabicyclo[2.2.1]heptane-2-carboxylate (5.83 g, 27.6 mmol) in Tol. (12.5 mL) was added into above reaction mixture at -70 °C and stirred at -70 °C for 1 h under N₂. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by aq. NH₄Cl (80 mL) and extracted with EtOAc (100 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 2/1) to give compound **I-46-1** (6.10 g, 18.7 mmol, 60.9% yield, 90.5% purity) as a yellow solid.

[0425] **Synthesis of tert-butyl 5-(5-bromothiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (I-46-2)** To a solution of compound **I-46-1** (3.03 g, 10.3 mmol) in DMF (35 mL) was added NBS (2.01 g, 11.3 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction was added water (30 mL) and extracted with EtOAc (50 mL* 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 100/1 to 7/1) to give compound **I-46-2** (2.68 g, 6.62 mmol, 64.5% yield, 92.4% purity) as a white solid.

[0426] **Synthesis of tert-butyl 5-(5-acetylthiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate (I-46-3)** To a solution of compound **I-46-2** (4.00 g, 10.7 mmol), tributyl(1-ethoxyvinyl)stannane (7.82 g, 21.7 mmol, 7.32 mL) in dioxane (40 mL) was added TEA (2.16 g, 21.4 mmol, 2.97 mL) and Pd(PPh₃)₂Cl₂ (750 mg, 1.07 mmol) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction was quenched by aq. KF (60 mL) and extracted with EtOAc (100 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 100/1 to 4/1) to give compound **I-46-3** (2.03 g, 4.05 mmol, 37.9% yield, 72.9% purity) as a white solid.

[0427] **[0423] Synthesis of tert-butyl (1S,4S,5S)-5-(5-(2-bromoacetyl)thiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate and tert-butyl (1R,4R,5R)-5-(5-(2-bromoacetyl)thiophen-2-yl)-5-hydroxy-2-azabicyclo[2.2.1]heptane-2-carboxylate mixture (I-46)** To a solution of compound **I-46-3** (1.00 g, 2.96 mmol) in DCM (4.80 mL) and MeOH (12.0 mL) was added TBATB (1.50 g, 3.11 mmol). The mixture was stirred at 25 °C for 4 h. The reaction was added water (20 mL) and extracted with DCM (20 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-46** (1.26 g, 1.55 mmol, 52.3% yield, 51.2% purity) as a yellow solid.

[0428] **Synthesis of 2-bromo-1-(5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)thiophen-2-yl)ethan-1-one (I-47):**



[0429] **Synthesis of tetrahydro-1H-pyrrolizine-7a(5H)-carbaldehyde (I-47-1)** To a solution of (tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (10.0 g, 70.8 mmol) in DCM (300 mL) was added Dess-Martin (60.1 g, 142 mmol, 43.9 mL) at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction was quenched by aq. NaHCO₃ (600 mL) and

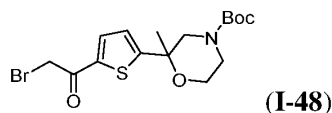
extracted with DCM (1000 mL x 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-47-1** (18 g, crude) as a yellow solid.

[0430] **Synthesis of (5-bromothiophen-2-yl)(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (I-47-2)** To a solution of 2,5-dibromothiophene (1.00 g, 4.13 mmol, 466 µL) in Tol. (10 mL) was added n-BuLi (2.50 M, 1.82 mL) at -70 °C under N₂. The mixture was stirred at -70 °C for 1 h under N₂. A solution of compound **I-47-1** (1.50 g, 10.8 mmol) in Tol. (10 mL) was added into above reaction mixture at -70 °C and stirred at -70 °C for 1 h under N₂. The mixture was stirred at 25 °C for 16 h. The reaction was quenched by aq. NH₄Cl (30 mL) at 0 °C and extracted with DCM (100 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 100/1 to 0/1) to give compound **I-47-2** (225 mg, 744 µmol, 18.0% yield) as a brown oil.

[0431] **Synthesis of (5-(1-ethoxyvinyl)thiophen-2-yl)(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methanol (I-47-3)** To a solution of compound **I-47-2** (225 mg, 744 µmol) in dioxane (3.50 mL) was added tributyl(1-ethoxyvinyl)stannane (403 mg, 1.12 mmol, 377 µL), TEA (151 mg, 1.49 mmol, 207 µL) and Pd(PPh₃)₂Cl₂ (52.3 mg, 74.5 µmol) under N₂. The mixture was stirred at 90 °C for 16 h under N₂. The reaction was quenched by aq. KF (10 mL) and extracted with EtOAc (20 mL * 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-47-3** (721 mg, crude) as a brown oil.

[0432] **Synthesis of 2-bromo-1-(5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)thiophen-2-yl)ethan-1-one (I-47)** To a solution of compound **I-47-3** (721 mg, 2.46 mmol) in THF (7 mL) and H₂O (3 mL) was added NBS (219 mg, 1.23 mmol,) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction was extracted with EtOAc (10 mL*2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-47** (670 mg, crude) as a brown oil.

[0433] Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-2-methylmorpholine-4-carboxylate (I-48):



[0434] **Synthesis of ethyl 2-hydroxy-2-(thiophen-2-yl)propanoate (I-48-1)** To a solution of ethyl 2-oxo-2-(2-thienyl)acetate (50 g, 271 mmol) in THF (500 mL) was added MeMgBr (3 M, 109 mL) at -78 °C under N₂ atmosphere. The mixture was stirred at -78 °C for 3 h. The reaction mixture was quenched by addition Saturated ammonium chloride solution 1000 mL at 0 °C, and then diluted with H₂O 1000 mL and extracted with EtOAc 3000 mL (1500 mL * 3), dried over MgSO₄, filtered and concentrated under reduced pressure to give **I-48-1** (60 g, crude) was obtained as a yellow oil.

[0435] **Synthesis of ethyl 2-(5-bromothiophen-2-yl)-2-hydroxypropanoate (I-48-2)** To a solution of **I-48-1** (54.4 g, 271 mmol) in DMF (500 mL) was added NBS (72.5 g, 407 mmol). The mixture was stirred at 25 °C for 6 hrs. The reaction mixture was partitioned between EtOAc 800 mL and H₂O 600 mL. The organic phase was separated, washed with brine 800 mL (400 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~4% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound **I-48-2** (67 g, 88.4% yield) was obtained as a red oil.

[0436] **Synthesis of 2-(5-bromothiophen-2-yl)-2-hydroxypropanoic acid (I-48-3)** To a solution of **I-48-2** (40 g, 143 mmol) in THF (200 mL) and EtOH (200 mL) at 0 °C. and then KOH (16.1 g, 287 mmol) in H₂O (200 mL) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove organic solvent. The combined water layers were washed with DCM 300 mL, The reaction mixture was poured into 1N HCl solution (pH<7), The reaction mixture was partitioned between DCM 600 mL and H₂O 500 mL. The organic phase was separated, washed with brine 600 mL (300 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash

silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/Petroleum ether gradient @ 90 mL/min) to give Compound **I-48-3** (35 g, 97.3% yield) as a brown solid.

[0437] **Synthesis of 2-(5-bromothiophen-2-yl)-N-(2-chloroethyl)-2-hydroxypropanamide (I-48-4)** To a solution of **I-48-3** (0.5 g, 1.99 mmol) in DMF (50 mL) was added 2-chloroethan-1-amine (346 mg, 2.99 mmol), HATU (1.14 g, 2.99 mmol), DIEA (772.1 mg, 5.97 mmol). The mixture was stirred at 25 °C for 12 h. The reaction mixture was partitioned between EtOAc 60 mL and H₂O 60 mL. The organic phase was separated, washed with brine 80 mL (40 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound **I-48-4** (460 mg, 73.9% yield) was obtained as a white oil.

[0438] **Synthesis of 2-(5-bromothiophen-2-yl)-2-methylmorpholin-3-one (I-48-5)** To a solution of **I-48-4** (81.3 mg, 0.26 mmol) in DMF (10 mL) was added t-BuOK (29.2 mg, 0.26 mmol) under N₂. The mixture was stirred at 25 °C for 1 h. The reaction mixture was extracted with EtOAc 15 mL (5 mL*3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give compound **I-48-5** (32 mg, 0.16 mmol, 44.5 % yield) as a yellow oil.

[0439] **Synthesis of 2-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-methylmorpholin-3-one (I-48-6)** To a solution of **I-48-5** (2 g, 7.24 mmol) in dioxane (100 mL) was added tributyl(1-ethoxyvinyl)stannane (5.23 g, 14.48 mmol, 4.89 mL), TEA (2.20 g, 21.73 mmol, 3.02 mL) and Pd(PPh₃)₂Cl₂ (508.34 mg, 724.24 μmol) under N₂. The mixture was stirred at 80 °C for 16 h. The reaction mixture was quenched with saturated KF solution (50 mL), extracted with EtOAc 150 mL (50 mL*3). The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **I-48-6** (6.0 g, crude) as a black oil.

[0440] **Synthesis of 2-(5-(2-bromoacetyl)thiophen-2-yl)-2-methylmorpholin-3-one (I-48-7)** To a solution of **I-48-6** (1 g, 3.95 mmol) in THF (10 mL) and H₂O (4 mL) was

added NBS (702.61 mg, 3.95 mmol). The mixture was stirred at 0 °C for 2 h. LCMS showed the desired product was formed and the starting material was consumed completely. The reaction mixture was quenched with H₂O (10 mL), extracted with EtOAc 15 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 SepaFlash® Silica Flash Column, Eluent of 0~40 % EtOAc/Petroleum ether gradient @ 80 mL/min) to give compound **I-48-7** (1.4 g, crude) as a yellow oil.

[0441] **Synthesis of 2-(5-bromothiophen-2-yl)-2-methylmorpholine (I-48-8)** To a solution of compound **I-48-7** (700 mg, 2.53 mmol) in THF (7 mL) was added BH₃.THF (1.00 M, 5.07 mL) at -70 °C under N₂. The mixture was stirred at 25 °C for 16 h. The reaction mixture was quenched by 2N HCl (7 mL) and stirred at 25 °C for 20 min. The mixture was adjusted pH=11 with 4N NaOH and extracted with DCM (15 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **I-48-8** (887 mg, crude) as a yellow oil.

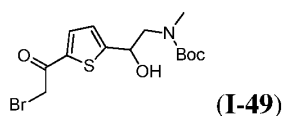
[0442] **Synthesis of tert-butyl 2-(5-bromothiophen-2-yl)-2-methylmorpholine-4-carboxylate (I-48-9)** To a solution of compound **I-48-8** (867 mg, 3.31 mmol) in THF (9 mL) and H₂O (4.5 mL) was added Boc₂O (1.44 g, 6.61 mmol, 1.52 mL) and K₂CO₃ (914 mg, 6.61 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was added water (10 mL) and extracted with EtOAc (10 mL* 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 4/1) to give compound **I-48-9** (897 mg, 2.43 mmol, 73.5% yield, 98.1% purity) as a yellow oil.

[0443] **Synthesis of tert-butyl 2-(5-acetylthiophen-2-yl)-2-methylmorpholine-4-carboxylate (I-48-10)** To a solution of compound **I-48-9** (897 g, 2.43 mmol) and tributyl(1-ethoxyvinyl)stannane (2.13 g, 5.90 mmol, 1.99 mL) in dioxane (10.0 mL) was added TEA (564 mg, 5.58 mmol, 776 µL) and Pd(PPh₃)₂Cl₂ (196 mg, 279 µmol,) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction was quenched by aq. KF (20 mL) and extracted with EtOAc (20 mL* 2). The combined organic layer was dried over

Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 100/1 to 5/1) to give compound **I-48-10** (578 mg, 1.64 mmol, 58.9% yield, 92.4% purity) as a yellow oil.

- [0444] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-2-methylmorpholine-4-carboxylate (I-48)** To a solution of compound **I-48-10** (478 mg, 1.47 mmol) in DCM (3.00 mL) and MeOH (7.50 mL) was added TBATB (744 mg, 1.54 mmol). The mixture was stirred at 25 °C for 2 h. The reaction was added water (5 mL) and extracted with DCM (10 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-48** (689 mg, crude) as a brown oil.

- 10 [0445] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)-2-hydroxyethyl)(methyl)carbamate (I-49):**

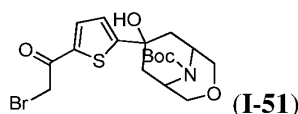


- [0446] **Synthesis of tert-butyl (2-(5-bromothiophen-2-yl)-2-hydroxyethyl)(methyl)carbamate (I-49-1)** To a solution of 2,5-dibromothiophene (15 g, 62.0 mmol) in THF (150 mL) was added dropwise n-BuLi (2.5 M, 27.3 mL) at -78 °C. After addition, the mixture was stirred at this temperature for 0.5 h, and then tert-butyl N-methyl-N-(2-oxoethyl)carbamate (12.9 g, 74.4 mmol) in THF (60 mL) was added dropwise at -78 °C. The resulting mixture was stirred at 25 °C for 2.5 h. The reaction mixture was quenched by addition saturated NH₄Cl aqueous solution 500 mL at 0 °C, and then diluted with H₂O 1000 mL and extracted with EtOAc 2000 mL (1000 mL * 2). The combined organic layers were washed with brine 1000 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 70 mL/min) to give Compound **I-49-1** (16.2 g, 77.8% yield) as a yellow solid.

[0447] **Synthesis of tert-butyl (2-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-hydroxyethyl)(methyl)carbamate (I-49-2)** A mixture of **I-49-1** (12 g, 35.7 mmol), tributyl(1-ethoxyvinyl)stannane (26.0 g, 72.0 mmol), TEA (10.8 g, 107 mmol) and Pd(PPh₃)₂Cl₂ (2.50 g, 3.57 mmol) in dioxane (150 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 500 mL at 25 °C, and then diluted with H₂O 600 mL and extracted with EtOAc 800 mL (400 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-49-2** (25 g, crude) was obtained as a black oil.

[0448] **Synthesis of tert-butyl (2-(5-(2-bromoacetyl)thiophen-2-yl)-2-hydroxyethyl)(methyl)carbamate (I-49)** To a solution of **I-49-2** (14 g, 42.8 mmol) in THF (150 mL) and H₂O (70 mL) was added NBS (7.61 g, 42.8 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was partitioned between EtOAc 800 mL and H₂O 600 mL. The organic phase was separated, washed with brine 1200 mL (600 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-49** (8.1 g, 35.0% yield, 69.8% purity) as a brown oil.

[0449] **Synthesis of tert-butyl 7-(5-(2-bromoacetyl)thiophen-2-yl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I-51):**



[0450] **Synthesis of tert-butyl 7-hydroxy-7-(thiophen-2-yl)-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I-51-1)** To a solution of tert-butyl 7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (4.67 g, 19.4 mmol) and in THF (100 mL) was added dropwise CeCl₃ (14.3 g, 58.1 mmol) at 25 °C. After addition, the mixture was stirred at this temperature for 1 h, and then bromo(2-thienyl)magnesium (1 M, 58.0 mL)

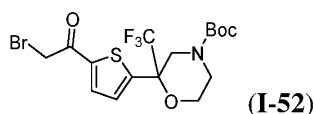
was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. TLC indicated Reactant 1 was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was quenched by addition 20% aqueous AcOH solution 100 mL at 0 °C, and then diluted with H₂O 200 mL and extracted with EtOAc 600 mL (300 mL * 2). The combined organic layers were washed with saturated NaHCO₃ aqueous solution 300 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-51-1** (5.7 g, 90.5% yield) as a white solid.

[0451] **Synthesis of tert-butyl 7-(5-bromothiophen-2-yl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I-51-2)** To a solution of **I-51-1** (5.7 g, 17.5 mmol) in DMF (50 mL) was added NBS (3.74 g, 21.0 mmol). The mixture was stirred at 0 °C for 1h. TLC indicated **I-51-1** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between EtOAc 200 mL and H₂O 200 mL. The organic phase was separated, washed with brine 200 mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~6% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-51-2** (6.4 g, 90.4% yield) was obtained as a white solid.

[0452] **Synthesis of tert-butyl 7-(5-(1-ethoxyvinyl)thiophen-2-yl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I-51-3)** A mixture of **I-51-2** (6 g, 14.8 mmol), tributyl(1-ethoxyvinyl)stannane (10.7 g, 29.7 mmol), TEA (4.50 g, 44.5 mmol) and Pd(PPh₃)₂Cl₂ (1.04 g, 1.48 mmol) in dioxane (100 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 3h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 500 mL at 25 °C, and then diluted with H₂O 300 mL and extracted with EtOAc 600 mL (300 mL * 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give Compound **I-51-3** (10 g, crude) as a black oil.

[0453] **Synthesis of tert-butyl 7-(5-(2-bromoacetyl)thiophen-2-yl)-7-hydroxy-3-oxa-9-azabicyclo[3.3.1]nonane-9-carboxylate (I-51)** To a solution of **I-51-3** (5.87 g, 14.8 mmol) in THF (50 mL) and H₂O (25 mL) was added NBS (3.96 g, 22.3 mmol). The mixture was stirred at 0 °C for 1 h. TLC indicated **I-51-3** was consumed completely and one new spot formed. The reaction was clean according to TLC. The reaction mixture was partitioned between EtOAc 80 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~25% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to give Compound **I-51** (3.92 g, 59.2% yield) as a white solid.

[0454] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-2-(trifluoromethyl)morpholine-4-carboxylate (I-52):**



[0455] **Synthesis of 1,1,1-trifluoro-3-nitro-2-(thiophen-2-yl)propan-2-ol (I-52-1)** To a solution of 2,2,2-trifluoro-1-(2-thienyl)ethanone (10 g, 55.5 mmol) in nitromethane (184 g, 3.01 mol) was added TEA (8.43 g, 83.3 mmol). The mixture was stirred at 35 °C for 16 h. After the reaction was completed, water (500 mL) was added, successively with 1 N HCl to adjust pH to 5-6. The organic phase was separated and the aqueous phase was extracted with EtOAc (300 mL * 2). The combined organic phase was washed with water (200 mL) then dried (Na₂SO₄), filtered and concentrated under reduced pressure to give Compound **I-52-1** (13 g, 97.1% yield) as a yellow solid.

[0456] **Synthesis of 3-amino-1,1,1-trifluoro-2-(thiophen-2-yl)propan-2-ol (I-52-2)** To a solution of **I-52-1** (12 g, 49.8 mmol) in EtOH (200 mL) was added PtO₂ (1.13 g, 4.98 mmol) under N₂ atmosphere. The suspension was degassed and purged with H₂ for 2 times. The mixture was stirred under H₂ (50 Psi) at 25 °C for 18 h. The mixture was filtered through a pad of celite and washed with MeOH (500 mL). The filtrate was concentrated under reduced pressure to give a residue. The residue was purified by flash

silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~50% THF/Petroleum ether gradient @ 70 mL/min) to give Compound **I-52-2** (7.8 g, 74.2% yield) was obtained as a white solid.

[0457] **Synthesis of 2-chloro-N-(3,3,3-trifluoro-2-hydroxy-2-(thiophen-2-yl)propyl)acetamide (I-52-3)** To a solution of **I-52-2** (7.2 g, 34.1 mmol) in DCM (30 mL) was added TEA (4.48 g, 44.3 mmol) and 2-chloroacetyl chloride (4.62 g, 40.9 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was partitioned between DCM 30 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% THF/Petroleum ether gradient @ 60 mL/min) to give Compound **I-52-3** (9.7 g, 33.7 mmol, 98.9% yield) as a colourless oil.

[0458] **Synthesis of 6-(thiophen-2-yl)-6-(trifluoromethyl)morpholin-3-one (I-52-4)** A solution of **I-52-3** (8.7 g, 30.2 mmol) in THF (100 mL) was degassed and purged with N₂ for 3 times at 0 °C. and then NaH (2.42 g, 60.5 mmol, 60% purity) was added dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition Saturated ammonium chloride solution 100 mL at 0 °C, and then diluted with H₂O 100 mL and extracted with EtOAc 600 mL (200 mL * 3), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~20% Ethyl acetate/Petroleum ether gradient @ 70 mL/min) to give Compound **I-52-4** (6 g, 60.8% yield, 77% purity) as a colorless oil.

[0459] **Synthesis of 2-(thiophen-2-yl)-2-(trifluoromethyl)morpholine (I-52-5)** To a solution of **I-52-4** (5.5 g, 21.9 mmol, 1 eq) in THF (50 mL) was degassed and purged with N₂ for 3 times at 0 °C. and then LiAlH₄ (2.08 g, 54.7 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 70 °C for 3 h. The reaction mixture was quenched by addition Na₂SO₄ 10 H₂O (10 g) at 0 °C, the reaction liquid is filtered directly and the filtrate was concentrated. Compound **I-52-5** (6 g, crude) was obtained as a colourless oil.

[0460] **Synthesis of tert-butyl 2-(thiophen-2-yl)-2-(trifluoromethyl)morpholine-4-carboxylate (I-52-6)** To a solution of **I-52-5** (5.19 g, 21.9 mmol) in MeOH (200 mL) was added TEA (3.32 g, 32.8 mmol) and Boc₂O (7.16 g, 32.8 mmol). The mixture was stirred at 25 °C for 16h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 5 80 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 60 mL/min) to give Compound **I-52-6** (6.3 g 85.4% yield) as a colourless oil.

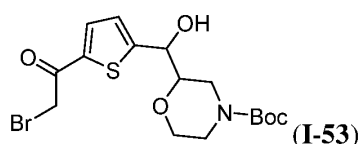
[0461] **Synthesis of tert-butyl 2-(5-bromothiophen-2-yl)-2-(trifluoromethyl)morpholine-4-carboxylate (I-52-7)** To a solution of **I-52-6** (5.2 g, 10 15.4 mmol) in DMF (50 mL) was added NBS (3.29 g, 18.5 mmol). The mixture was stirred at 70 °C for 2 h. The reaction mixture was partitioned between EtOAc 200 mL and H₂O 300 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g 15 SepaFlash® Silica Flash Column, Eluent of 0~15% THF/Petroleum ether gradient @ 60 mL/min) to give Compound **I-52-7** (6.3 g, 98.2% yield) was obtained as a yellow oil.

[0462] **Synthesis of tert-butyl 2-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-(trifluoromethyl)morpholine-4-carboxylate (I-52-8)** A mixture of **I-52-7** (6.3 g, 15.1 mmol), tributyl(1-ethoxyvinyl)stannane (11.5 g, 31.7 mmol), TEA (4.59 g, 45.4 mmol) 20 and Pd(PPh₃)₂Cl₂ (1.06 g, 1.51 mmol) in dioxane (60 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 6 h under N₂ atmosphere. The reaction mixture was quenched by addition saturated KF aqueous solution 500 mL at 25 °C, and then diluted with H₂O 300 mL and extracted with EtOAc 200 mL (100 mL * 2). dried over MgSO₄, filtered and concentrated under reduced pressure to give 25 Compound **I-52-8** (12 g, crude) was obtained as a black oil.

[0463] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-2-(trifluoromethyl)morpholine-4-carboxylate (I-52)** To a solution of **I-52-8** (6 g, 14.7 mmol, 1 eq) in THF (60 mL) and H₂O (30 mL) was added NBS (5.24 g, 29.5 mmol), The mixture was stirred at 0 °C for 1 h. TLC indicated **I-52-8** was consumed completely and 30 one new spot formed. The reaction was clean according to TLC. The reaction mixture

was partitioned between EtOAc 80 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 80 g SepaFlash® Silica Flash Column, Eluent of 0~12% Ethyl acetate/Petroleum ether gradient @ 60 mL/min) to Compound **I-52** (3.1 g, 45.9% yield) as a yellow solid.

[0464] **Synthesis of tert-butyl 2-((5-(2-bromoacetyl)thiophen-2-yl)(hydroxy)methyl)morpholine-4-carboxylate (I-53):**



[0465] **Synthesis of tert-butyl 2-formylmorpholine-4-carboxylate (I-53-1)** A solution of (COCl)₂ (29.2 g, 230 mmol, 20.1 mL) in DCM (250 mL) was treated with DMSO (27.0 g, 345 mmol, 27.0 mL) for 0.5 h at -78 °C under nitrogen atmosphere followed by the addition of tert-butyl 2-(hydroxymethyl)morpholine-4-carboxylate (25.0 g, 115 mmol) in DCM (250 mL) dropwise at -78 °C. The resulting mixture was stirred for 1 h at -78 °C, and then TEA (34.9 g, 345 mmol, 48.1 mL) was added dropwise at -78 °C. The reaction was maintained at -78 °C for 1 h and then warmed to 25°C for 24 h. The residue was diluted with H₂O 500 mL and extracted with DCM 1500 mL (500mL *3). The combined organic layers were washed with brine 2000 mL (1000 mL *2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-53-1** (24.0 g, 105 mmol, 91.6% yield, 94.5% purity) was obtained as a yellow oil.

[0466] **Synthesis of tert-butyl 2-(hydroxy(thiophen-2-yl)methyl)morpholine-4-carboxylate (I-53-2)** To a solution of 2-bromothiophene (7.35 g, 45.1 mmol) in THF (100 mL) was added dropwise n-BuLi (2.5 M, 19.8 mL, 1.1 eq) at -78 °C for 10 min. After addition, the mixture was stirred at this temperature for 30min, and then **I-53-1** (4.50 g, 20.9 mmol) in THF (100 mL) was added dropwise at -78 °C. The resulting mixture was stirred at 25 °C for 24 h. The residue was diluted with H₂O 100 mL and extracted with EtOAc 200 mL (100 mL *2). The combined organic layers were washed with brine 200

mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=3/1). Compound **I-53-2** (3.00 g, 6.92 mmol, 15.4% yield, 69.1% purity) was obtained as a red oil.

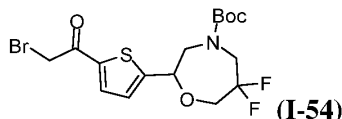
- 5 [0467] **Synthesis of tert-butyl 2-((5-bromothiophen-2-yl)(hydroxy)methyl)morpholine-4-carboxylate (I-53-3)** To a solution of **I-53-2** (2.86 g, 9.55 mmol) in DMF (30 mL) was added NBS (1.87 g, 10.5 mmol). The mixture was stirred at 0 °C for 3 h. The residue was diluted with H₂O 200 mL and extracted with EtOAc 400 mL (200 mL *2). The combined organic layers were washed with brine 400 mL (200 mL*2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1). Compound **I-53-3** (2.60 g, 4.81 mmol, 50.3% yield, 69.9% purity) was obtained as a red oil.

- 15 [0468] **Synthesis of tert-butyl 2-((5-(1-ethoxyvinyl)thiophen-2-yl)(hydroxy)methyl)morpholine-4-carboxylate (I-53-4)** To a solution of **I-53-3** (2.40 g, 6.34 mmol) and tributyl(1-ethoxyvinyl)stannane (4.58 g, 12.7 mmol) in dioxane (80 mL) was added TEA (1.93 g, 19.0 mmol) and Pd(PPh₃)₂Cl₂ (445 mg, 634 μmol) under N₂. The mixture was stirred at 80 °C for 2 h. The reaction was quenched with H₂O (100 mL) and stirred at 25 °C for 1 h. The reaction mixture was extracted with EtOAc 200 mL. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-53-4** (4.00 g, 5.97 mmol, 94.1% yield, 55.1% purity) was obtained as a black oil.

- 25 [0469] **Synthesis of tert-butyl 2-((5-(2-bromoacetyl)thiophen-2-yl)(hydroxy)methyl)morpholine-4-carboxylate (I-53)** To a solution of **I-53-4** (2.34 g, 6.33 mmol) in THF (70 mL) and H₂O (35 mL) was added NBS (1.13 g, 6.33 mmol). The mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched by addition sat. NH₄Cl solution 10 mL at 25 °C, and then diluted with H₂O 100 mL and extracted with EtOAc 200 mL (100 mL * 2). The combined organic layers were washed with brine 200 mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-53** (7.00 g, 3.27 mmol, 51.6% yield, 19.6% purity) was
- 30

obtained as a white solid.

[0470] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-6,6-difluoro-1,4-oxazepane-4-carboxylate (I-54):**



- 5 [0471] **Synthesis of 3-(benzylamino)-2,2-difluoropropan-1-ol (I-54-1)** To a solution of 3-amino-2,2-difluoropropan-1-ol (5.00 g, 45.0 mmol) in DCM (50 mL) was added benzaldehyde (4.78 g, 45.0 mmol, 4.55 mL) and AcOH (270 mg, 4.50 mmol) at 25 °C. After addition, the mixture was stirred at 25 °C for 0.5 hr, and then NaBH(OAc)₃ (28.6 g, 135 mmol) was added at 25 °C. The resulting mixture was stirred at 25 °C for 2 h.
- 10 the reaction mixture was quenched by addition H₂O 100 mL at 0 °C, extracted with DCM 400 mL (200 mL * 2). The aqueous layers adjust the pH to 7 with NaHCO₃, and extracted with DCM 500 mL (250 mL * 2). The organic layers were washed with brine 1000 mL (500 mL*2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-54-1** (3.80 g, 16.1 mmol, 35.7% yield, 85% purity) was obtained
- 15 as a white solid.

- [0472] **Synthesis of 2-(benzyl(2,2-difluoro-3-hydroxypropyl)amino)-1-(5-bromothiophen-2-yl)ethan-1-one (I-54-2)** To a solution of **I-54-1** (3.80 g, 18.9 mmol) in THF (100 mL) was added DIEA (4.88 g, 37.8 mmol, 6.58 mL) and 2-bromo-1-(5-bromothiophen-2-yl)ethan-1-one (5.36 g, 18.9 mmol). The mixture was stirred at 70 °C
- 20 for 3 h. The residue was diluted with H₂O 100 mL and extracted with EtOAc 400 mL (200 mL * 2). The combined organic layers were washed with brine 500 mL (250 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=5/1). Compound **I-54-2** (5.50 g, 11.5 mmol, 60.9% yield, 84.6% purity) was obtained as a
- 25 white solid.

[0473] **Synthesis of 3-(benzyl(2-(5-bromothiophen-2-yl)-2-hydroxyethyl)amino)-2,2-difluoropropan-1-ol (I-54-3)** To a solution of **I-54-2** (5.22 g, 12.9 mmol) in THF (50

mL) was added NaBH₄ (735 mg, 19.4 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition NH₄Cl 50 mL at 0 °C, and then diluted with H₂O 50 mL and extracted with EtOAc 150 mL (50 mL * 3). The combined organic layers were washed with brine 200 mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-54-3** (5 g, 9.99 mmol, 77.4% yield, 81.2% purity) was obtained as a yellow oil.

[0474] **Synthesis of 4-benzyl-2-(5-bromothiophen-2-yl)-6,6-difluoro-1,4-oxazepane (I-54-4)** A mixture of **I-54-3** (5.00 g, 12.3 mmol) in HCl (50 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 8 h under N₂ atmosphere. The residue was diluted with H₂O 100 mL and extracted with EtOAc 200 mL (100 mL * 2). The combined organic layers were washed with brine 200 mL (100 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=10/1). Compound **I-54-4** (2.20 g, 5.67 mmol, 46.0% yield, 100% purity) was obtained as a white solid.

[0475] **Synthesis of 2-(5-bromothiophen-2-yl)-6,6-difluoro-1,4-oxazepane (I-54-5)** To a solution of **I-54-4** (2.20 g, 5.67 mmol) in DCE (20 mL) was added 1-chloroethyl carbonochloridate (4.05 g, 28.3 mmol) at 0 °C. The mixture was stirred at 80 °C for 18 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was added MeOH (20 mL) and stirred at 80 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove MeOH. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=1/1). Compound **I-54-5** (1.38 g, 4.11 mmol, 72.6% yield, 88.9% purity) was obtained as a black oil.

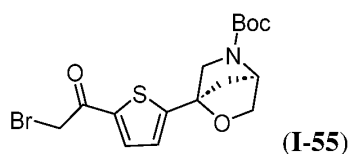
[0476] **Synthesis of tert-butyl 2-(5-bromothiophen-2-yl)-6,6-difluoro-1,4-oxazepane-4-carboxylate (I-54-6)** To a solution of **I-54-5** (625 mg, 2.10 mmol) in DCM (10 mL) was added Boc₂O (915 mg, 4.19 mmol, 963 µL) and TEA (636 mg, 6.29 mmol, 875 µL). The mixture was stirred at 25 °C for 8 h. The residue was diluted with H₂O 10 mL and extracted with DCM 40 mL (20 mL * 2). The combined organic layers were washed with brine 50 mL (25 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography

(SiO₂, Petroleum ether/Ethyl acetate=10/1). Compound **I-54-6** (550 mg, 1.33 mmol, 63.5% yield, 96.4% purity) was obtained as a white solid.

[0477] **Synthesis of tert-butyl 2-(5-(1-ethoxyvinyl)thiophen-2-yl)-6,6-difluoro-1,4-oxazepane-4-carboxylate (I-54-7)** To a solution of **I-54-6** (550 mg, 1.41 mmol) and tributyl(1-ethoxyvinyl)stannane (762 mg, 2.11 mmol, 713 μ L) in dioxane (20 mL) was added TEA (427 mg, 4.22 mmol) and Pd(PPh₃)₂Cl₂ (98.7 mg, 141 μ mol) under N₂. The mixture was stirred at 80 °C for 2 h. The reaction was quenched with H₂O (100 mL) and stirred at 25 °C for 1 h. The reaction mixture was extracted with EtOAc 200 mL. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **I-54-7** (1.50 g, 1.32 mmol, 94.2% yield, 34.4% purity) was obtained as a black oil.

[0478] **Synthesis of tert-butyl 2-(5-(2-bromoacetyl)thiophen-2-yl)-6,6-difluoro-1,4-oxazepane-4-carboxylate (I-54)** To a solution of **I-54-7** (1.62 g, 1.43 mmol) in THF (2.5 mL) was added NBS (280 mg, 1.57 mmol) and H₂O (2.50 mL). The mixture was stirred at 0 °C for 2 h. The reaction was quenched with H₂O (100 mL), extracted with EtOAc 200 mL. The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=10/1). Compound **I-54** (400 mg, 723 μ mol, 50.6% yield, 79.6% purity) was obtained as a yellow oil.

[0479] **Synthesis of tert-butyl (1R,4R)-1-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-55):**



[0480] **Synthesis of (2R,4R)-1-(tert-butoxycarbonyl)-4-hydroxy-4-(thiophen-2-yl)pyrrolidine-2-carboxylic acid (I-55-1)** To a solution of (R)-1-(tert-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid (10 g, 43.62 mmol) in THF (200 mL) was added thiophen-2-ylmagnesium bromide (1 M, 52.35 mL) dropwise at -70 °C under N₂. The

mixture was stirred at 25 °C for 2 h under N₂. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (50 mL) dropwise at 0 °C under N₂ and extracted with EtOAc (250 mL *2). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 2/1) to give **I-55-1** (9.5 g, 30.32 mmol, 69.49% yield) as a white solid.

[0481] **Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-(hydroxymethyl)-4-(thiophen-2-yl)pyrrolidine-1-carboxylate (I-55-2)** To a solution of **I-55-1** (5 g, 15.96 mmol) in THF (10.0 mL) was added BH₃.THF (1 M, 15.96 mL). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by addition of MeOH (20 mL) and extracted with EtOAc (200 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated in vacuum to give **I-55-2** (3 g, 10.02 mmol, 62.80% yield) as white oil

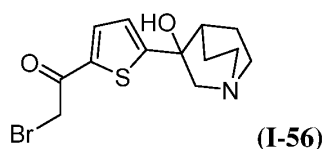
[0482] **Synthesis of tert-butyl (1R,4R)-1-(thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-55-3)** To a solution of compound **I-55-2** (3.0 g, 1.00 mmol) in toluene (30 mL) added 2-(tributyl-phosphanylidene)acetonitrile (4.8 g, 20.04 mmol) at 25 °C. The mixture was stirred at 100 °C for 1 h. The reaction mixture was diluted with H₂O (50 mL) and extracted with DCM (50 mL* 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 5/1) to give compound **I-55-3** (2.5 g, 8.89 mmol, 95.00% yield) as a yellow oil.

[0483] **Synthesis of tert-butyl (1R,4R)-1-(5-bromothiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-55-4)** To a solution of compound **I-55-3** (2.5 g, 8.89 mmol) in DMF (30 mL) was added NBS (2.06 g, 11.55 mmol) and the mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by H₂O (70 mL) and extracted with EtOAc (100 mL* 3). The combined organic layers were washed with H₂O (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **I-55-4** (2.8 g, 7.77 mmol, 87.47% yield) as a light yellow solid.

[0484] **Synthesis of tert-butyl (1R,4R)-1-(5-(1-ethoxyvinyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-55-5)** To a solution of compound **I-55-4** (2.8 g, 7.77 mmol) in dioxane (30.0 mL) was added tributyl(1-ethoxyvinyl)stannane (5.61 g, 15.54 mmol, 5.25 mL), TEA (2.36 g, 23.32 mmol, 3.25 mL) and Pd(PPh₃)₂Cl₂ (818.27 mg, 1.17 mmol) under N₂. The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by H₂O (20 mL) and was extracted with EtOAc (30 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **I-55-5** (4.4 g, crude) as a brown oil.

Synthesis of tert-butyl (1R,4R)-1-(5-(2-bromoacetyl)thiophen-2-yl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-55) To a solution of compound **I-55-5** (2.73 g, 7.77 mmol) in THF (30 mL) and H₂O (10 mL) was added NBS (2.77 g, 15.54 mmol). The mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched by H₂O (20 mL) and was extracted with EtOAc (30 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 50/1 to 4/1) to give compound **I-55** (3.1 g, crude) as a yellow oil.

[0485] **Synthesis of 2-bromo-1-[5-(3-hydroxyquinuclidin-3-yl)-2-thienyl]ethanone (I-56):**



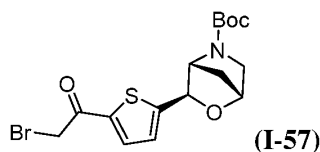
[0486] **Synthesis of 3-(2-thienyl)quinuclidin-3-ol (I-56-1):** To a solution of 2,5-dibromothiophene (9.73 g, 40.2 mmol, 4.53 mL) in THF (100 mL) was added n-BuLi (2.5 M, 13.6 mL) at -60 °C dropwise and the mixture was stirred at -60 °C for 1 h. a solution of quinuclidin-3-one (5.00 g, 30.9 mmol, 1 eq, HCl) in THF (50 mL) was added dropwise at -60 °C. The mixture was stirred at 25 °C for 2 h. The residue was poured into sat. NH₄Cl (150 mL) and extracted with EtOAc (300 mL). The combined organic layers were washed with brine (100 mL), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give the residue. The residue was purified by flash silica gel

chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~100% Ethyl acetate/Petroleum ether gradient) to give **I-56-1** (1.8 g, 8.60 mmol, 27.80% yield) as light pink solid.

[0487] **Synthesis of 3-[5-(1-ethoxyvinyl)-2-thienyl]quinuclidin-3-ol (I-56-2):** A mixture of tributyl(1-ethoxyvinyl)stannane (2.00 g, 5.55 mmol), **I-56-1** (0.8 g, 2.78 mmol), TEA (843 mg, 8.33 mmol, 1.16 mL) and Pd(PPh₃)₂Cl₂ (195 mg, 278 μmol) in dioxane (10 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by CsF addition 10 mL, and extracted with EtOAc 50 mL. The combined organic layers were washed with brine 20 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product **I-56-2** (0.8 g, crude) was obtained as orange oil.

[0488] **Synthesis of 2-bromo-1-[5-(3-hydroxyquinuclidin-3-yl)-2-thienyl]ethanone (I-56):** To a solution of **I-56-2** (0.5 g, 1.99 mmol) in THF (5 mL) and H₂O (1 mL) was added NBS (637 mg, 3.58 mmol). The mixture was stirred at 80 °C for 3 h. The reaction mixture was quenched by H₂O (20 mL) and was extracted with EtOAc (30 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give the crude product **I-56** (0.4 g, crude) as brown oil.

[0489] **Synthesis of tert-butyl (1R,3R,4R)-3-[5-(2-bromoacetyl)-2-thienyl]-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-57):**



[0490] **Synthesis of tert-butyl (1R,4R)-3-oxo-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-57-1):** To a solution of (2R,4S)-1-tert-butoxycarbonyl-4-hydroxy-pyrrolidine-2-carboxylic acid (10 g, 43.24 mmol) in THF (100 mL) was added PPh₃ (17.0 g, 64.9 mmol) and DIAD (13.1 g, 64.9 mmol, 12.6 mL) at 0 °C under N₂ atmosphere. The mixture was stirred at 25 °C for 16 h under N₂ atmosphere. TLC (EA:PE is 2:1, UV

254 nm) indicated starting material was consumed completely. The mixture was diluted with H₂O 100 mL, then extracted with EtOAc 200 mL, the organic phase was combined and concentrated in vacuum to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~70% Ethyl acetate/Petroleum ether gradient) to give the compound **I-57-1** (7.8 g, 21.95 mmol, 50.75% yield, 60% purity) as colorless oil.

[0491] **Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-(thiophene-2-carbonyl)pyrrolidine-1-carboxylate (I-57-2):** To the solution of **I-57-1** (1.50 g, 7.03 mmol) in THF (20 mL) was added bromo(2-thienyl)magnesium (1 M, 8.44 mL) at -78 °C under N₂ atmosphere slowly, then the mixture was degassed and purged with N₂ for 3 times, and stirred at 25 °C for 16 h under N₂ atmosphere. The mixture was clear. TLC (UV 254 nm) indicated starting material was consumed completely and one new spot formed. The mixture was quenched with NH₄Cl.aq 30 mL, and then extracted with EtOAc 30 mL, the organic phase was combined and concentrated to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give the compound **I-57-2** (0.55 g, 1.85 mmol, 26.3% yield) as orange solid.

[0492] **Synthesis of tert-butyl (2R,4R)-4-hydroxy-2-[(R)-hydroxy(2-thienyl)methyl]pyrrolidine-1-carboxylate (I-57-3):** The solution of **I-57-2** (0.55 g, 1.85 mmol) in MeOH (10 mL) was cooled to 0 °C under N₂ atmosphere, and then NaBH₄ (280 mg, 7.40 mmol) was added at 0 °C slowly. The mixture was stirred at 25 °C for 2 h. The mixture was cooled to 0 °C and quenched with 1N HCl.aq slowly till the pH is 4~5. Then extracted with EtOAc 50 mL, the organic phase was combined and concentrated in vacuum to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give the compound **I-57-3** (0.54 g, 1.80 mmol, 97.5% yield) was obtained as a colorless oil.

[0493] **Synthesis of tert-butyl (1R,3R,4R)-3-(2-thienyl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-57-4):** A mixture of **I-57-3** (0.54 g, 1.80 mmol) and 2-(tributyl-phosphanylidene)acetonitrile (1.09 g, 4.51 mmol) in toluene (10

mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 100 °C for 16 h under N₂ atmosphere. The mixture was diluted with H₂O 100 mL, then extracted with EtOAc 200 mL, the organic phase was combined and concentrated in vacuum to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give the **I-57-4** (0.35 g, 1.24 mmol, 68.96% yield) as a colourless oil.

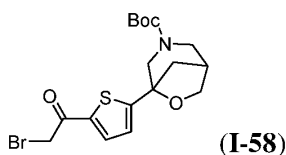
[0494] **Synthesis of tert-butyl (1R,3R,4R)-3-(5-bromo-2-thienyl)-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-57-5):** To a solution of **I-57-4** (0.22 g, 782 μmol) in DMF (5 mL) was added NBS (209 mg, 1.17 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The mixture was concentrated in vacuum to give the residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give the compound **I-57-5** (0.16 g, 444.12 μmol, 56.80% yield) as colourless oil.

[0495] **Synthesis of ethyl 2-[5-(2-bromoacetyl)-2-thienyl]-3,3,3-trifluoro-2-hydroxy-propanoate (I-57-6):** A mixture of **I-57-5** (0.16 g, 0.44 mmol), tributyl(1-ethoxyvinyl)stannane (0.54 g, 0.88 mmol, 0.5 mL), TEA (230 mg, 1.32 mmol) and Pd(PPh₃)₂Cl₂ (108 mg, 44.4 μmol) in dioxane (5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80 °C for 16 h under N₂ atmosphere. The reaction mixture was quenched by CsF addition 30 mL, and extracted with EtOAc 30 mL. The combined organic layers were washed with brine 30 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give the crude product **I-57-6** (0.5 g, crude) as black oil.

[0496] **Synthesis of tert-butyl (1R,3R,4R)-3-[5-(2-bromoacetyl)-2-thienyl]-2-oxa-5-azabicyclo[2.2.1]heptane-5-carboxylate (I-57):** The solution of **I-57-6** (0.56 g, 1.59 mmol) in THF (10 mL) and H₂O (5 mL) was added NBS (284 mg, 1.59 mmol). The mixture was stirred at 0 °C for 2 h. The mixture was diluted with H₂O 10 mL, and then extracted with EtOAc 10 mL. The organic phase was combined and concentrated in vacuum to give the residue. The residue was purified by flash silica gel chromatography

(ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient) to give compound **I-57** (0.075 g, 186 μ mol, 11.70% yield) as a yellow oil.

[0497] **Synthesis of tert-butyl 5-(5-(2-bromoacetyl)thiophen-2-yl)-6-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate (I-58):**



[0498] **Synthesis of 1-(tert-butyl) 3-methyl 5-oxopiperidine-1,3-dicarboxylate (I-58-1)** To a solution of (COCl)₂ (14.2 g, 112 mmol, 9.80 mL, 1.45 *eq*) in DCM (400 mL) was added DMSO (15.8 g, 202 mmol, 15.8 mL, 2.62 *eq*) at -78 °C under N₂. The mixture was stirred at -78 °C for 0.5 h. A solution of O1-tert-butyl O3-methyl 5-hydroxypiperidine-1,3-dicarboxylate (20.0 g, 77.1 mmol, 1.00 *eq*) in DCM (60.0 mL) was added to the above reaction solution at -78 °C under N₂. The mixture was stirred at -78 °C for 0.5 h under N₂. TEA (34.9 g, 344 mmol, 48.0 mL, 4.47 *eq*) was added to the above reaction solution at -78 °C under N₂. The mixture was stirred at 25 °C for 2 h. The mixture was diluted with DCM (400 mL), washed with aq. NaHCO₃ (500 mL) and brine (500 mL). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give **I-58-1** (19.9 g, crude) as a yellow oil.

[0499] **Synthesis of 1-(tert-butyl) 3-methyl 5-hydroxy-5-(thiophen-2-yl)piperidine-1,3-dicarboxylate (I-58-2)** To a solution of **I-58-1** (19.9 g, 77.4 mmol, 1.00 *eq*) in THF (250 mL) was added bromo(2-thienyl)magnesium (1.00 M, 106 mL, 1.37 *eq*) dropwise at -70 °C under N₂. The mixture was stirred at -70 °C for 2 h under N₂. The reaction was quenched by aq. NH₄Cl (300 mL) at 0 °C and extracted with EtOAc (300 mL x 2). The combined organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 100/1 to 4/1) to give compound **I-58-2** (7.25 g, 21.2 mmol, 27.5% yield) as a yellow oil.

[0500] **Synthesis of tert-butyl 3-hydroxy-5-(hydroxymethyl)-3-(thiophen-2-**

yl)piperidine-1-carboxylate (I-58-3) To a solution of compound **I-58-2** (7.05 g, 20.7 mmol, 1.00 *eq*) in THF (70.0 mL) was added LiAlH₄ (2.50 M, 24.8 mL, 3.00 *eq*) at 0 °C under N₂. The mixture was stirred at 25 °C for 1 h under N₂. The reaction was quenched by Na₂SO₄·10H₂O (12 g), filtered and concentrated in vacuum to give compound **I-58-3** (6.33 g, crude) as a yellow oil.

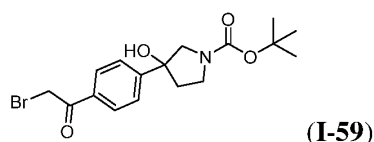
[0501] **Synthesis of tert-butyl 5-(thiophen-2-yl)-6-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate (I-58-4)** To a solution of compound **I-58-3** (6.33 g, 20.2 mmol, 1.00 *eq*) and PPh₃ (7.95 g, 30.3 mmol, 1.50 *eq*) in Tol. (65.0 mL) was added DIAD (7.00 g, 34.6 mmol, 6.71 mL, 1.71 *eq*) at 0 °C under N₂. The mixture was stirred at 25 °C for 16 h under N₂. The reaction mixture concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 50/1 to 4/1) to give compound **I-58-4** (5.42 g, 13.3 mmol, 65.6% yield, 72.2% purity) as a yellow oil.

[0502] **Synthesis of tert-butyl 5-(5-bromothiophen-2-yl)-6-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate (I-58-5)** To a solution of compound **I-58-4** (5.22 g, 17.7 mmol, 1.00 *eq*) in DMF (52.0 mL) was added NBS (3.46 g, 19.4 mmol, 1.10 *eq*) at 0 °C. The mixture was stirred at 0 °C for 4 h. The reaction mixture was quenched by H₂O (70.0 mL) and was extracted with EtOAc (70.0 mL x 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 50/1 to 6/1) to give compound **I-58-5** (2.33 g, 5.77 mmol, 32.7% yield, 92.7% purity) as a yellow oil.

[0503] **Synthesis of tert-butyl 5-(5-(1-ethoxyvinyl)thiophen-2-yl)-6-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate (I-58-6)** To a solution of compound **I-58-5** (2.32 g, 6.20 mmol, 1.00 *eq*) and tributyl(1-ethoxyvinyl)stannane (4.80 g, 13.3 mmol, 4.49 mL, 2.14 *eq*) in dioxane (23.0 mL) was added TEA (1.88 g, 18.6 mmol, 2.59 mL, 3.00 *eq*) and Pd(PPh₃)₂Cl₂ (435 mg, 620 µmol, 0.100 *eq*) under N₂. The mixture was stirred at 90 °C for 16 h. The reaction was quenched by aq. KF (30.0 mL) and extracted with EtOAc (50.0 mL x 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give compound **I-58-6** (6.37 g, crude) as a yellow oil.

[0504] **Synthesis of tert-butyl 5-(5-(2-bromoacetyl)thiophen-2-yl)-6-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate (I-58)** To a solution of compound **I-58-6** (6.00 g, 16.4 mmol, 1.00 *eq*) in THF (60.0 mL) and H₂O (30.0 mL) was added NBS (2.92 g, 16.4 mmol, 1.00 *eq*) at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by H₂O (70.0 mL) and was extracted with EtOAc (70.0 mL x 2). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/THF = 50/1 to 3/1) to give compound **I-58** (1.63 g, 3.09 mmol, 18.8% yield, 78.9% purity) as a yellow oil.

10 [0505] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)phenyl)-3-hydroxypyrrolidine-1-carboxylate (I-59):**



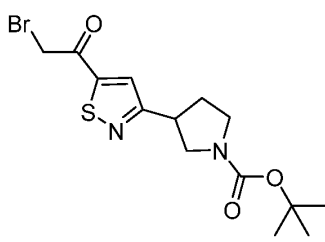
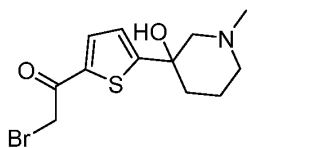
[0506] **Synthesis of tert-butyl 3-(4-bromophenyl)-3-hydroxypyrrolidine-1-carboxylate (I-59-1)** To a solution of 5-bromo-2-iodo-pyrimidine (9.50 g, 33.4 mmol,) in toluene (95 mL) was added n-BuLi (2.50 M, 14.7 mL) slowly at -78 °C under N₂ atmosphere. After 1 h, a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (6.79 g, 36.7 mmol) in toluene (50 mL) was added slowly. The mixture was stirred at -78 °C for 4 h. The reaction mixture was added H₂O 200 mL at 0°C. The reaction mixture was extracted with EtOAc 600 mL (300 mL * 2). The combined organic layers were washed with brine 200 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (SiO₂, Eluent of 0~50% Ethyl acetate/Petroleum ether gradient). Compound **I-59-1** (1.95 g, 4.53 mmol, 13.6% yield, 80% purity) was obtained as a yellow solid.

[0507] **Synthesis of tert-butyl 3-(4-(1-ethoxyvinyl)phenyl)-3-hydroxypyrrolidine-1-carboxylate (I-59-2)** To a solution of compound **I-59-1** (250 mg, 726 μmol) and tributyl(1-ethoxyvinyl)stannane (540 mg, 1.50 mmol, 505 μL) in dioxane (4.00 mL) was added Pd(PPh₃)₂Cl₂ (10.2 mg, 14.5 μmol) and TEA (147 mg, 1.45 mmol, 202 μL). The

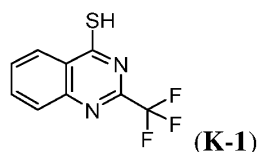
mixture was stirred at 90 °C for 16 h. The reaction mixture was added H₂O 10 mL at 0°C, extracted with EtOAc 30 mL (10 mL * 3). The combined organic layers were washed with brine 30 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by
 5 flash silica gel chromatography (SiO₂, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient). Compound **I-59-2** (180 mg, 494 µmol, 68.0 % yield, 92.0% purity) was obtained as a yellow oil.

[0508] **Synthesis of tert-butyl 3-(4-(2-bromoacetyl)phenyl)-3-hydroxypyrrolidine-1-carboxylate (I-59)** To a solution of compound **I-59-2** (1.15 g, 3.43 mmol) in THF (15
 10 mL) and H₂O (5 mL) was added NBS (610 mg, 3.43 mmol,). The mixture was stirred at 25 °C for 2h. The reaction mixture was added H₂O 10 mL at 0°C, extracted with EtOAc 30 mL (10 mL * 3). The combined organic layers were washed with brine 30 mL. The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography
 15 (SiO₂, Eluent of 0~30% Ethyl acetate/Petroleum ether gradient). Compound **I-59** (1.10 g, 2.85 mmol, 83.1 % yield) was obtained as a yellow solid.

[0509] Intermediates below were prepared using similar methods as described above, or via methods described in literature.

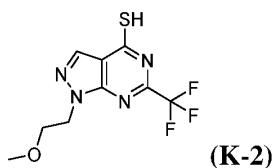
Cpd number	Structure	Name
	I-60	tert-butyl 3-(5-(2-bromoacetyl)isothiazol-3-yl)pyrrolidine-1-carboxylate
	I-61	2-bromo-1-(5-(3-hydroxy-1-methylpiperidin-3-yl)thiophen-2-yl)ethan-1-one

[0510] **Synthesis of 2-(trifluoromethyl)quinazoline-4-thiol (K-1):**



- [0511] **Synthesis of 2-(trifluoromethyl)quinazolin-4-ol (K-1-1)** To a solution of 2-aminobenzamide (50.0 g, 367 mmol) in EtOH (500 mL) was added NaH (103 g, 2.57 mol, 60.0% purity) and ethyl 2,2,2-trifluoroacetate (209 g, 1.47 mol, 202 mL) at 0 °C.
- 5 The reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched by addition of sat. NH₄Cl aq. (400 g in 1500 mL) at 0 °C and extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was triturated with MTBE/PE = 1/1 (200 mL) at 25 °C for 30 min to give compound **K-1-1** (112 g, crude) as a yellow solid.
- 10 [0512] **Synthesis of 2-(trifluoromethyl)quinazoline-4-thiol (K-1)** To the solution of compound **K-1-1** (112 g, 523 mmol) in toluene (784 mL) was added P₂S₅ (128 g, 575 mmol, 61.2 mL) under N₂ and the mixture was stirred at 120 °C for 12 h. The reaction mixture was concentrated in vacuum. The residue was triturated with H₂O (50.0 mL) at 25 °C for 30 min to give crude product. The crude product was triturated with EtOAc
- 15 (50.0 mL) at 25 °C for 30 min to give compound **K-1** (63.0 g, crude) as a light yellow solid.

[0513] **Synthesis of 1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-2):**



- 20 [0514] **Synthesis of 5-amino-1-(2-methoxyethyl)-1H-pyrazole-4-carbonitrile (K-2-1)** To a solution of 5-amino-1H-pyrazole-4-carbonitrile (16.0 g, 148 mmol) in DMF (140 mL) was added K₂CO₃ (40.9 g, 296 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Then 1-bromo-2-methoxyethane (24.7 g, 178 mmol, 16.7 mL) was added into the above solution. The mixture was stirred at 90 °C for 10 h. The reaction mixture
- 25 was quenched by addition of H₂O (200 mL) at 5 °C and extracted with EtOAc (100 mL

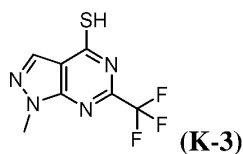
x 3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by reversed-phase HPLC (0.100% NH₃•H₂O) to give 3-amino-1-(2-methoxyethyl)-1H-pyrazole-4-carbonitrile (5.50 g, 22.3% yield) and 5-amino-1-(2-methoxyethyl)-1H-pyrazole-4-carbonitrile **K-2-1** (2.00 g, 8.13% yield, 98.0% purity) as a white solid.

[0515] **Synthesis of 5-amino-1-(2-methoxyethyl)-1H-pyrazole-4-carboxamide (K-2-2)** A solution of compound **K-2-1** (20.0 g, 120 mmol) was added H₂SO₄ (50.0 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with H₂O (30.0 mL) at 0 °C and adjusted to pH = 7~8 with NH₃•H₂O. The solid was collected by filtration to give compound **K-2-2** (12.0 g, 54.1% yield, 98.5% purity) was obtained as a white solid.

[0516] **Synthesis of 1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (K-2-3)** To a solution of NaH (16.3 g, 407 mmol, 60.0% purity) in EtOH (107 mL) was added compound **K-2-2** (10.7 g, 58.1 mmol) and CF₃COOEt (33.0 g, 232 mmol, 31.9 mL) at 0 °C and the mixture purged with N₂ for 3 times. The mixture was stirred at 90 °C for 16 h under N₂ atmosphere. The crude product was triturated with MTBE (100 mL) at 25 °C for 30 min to give compound **K-2-3** (9.10 g, 59.8% yield, 100% purity) as a white solid.

[0517] **Synthesis of 1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-2)** To a solution of compound **K-2-3** (8.60 g, 32.8 mmol) in toluene (100 mL) was added P₂S₅ (10.9 g, 49.2 mmol, 5.23 mL) and the mixture purged with N₂ for 3 times. The mixture was stirred at 110 °C for 12 h under N₂ atmosphere. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure. The reaction mixture was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with sat NaCl 100 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ ethyl acetate = 50/1 to 1/1) to give compound **K-2** (7.90 g, 86.1% yield, 99.5% purity) was obtained as a white solid.

[0518] **Synthesis of 1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-3):**

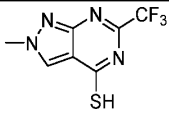
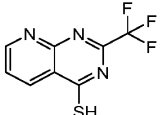


[0519] **Synthesis of 5-amino-1-methyl-1H-pyrazole-4-carboxamide (K-3-1)** A solution of 5-amino-1-methyl-pyrazole-4-carbonitrile (10.0 g, 81.9 mmol) was added H₂SO₄ (20.0 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was diluted with H₂O (30.0 mL) at 0 °C and adjusted to pH = 7 ~8 with NH₃·H₂O. The solid was collected by filtration to give compound **K-3-1** (12.5 g, 94.1% yield, 86.4% purity) as a brown-yellow solid.

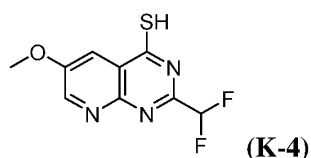
[0520] **Synthesis of 1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ol (K-3-2)** To a solution of NaH (25.0 g, 624 mmol, 60.0% purity) in EtOH (250 mL) was added compound **K-3-1** (12.5 g, 89.2 mmol) and CF₃COOEt (50.7 g, 357 mmol, 49.2 mL) at 0 °C. The mixture was stirred at 90 °C for 12 h. The reaction mixture was adjusted to pH = 3 with 1 M HCl (600 mL) and extracted with EtOAc (200 mL x 3). The organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was trituration with heptane/MTBE (5/1, 10 V) at 25 °C for 2 h to give compound **K-3-2** (5.77 g, 28.8% yield, 97.0% purity) was obtained as a brown oil.

[0521] **Synthesis of 1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-3)** To a solution of compound **K-3-2** (5.77 g, 26.5 mmol) in toluene (40.0 mL) was added P₂S₅ (6.47 g, 29.1 mmol) and the mixture was stirred at 110 °C for 4 h. The reaction mixture was quenched by H₂O (30.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **K-3** (5.65 g, 89.5% yield, 98.1% purity) as a light yellow solid.

[0522] The following intermediate compounds **K** have been prepared using the experimental conditions described above from the reaction of substituted amino carboxamide aryls and heteroaryls, and trifluoroacetic anhydride or CHF₂-based reagents. Alternatively, they were prepared from art known or commercial hydroxy-substituted heteroaryls of formula **Y**¹-OH by thionation using P₂S₅ reagent or Lawesson's reagent.

Cpd number	Structure	Name
K-8		2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidine-4-thiol
K-6		2-(trifluoromethyl)pyrido[2,3-d]pyrimidine-4-thiol

[0523] **Synthesis of 2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidine-4-thiol (K-4):**



[0524] **Synthesis of 2-fl uoro-5-methoxynicotinic acid (K-4-1)** To a solution of DIPA (37.4 g, 370 mmol) in THF (1500 mL) was added n-BuLi (1.60 M, 231 mL) at -78 °C under N₂. The mixture was stirred at -78 °C for 45 min. To the mixture was added a solution of 2-fluoro-5-methoxy-pyridine (47.0 g, 370 mmol) in THF (160 mL) and stirring was continued at -78 °C for 1.5 h. Then to the mixture was added CO₂ (81.4 g, 1.85 mol) and stirring was continued at -78 °C for 30 min. The mixture was warmed to 0 °C and H₂O (500 mL) was added at 0 °C. Then the mixture was concentrated to remove THF and added HCl (2 N, 180 mL). The mixture was stirred for 1 h at 25 °C and filtered to give compound **K-4-1** (38.0 g, 60.1% yield) as a yellow solid.

[0525] **Synthesis of 2-amino-5-methoxynicotinic acid (K-4-2)** To a solution of compound **K-4-1** (5.00 g, 29.2 mmol) in NH₃·H₂O (50.0 mL) was stirred at 140 °C for 48 h for 4 batch. The mixture was concentrated under reduced pressure to give compound **K-4-2** (24.0 g, 79.4% yield, 65.0% purity) as a yellow solid.

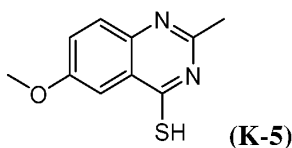
[0526] **Synthesis of 2-amino-5-methoxynicotinamide (K-4-3)** To a solution of compound **K-4-2** (1.00 g, 5.95 mmol) in DMF (10.0 mL) was added HOBt (884 mg, 6.54 mmol) and EDCI (1.37 g, 7.14 mmol). The mixture was stirred at 25 °C for 2 h. Then the mixture was added NH₃·H₂O (5.00 mL) and stirred at 25 °C for 1 h. The reaction was quenched by H₂O (3.00 mL) and extracted with EtOAc (9.00 mL). The combined organic

layers were dried over Na₂SO₄, filtered, and concentrated to give compound **K-4-3** (634 mg, 63.8% yield) as a yellow solid.

[0527] **Synthesis of 2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-ol (K-4-4)** To a solution of NaH (607 mg, 15.2 mmol, 60.0% purity) in EtOH (7.00 mL) was added compound **K-4-3** (634 mg, 3.79 mmol) and ethyl 2,2-difluoroacetate (941 mg, 7.59 mmol). The mixture was stirred at 90 °C for 16 h. The reaction was quenched by H₂O (3.00 mL) and extracted with EtOAc (9.00 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was triturated with MTBE (1.00 mL) at 25 °C for 20 min to give compound **K-4-4** (220 mg, 25.5% yield) as a brown solid.

[0528] **Synthesis of 2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidine-4-thiol (K-4)** To a solution of compound **K-4-4** (220 mg, 968 µmol) in toluene (2.00 mL) was added 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (470 mg, 1.16 mmol). The mixture was stirred at 110 °C for 5 h. The reaction was quenched by H₂O (3.00 mL) and extracted with EtOAc (9.00 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated. The crude product was triturated with MTBE (1.00 mL) at 25 °C for 20 min to give compound **K-4** (140 mg, 59.4% yield) as a brown solid.

[0529] **Synthesis of 6-methoxy-2-methylquinazoline-4-thiol (K-5)**

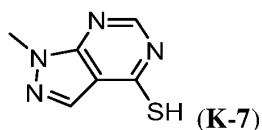


[0530] **Synthesis of 6-methoxy-2-methylquinazolin-4-ol (K-5-1)** To EtOH (500 mL) was added NaH (42.1 g, 1.05 mol, 60% purity) in portions at 0 °C and then 2-amino-5-methoxybenzamide (25.0 g, 150 mmol) was added followed by EtOAc (53.0 g, 601 mmol, 58.91 mL). The resulting mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched by 1 M HCl (500 mL) and filtered. The filter cake was collected. The collected filter cake was dissolved in EtOAc/MeOH (V/V = 1/1, 200 mL) and filtered. The filtrate was concentrated in vacuum to give compound **K-5-1** (34.0 g, crude) as an off-white solid.

¹H NMR: (400 MHz, DMSO-*d*₆) δ 12.2 (s, 1H), 7.51 (d, *J* = 9.2 Hz, 1H), 7.45 (d, *J* = 2.8 Hz), 7.36 (dd, *J* = 8.8 Hz, 1H), 3.84 (s, 1H), 2.32 (s, 3H).

[0531] **Synthesis of 6-methoxy-2-methylquinazoline-4-thiol (K-5)** To a solution of compound **K-5-1** (20.0 g, 105 mmol) in toluene (140 mL) was added Lawesson's reagent (46.8 g, 115 mmol) and the mixture was stirred at 120 °C for 12 h under N₂ atmosphere. Two additional runs were done of this reaction on 18.0 g scale and 7.20 g scale of **K-5-1**, and the crude mixtures of all three runs were combined for work-up. The reaction mixture was concentrated in vacuum to remove solvent. The residue was triturated with EtOAc/MeOH (V/V = 10/1, 10 V, 3 times) at 25 °C for 6 h to give compound **K-5** (25.5 g, 72% yield, 85.3% purity) as a yellow solid. ¹H NMR: (400 MHz, DMSO-*d*₆) δ 13.9 (s, 1H), 7.91 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.51 (dd, *J* = 8.8 Hz, 1H), 3.87 (s, 3H), 2.48 (s, 3H).

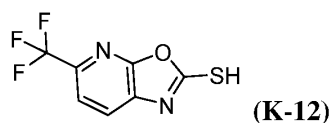
[0532] **Synthesis of 1-methyl-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-7)**



[0533] **Synthesis of 1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-ol (K-7-1)** A solution mixture of ethyl 5-amino-1-methyl-1H-pyrazole-4-carboxylate (10 g, 59.1 mmol) in formamide (40 mL) was stirred at 180 °C for 4 h. The reaction mixture was cooled to rt, after which a precipitate formed. The resulting precipitate was filtered in vacuo, washed with hexane and dried in vacuo to afford **K-7-1** (7.2 g, Yield: 79%) as an off-white solid.

[0534] **Synthesis of 1-methyl-1H-pyrazolo[3,4-d]pyrimidine-4-thiol (K-7)** To a solution of compound **K-7-1** (3.4 g, 22.6 mmol) in toluene (50.0 mL) was added Lawesson's reagent (5.4 g, 13.5 mmol) at 0 °C. The reaction mixture was stirred for 2 h at 120 °C. Next, the mixture was concentrated in vacuo, and the residue was purified by column chromatography over silica gel (60-120 mesh) eluting with 10% EtOAc in hexane to afford **K-7** (3.0 g, Yield: 81%) as a pale-yellow solid.

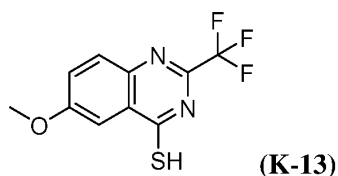
[0535] **Synthesis of 5-(trifluoromethyl)oxazolo[5,4-b]pyridine-2-thiol (K-12)**



[0536] **Synthesis of 3-amino-6-(trifluoromethyl)pyridin-2-ol (K-12-1)** To a stirred solution of 3-nitro-6-(trifluoromethyl)pyridin-2-ol (200 mg, 0.961 mmol) in MeOH (1 mL) was added 15% Pd-C (30 mg). Then H₂ gas was inserted for 3 h at 60 psi., after which the mixture was heated to 50 °C for 3 h. The reaction mixture was filtered through a celite bed under vacuum. The solvent was evaporated under reduced pressure to get title compound **K-12-1** (142 mg, 75% yield).

[0537] **Synthesis of 5-(trifluoromethyl)oxazole[5,4-b]pyridine-2-thiol (K-12-2)** To a solution of 3-amino-6-(trifluoromethyl)pyridin-2-ol **K-12-1** (1.8 g, 0.010 mol) in EtOH (18 mL) was added KOH (1.13 g, 0.0202 mol) followed by CS₂ (1.13 mL, 0.0202 mol) at 0 °C. The reaction mixture was stirred at 80 °C for 16 h. After completion of the reaction, the solvent was evaporated under reduced pressure and purified by C18-reversed phase combi-flash chromatography (eluent: 0.1% formic acid in ACN) to get title compound **K-12** (1.8 g, 81% yield) as an off-white solid.

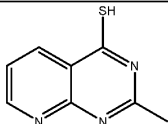
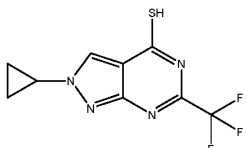
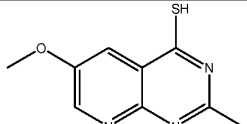
[0538] **Synthesis of 6-methoxy-2-(trifluoromethyl)quinazoline-4-thiol (K-13)**



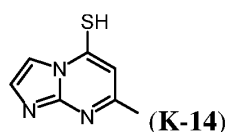
Synthesis of 6-methoxy-2-(trifluoromethyl)quinazoline-4-thiol (K-13-1) To a stirred solution of 6-methoxy-2-(trifluoromethyl)quinazolin-4-ol (900 mg, 3.673 mmol) in dry 1,4-dioxane (10 mL) added the Lawesson's reagent (1.6 g, 2.336 mmol) under an atmosphere of dry argon. The reaction was heated under reflux for 16 h. A solution of 3 N NaOH (20 mL) was added to the mixture and the mixture neutralized with 1 N HCl. The solid was filtered and dried under vacuum to afford title **K-13** (410 mg, 42% yield) as an off white solid.

[0539] The following intermediate compounds **K** have been prepared using the experimental conditions described above. Alternatively, they were prepared from art

known or commercial hydroxy-substituted heteroaryls of formula Y^1 -OH by thionation using P_2S_5 reagent or Lawesson's reagent.

Cpd number	Structure	Name
K-9		2-methylpyrido[2,3-d]pyrimidine-4-thiol
K-10		2-cyclopropyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidine-4-thiol
K-11		6-methoxy-2-methylpyrido[2,3-d]pyrimidine-4-thiol

[0540] **Synthesis of 7-methylimidazo[1,2-a]pyrimidine-5-thiol (K-14):**

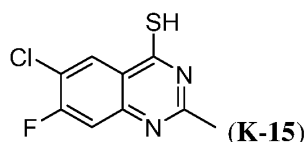


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[0541] **Synthesis of 7-methylimidazo[1,2-a]pyrimidine-5-thiol (K-14)** To a solution of 7-methylimidazo[1,2-a]pyrimidin-5-ol (0.45 g, 3.02 mmol) and P_2S_5 (670.62 mg, 3.02 mmol, 320.87 μ L) in anisole (4 mL) was added trimethyl(trimethylsilyloxy)silane (2.45 g, 15.09 mmol, 3.21 mL). The mixture was stirred at 120 °C for 3 h. TLC (petroleum ether/ethyl acetate = 1/1, compound I-2-1 R_f = 0.42) showed the compound starting material was consumed and one new spot was formed. The mixture was filtered, and the solid was dried in vacuum to give compound **K-14** (0.4 g, 2.42 mmol, 80.25% yield) as a gray solid.

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[0542] **Synthesis of 6-chloro-7-fluoro-2-methylquinazoline-4-thiol (K-15):**

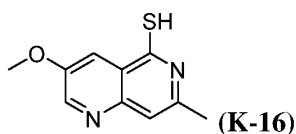


[0543] **Synthesis of 2-amino-5-chloro-4-fluorobenzoic acid (K-15-1)** To a solution of 2-amino-4-fluoro-benzoic acid (50.0 g, 322 mmol) in DMF (700 mL) was added NCS (41.0 g, 307 mmol). The reaction mixture was stirred at 50 °C for 5 h. The mixture was poured into water (2000 mL) and filtered. The filter cake was washed with water and dried to give compound **K-15-1** (56.7 g, 254 mmol, 78.7% yield, 84.8% purity) as a brown solid.

[0544] **Synthesis of 6-chloro-7-fluoro-2-methylquinazolin-4(3H)-one (K-15-2)** To a solution of compound **K-15-1** (55.7 g, 249 mmol) in 2-methoxyethanol (557 mL) was added acetamidine;hydrochloride (58.9 g, 623 mmol) and NaOAc (51.1 g, 623 mmol). The mixture was stirred at 130 °C for 16 h. The mixture was poured into water (2000 mL) and filtered. The filter cake was washed with water and dried to give compound **K-15-2** (34.9 g, 154 mmol, 61.7% yield, 93.7% purity) as a brown solid.

[0545] **Synthesis of 6-chloro-7-fluoro-2-methylquinazoline-4-thiol (K-15)** To a solution of compound **K-15-2** (20.0 g, 94.1 mmol) in Tol. (400 mL) was added 2,4-bis(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4dithiadiphosphetane (47.6 g, 118 mmol). The mixture was stirred at 120 °C for 2 h. The mixture was poured into water (500 mL) and filtered. The filter cake was washed with water and dried to give a residue. The residue was purified by re-crystallization from H₂O (1000 mL) and EtOAc (300 mL) at 25 °C for 1 h to give compound **K-15** (13.5 g, 57.8 mmol, 61.4% yield, 97.6% purity) as a yellow solid.

[0546] **Synthesis of 3-methoxy-7-methyl-1,6-naphthyridine-5-thiol (K-16):**



[0547] **Synthesis of 5,7-dichloro-3-iodo-1,6-naphthyridine (K-16-1)** To a solution of 5,7-dichloro-1,6-naphthyridine (4.00 g, 20.1 mmol) in AcOH (60.0 mL) was added NIS (9.04 g, 40.2 mmol) under N₂. The mixture was stirred at 100 °C for 16 h. The mixture was concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/Ethyl acetate = 100/1 to 20/1) to give compound **K-16-1** (3.14 g, 8.79 mmol, 43.8% yield, 91.2% purity) as a yellow solid.

[0548] **Synthesis of (5,7-dichloro-1,6-naphthyridin-3-yl)boronic acid (K-16-2)** To a solution of compound **K-16-1** (5.08 g, 15.6 mmol) and B₂Pin₂ (4.37 g, 17.2 mmol) in dioxane (51.0 mL) was added KOAc (3.07 g, 31.3 mmol) and Pd(dppf)Cl₂ (1.14 g, 1.56 mmol) under N₂. The mixture was stirred at 90 °C for 16 h. The mixture was quenched by water (100 mL) and was extracted with EtOAc (200 mL*3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ Ethyl acetate = 100/1 to 25/2) to give compound **K-16-2** (2.90 g, 11.1 mmol, 71.0% yield, 93.0% purity) was obtained as a yellow solid.

[0549] **Synthesis of 5,7-dichloro-1,6-naphthyridin-3-ol (K-16-3)** To a solution of compound **K-16-2** (2.90 g, 11.9 mmol) in DCM (15.0 mL) was added H₂O₂ (7.30 g, 64.4 mmol, 6.19 mL, 30.0% purity) at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was filtered and the filter cake was concentrated to give compound **K-16-3** (2.45 g, 11.3 mmol, 94.5% yield, 99.0% purity) as a white solid.

[0550] **Synthesis of 5,7-dichloro-3-methoxy-1,6-naphthyridine (K-16-4)** To a solution of compound **K-16-3** (2.45 g, 11.4 mmol) in DMF (25.0 mL) was added K₂CO₃ (4.72 g, 34.2 mmol) and MeI (3.23 g, 22.8 mmol, 1.42 mL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was added water (70 mL) and extracted with EtOAc (100 mL * 2). The combined organic layer was washed with brine (400 mL * 2), dried over Na₂SO₄, filtered and concentrated in vacuum to give compound **K-16-4** (2.24 g, 9.73 mmol, 85.4% yield, 99.5% purity) as a yellow solid.

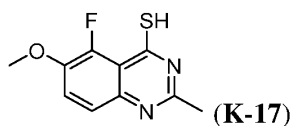
[0551] **Synthesis of 7-chloro-3-methoxy-5-((4-methoxybenzyl)thio)-1,6-naphthyridine (K-16-5)** To a solution of compound **K-16-4** (2.24 g, 9.73 mmol) in

dioxane (23.0 mL) was added (4-methoxyphenyl)methanethiol (2.25 g, 14.6 mmol, 2.03 mL) and Cs_2CO_3 (6.34 g, 19.5 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was added water (50 mL) and extracted with EtOAc (100 mL*2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/Ethyl acetate = 100/1 to 20/1) to give compound **K-16-5** (2.01 g, 5.59 mmol, 57.5% yield, 96.5% purity) as a yellow solid.

[0552] **Synthesis of 3-methoxy-5-((4-methoxybenzyl)thio)-7-methyl-1,6-naphthyridine (K-16-6)** To a solution of compound **K-16-5** (1.90 g, 5.29 mmol) and methylboronic acid (633 mg, 10.6 mmol) in DMF (19.0 mL) was added K_3PO_4 (3.37 g, 15.9 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (611 mg, 529 μmol) under N_2 . The mixture was stirred at 110 °C for 2 h. The reaction mixture was added water (50 mL) and extracted with EtOAc (100 mL*2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/Ethyl acetate = 100/1 to 20/1) to give compound **K-16-6** (1.43 g, 3.96 mmol, 74.8% yield, 90.3% purity) as a yellow solid.

[0553] **Synthesis of 3-methoxy-7-methyl-1,6-naphthyridine-5-thiol (K-16)** To a solution of compound **K-16-6** (500 mg, 1.53 mmol) in TFA (5.00 mL) was added m-cresol (166 mg, 1.53 mmol, 160 μL). The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched by addition H_2O (10 mL), and extracted with EtOAc (15 mL * 3). The combined organic layer was washed with brine (30 mL x 3), dried over Na_2SO_4 , filtered and concentrated to give compound **K-16** (735 mg, crude) as a red solid.

[0554] **Synthesis of 5-fluoro-6-methoxy-2-methylquinazoline-4-thiol (K-17):**



[0555] **Synthesis of 6-bromo-2-fluoro-3-methoxybenzoic acid (K-17-1)** To a solution of 2-fluoro-3-methoxybenzoic acid (100 g, 588 mmol) in AcOH (500 mL) and H_2O (500 mL) was added dropwise Br_2 (188 g, 1.18 mol) at 0 °C. The resulting mixture was stirred

at 25 °C for 16 h. The reaction mixture was quenched by addition H₂O (2.5 L) at 25 °C, the precipitate was filtered and the filter cake was wash with water. Compound **K-17-1** (127 g, 86.8% yield, 100% purity) was obtained as a white solid.

[0556] **Synthesis of ethyl 6-bromo-2-fluoro-3-methoxybenzoate (K-17-2)** To a solution of **K-17-1** (127 g, 510 mmol) in ACN (1000 mL) was added Cs₂CO₃ (199 g, 612 mmol) and iodoethane (119 g, 765 mmol). The mixture was stirred at 25 °C for 72 h. The mixture was filtered through celite, washed with MeCN (500 mL) and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound **K-17-2** (137 g, 96.5% yield, 99.5% purity) was obtained as a yellow oil.

[0557] **Synthesis of ethyl 6-((tert-butoxycarbonyl)amino)-2-fluoro-3-methoxybenzoate (K-17-3)** **K-17-2** (100 g, 361 mmol) was dissolved in dioxane (1000 mL). tert-butyl carbamate (50.7 g, 433 mmol), Xantphos (20.9 g, 36.1 mmol), Pd(OAc)₂ (8.10 g, 36.1 mmol) and Cs₂CO₃ (235 g, 722 mmol) were added and the mixture was stirred for 16 h at 100 °C. The mixture was cooled, diluted with EtOAc (1000 mL) and filtered through Celite washing with EtOAc (1000 mL). The combined filtrates were concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 330 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min). Compound **K-17-3** (97 g, 82.9% yield, 96.6% purity) was obtained as a yellow solid.

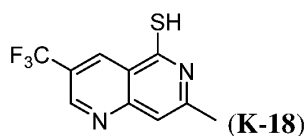
[0558] **Synthesis of ethyl 6-amino-2-fluoro-3-methoxybenzoate (K-17-4)** To a solution of **K-17-3** (97 g, 310 mmol) in dioxane (200 mL) was added HCl/dioxane (2 M, 619 mL). The mixture was stirred at 25 °C for 16 h. The reaction liquid is filtered directly and the solids are collected. Compound **K-17-4** (74 g, 95.7% yield, 100% purity, HCl) was obtained as a white solid.

[0559] **Synthesis of 5-fluoro-6-methoxy-2-methylquinazolin-4-ol (K-17-5)** To a solution of **K-17-4** (55 g, 258 mmol, 1 eq) in ACN (500 mL) was added HCl (12 M, 215 mL). The mixture was stirred at 100 °C for 16 h. The reaction mixture was quenched by

addition $\text{NH}_3\text{H}_2\text{O}$ 220 mL at 20 °C. The reaction liquid is filtered directly and the solids are collected. Compound **K-17-5** (42 g, 78.2% yield) was obtained as a white solid.

[0560] **Synthesis of 5-fluoro-6-methoxy-2-methylquinazoline-4-thiol (K-17)** To a solution of **K-17-5** (5 g, 24.0 mmol) in anisole (50 mL) was added P_2S_5 (2.67 g, 12.0 mmol) and trimethyl(trimethylsilyloxy)silane (19.5 g, 120 mmol). The mixture was stirred at 110 °C for 16 h. The mixture was cooled to 0 °C and quenched by addition of K_2CO_3 aqueous solution (5.3 M, 300 mL) at 0 °C, then acetone (200 mL) was added. The mixture was stirred at 0 °C for 1 h. The crude product was triturated with MeCN (200 mL) at 25 °C for 12 h. The mixture was filtered and the filter cake was washed with MeCN (100 mL*3) and collected. Compound **K-17** (5 g, 86.3% yield, 93% purity) was obtained as a yellow solid.

[0561] **Synthesis of 7-methyl-3-(trifluoromethyl)-1,6-naphthyridine-5-thiol (K-18):**



[0562] **Synthesis of 5,7-dichloro-3-iodo-1,6-naphthyridine (K-18-1)** To a solution of 5,7-dichloro-1,6-naphthyridine (5.00 g, 25.1 mmol) in AcOH (75.0 mL) was added NIS (11.3 g, 50.2 mmol) under N_2 . The mixture was stirred at 100 °C for 16 h. The reaction mixture was concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 19/1) to give compound **K-18-1** (5.12 g, 15.3 mmol, 61.0% yield, 97.3% purity) as a brown solid.

[0563] **Synthesis of 5,7-dichloro-3-(trifluoromethyl)-1,6-naphthyridine (K-18-2)** To a solution of compound **K-18-1** (2.00 g, 5.99 mmol) in DMF (20.0 mL) was added CuI (2.85 g, 15.0 mmol) and HMPA (5.37 g, 29.9 mmol, 5.24 mL) under N_2 . The mixture was heated to 90 °C. methyl 2,2-difluoro-2-fluorosulfonyl-acetate (2.30 g, 12.0 mmol, 1.52 mL) was added into above reaction mixture at 90 °C and stirred at 90 °C for 2 h under N_2 . The reaction mixture was added water (20 mL) and extracted with EtOAc (30 mL* 3). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2 ,

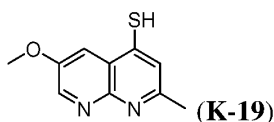
petroleum ether/ethyl acetate = 100/1 to 19/1) to give compound **K-18-2** (820 mg, 2.93 mmol, 48.9% yield, 95.4% purity) as a yellow solid.

[0564] **Synthesis of 7-chloro-5-((4-methoxybenzyl)thio)-3-(trifluoromethyl)-1,6-naphthyridine (K-18-3)** To a solution of compound **K-18-2** (800 mg, 2.70 mmol) and PMBSH (457 mg, 2.97 mmol, 413 μ L) in dioxane (16.0 mL) was added Cs_2CO_3 (879 mg, 2.70 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was added water (10 mL) and extracted with EtOAc (20 mL *2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 19/1) to give compound **K-18-3** (736 mg, 1.71 mmol, 63.6% yield, 89.6% purity) as a white solid.

[0565] **Synthesis of 5-((4-methoxybenzyl)thio)-7-methyl-3-(trifluoromethyl)-1,6-naphthyridine (K-18-4)** To a solution of compound **K-18-3** (716 mg, 1.80 mmol) and methylboronic acid (215 mg, 3.59 mmol) in DMF (8.00 mL) was added K_3PO_4 (1.14 g, 5.39 mmol,) and $\text{Pd}(\text{PPh}_3)_4$ (207 mg, 180 μ mol) under N_2 . The mixture was stirred at 110 °C for 2 h. The reaction mixture was added water (15 mL) and extracted with EtOAc (20 mL*2). The combined organic layer was dried over Na_2SO_4 , filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 19/1) to give compound **K-18-4** (182 mg, 471 μ mol, 26.2% yield, 94.3% purity) as a yellow solid.

[0566] **Synthesis of 7-methyl-3-(trifluoromethyl)-1,6-naphthyridine-5-thiol (K-18)** To a solution of compound **K-18-4** (182 mg, 471 μ mol) in TFA (2.00 mL) was added m-cresol (50.9 mg, 471 μ mol, 49.3 μ L). The mixture was stirred at 80 °C for 2 h. The reaction mixture was added water (5 mL) and extracted with EtOAc (5 mL*3). The combined organic layer was washed with brine (10 mL * 3), dried over Na_2SO_4 , filtered and concentrated in vacuum to give compound **K-18** (202 mg, crude) as a red solid.

[0567] **Synthesis of 2-methylquinazoline-4-thiol (K-19):**



[0568] **Synthesis of 2-amino-5-bromo-pyridine-3-carboxylic acid (K-19-1)** To a solution of ethyl 2-amino-5-bromo-pyridine-3-carboxylate (20.0 g, 81.6 mmol) in THF (200 mL) was added NaOH (9.79 g, 245 mmol) in H₂O (60 mL). The mixture was stirred at 25 °C for 16 h. The reaction mixture was concentrated and added HCl (1 N, 50 mL). The solid was filtered and concentrated to give compound **K-19-1** (17.0 g, 78.3 mmol, 96.0 % yield) as a white solid.

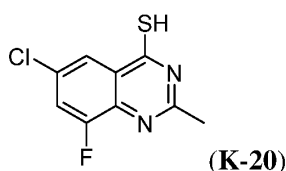
[0569] **Synthesis of 6-bromo-4-chloro-2-methyl-1,8-naphthyridine (K-19-2)** To a solution of **K-19-1** (13.0 g, 59.9 mmol) in POCl₃ (150 mL) was added acetone (13.9 g, 240 mmol). The mixture was stirred at 80 °C for 2 h. The reaction mixture was concentrated under reduced pressure to remove POCl₃. The residue was poured into ice water 100 mL, dropwise added NaOH solution (2 N) and extracted with EtOAc (100 mL*3). The combined organic layers were washed with NaCl 50 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~30% THF/Petroleum ether gradient @ 100 mL/min) to give compound **K-19-2** (4.70 g, 14.6 mmol, 24.4 % yield, 80 % purity) as a yellow solid.

[0570] **Synthesis of 6-bromo-4-[(4-methoxyphenyl)methylsulfanyl]-2-methyl-1,8-naphthyridine (K-19-3)** To a solution of **K-19-2** (4.50 g, 17.5 mmol) in dioxane (50 mL) was added Cs₂CO₃ (5.69 g, 17.5 mmol) and (4-methoxyphenyl)methanethiol (2.70 g, 17.5 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was quenched with saturated H₂O (50 mL) and was extracted with EtOAc (100 mL). The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~60% THF/Petroleum ether gradient @ 80 mL/min) to give compound **K-19-3** (4.70 g, 12.5 mmol, 71.7 % yield) as a yellow solid.

[0571] **Synthesis of 6-methoxy-4-[(4-methoxyphenyl)methylsulfanyl]-2-methyl-1,8-naphthyridine (K-19-4)** To a solution of **K-19-3** (2.70 g, 7.19 mmol) in dioxane (10 mL) was added RockPhos Pd G3 (302 mg, 360 μ mol), MeOH (2.31 g, 72.0 mmol) and t-BuONa (415 mg, 4.32 mmol) under N₂. The mixture was stirred at 70 °C for 2 h. The reaction mixture was quenched with saturated H₂O (10 mL) and was extracted with EtOAc 30 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~27% THF/Petroleum ether gradient @ 40 mL/min) to give compound **K-19-4** (960 mg, 2.35 mmol, 32.7 % yield, 80 % purity) as a yellow solid.

[0572] **Synthesis of 6-methoxy-2-methyl-1,8-naphthyridine-4-thiol (K-19)** To a solution of **K-19-4** (960 mg, 2.94 mmol) in TFA (2 mL) was added TfOH (441 mg, 2.94 mmol). The mixture was stirred at 70 °C for 1 h. The reaction mixture was quenched with saturated H₂O (10 mL) and was extracted with EtOAc 30 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The crude product was triturated with MTBE at 20 °C for 30 min to give compound **K-19** (800 mg, 2.71 mmol, 92.3 % yield, 70 % purity) as a yellow solid.

[0573] **Synthesis of 6-chloro-8-fluoro-2-methyl-quinazoline-4-thiol (K-20):**

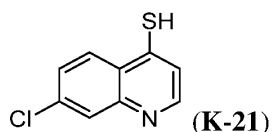


[0574] **Synthesis of 6-chloro-8-fluoro-2-methyl-quinazolin-4-ol (K-20-1)** To a solution of NaH (34.1 g, 854 mmol, 60.0% purity) in EtOH (400 mL) at 0 °C was added 2-amino-5-chloro-3-fluoro-benzamide (23.0 g, 122 mmol) and EtOAc (43.0 g, 488 mmol, 47.8 mL) and purged with N₂ for 3 times, and then the mixture was stirred at 90 °C for 12 h under N₂ atmosphere. The reaction mixture was added H₂O 500 mL at 0 °C. The reaction mixture was extracted with EtOAc 1500 mL (500 mL * 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product

was purified by re-crystallization from MTBE (200 mL) at 25 °C. Compound **K-20-1** (18.0 g, 84.7 mmol, 69.4 % yield) was obtained as a yellow solid.

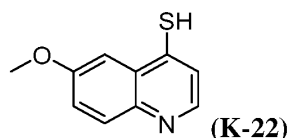
- [0575] **Synthesis of 6-chloro-8-fluoro-2-methyl-quinazoline-4-thiol (K-20)** To a solution of compound **K-20-1** (18.0 g, 84.7 mmol) in toluene (200 mL) was added P₂S₅ (28.2 g, 127 mmol, 13.5 mL). The mixture was stirred at 110 °C for 6 h under N₂ atmosphere. The reaction mixture was filtered and the filter cake was concentrated under reduced pressure to give a residue. The reaction mixture was extracted with EtOAc 1500 mL (500 mL * 3). The combined organic layers were washed with brine 1000 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by re-crystallization from MTBE (200 mL) at 25 °C. Compound **K-20** (15.0 g, 58.4 mmol, 69.0 % yield, 89.0 % purity) was obtained as a yellow solid.

[0576] **Synthesis of 7-chloroquinoline-4-thiol (K-21):**



- 15 [0577] **Synthesis of 7-chloroquinoline-4-thiol (K-21)** To a solution of 4,7-dichloroquinoline (3 g, 15.15 mmol) in DMF (10 mL) was added NaHS (4.25 g, 75.74 mmol). The mixture was stirred at 80 °C for 2 h. The mixture was poured into water (100 mL) and filtered. The filter cake was washed with water and dried to give compound **K-21** (2 g, 10.22 mmol, 67.48% yield) as a brown solid.

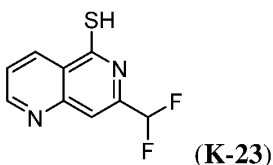
20 [0578] **Synthesis of 6-methoxyquinoline-4-thiol (K-22):**



[0579] **Synthesis of 6-methoxyquinoline-4-thiol (K-22)** To a solution of 4-chloro-6-methoxy-quinoline (3 g, 15.49 mmol) in DMF (2 mL) was added NaHS (4.34 g, 77.47

mmol). The mixture was stirred at 80 °C for 2 h. The mixture was poured into water (100 mL) and filtered. The filter cake was washed with water and dried to give compound **K-22** (2 g, 10.46 mmol, 67.50% yield) as a yellow solid.

[0580] **Synthesis of 7-(difluoromethyl)-1,6-naphthyridine-5-thiol (K-23):**



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[0581] **Synthesis of 5-oxo-5,6-dihydro-1,6-naphthyridine-7-carbaldehyde (K-23-1)**

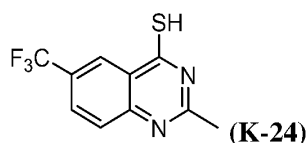
To a solution of 7-methyl-1,6-naphthyridin-5(6H)-one (2 g, 12.49 mmol,) in dioxane (50 mL) was added SeO₂ (2.77 g, 24.97 mmol). The reaction mixture was stirred at 110 °C for 2 h. The reaction mixture was extracted with EtOAc (50 mL *3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). to give compound **K-23-1** (1.5 g, 8.61 mmol, 68.98% yield) was obtained as yellow solid.

15 [0582] **Synthesis of 7-(difluoromethyl)-1,6-naphthyridin-5-ol (K-23-2)** To the solution of compound **K-23-1** (70 mg, 356.86 µmol) in POCl₃ (5 mL) under N₂ and the mixture was stirred at 110 °C for 2 h. TLC (Petroleum ether: Ethyl acetate = 1/1, product R_f = 0.24) indicated compound **K-23-1** was consumed and one new spot was formed. The reaction mixture was concentrated in vacuum to give a residue. The reaction mixture
20 was extracted with EtOAc (50 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~80% Ethylacetate/Petroleum ether gradient @ 60 mL/min). to give compound **K-23-2** (50 mg, 70% yield) was obtained as yellow solid.

25 [0583] **Synthesis of 7-(difluoromethyl)-1,6-naphthyridine-5-thiol (K-23)** To a solution of compound **K-23-2** (5.77 g, 26.5 mmol) in Tol. (40.0 mL) was added P₂S₅

(6.47 g, 29.1 mmol) and the mixture was stirred at 110 °C for 4 h. The reaction mixture was quenched by H₂O (30.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **K-23** (5.1 g, 80% yield) as a yellow solid.

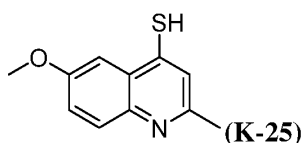
5 [0584] **Synthesis of 2-methyl-6-(trifluoromethyl)quinazoline-4-thiol (K-24):**



[0585] **Synthesis of 2-methyl-6-(trifluoromethyl)quinazolin-4(3H)-one (K-24-1)** To a solution of ethyl 2-amino-5-(trifluoromethyl)benzoate (22 g, 100.38 mmol) in MeCN (300 mL) was added methanesulfonic acid (60 mL) at 0 °C. The reaction mixture was stirred at 100 °C for 12 h. The reaction mixture was quenched by addition of H₂O (200 mL) at 5 °C and extracted with EtOAc (100 mL*3). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethylacetate/Petroleum ether gradient @ 80 mL/min). to give compound **K-24-1** (12 g, 52.59 mmol, 52.39% yield) was obtained as a white solid.

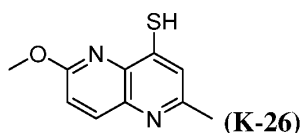
[0586] **Synthesis of 2-methyl-6-(trifluoromethyl)quinazoline-4-thiol (K-24)** To a solution of compound **K-24-1** (1 g, 4.38 mmol) in THF (40.0 mL) was added P₂S₅ (6.47 g, 29.1 mmol) and the mixture was stirred at 80 °C for 4 h. The reaction mixture was quenched by H₂O (30.0 mL) and extracted with EtOAc (10.0 mL * 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **K-24** (750 mg, 70% yield) as a yellow solid.

[0587] **Synthesis of 6-methoxy-2-methylquinoline-4-thiol (K-25):**



[0588] **Synthesis of 6-methoxy-2-methylquinoline-4-thiol (K-25)** A solution of 6-methoxy-2-methylquinolin-4-ol (1 g, 5.29 mmol) in THF (40 mL) was added Lawesson's Reagent (2.14 g, 5.29 mmol) dropwise at 25 °C. The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched by H₂O (30.0 mL) and extracted with EtOAc (30.0 mL* 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **K-25** (720 mg, crude) as a yellow solid.

[0589] **Synthesis of 6-methoxy-2-methyl-1,5-naphthyridine-4-thiol (K-26):**

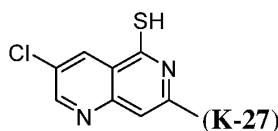


[0590] **Synthesis of ethyl 3-((6-methoxypyridin-3-yl)imino)butanoate (K-26-1)** A solution of 6-methoxypyridin-3-amine (5 g, 40.28 mmol) in ethyl 3-oxobutanoate (5 mL) was stirred at 130 °C for 3 h. TLC indicated the starting material was consumed completely and one new spot was formed. The mixture was concentrated under reduced pressure to give compound **K-26-1** (4.0 g, crude) as a black solid.

[0591] **Synthesis of 6-methoxy-2-methyl-1,5-naphthyridin-4-ol (K-26-2)** To a solution of compound **K-26-1** (4 g, 16.93 mmol) in 1,1'-biphenyl,phenoxybenzene (50 mL) The mixture was stirred at 250 °C for 1 h. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~40% Ethylacetate/Petroleum ether gradient @ 80 mL/min) to give compound **K-26-2** (1.2 g, 6.31 mmol,) as a black solid.

[0592] **Synthesis of 6-methoxy-2-methyl-1,5-naphthyridine-4-thiol (K-26)** To a solution of compound **K-26-2** (1.2 g, 6.31 mmol) in THF (40.0 mL) was added Lawesson's Reagent (2.55 g, 6.31 mmol) dropwise at 25 °C. The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched by H₂O (30.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give compound **K-26** (1.1 g, 5.33 mmol) as a yellow solid.

[0593] **Synthesis of 3-chloro-7-methyl-1,6-naphthyridine-5-thiol (K-27):**



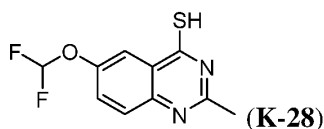
[0594] **Synthesis of 3,5,7-trichloro-1,6-naphthyridine (K-27-1)** To a solution of 5,7-dichloro-1,6-naphthyridine (19.2 g, 96.5 mmol) in DMF (100 mL) was added a solution of NCS (16.0 g, 120 mmol) in DMF (60.0 mL). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by water (300 mL) and extracted with EtOAc (300 mL * 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 49/1) to give compound **K-27-1** (25.4 g, 69.6 mmol, 72.1% yield, 64.0% purity) as a white solid.

[0595] **Synthesis of 3,7-dichloro-5-((4-methoxybenzyl)thio)-1,6-naphthyridine (K-27-2)** To a solution of compound **K-27-1** (25.4 g, 69.6 mmol) and PMBSH (11.8 g, 76.5 mmol, 10.7 mL) in dioxane (260 mL) was added Cs₂CO₃ (22.7 g, 69.6 mmol). The mixture was stirred at 50 °C for 2 h. The reaction mixture was added water (300 mL) and extracted with EtOAc (500 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 8/1) to give compound **K-27-2** (19.1 g, 53.5 mmol, 76.9% yield, 92.6% purity) as a yellow solid.

[0596] **Synthesis of 3-chloro-5-((4-methoxybenzyl)thio)-7-methyl-1,6-naphthyridine (K-27-3)** To a solution of compound **K-27-2** (3.00 g, 7.77 mmol) and methylboronic acid (810 mg, 13.5 mmol) in DMF (30.0 mL) was added K₃PO₄ (4.95 g, 23.3 mmol) and Pd(PPh₃)₄ (898 mg, 777 μmol) under N₂. The mixture was stirred at 110 °C for 1 h. The reaction mixture was added water (50 mL) and extracted with EtOAc (50 mL * 3). The combined organic layer was dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 32/1) to give compound **K-27-3** (1.21 g, 3.30 mmol, 42.4% yield, 90.1% purity) as a yellow solid.

[0597] **Synthesis of 3-chloro-7-methyl-1,6-naphthyridine-5-thiol (K-27)** To a solution of compound **K-27-3** (1.21 g, 3.30 mmol) in TFA (12.0 mL) was added m-cresol (356 mg, 3.30 mmol, 345 μ L). The mixture was stirred at 80 °C for 2 h. The reaction mixture was added water (20 mL) and extracted with EtOAc (20 mL * 2). The combined organic layer was washed with brine (50 mL * 3), dried over Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1) to give compound **K-27** (622 mg, 1.95 mmol, 59.1% yield, 66.0% purity) as a yellow solid.

[0598] **Synthesis of 6-(difluoromethoxy)-2-methylquinazoline-4-thiol (K-28):**



10

[0599] **Synthesis of methyl 5-hydroxy-2-nitrobenzoate (K-28-1)** To a solution of 5-hydroxy-2-nitro-benzoic acid (15.0 g, 81.9 mmol) in MeOH (150 mL) was added SOCl₂ (9.75 g, 81.9 mmol, 5.95 mL). The mixture was stirred at 25°C for 18 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=5/1). Compound **K-28-1** (16.0 g, 81.2 mmol, 99.1% yield) was obtained as a yellow oil.

[0600] **Synthesis of 5-(difluoromethoxy)-2-nitrobenzoic acid (K-28-2)** To a solution of 1-[[bromo(difluoro)methyl]-ethoxy-phosphoryl]oxyethane (40.6 g, 152.2 mmol) in MeCN (200 mL) and H₂O (200 mL) was added dropwise KOH (85.4 g, 1.52 mol) at 0 °C. After addition, the mixture was stirred at this temperature for 1 h, and then **K-28-1** (15.0 g, 76.1 mmol) was added dropwise at 0 °C. The resulting mixture was stirred at 25 °C for 18 h. The residue was diluted with H₂O 300 mL and extracted with EtOAc 1000 mL (500 mL * 2). The combined organic layers were washed with brine 1000 mL (500 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **K-28-2** (17.0 g, 19.5 mmol, 25.7% yield, 26.8% purity) was obtained as a yellow oil.

[0601] **Synthesis of methyl 5-(difluoromethoxy)-2-nitrobenzoate (K-28-3)** To a

solution of **K-28-2** (17.0 g, 19.5 mmol) in DMF (170 mL) was added MeI (5.55 g, 39.1 mmol, 2.43 mL) and K₂CO₃ (5.40 g, 39.1 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H₂O 200 mL and extracted with EtOAc 400 mL (200 mL * 2). The combined organic layers were washed with brine 300 mL (150 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=10/1). Compound **K-28-3** (4.80 g, 18.0 mmol, 91.8% yield, 92.4% purity) was obtained as a white oil.

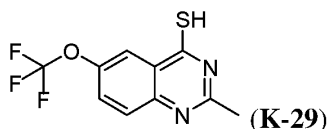
[0602] **Synthesis of methyl 2-amino-5-(difluoromethoxy)benzoate (K-28-4)** To a solution of **K-28-3** (4.20 g, 17.0 mmol) in EtOH (40.0 mL) and H₂O (8.50 mL) was added NH₄Cl (1.82 g, 34.0 mmol), Fe (2.85 g, 50.98 mmol) at 25 °C. The resulting mixture was stirred at 80 °C for 2 h. The reaction was filtered and the filtrate was concentrated under the reduced pressure to give a residue. The residue was diluted with H₂O 100 mL and extracted with EtOAc 300 mL (150 mL * 2). The combined organic layers were washed with brine 300 mL (150 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. Compound **K-28-4** (2.90 g, 11.8 mmol, 69.5% yield, 88.5% purity) was obtained as a brown oil.

[0603] **Synthesis of 6-(difluoromethoxy)-2-methylquinazolin-4-ol (K-28-5)** To a solution of acetamidine (2.54 g, 43.7 mmol) in 2-methoxyethanol (50.0 mL) was added AcONa (3.59 g, 43.7 mmol) and **K-28-4** (1.90 g, 8.75 mmol). The mixture was stirred at 130 °C for 24 h. The reaction mixture was diluted with H₂O 50 mL and extracted with EtOAc 200 mL (100 mL *2). The combined organic layers were washed with brine 300 mL, dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with MTBE (100 mL) at 25 °C for 30 min. Compound **K-28-5** (1.10 g, 4.86 mmol, 55.6% yield) was obtained as a white solid.

[0604] **Synthesis of 6-(difluoromethoxy)-2-methylquinazoline-4-thiol (K-28)** To a solution of **K-28-5** (1.10 g, 4.86 mmol) in toluene (10 mL) was added Lawesson's reagent (2.95 g, 7.30 mmol). The mixture was stirred at 100 °C for 3 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, Petroleum ether/THF=3/1). Compound **K-28** (1.20 g,

4.43 mmol, 91.2% yield, 89.5% purity) was obtained as a white solid.

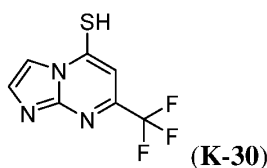
[0605] **Synthesis of 2-methyl-6-(trifluoromethoxy)quinazoline-4-thiol (K-29):**



[0606] **Synthesis of 2-methyl-6-(trifluoromethoxy)quinazolin-4-ol (K-29-1)** To a solution of 2-amino-5-(trifluoromethoxy)benzoic acid (10.0 g, 45.2 mmol) in 2-methoxyethanol (100 mL) was added acetamidine hydrochloride (10.7 g, 113 mmol) and NaOAc (9.27 g, 113 mmol, 2.50 eq). The mixture was stirred at 130 °C for 6 h. The mixture was added (300 mL) and filtered. The filter cake was washed with water and dried to give compound **K-29-1** (7.50 g, 30.7 mmol, 67.9% yield, 92.0% purity) as a brown solid.

[0607] **Synthesis of 2-methyl-6-(trifluoromethoxy)quinazoline-4-thiol (K-29)** To a solution of compound **K-29-1** (5.25 g, 21.5 mmol, 1.00 eq) in pyridine (53.0 mL) was added Lawesson's reagent (17.4 g, 43.0 mmol). The mixture was stirred at 145 °C for 16 h. The mixture was poured into water (200 mL) and filtered. The filter cake was washed with water and dried to give compound **K-29** (5.44 g, 20.9 mmol, 97.2% yield) as a yellow solid.

[0608] **Synthesis of 7-(trifluoromethyl)imidazo[1,2-a]pyrimidine-5-thiol (K-30):**



[0609] **Synthesis of 7-(trifluoromethyl)-1H-imidazo[1,2-a]pyrimidin-5-one (K-30-1)** 2-bromo-1,1-diethoxy-ethane (11.0 g, 55.8 mmol, 8.40 mL) was added to a stirred solution of 2-amino-6-(trifluoromethyl)-1H-pyrimidin-4-one (5.00 g, 27.9 mmol, 1 eq) and K₂CO₃ (9.65 g, 69.8 mmol, 2.5 eq) in DMF (40 mL) at 25 °C. The reaction mixture was heated at 80 °C for 16 h, then cooled to 25 °C and partitioned between water (100

mL) and EtOAc (200 mL). The organic phase was washed with water and brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in AcOH (28.5 g, 475 mmol, 27.2 mL) and heated at 120 °C for 1 h. The mixture was cooled to 25 °C, diluted with water and extracted with EtOAc (50 mL), dried over

5 Na₂SO₄, filtered and concentrated under vacuum to give the crude **K-30-1** (2.5 g, 9.11 mmol, 32.6% yield, 74% purity) as white solid.

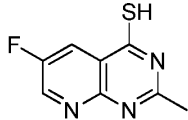
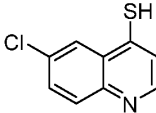
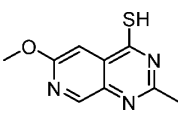
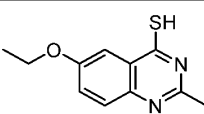
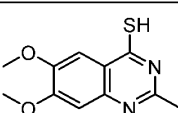
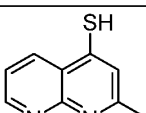
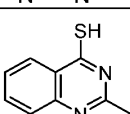
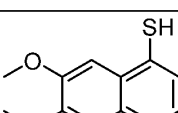
[0610] **Synthesis of 7-(trifluoromethyl)imidazo[1,2-a]pyrimidine-5-thiol (K-30):** A mixture of **K-30-1** (2.3 g, 11.3 mmol, 1 eq) and Lawesson's reagent (4.6 g, 11.3 mmol, 1 eq) in toluene (30 mL) was degassed and purged with N₂ for 3 times, and then the mixture

10 was stirred at 120 °C for 16 h under N₂ atmosphere. The mixture was filtered and the cake was dried in vacuum to give the crude product **K-30** (2 g, 6.39 mmol, 56.41% yield, 70% purity) as yellow solid.

[0611] The following intermediate compounds **K** have been prepared similarly using the experimental conditions described above or art known conditions. Alternatively, they

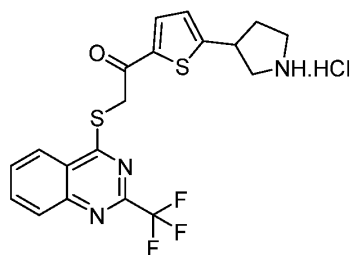
15 were prepared from art known or commercial hydroxy-substituted heteroaryls of formula **Y¹-OH** by thionation using P₂S₅ reagent or Lawesson's reagent.

Cpd number	Structure	Name
K-31		7-methoxy-2-methylquinazoline-4-thiol
K-32		7-methoxyquinoline-4-thiol
K-33		2-methyl-6-(trifluoromethyl)-1,8-naphthyridine-4-thiol
K-34		5-methoxy-2-methyl-quinazoline-4-thiol
K-35		6-methoxyquinoline-4-thiol

K-36		6-fluoro-2-methylpyrido[2,3-d]pyrimidine-4-thiol
K-37		6-chloroquinoline-4-thiol
K-38		6-methoxy-2-methylpyrido[3,4-d]pyrimidine-4-thiol
K-39		6-ethoxy-2-methylquinazoline-4-thiol
K-40		6,7-dimethoxy-2-methylquinazoline-4-thiol
K-41		2-methyl-1,8-naphthyridine-4-thiol
K-42		2-methylquinazoline-4-thiol
K-43		6,7-dimethoxyquinoline-4-thiol

Preparation of example compounds

[0612] **Synthesis of 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride (Example 1):**

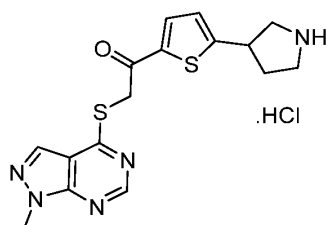


(Example 1)

[0613] **Synthesis of tert-butyl 3-(5-(2-((2-(trifluoromethyl)quinazolin-4-yl)thio)acetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (M-1)** To a solution of 2-(trifluoromethyl)quinazoline-4-thiol **K-1** (123 mg, 0.536 mmol) in DMF, added NaOMe (35 mg, 0.643 mmol) at 0° C and the mixture was stirred for 30 min. tert-Butyl 3-(5-(2-bromoacetyl)thiophen-2-yl)pyrrolidine-1-carboxylate **I-1** (200 mg, 0.536 mmol) was added and stirring was continued at rt for 2 h. The reaction mixture was then concentrated, and the crude was purified by combi flash C18-reverse-phase column (0.1% FA in ACN) chromatography to afford **M-1** (82 mg, 29% yield) as a white solid.

[0614] **Synthesis of 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride (Example 1)** To a solution mixture of **M-1** (30 mg) in dioxane (0.3 mL) was added 4 N HCl dioxane (0.2 mL) at 0 °C and continuous at rt for 2 h. The solvent was evaporated, and the residue was washed with n-pentane and dried in vacuo to afford title compound **Example 1** HCl salt (5 mg, 25% yield) as an off white solid.

[0615] **Synthesis of 2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one (Example 5)**

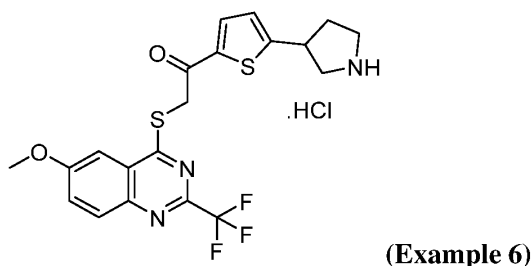


(Example 5)

[0616] **Synthesis of tert-butyl 3-(5-(2-((1-methyl-1H-pyrazolo[3,4-d] pyrimidin-4-yl)thio) acetyl) thiophen-2-yl)pyrrolidine-1-carboxylate (M-34)** To a solution of 1-methyl-1H-pyrazolo[3,4-d] pyrimidine-4-thiol **3** (112 mg, 0.301 mmol 1.0 eq) in DMF cooled to 0 °C was added NaOMe (48 mg, 0.903 mmol, 3 eq). This mixture was stirred for 30 min, then tert-butyl 3-(5-(2-bromoacetyl) thiophen-2-yl) pyrrolidine-1-carboxylate (50 mg, 0.301 mmol, 1.0 eq) was added and stirring continued at rt for 2 h. After concentrating, the crude mixture was purified by C18 reverse-phase combi flash chromatography (0.1% FA in ACN) to afford the title compound **M-34** (72 mg, 52% yield) as a white solid.

[0617] **Synthesis of 2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one hydrochloride (Example 5)** To a solution mixture of *tert*-butyl 3-(5-(2-((1-methyl-1H-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)acetyl)thiophen-2-yl)pyrrolidine-1-carboxylate **M-34** (100 mg) in dioxane (2.0 mL) was added 4 N HCl in dioxane (0.5 mL) at 0 °C, and the mixture was stirred at rt for 2 h. The reaction mixture was evaporated in vacuo. The crude compound was washed with *n*-pentane and dried in vacuo to afford **Example 5** (15 mg, 18% yield) as an off white solid.

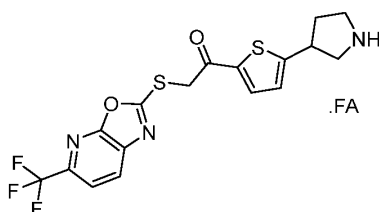
[0618] **Synthesis of 2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one hydrochloride (Example 6):**



[0619] **Synthesis of *tert*-butyl 3-(5-(2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)acetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (M-35):** To a solution of 6-methoxy-2-(trifluoromethyl)quinazoline-4-thiol **K-13** (500 mg, 1.915 mmol, 1.0 eq) in DMF cooled to 0 °C was added NaOMe (517 mg, 9.575 mmol, 5.0 eq) and the mixture was stirred for 30 min at rt. Then **I-1** (714 mg, 1.915 mmol, 1.0 eq) was added and stirring continued at rt for 2 h. After concentrating, the crude was purified by C18 reverse-phase combi flash chromatography (0.1% FA in ACN) to afford title compound **M-35** (620 mg, 62% yield) as a white solid.

[0620] **Synthesis of 2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one hydrochloride (Example 6):** To a solution mixture of *tert*-butyl **M-35** (50 mg) in dioxane (1.0 mL) was added 4 N HCl in dioxane (0.5 mL) at 0 °C and subsequently for 2 h at rt. The reaction mixture was evaporated in vacuo. The residue was washed with *n*-pentane and dried in vacuo to afford title compound **Example 6** (10 mg, 24% yield) as an off white solid.

[0621] Synthesis of 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one formic acid salt (Example 4)



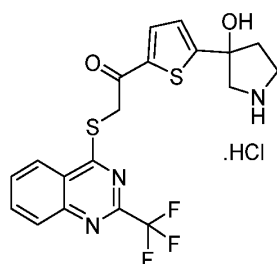
(Example 4)

- 5 [0622] **Synthesis of *tert*-butyl 3-(5-(2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)acetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (M-33)** To a solution of 5-(trifluoromethyl)oxazole[5,4-b] pyridine-2-thiol **K-12** (271 mg, 0.727 mmol) in DMF (3 mL) was added NaOMe (196 mg, 3.635 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C after which compound **I-1** (160 mg, 0.727 mmol) was added. The reaction mixture was stirred for at rt 2 h. After concentrating, the reaction mixture purified by C18 reverse-phase combi flash chromatography (0.1% FA in ACN) to get title compound **M-33** (381 mg, 60% yield) as an off-white solid.

- [0623] **Synthesis of 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one formic acid salt (Example 4):** Compound **M-33** (100 mg, 0.194 mmol) was taken in 1,4-dioxane (10 vol) and cooled to 0 °C. To the reaction mixture 4 N HCl in 1,4-dioxane was added (10 vol), and stirring was continued at room temperature for 2 h. After completion of reaction (TLC monitoring), solvents were evaporated under reduced pressure. The residue was purified by C18 reverse-phase combi-flash chromatography (0.1% FA in ACN) to get **Example 4** (16 mg, 15% yield) as an off-white solid.

[0624] Synthesis of 1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride (Example 18)

236

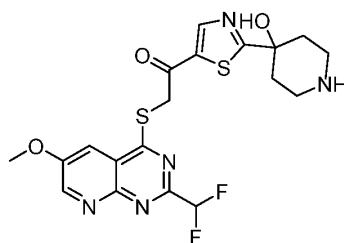


(Example 18)

[0625] **Synthesis of tert-butyl 3-hydroxy-3-(5-(2-((2-(trifluoromethyl)quinazolin-4-yl)thio)acetyl)thiophen-2-yl)pyrrolidine-1-carboxylate (M-2)** To a solution of **K-1** (140 mg, 359 μmol) in MeCN (2 mL) was added K_2CO_3 (49.6 mg, 359 μmol) and **I-8** (82.6 mg, 359 μmol). The mixture was stirred at 25 $^\circ\text{C}$ for 2 h. The reaction mixture was quenched by addition H_2O (10.0 mL) at 25 $^\circ\text{C}$, and then extracted with EtOAc (5.00 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 4 g SepaFlash® Silica Flash Column, Eluent of 0~18% ethyl acetate/petroleum ether gradient @ 40 mL/min) to give compound (**M-2**) (160 mg, 237 μmol , 66.1% yield, 80% purity) as a yellow solid.

[0626] **Synthesis of 1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride (Example 18)** To a mixture of compound **M-2** (160 mg, 237 μmol , 80% purity) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 2 mL), and then the mixture was stirred at 25 $^\circ\text{C}$ for 2 h. The mixture was filtered and the residue was concentrated under reduced pressure to give **Example 18** (80.0 mg, 182 μmol , 76.7% yield, 99.0% purity) as a yellow solid.

[0627] **Synthesis of 2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)ethan-1-one (Example 59)**



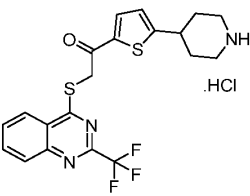
(Example 59)

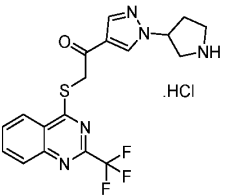
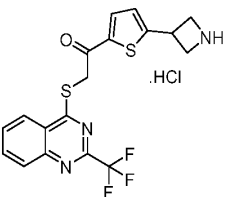
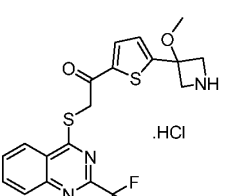
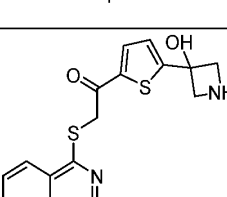
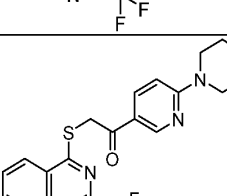
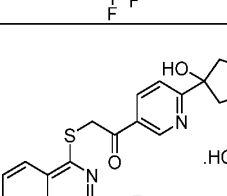
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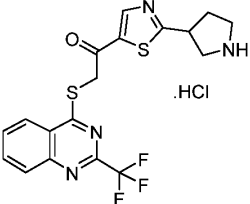
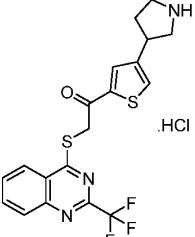
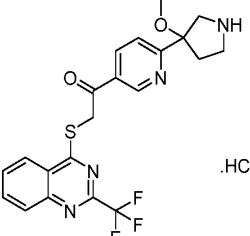
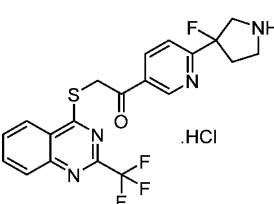
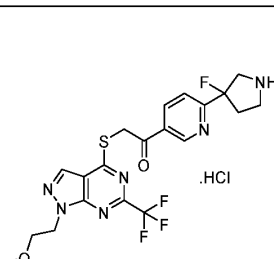
[0628] **tert-butyl 4-[5-[2-[2-(difluoromethyl)-6-methoxy-pyrido[2,3-d]pyrimidin-4-yl]sulfanylacetyl]thiazol-2-yl]-4-hydroxy-piperidine-1-carboxylate (M-103)** To a solution of **K-4** (180 mg, 740 μ mol) in MeCN (3 mL) was added K_2CO_3 (102 mg, 740 μ mol) and), **I-25** (300 mg, 740 μ mol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H_2O (3 mL) and was extracted with EtOAc 30 mL (10 mL*3). The combined organic layers are dried over Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~35% EtOAc/Petroleum ether gradient @ 40 mL/min) to give compound **M-103** (160 mg, 282 μ mol, 38.1 % yield) as a yellow solid.

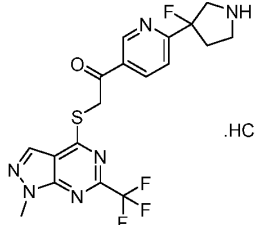
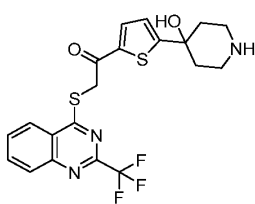
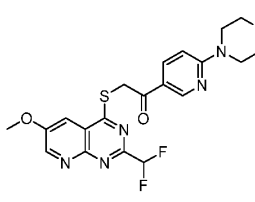
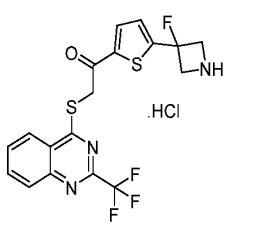
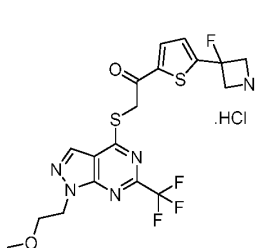
[0629] **Synthesis of 2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)ethan-1-one (Example 59)** To a solution of **M-103** (150 mg, 264 μ mol) in EtOAc (3 mL) was added HCl/EtOAc (4 M, 3 mL). The mixture was stirred at 20 °C for 2 h. The mixture was filtered and the solid was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: C18 150×30mm;mobile phase: [Water(FA)-MeCN];gradient:0%-40% B over 9 min) to give compound **Example 59** (120 mg, 257 μ mol, 97.1 % yield) as a yellow solid.

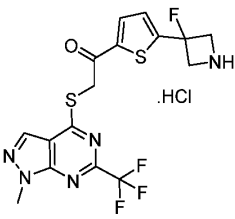
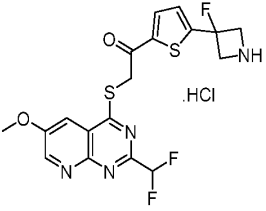
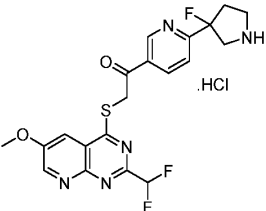
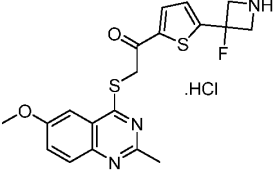
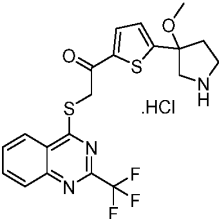
[0630] The Examples below have been prepared using the experimental conditions described above from the reaction of compounds **K** of Formula **Y¹-SH** with bromo-ketones **I** giving N-Boc intermediates (Int.) **M**, followed by de-protection of the Boc protecting group.

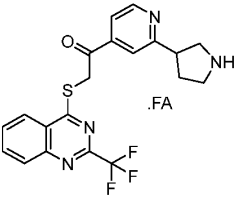
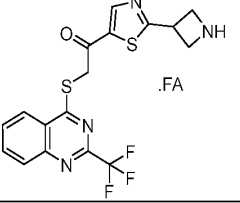
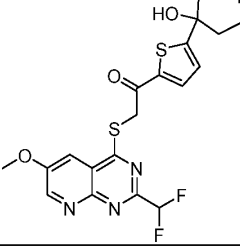
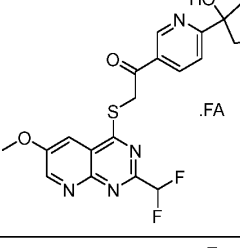
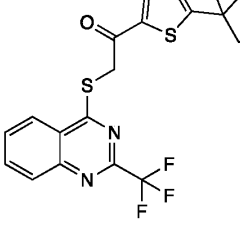
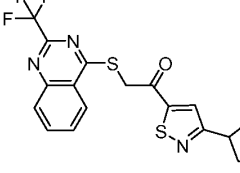
Ex.	Structure	Cpd. K	Cp d. I	N-Boc Int. M	IUPAC name
2		K-1	I-23	M-30	1-(5-(piperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride

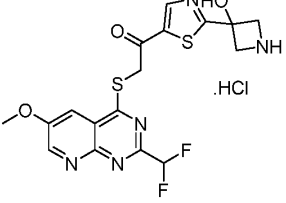
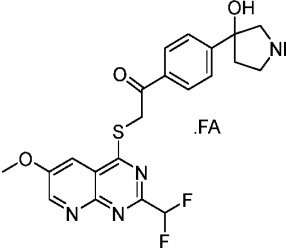
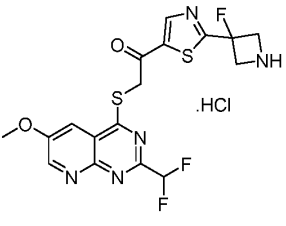
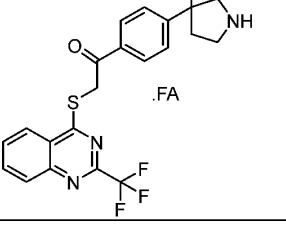
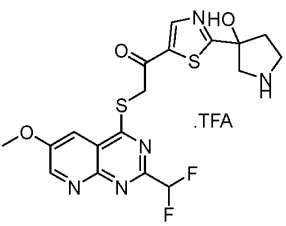
9		K-1	I-3	M-36	1-(1-(pyrrolidin-3-yl)-1H-pyrazol-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride
10		K-1	I-2	M-37	1-(5-(azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride
13		K-1	I-6	M-4	1-(5-(3-methoxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride
14		K-1	I-5	M-5	1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
15		K-1	I-15	M-6	1-(6-(piperazin-1-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
16		K-1	I-11	M-7	1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride

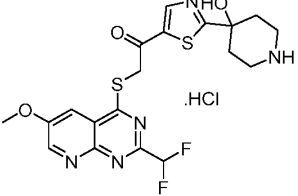
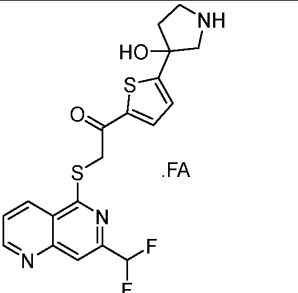
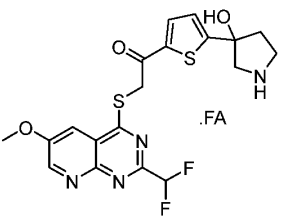
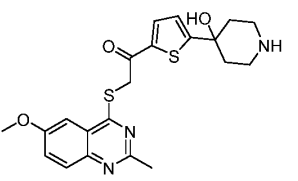
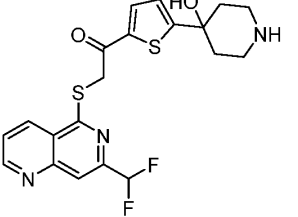
17		K-1	I-4	M-8	1-(2-(pyrrolidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one hydrochloride
19		K-1	I-16	M-9	1-(4-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one hydrochloride
22		K-1	I-12	M-10	1-(6-(3-methoxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one hydrochloride
23		K-1	I-13	M-11	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one hydrochloride
24		K-2	I-13	M-12	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)ethan-1-one hydrochloride

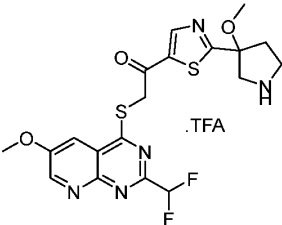
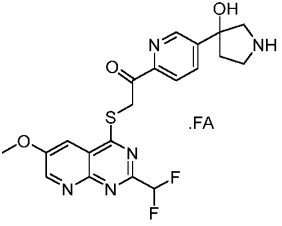
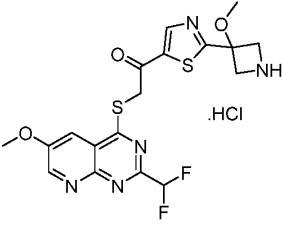
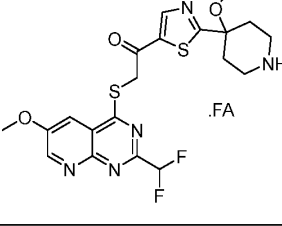
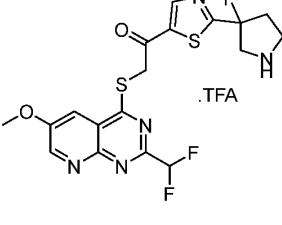
25		K-3	I-13	M-13	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)ethan-1-one hydrochloride
26		K-1	I-10	M-14	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one
27		K-4	I-15	M-15	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-ylthio)-1-(6-(piperazin-1-yl)pyridin-3-yl)ethan-1-one
28		K-1	I-7	M-16	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-ylthio)ethan-1-one hydrochloride
29		K-2	I-7	M-17	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylthio)ethan-1-one hydrochloride

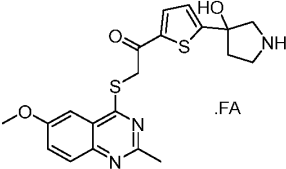
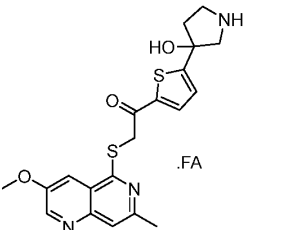
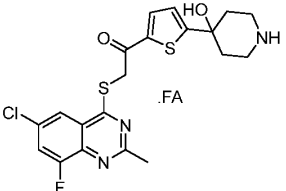
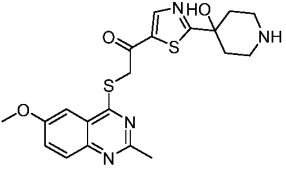
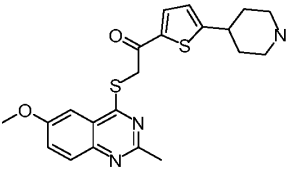
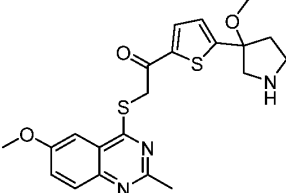
30		K-3	I-7	M-18	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one hydrochloride
31		K-4	I-7	M-19	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)ethan-1-one hydrochloride
32		K-4	I-13	M-20	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)ethan-1-one hydrochloride
33		K-5	I-7	M-21	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one hydrochloride
34		K-1	I-9	M-22	1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride

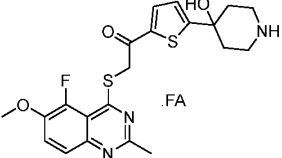
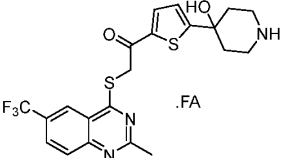
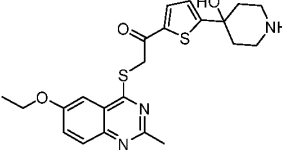
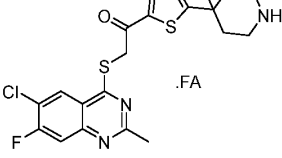
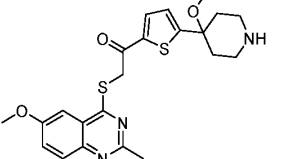
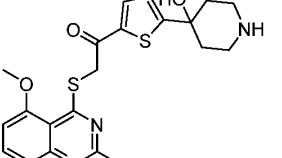
35		K-1	I-17	M-23	1-(2-(pyrrolidin-3-yl)pyridin-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one formic acid salt
36		K-1	I-18	M-24	1-(2-(azetidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one formic acid salt
37		K-4	I-10	M-25	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
38		K-4	I-8	M-26	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)ethan-1-one formic acid salt
52		K-1	I-33	M-45	1-(5-(3-fluoropyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one formic acid salt
53		K-1	I-60	M-46	1-(3-(pyrrolidin-3-yl)isothiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one

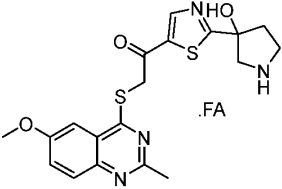
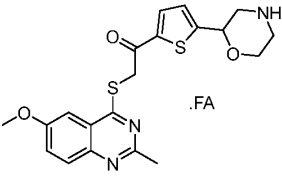
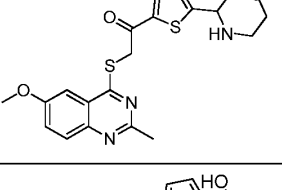
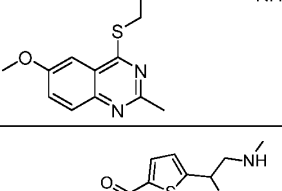
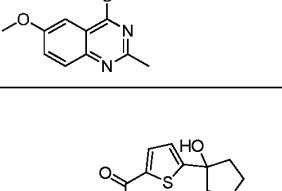
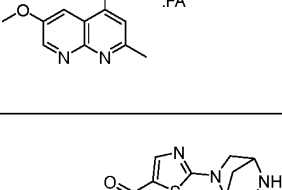
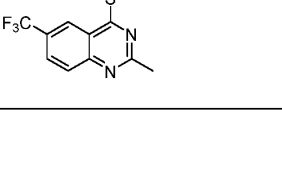
54		K-4	I-30	M-47	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxyazetidin-3-yl)thiazol-5-yl)ethan-1-one hydrochloride
55		K-4	I-59	M-48	2-[[7-(difluoromethyl)-3-methoxy-5-quinolyl]sulfanyl]-1-[2-(3-hydroxypyrrolidin-3-yl)pyrimidin-5-yl]ethenone formic acid salt
56		K-4	I-32	M-49	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoroazetidin-3-yl)thiazol-5-yl)ethan-1-one hydrochloride
57		K-1	I-59	M-50	1-[4-(3-hydroxypyrrolidin-3-yl)phenyl]-2-[2-(trifluoromethyl)quinazolin-4-yl]sulfanyl-ethanone formic acid salt
58		K-4	I-27	M-51	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)ethenone trifluoroacetic acid salt

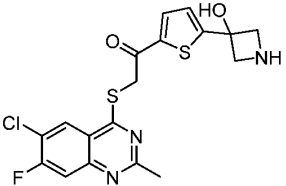
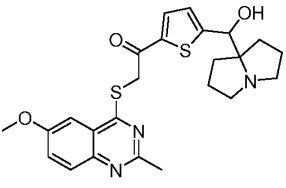
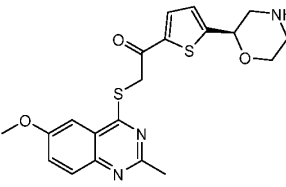
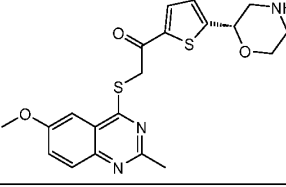
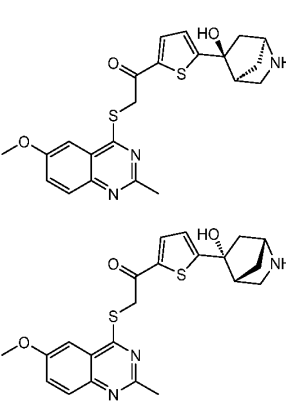
59		K-4	I-25	M-103	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)ethan-1-one hydrochloride
60		K-23	I-8	M-53	2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one formic acid salt
61		K-4	I-8	M-54	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one formic acid salt
62		K-5	I-10	M-55	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
63		K-23	I-10	M-56	2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one

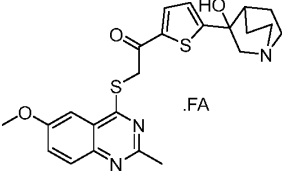
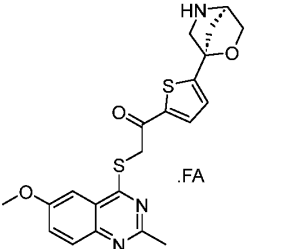
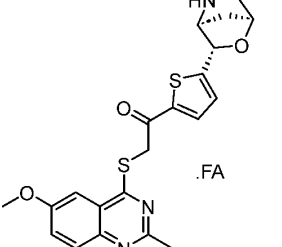
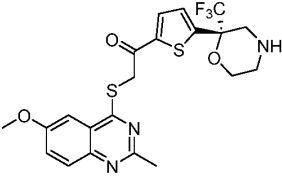
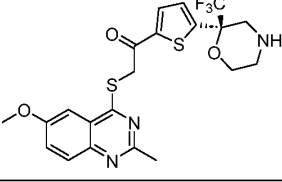
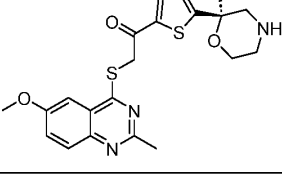
64		K-4	I-28	M-57	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-methoxypyrrolidin-3-yl)thiazol-5-yl)ethenone trifluoroacetic acid salt
65		K-4	I-35	M-58	2-[2-(difluoromethyl)-6-methoxy-pyrido[2,3-d]pyrimidin-4-yl]sulfanyl-1-[5-(3-hydroxypyrrolidin-3-yl)-2-pyridyl]ethenone formic acid salt
66		K-4	I-31	M-59	1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one hydrochloride
67		K-4	I-26	M-60	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-methoxypiperidin-4-yl)thiazol-5-yl)ethan-1-one formic acid salt
68		K-4	I-29	M-61	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoropyrrolidin-3-yl)thiazol-5-yl)ethenone trifluoroacetic acid salt

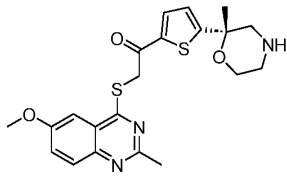
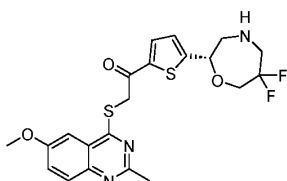
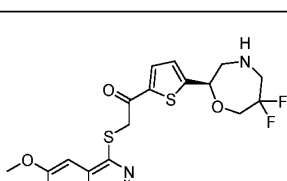
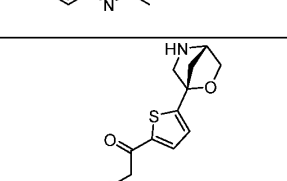
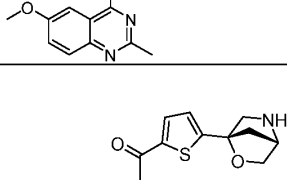
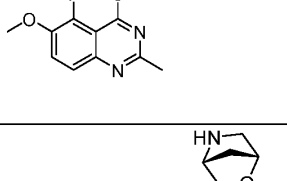
70		K-5	I-8	M-62	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
71		K-16	I-8	M-63	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one formic acid salt
73		K-20	I-10	M-64	2-(6-chloro-8-fluoro-2-methyl-quinazolin-4-yl)sulfanyl-1-[5-(4-hydroxy-4-piperidyl)-2-thienyl]ethanone formic acid salt
74		K-5	I-25	M-65	1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
76		K-5	I-23	M-66	2-(6-methoxy-2-methyl-pyrido[2,3-d]pyrimidin-4-yl)sulfanyl-1-[5-(4-piperidyl)-2-thienyl]ethanone
77		K-5	I-9	M-67	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one

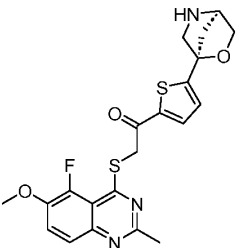
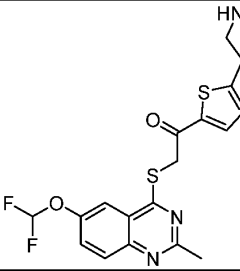
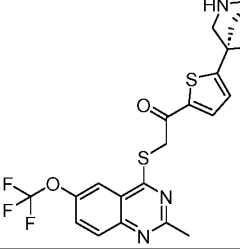
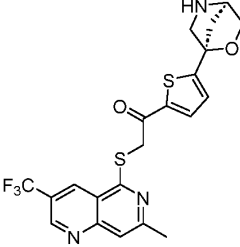
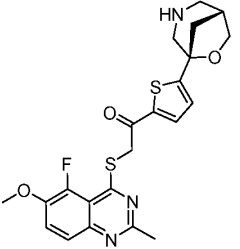
80		K-17	I-10	M-68	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethanone formic acid salt
81		K-24	I-10	M-69	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one formic acid salt
83		K-39	I-10	M-104	2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
84		K-15	I-10	M-70	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one formic acid salt
85		K-5	I-24	M-71	2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanyl-1-[5-(4-methoxy-4-piperidyl)-2-thienyl]ethanone
89		K-34	I-10	M-72	1-[5-(4-hydroxy-4-piperidyl)-2-thienyl]-2-(5-methoxy-2-methyl-quinazolin-4-yl)sulfanyl-ethanone

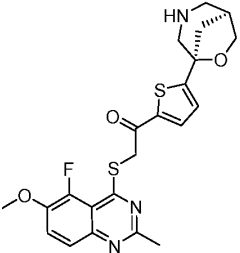
78		K-5	I-27	M-73	1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone formic acid salt
95		K-5	I-45	M-74	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one formic acid salt
101		K-5	I-43	M-75	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-3-yl)thiophen-2-yl)ethanone
129		K-5	I-5	M-76	1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
132		K-5	I-49	M-77	1-(5-(1-hydroxy-2-(methylamino)ethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
133		K-19	I-8	M-78	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one formic acid salt
134		K-24	I-40	M-79	1-(2-(2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one

136		K-15	I-5	M-80	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)ethan-1-one
148		K-5	I-47	M-81	1-(5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
157 or 158		K-5	I-45	M-82	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
157 or 158		K-5	I-45	M-83	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
162		K-5	I-46	M-84	1-(5-((1S,4S,5S)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((1R,4R,5R)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

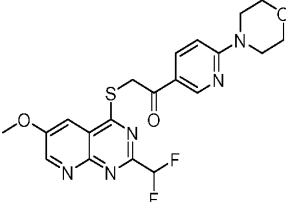
163		K-5	I-56	M-85	1-(5-(3-hydroxyquinuclidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
165		K-5	I-55	M-86	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
166		K-5	I-41	M-87	1-(5-((1S,3S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
167 or 168		K-5	I-52	M-88	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethanone
167 or 168		K-5	I-52	M-89	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethanone
169 or 170		K-5	I-48	M-90	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one

160 or 170		K-5	I-48	M-91	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
171 or 172		K-5	I-54	M-92	(S)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
171 or 172		K-5	I-54	M-93	(R)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
173		K-5	I-42	M-94	1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
175		K-17	I-42	M-95	1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
177		K-5	I-57	M-96	1-(5-((1R,3R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt

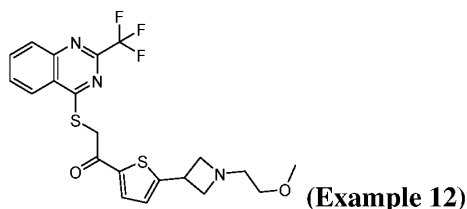
179		K-17	I-55	M-97	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
180		K-28	I-55	M-98	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)ethan-1-one
183		K-29	I-55	M-99	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
185		K-18	I-55	M-100	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
187 or 188		K-17	I-58	M-101	1-(5-((1R,5S)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

187 or 188		K-17	I-58	M-102	1-(5-((1S,5R)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
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[0631] The Examples below have been prepared using the experimental conditions described above from the reaction of compounds **K** of Formula **Y¹-SH** with bromo-ketones **I**.

Ex.	Structure	Cpd. Y ¹ -SH	Cpd. I	IUPAC name
21		K-4	I-14	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-morpholinopyridin-3-yl)ethan-1-one

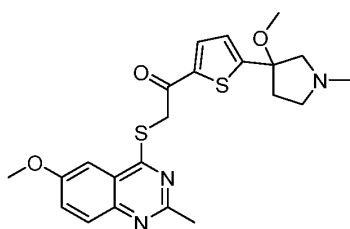
- [0632] **Synthesis of 1-(5-(1-(2-methoxyethyl)azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one (Example 12)**



- [0633] To a solution of (COCl)₂ (18.4 mg, 145 μmol, 12.6 μL) in DCM (1.00 mL) was added dropwise DMSO (22.6 mg, 289 μmol, 22.6 μL) at -78 °C. After addition, 2-methoxyethanol (10.0 mg, 131 μmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h, and then TEA (39.9 mg, 394 μmol, 54.9 μL) was added dropwise at -78 °C. The resulting mixture was stirred at 25 °C for 1.5 h. To the mixture was added compound **Example 10** (30.0 mg, 73.3 μmol), AcOH (2.20 mg, 36.6 μmol, 2.10 μL), NaBH(OAc)₃ (15.5 mg, 73.3 μmol). The mixture was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 18 h under N₂ atmosphere. The reaction mixture was purified directly by prep-HPLC (column: Waters

X bridge BEH C18 100 x 30 mm x 10 μ m; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 45%-70% B over 8.0 min) to give **Example 12** (2.89 mg, 7.51% yield, 89.0% purity) as a light yellow solid.

[0634] **Synthesis of 1-(5-(3-methoxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 86)**



(Example 86)

[0635] **Synthesis of tert-butyl 3-methoxy-3-[5-[2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanylacetyl]-2-thienyl]pyrrolidine-1-carboxylate (M-67)** To a solution of **K-5** (245 mg, 1.19 mmol) in MeCN (10 mL) was added K₂CO₃ (164 mg, 1.19 mmol) and **I-9** (800 mg, 1.19 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H₂O (3 mL) and was extracted with EtOAc 30 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 12 g SepaFlash® Silica Flash Column, Eluent of 0~60% Ethyl acetate/Petroleum ether gradient @ 40 mL/min) to give compound **M-67** (332 mg, 627 μ mol, 52.8 % yield) as a yellow solid.

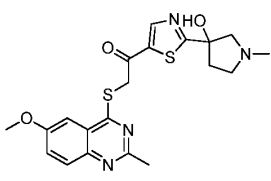
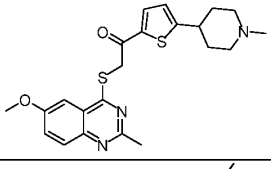
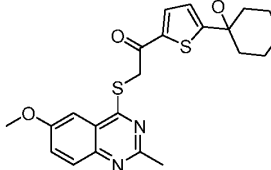
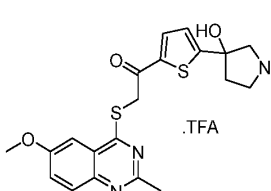
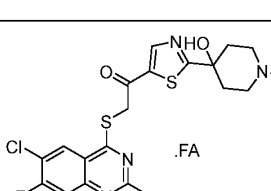
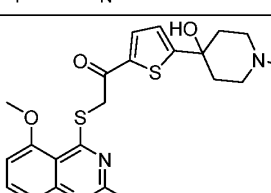
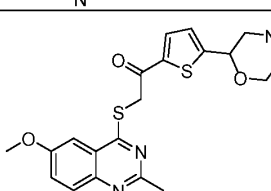
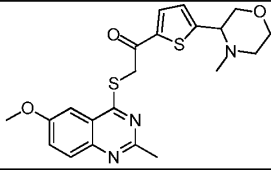
[0636] **Synthesis of 2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanyl-1-[5-(3-methoxypyrrolidin-3-yl)-2-thienyl]ethanone (Example 77)** To a solution of **M-67** (320 mg, 604 μ mol) in EtOAc (3 mL) was added HCl/EtOAc (2 M, 3 mL). The mixture was stirred at 25 °C for 16 h. The mixture was filtered and the solid was concentrated under reduced pressure to give compound **Example 77** (250 mg, 582 μ mol, 96.3 % yield) as a yellow solid.

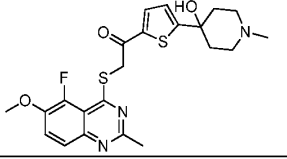
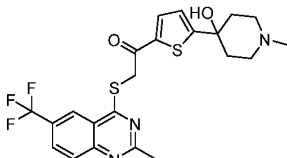
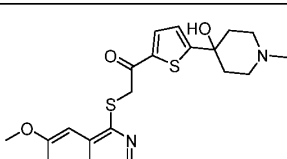
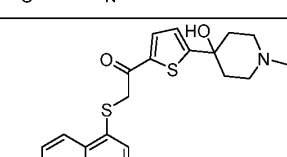
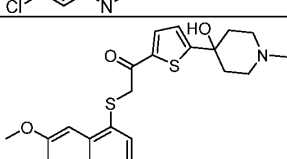
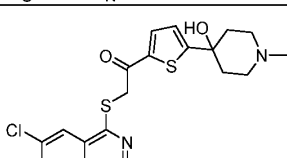
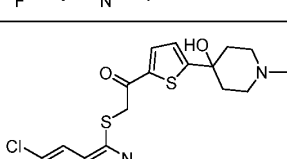
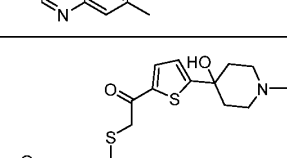
[0637] **Synthesis of 1-(5-(3-methoxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 86)** To a solution of **Example 77** (100 mg, 233 μ mol) in DCM (0.5 mL) was added AcOH (41.9 mg, 698 μ mol) and HCHO (34.9 mg, 1.16 mmol). The mixture was stirred at 25 °C for 1 h. Then

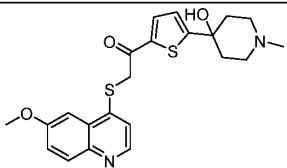
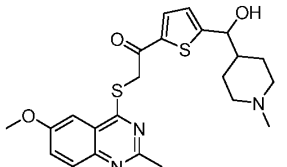
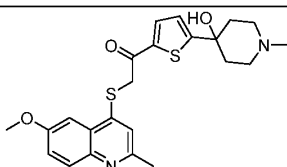
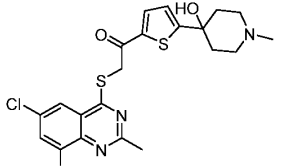
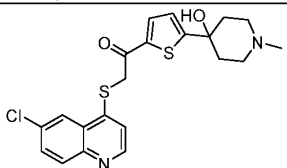
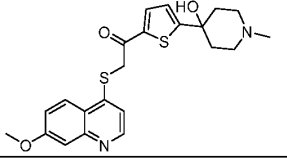
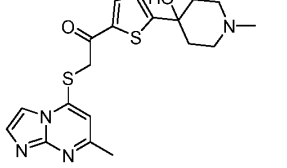
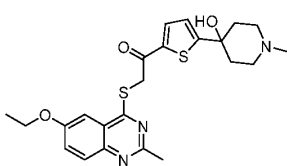
the mixture was added NaBH(OAc)₃ (148 mg, 698 μmol) and stirred at 25°C for 1 h. The reaction mixture was quenched with H₂O (3 mL) and was extracted with EtOAc 10 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (column: Boston Prime C18 5 150*30mm*5μm; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 18%-38% B over 10 min) to give compound **Example 86** (28.0 mg, 63.1 μmol, 27.1 % yield) as a yellow solid.

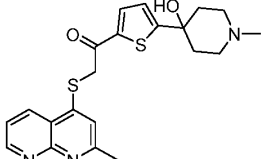
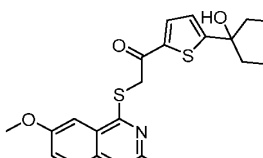
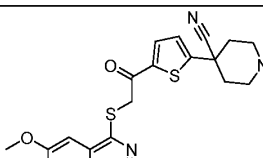
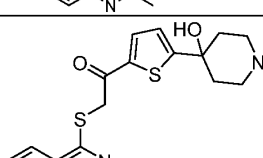
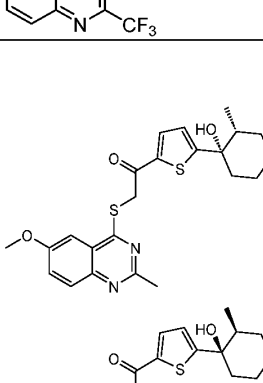
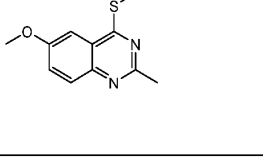
[0638] The Examples below have been prepared using the experimental conditions described above.

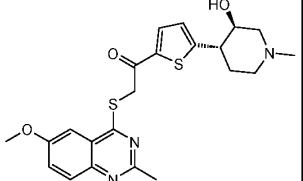
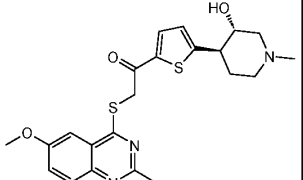
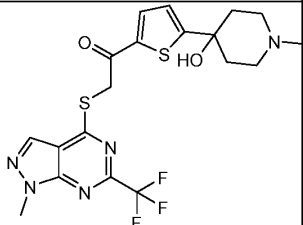
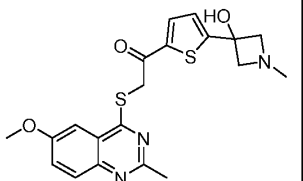
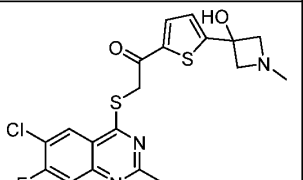
Cpd. P	Structure	Cpd. Y ¹ -SH	Cpd. I	IUPAC name
11		K-1	I-2	1-(5-(1-methylazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
69		K-4	I-10	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
72		K-5	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
75		K-5	I-25	1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

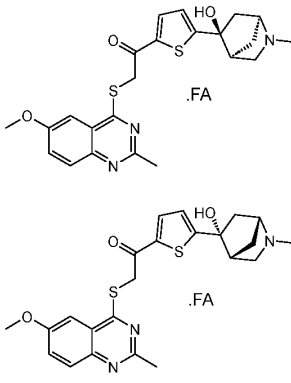
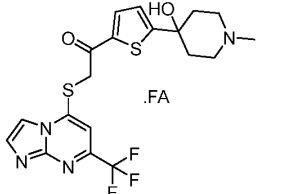
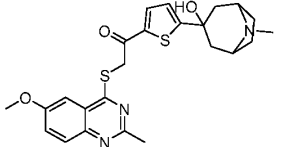
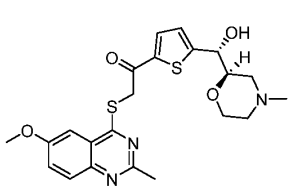
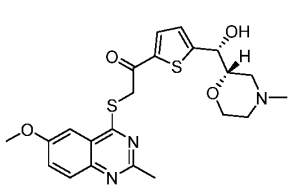
79		K-5	I-27	1-(2-(3-hydroxy-1-methylpyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
82		K-5	I-23	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
88		K-5	I-24	1-[5-(4-methoxy-1-methyl-4-piperidyl)-2-thienyl]-2-(6-methoxy-2-methylquinazolin-4-yl)sulfanyl-ethanone
87		K-5	I-8	1-(5-(3-hydroxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one trifluoroacetic acid salt
90		K-15	I-10	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)ethan-1-one formic acid salt
91		K-34	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-(5-methoxy-2-methylquinazolin-4-yl)sulfanyl-ethanone
96		K-5	I-45	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
102		K-5	I-43	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-3-yl)thiophen-2-yl)ethanone

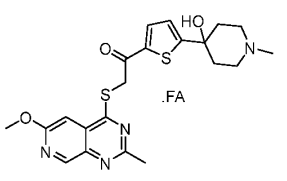
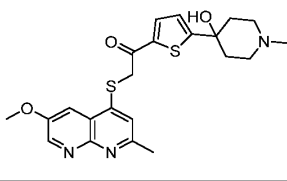
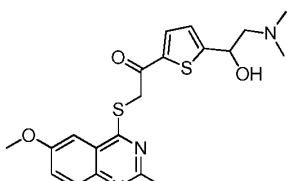
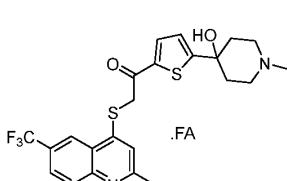
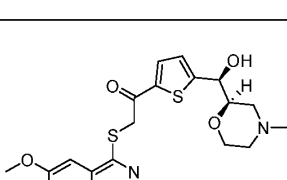
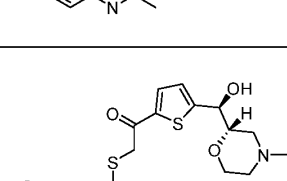
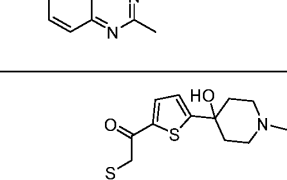
103		K-17	I-10	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethanone
104		K-24	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
105		K-40	I-10	2-((6,7-dimethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
106		K-21	I-10	2-[(7-chloro-4-quinolyl)sulfanyl]-1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]ethanone
107		K-43	I-10	2-((6,7-dimethoxyquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
108		K-15	I-10	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
109		K-27	I-10	2-((3-chloro-7-methyl-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
110		K-16	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one

111		K-22	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-[(6-methoxy-4-quinolyl)sulfanyl]ethanone
112		K-5	I-38	1-(5-(hydroxy(1-methylpiperidin-4-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
113		K-25	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinolin-4-yl)thio)ethan-1-one
114		K-20	I-10	2-(6-chloro-8-fluoro-2-methyl-quinazolin-4-yl)sulfanyl-1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]ethanone
115		K-37	I-10	2-[(6-chloro-4-quinolyl)sulfanyl]-1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]ethanone
116		K-32	I-10	2-[(6-chloro-4-quinolyl)sulfanyl]-1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]ethanone
117		K-14	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methylimidazo[1,2-a]pyrimidin-5-yl)thio)ethan-1-one
118		K-39	I-10	2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one

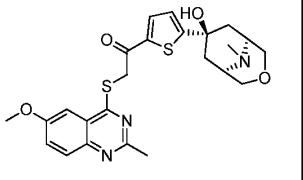
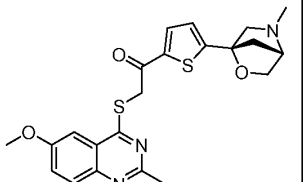
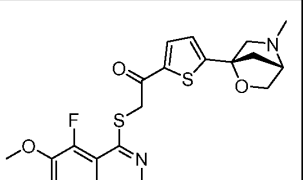
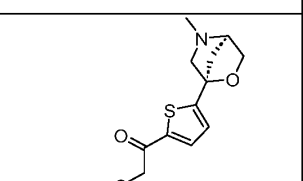
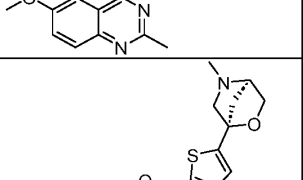
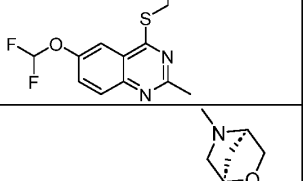
119		K-41	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
120		K-5	I-61	1-(5-(3-hydroxy-1-methylpiperidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
121		K-5	I-39	4-(5-(2-((6-methoxy-2-methylquinazolin-4-yl)thio)acetyl)thiophen-2-yl)-1-methylpiperidine-4-carbonitrile
122		K-1	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
123		K-5	I-36	1-(5-((3R,4S)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((3S,4R)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
125		K-42	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethan-1-one

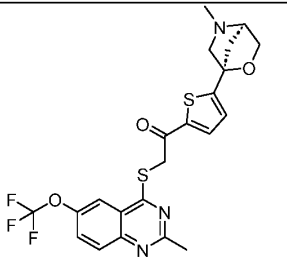
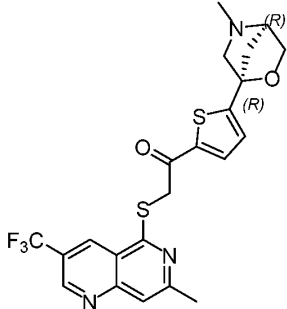
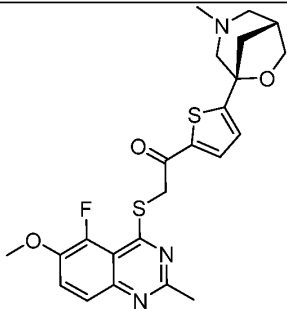
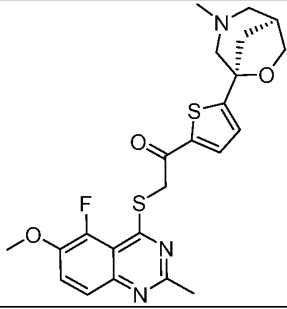
126 or 127		K-5	I-44	1-(5-((3R,4S)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
126 or 127		K-5	I-44	1-(5-((3S,4R)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
128		K-3	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
130		K-5	I-5	1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
137		K-15	I-5	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)ethan-1-one

139		K-5	I-46	1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt and 1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
140		K-30	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-[7-(trifluoromethyl)imidazo[1,2-a]pyrimidin-5-yl]sulfanylethanone formic acid salt
141		K-5	I-37	1-[5-(3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2-thienyl]-2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanylethanone
142 or 143 or 149 or 150		K-5	I-53	1-(5-((R)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150		K-5	I-53	1-(5-((R)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

144		K-38	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-(6-methoxy-2-methyl-pyrido[3,4-d]pyrimidin-4-yl)sulfanyl-ethanone formic acid salt
145		K-19	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
146		K-5	I-49	1-(5-(2-(dimethylamino)-1-hydroxyethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
147		K-25	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinolin-4-yl)thio)ethanone formic acid salt
142 or 143 or 149 or 150		K-5	I-53	1-(5-((S)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150		K-5	I-53	1-(5-((S)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
151		K-26	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,5-naphthyridin-4-yl)thio)ethan-1-one

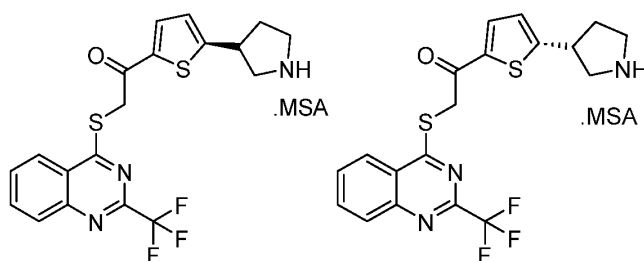
153		K-18	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
154		K-33	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-[[2-methyl-6-(trifluoromethyl)-1,8-naphthyridin-4-yl]sulfanyl]ethanone
155		K-8	I-10	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
156		K-36	I-10	2-((6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethanone
159 or 160		K-5	I-46	1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
159 or 160		K-5	I-46	1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
161		K-31	I-10	1-[5-(4-hydroxy-1-methyl-4-piperidyl)-2-thienyl]-2-(7-methoxy-2-methylquinazolin-4-yl)sulfanyl-ethanone hydrochloride

164		K-5	I-51	1-(5-((1R,5S,7s)-7-hydroxy-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
174		K-5	I-42	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
176		K-17	I-42	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
178		K-5	I-55	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
181		K-28	I-55	2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
182		K-17	I-55	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one

184		K-29	I-55	1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
185		K-18	I-55	1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
189 or 190		K-17	I-58	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,5S)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one
189 or 190		K-17	I-58	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,5R)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one

[0639] Compounds obtained as racemic or diastereomeric mixtures were separated into pure enantiomers and/or diastereomers according to the general method below.

[0640] Synthesis of (R)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one methanesulfonate and (S)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one methanesulfonate (Example 7 and 8).



5

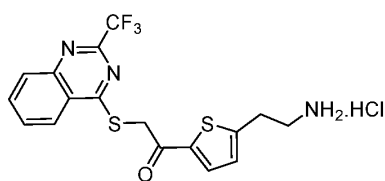
(Example 7 and 8)

[0641] The enantiomers were separated by chiral HPLC of compound (rac)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one (**Example 1**) over a CHIRALPAK IG, 250 x 30 mm, 5 μ m column; mobile phase: n-hexane/DCM/EtOH/MSA (55:35:10:0.10); flow rate: 20.0 mL/min; column temperature: 40°C. After evaporation of the eluent both enantiomers were isolated as MSA salts. LCMS analysis method: CHIRALPAK IG, 250 x 4.6 mm, 5 μ m; mobile phase: n-hexane/DCM/EtOH/MSA (55:35:10:0.10); flow rate: 1.0 mL/min; column temperature: 40°C; **Enantiomer 1**: retention time 13.4 min; **Enantiomer 2**: 18.3 min.

10

[0642] Synthesis of 1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride (Example 39)

15



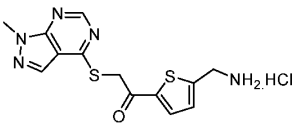
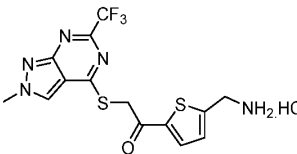
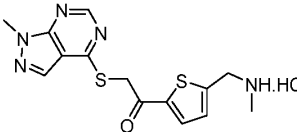
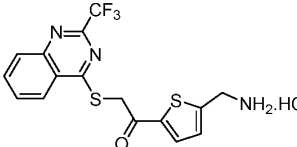
(Example 39)

[0643] To a solution mixture of compound **K-1** (390 mg, 130 mmol) in DMF (5 mL) is added NaOMe (77 mg, 1.43 mmol) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and was added compound **I-21** (549 mg, 156 mmol). The reaction mixture was stirred for 2 h at rt. The reaction mixture was quenched with cold water and extracted with EtOAc (2 x 50 mL). The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude compound was purified by column chromatography over silica gel (60-

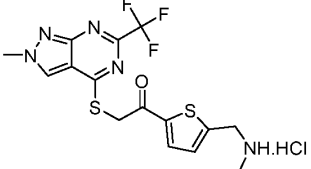
20

120 mesh). The compound was eluted using 30% EtOAc in hexane to afford compound **M-3**. To a solution mixture of compound **M-3** in dioxane (3.0 mL) was added 4 M HCl in dioxane (6.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at rt. The reaction mixture was concentrated in vacuo. The crude compound was washed with n-pentane and dried in vacuo to afford the hydrochloride salt of compound (**Example 39**) as a white solid.

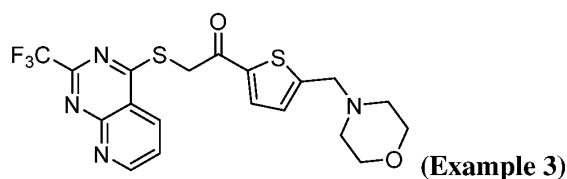
[0644] The following Examples have been prepared using the experimental conditions described above from the reaction of compounds **K** of Formula **Y¹-SH** with bromo-ketone compounds **I** yielding N-Boc intermediates (Int.) **M**, followed by deprotection of the Boc protecting group to provide a terminal amino group.

<i>Cpd #</i>	<i>Structure</i>	<i>Cpd. K</i>	<i>Cpd. I</i>	<i>N-Boc Int. M</i>	<i>Name</i>
40		K-7	I-20	M-27	1-(5-(aminomethyl)thiophen-2-yl)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone hydrochloride
41		K-8	I-20	M-43	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone hydrochloride
42		K-7	I-22	M-39	2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethanone hydrochloride
43		K-1	I-20	M-38	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethanone hydrochloride

44		K-9	I-20	M-44	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one hydrochloride
45		K-10	I-20	M-40	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-cyclopropyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one hydrochloride
46		K-11	I-20	M-31	1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one hydrochloride
47		K-11	I-22	M-32	2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one hydrochloride
48		K-6	I-20	M-41	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one hydrochloride
49		K-5	I-20	M-29	1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone hydrochloride
50		K-12	I-20	M-42	1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one hydrochloride

51		K-8	I-22	M-28	2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-((methylamino)methyl)thiophen-2-yl)ethan-1-one hydrochloride
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[0645] **Synthesis of 1-(5-(morpholinomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one (Example 3)**



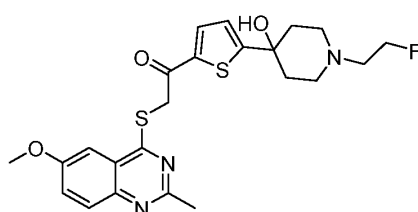
[0646] **Synthesis of 1-(5-(hydroxymethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one (L-1)** To a solution of compound **K-6** (197 mg, 850 μ mol) in DMF (2.00 mL) was added NaOMe (48.3 mg, 893 μ mol) at 0 °C. After addition, the mixture was stirred at this temperature for 30 min, and then compound **I-19** (200 mg, 851 μ mol) was added at 0 °C. The resulting mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by addition H₂O (10.0 mL) at 25 °C, and then the mixture was filtered, the filter cake was concentrated under reduced pressure to give compound **L-1** (200 mg, 54.2% yield, 89.0% purity) was obtained as a light yellow solid.

[0647] **Synthesis of 5-(2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)acetyl)thiophene-2-carbaldehyde (L-2)** A mixture of compound **L-1** (110 mg, 285.43 μ mol), Dess-Martin periodinane (182 mg, 428 μ mol, 133 μ L) in DCM (2.00 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 12 h under N₂ atmosphere. The reaction mixture was filtered and concentrated under reduced pressure to give compound **L-3** (70.0 mg, 63.9% yield) was obtained as a white solid.

[0648] **Synthesis of 1-(5-(morpholinomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one (Example 3)** A mixture of compound **L-3** (70.0 mg, 183 μ mol), morpholine (14.3 mg, 164 μ mol, 14.5

μL), sodium triacetoxyborohydride (38.7 mg, 183 μmol) in DCM (0.70 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 25 °C for 18 h under N₂ atmosphere. The reaction mixture was quenched by addition H₂O (10.0 mL) at 25 °C, and then the mixture was filtered, the filter cake was concentrated under reduced pressure. The crude product was purified by prep-HPLC (The crude product was purified by prep-HPLC (column: C18-1 150 x 30 mm x 5 μm; mobile phase: [Water-ACN]; B%: 20%-50%, 20 min) to give **Example 3** (7.71 mg, 8.84% yield, 95.1% purity) as a light yellow solid.

[0649] **Synthesis of 1-(5-(1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 92)**



(Example 92)

[0650] **Synthesis of tert-butyl 4-hydroxy-4-[5-[2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanylacetyl]-2-thienyl]piperidine-1-carboxylate (M-55)** To a solution of **K-5** (1.28 g, 6.18 mmol) in MeCN (25 mL) was added K₂CO₃ (1.71 g, 12.4 mmol) and **I-10** (2.50 g, 6.18 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched with H₂O (30 mL) and was extracted with EtOAc 50 mL. The combined organic layers are dried over Na₂SO₄, filtered and concentrated to give compound **M-55** (3.20 g, 6.04 mmol, 97.7 % yield) as a yellow solid.

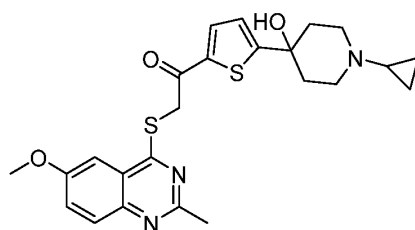
[0651] **Synthesis of 1-[5-(4-hydroxy-4-piperidyl)-2-thienyl]-2-(6-methoxy-2-methyl-quinazolin-4-yl)sulfanyl-ethanone (Example 62)** To a solution of **M-55** (3.30 g, 6.23 mmol) in EtOAc (30 mL) was added HCl/EtOAc (2 M, 30 mL). The mixture was stirred at 25 °C for 16 h. The mixture was filtered and the solid was concentrated under reduced pressure to give compound **Example 62** (2.80 g, 6.13 mmol, 98.3 % yield, 94 % purity) as a yellow solid.

[0652] **Synthesis of 1-(5-(1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 92)** To a solution of **Example 62** (200 mg, 466 μ mol) in DMF (2 mL) was added K_2CO_3 (161 mg, 1.16 mmol) and 1-bromo-2-fluoro-ethane (177 mg, 1.40 mmol). The mixture was stirred at 60 °C for 2 h. The mixture was filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Prime C18 150 * 30 mm * 5 μ m; mobile phase: [water (ammonia hydroxide v/v)-ACN];gradient:38%-58% B over 5 min) to give compound **Example 92** (79 mg, 166 μ mol, 35.7 % yield) as a yellow solid.

10 [0653] The examples below were similarly prepared from **Example 62** as described above using N-alkylating reagents **Alk-X**.

Ex	Structure	Alk-X	IUPAC name
93			1-(5-(4-hydroxy-1-isopropylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
94			1-(5-(4-hydroxy-1-(2-methoxyethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
97			1-(5-(1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one formic acid salt
124			1-(5-(4-hydroxy-1-(2,2,2-trifluoroethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

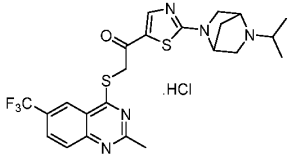
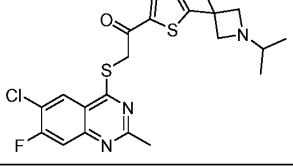
[0654] **Synthesis of 1-(5-(1-cyclopropyl-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 98)**



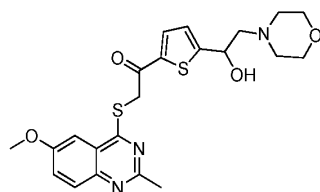
(Example 98)

[0655] **Synthesis of 1-(5-(1-cyclopropyl-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one (Example 98)** To a solution of **Example 62** (150 mg, 349 μ mol) in DCM (2 mL) was added (1-ethoxycyclopropoxy)-trimethyl-silane (122 mg, 698 μ mol), $\text{NaBH}(\text{OAc})_3$ (222 mg, 1.05 mmol) and AcOH (41.9 mg, 698 μ mol). The mixture was stirred at 25 $^{\circ}\text{C}$ for 16 h. The reaction mixture was quenched by addition NH_4Cl solution 4 mL at 25 $^{\circ}\text{C}$, and extracted with DCM 10 mL. The combined organic layers dried over MgSO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Boston Prime C18 150*30mm*5 μ m; mobile phase: [water (ammonia hydroxide v/v)-ACN]; gradient: 45%-65% B over 5 min) to give compound **Example 98** (37.0 mg, 78.8 μ mol, 22.5 % yield) as a yellow solid.

Ex	Structure	Starting Ex.	Cpd. -X	IUPAC name
99		62		1-(5-(1-cyclobutyl-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
100		62		1-(5-(4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
131		129		1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

135		134		1-((2-(5-isopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one hydrochloride
138		136		2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)ethan-1-one

[0656] **Synthesis of 1-(5-(1-hydroxy-2-morpholinoethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone (Example 152):**



(Example 152)

[0657] **Synthesis of tert-butyl (2-hydroxy-2-(5-(2-((6-methoxy-2-methylquinazolin-4-yl)thio)acetyl)thiophen-2-yl)ethyl)carbamate (Example 152-1)** To a solution of **I-34** (2 g, 3.73 mmol) in ACN (40 mL) was added K₂CO₃ (774.02 mg, 5.60 mmol) and **K-5** (770 mg, 3.73 mmol). The mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~75% Ethyl acetate/Petroleum ether gradient @ 60 mL/min). **Example 152-1** (1.6 g, 2.68 mmol, 71.8% yield, 82% purity) was obtained as a yellow solid.

[0658] **Synthesis of 1-(5-(2-amino-1-hydroxyethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone (Example 152-2)** To a solution of **Example 152-1** (1.6 g, 3.27 mmol) in DCM (20 mL) was added HCl/dioxane (2 M, 9.80 mL, 6 eq). The mixture was stirred at 25 °C for 3 h. The reaction liquid is filtered directly and the solids are collected. **Example 152-2** (1.35 g, 3.17 mmol, 97% yield, HCl) was obtained as a yellow solid.

[0659] **Synthesis of 1-(5-(1-hydroxy-2-morpholinoethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone (Example 152)** To a solution of **Example 152-2** (1 g, 2.35 mmol) in DMF (15 mL) was added DIEA (1.21 g, 9.39 mmol) and 1-bromo-2-(2-bromoethoxy)ethane (1.09 g, 4.70 mmol). The mixture was stirred at 120 °C for 1h. The reaction mixture was partitioned between EtOAc 80 mL and H₂O 60 mL. The organic phase was separated, washed with brine 120 mL (60 mL * 2), dried over MgSO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Xtimate C18 150*40mm*5um;mobile phase: [water(FA)-ACN];gradient:2%-42% B over 9 min) and prep-HPLC (column: C18 150x40mm;mobile phase: [water(NH₃H₂O+NH₄HCO₃)-ACN];gradient:20%-60% B over 9 min) to give **Example 152** (280 mg, 609 μmol, 26.0% yield, 100% purity) as a yellow solid.

Properties of examples compounds

<i>Ex.</i>	<i>Form</i>	<i>LC-MS m/z (Rt)</i>	<i>Method</i>	<i>¹H-NMR [400 MHz]</i>
1	off white solid	424.15 [M+1] ⁺ , (1.83 min)	3	δ (DMSO- <i>d</i> ₆): δ 1.62-1.12 (m, 3H), 2.93-3.21 (m, 3H), 3.41 (t, <i>J</i> = 7.2 Hz, 1H), 3.57 (t, <i>J</i> = 7.6 Hz, 1H), 4.72 (s, 1H), 6.96 (d, <i>J</i> = 4.0 Hz, 1H), 7.74 (t, <i>J</i> = 4.0 Hz, 1H), 7.88 (d, <i>J</i> = 4.0 Hz, 1H), 7.97 (t, <i>J</i> = 7.6 Hz, 1H), 8.10 (d, <i>J</i> = 4.0 Hz, 1H), 8.22 (d, <i>J</i> = 4.0 Hz, 1H).
2	off white solid	438.09 [M+1] ⁺ , (1.87 min)	4	δ (DMSO- <i>d</i> ₆): 2.04-2.23 (m, 4H), 2.94-3.14 (m, 3H), 3.47 (d, <i>J</i> = 12.8 Hz, 3H), 4.76 (s, 2H), 4.72 (s, 1H), 6.99 (d, <i>J</i> = 4.0 Hz, 1H), 7.76 (t, <i>J</i> = 7.2 Hz, 1H), 7.89 (d, <i>J</i> = 3.6 Hz, 1H), 7.99 (t, <i>J</i> = 6.8 Hz, 1H), 8.10 (d, <i>J</i> = 8.4 Hz, 1H), 8.21 (d, <i>J</i> = 8.0 Hz, 1H), 8.55 (s, 1H).
3	light yellow solid	455.1 [M+H] ⁺ , (2.69 min)	8	δ (DMSO- <i>d</i> ₆): 9.38 (t, <i>J</i> = 4.0 Hz, 1H), 8.83 (d, <i>J</i> = 8.4 Hz, 1H), 8.09 (d, <i>J</i> = 4.2 Hz, 1H), 7.93-7.90 (m, 1H), 7.18 (d, <i>J</i> = 4.0 Hz, 1H), 5.00 (s, 2H), 3.76 (s, 2H), 3.60-3.57 (m, 4H), 2.44 (m, 4H).

4	off-white solid	414.10 [M+1] ⁺ , (1.05 min)	3	δ (DMSO- <i>d</i> ₆): δ 1.99-2.05 (m, 1H), 2.44-2.55 (m, 1H), 3.13-3.38 (m, 3H), 3.67-3.84 (m, 2H), 5.13 (s, 2H), 7.28 (d, <i>J</i> = 3.6 Hz, 1H), 7.95 (d, <i>J</i> = 8.4 Hz, 1H), 8.13 (d, <i>J</i> = 4 Hz, 1H), 8.28 (d, <i>J</i> = 8.0 Hz, 1H), 8.94 (bs, 1H)
5	off white solid	360.25 [M+1] ⁺ , (1.36 min)	3	δ (DMSO- <i>d</i> ₆): δ 2.43-2.46 (m, 2H), 3.14-3.27 (m, 2H), 3.67-3.82 (m, 2H), 3.67-3.82 (m, 2H), 4.021 (s, 3H), 5.00 (s, 2H), 7.27 (d, <i>J</i> = 4.0 Hz, 1H), 8.13 (d, <i>J</i> = 4 Hz, 1H), 8.41 (s, 1H), 8.66 (s, 1H), 9.20
6	off white solid	454.13 [M+1] ⁺ , (1.93 min).	4	δ (DMSO- <i>d</i> ₆): δ 1.98-2.03 (m, 1H), 2.45-2.50 (m, 1H), 3.12-3.43 (m, 3H), 3.68-3.84 (m, 2H), 4.03 (s, 3H), 4.98 (s, 2H), 7.26 (d, <i>J</i> = 4.0 Hz, 1H), 7.44 (d, <i>J</i> = 2.8 Hz, 1H), 7.80 (dd, <i>J</i> = 2.8 Hz, 1H), 8.15 (dd, <i>J</i> = 4.0 Hz, 2H), 8.92 (bs, 2H)
9	white solid	408.1 [M+H] ⁺ , (1.851 min)	11	δ (DMSO- <i>d</i> ₆): 9.45 (s, 2H), 8.81 (s, 1H), 8.35 (d, <i>J</i> = 8.4 Hz, 1H), 8.05-8.25 (m, 3H), 7.96 (ddd, <i>J</i> = 8.0, 6.4, 1.6 Hz, 1H), 5.24-5.37 (m, 1H), 4.82 (s, 2H), 3.50-3.76 (m, 2H), 3.37-3.48 (m, 2H), 2.19-2.48 (m, 2H)
10	yellow solid	410.0 [M+H] ⁺ , (2.292 min)	11	δ (DMSO- <i>d</i> ₆): 9.56-9.00 (m, 2H), 8.35 (d, <i>J</i> = 8.4 Hz, 1H), 8.27-8.10 (m, 3H), 7.95 (d, <i>J</i> = 8.4 Hz, 1H), 7.42 (d, <i>J</i> = 3.6, 1H), 5.00 (s, 2H), 4.52-4.25 (m, 3H), 4.07 (s, 2H)
11	light yellow solid	424.0 [M+H] ⁺ , (3.051 min)	8	δ (DMSO- <i>d</i> ₆): 8.35 (d, <i>J</i> = 8.4 Hz, 1H), 8.20-8.11 (m, 2H), 8.08 (d, <i>J</i> = 4.0 Hz, 1H), 7.95 (d, <i>J</i> = 8.4 Hz, 1H), 7.17 (d, <i>J</i> = 4.0 Hz, 1H), 4.98 (s, 2H), 3.88 (t, <i>J</i> = 6.8 Hz, 1H), 3.63 (t, <i>J</i> = 7.2 Hz, 2H), 3.08 (t, <i>J</i> = 6.4 Hz, 2H), 2.25 (s, 3H)
12	light yellow solid	468.1 [M+H] ⁺ , (3.122 min)	8	δ (DMSO- <i>d</i> ₆): 8.35 (d, <i>J</i> = 8.4 Hz, 1H), 8.20-8.11 (m, 2H), 8.08 (d, <i>J</i> = 4.0 Hz, 1H), 7.99-7.87 (m, 1H), 7.16 (d, <i>J</i> = 3.6 Hz, 1H), 4.98 (s, 2H), 3.95-3.82 (m, 1H), 3.67 (t, <i>J</i> = 7.2 Hz, 2H), 3.34-3.32 (m, 2H), 3.22 (s, 3H), 3.12 (t, <i>J</i> = 6.8 Hz, 2H), 2.58 (t, <i>J</i> = 5.8 Hz, 3H)
13	White solid	440.0 [M+H] ⁺ , (2.745 min)	1	δ (DMSO- <i>d</i> ₆): 9.47 (m, 2 H) 8.35 (d, <i>J</i> = 8.25 Hz, 1 H) 8.26 (d, <i>J</i> = 4.00 Hz, 1 H) 8.16 (m, 2 H) 7.96 (t, <i>J</i> = 7.38 Hz, 1 H) 7.59 (d, <i>J</i> = 4.00 Hz, 1 H) 5.01 (s, 2 H) 4.31 (br d, <i>J</i> = 14.51 Hz, 4 H) 3.17 (s, 3 H)
14	Yellow solid	426.1 [M+H] ⁺ , (3.047 min)	1	δ (DMSO- <i>d</i> ₆): 8.35 (d, <i>J</i> =8.36 Hz, 1 H) 8.29 (s, 1 H) 8.11 - 8.21 (m, 3 H) 7.85 - 8.02 (m, 1 H) 7.46 (d, <i>J</i> =3.74 Hz, 1 H) 5.00 (s, 2 H) 3.94

				(br d, $J=8.80$ Hz, 1 H) 3.83 (br d, $J=8.36$ Hz, 2 H)
15	Yellow solid	434.1 [M+H] ⁺ , (3.202 min)	2	δ (DMSO- d_6): 8.88 (d, $J = 2.4$ Hz, 1H), 8.36 (d, $J = 8.1$ Hz, 1H), 8.20 - 8.11 (m, 2H), 8.05 (dd, $J = 2.5, 9.1$ Hz, 1H), 7.94 (ddd, $J = 1.9, 6.3, 8.3$ Hz, 1H), 6.89 (d, $J = 9.1$ Hz, 1H), 4.96 (s, 2H), 3.68 - 3.58 (m, 4H), 2.79 - 2.75 (m, 4H)
16	Yellow solid	435.1 [M+H] ⁺ , (2.491 min)	1	δ (DMSO- d_6): 9.70 (m, 2 H) 9.25 (d, $J = 1.76$ Hz, 1 H) 8.52 (dd, $J = 8.25, 2.09$ Hz, 1 H) 8.36 (d, $J = 8.36$ Hz, 1 H) 8.15 (m, 2 H) 7.96 (m, 2 H) 5.10 (s, 2 H) 3.67 (m, 2 H) 3.45 (m, 3 H) 2.39 (m, 1 H) 2.23 (br dd, $J = 13.09, 6.49$ Hz, 1 H)
17	Brown solid	425.1 [M+H] ⁺ , (2.195 min)	1	δ (DMSO- d_6): 9.29 - 9.54 (m, 2 H) 8.90 (s, 1 H) 8.34 (d, $J = 8.14$ Hz, 1 H) 8.09 - 8.22 (m, 2 H) 7.90 - 7.99 (m, 1 H) 5.00 (s, 2 H) 4.08 (t, $J = 7.81$ Hz, 1 H) 3.62 - 3.76 (m, 1 H) 3.46 (br s, 1 H) 3.29 (br d, $J = 5.72$ Hz, 2 H) 2.47 (br s, 1 H) 2.05 - 2.19 (m, 1 H)
18	Yellow solid	440.1 [M+H] ⁺ , (2.303 min)	1	δ (DMSO- d_6): 9.38 - 9.70 (m, 2 H) 8.35 (d, $J = 8.14$ Hz, 1 H) 8.09 - 8.24 (m, 3 H) 7.87 - 8.01 (m, 1 H) 7.35 (d, $J = 3.96$ Hz, 1 H) 6.68 (s, 1 H) 5.00 (s, 2 H) 3.37 - 3.54 (m, 4 H) 2.30 - 2.42 (m, 2 H)
19	White solid	424.1 [M+H] ⁺ , (2.611 min)	1	δ (DMSO- d_6): 9.27 - 9.53 (m, 2 H) 8.30 - 8.39 (m, 2 H) 8.09 - 8.22 (m, 2 H) 7.91 - 8.01 (m, 2 H) 4.99 (s, 2 H) 3.50 - 3.71 (m, 2 H) 3.36 - 3.43 (m, 1 H) 3.20 - 3.30 (m, 1 H) 3.06 - 3.17 (m, 1 H) 2.34 - 2.46 (m, 1 H) 1.92 - 2.06 (m, 1 H)
21	Yellow solid	448.2 [M+H] ⁺ , (3.056 min)	1	δ (DMSO- d_6): 9.10 (d, $J = 3.1$ Hz, 1H), 8.91 (d, $J = 2.4$ Hz, 1H), 8.11 (dd, $J = 2.4, 9.1$ Hz, 1H), 7.84 (d, $J = 3.0$ Hz, 1H), 7.00 - 6.70 (m, 2H), 5.02 (s, 2H), 4.08 (s, 3H), 3.69 (br d, $J = 3.3$ Hz, 8H)
22	White solid	449.1 [M+H] ⁺ , (2.385 min)	1	δ (DMSO- d_6): 9.41 (m, 2 H) 9.29 (d, $J = 1.76$ Hz, 1 H) 8.55 (dd, $J = 8.14, 2.20$ Hz, 1 H) 8.37 (d, $J = 8.14$ Hz, 1 H) 8.16 (m, 2 H) 7.96 (t, $J = 6.93$ Hz, 1 H) 7.80 (d, $J = 8.36$ Hz, 1 H) 5.09 (s, 2 H) 3.77 (m, 1 H) 3.63 (m, 1 H) 3.44 (br d, $J = 4.62$ Hz, 2 H) 3.09 (s, 3 H) 2.56 (br d, $J = 6.82$ Hz, 1 H) 2.36 (m, 1 H)
23	Yellow solid	437.1 [M+H] ⁺ , (2.623 min)	1	δ (DMSO- d_6): 10.15 (m, 2 H) 9.32 (s, 1 H) 8.58 (dd, $J = 8.25, 2.00$ Hz, 1 H) 8.35 (d, $J = 8.25$ Hz, 1 H) 8.14 (m, 2 H) 7.92 (m, 2 H) 5.11

				(s, 2 H) 3.84 (m, 2 H) 3.65 (m, 1 H) 3.50 (m, 1 H) 2.61 (m, 2 H)
24	White solid	485.1 [M+H] ⁺ , (2.501 min)	1	δ (DMSO- <i>d</i> ₆): 9.82 (br s, 2 H) 9.30 (s, 1 H) 8.68 (s, 1 H) 8.56 (dd, <i>J</i> = 8.32, 2.06 Hz, 1 H) 7.90 (d, <i>J</i> = 8.13 Hz, 1 H) 5.12 (s, 2 H) 4.61 (t, <i>J</i> = 5.13 Hz, 2 H) 3.88 (br s, 1 H) 3.81 (t, <i>J</i> = 5.19 Hz, 3 H) 3.64 (br s, 1 H) 3.49 (br s, 1 H) 3.17 (s, 3 H) 2.61 (m, 2 H)
25	Yellow solid	441.1 [M+H] ⁺ , (2.404 min)	1	δ (DMSO- <i>d</i> ₆): 9.91 (m, 2 H) 9.29 (s, 1 H) 8.64 (s, 1 H) 8.56 (br d, <i>J</i> = 8.25 Hz, 1 H) 7.89 (d, <i>J</i> = 8.13 Hz, 1 H) 5.11 (s, 2 H) 4.06 (s, 3 H) 3.83 (m, 2 H) 3.64 (br s, 1 H) 3.52 (m, 1 H) 2.60 (m, 2 H)
26	Brown solid	436.1 [M+H] ⁺ , (2.590 min)	1	δ (DMSO- <i>d</i> ₆): 8.40 (br s, 1H), 8.34 (d, <i>J</i> = 8.4 Hz, 1H), 8.20 - 8.12 (m, 2H), 8.09 (d, <i>J</i> = 4.0 Hz, 1H), 7.94 (ddd, <i>J</i> = 1.7, 6.4, 8.2 Hz, 1H), 7.15 (d, <i>J</i> = 4.0 Hz, 1H), 4.98 (s, 2H), 3.03 (br d, <i>J</i> = 7.0 Hz, 4H), 2.13 - 2.00 (m, 2H), 1.84 (br d, <i>J</i> = 13.0 Hz, 2H)
27	Yellow solid	447.1 [M+H] ⁺ , (2.506 min)	2	δ (DMSO- <i>d</i> ₆): 9.10 (d, <i>J</i> = 3.0 Hz, 1H), 8.89 (d, <i>J</i> = 2.3 Hz, 1H), 8.07 (dd, <i>J</i> = 2.4, 9.2 Hz, 1H), 7.84 (d, <i>J</i> = 3.1 Hz, 1H), 7.01 - 6.72 (m, 2H), 5.01 (s, 2H), 4.08 (s, 3H), 3.67 - 3.60 (m, 4H), 2.81 - 2.75 (m, 4H)
28	Yellow solid	428.0 [M+H] ⁺ , 2.533 min)	1	δ (DMSO- <i>d</i> ₆): 9.55 (br s, 2 H) 8.36 (d, <i>J</i> = 8.14 Hz, 1 H) 8.28 - 8.32 (m, 1 H) 8.14 - 8.21 (m, 2 H) 7.97 (t, <i>J</i> = 7.01 Hz, 1 H) 7.70 - 7.73 (m, 1 H) 5.05 (s, 2 H) 4.63 (s, 2 H) 4.58 (s, 2 H)
29	Yellow solid	476.1 [M+H] ⁺ , (2.363 min)	1	δ (DMSO- <i>d</i> ₆): 9.46 (br s, 2 H) 8.67 (s, 1 H) 8.27 - 8.29 (m, 1 H) 7.70 (br s, 1 H) 5.05 (s, 2 H) 4.60 - 4.66 (m, 4 H) 4.57 (s, 2 H) 3.82 (t, <i>J</i> = 5.17 Hz, 2 H) 3.18 (s, 3 H)
30	Yellow solid	432.0 [M+H] ⁺ , (2.287 min)	1	δ (DMSO- <i>d</i> ₆): 9.54 (br s, 2 H) 8.64 (s, 1 H) 8.26 - 8.29 (m, 1 H) 7.69 - 7.72 (m, 1 H) 5.04 (s, 2 H) 4.62 (s, 2 H) 4.57 (s, 2 H) 4.08 (s, 3 H)
31	Yellow solid	441.1 [M+H] ⁺ , (1.954 min)	1	δ (DMSO- <i>d</i> ₆): 9.71 (br s, 2 H) 9.08 - 9.13 (m, 1 H) 8.27 - 8.33 (m, 1 H) 7.83 (d, <i>J</i> = 3.01 Hz, 1 H) 7.72 - 7.78 (m, 1 H) 6.81 (t, <i>J</i> = 53.97 Hz, 1 H) 5.08 (s, 2 H) 4.51 - 4.65 (m, 4 H) 4.02 - 4.10 (m, 3 H)
32	Yellow solid	450.1 [M+H] ⁺ , (1.873 min)	1	δ (DMSO- <i>d</i> ₆): 9.70 (br s, 2 H) 9.31 (s, 1 H) 9.11 (d, <i>J</i> = 3.08 Hz, 1 H) 8.59 (dd, <i>J</i> = 8.25, 2.09 Hz, 1 H) 7.87 (m, 2 H) 6.77 (m, 1 H) 5.13 (s, 2 H) 4.09 (s, 3 H) 3.85 (m, 2 H) 3.65 (br s, 1 H) 3.50 (br s, 1 H) 2.61 (m, 2 H)

33	Yellow solid	404.0 [M+H] ⁺ , (2.126 min)	1	δ (DMSO- <i>d</i> ₆): 9.88 (br s, 2 H) 8.30 - 8.35 (m, 1 H) 7.85 (d, <i>J</i> = 9.24 Hz, 1 H) 7.72 - 7.76 (m, 1 H) 7.65 (d, <i>J</i> = 9.18 Hz, 1 H) 7.32 (d, <i>J</i> = 2.64 Hz, 1 H) 4.94 (s, 2 H) 4.63 (br s, 2 H) 4.51 - 4.60 (m, 2 H) 3.97 (s, 3 H) 2.39 - 2.44 (m, 3 H)
34	White solid	454.1 [M+H] ⁺ , (2.520 min)	1	δ (DMSO- <i>d</i> ₆): 9.26 - 9.86 (m, 2 H) 8.34 (d, <i>J</i> = 8.36 Hz, 1 H) 8.10 - 8.25 (m, 3 H) 7.90 - 8.00 (m, 1 H) 7.41 (d, <i>J</i> = 3.96 Hz, 1 H) 5.00 (s, 2 H) 3.73 (br d, <i>J</i> = 11.88 Hz, 1 H) 3.44 (br d, <i>J</i> = 9.46 Hz, 1 H) 3.37 (br s, 1 H) 3.27 - 3.32 (m, 1 H) 3.10 (s, 3 H) 2.61 (br dd, <i>J</i> = 13.53, 6.71 Hz, 1 H) 2.28 - 2.41 (m, 1 H)
35	Yellow solid	419.1 [M+H] ⁺ , (2.331 min)	1	δ (DMSO- <i>d</i> ₆): 8.81 (d, <i>J</i> = 5.25 Hz, 1 H) 8.36 (d, <i>J</i> = 8.00 Hz, 1 H) 8.31 (s, 1 H) 8.12 - 8.21 (m, 2 H) 7.90 - 8.00 (m, 2 H) 7.83 (br d, <i>J</i> = 3.50 Hz, 1 H) 5.07 (s, 2 H) 3.63 - 3.69 (m, 2 H) 3.14 (br d, <i>J</i> = 3.38 Hz, 2 H) 2.24 - 2.40 (m, 2 H) 1.94 - 2.09 (m, 1 H)
36	Yellow solid	411.1 [M+H] ⁺ , (2.442 min)	1	δ (DMSO- <i>d</i> ₆): 8.91 (s, 1H), 8.37 - 8.27 (m, 2H), 8.20 - 8.11 (m, 2H), 7.95 (br t, <i>J</i> = 7.6 Hz, 1H), 5.01 (s, 2H), 4.45 - 4.36 (m, 1H), 4.07 (br s, 2H), 3.92 (br s, 2H)
37	Yellow solid	467.1 [M+H] ⁺ , (1.835 min)	1	δ (DMSO- <i>d</i> ₆): 9.11 (d, <i>J</i> = 3.1 Hz, 1H), 8.08 (d, <i>J</i> = 4.0 Hz, 1H), 7.84 (d, <i>J</i> = 3.1 Hz, 1H), 7.20 - 7.11 (m, 1H), 6.83 (t, <i>J</i> = 54.1 Hz, 1H), 5.70 (s, 1H), 5.03 (s, 2H), 4.08 (s, 3H), 2.97 - 2.86 (m, 2H), 2.84 - 2.75 (m, 2H), 1.94 - 1.81 (m, 2H), 1.77 - 1.69 (m, 2H)
38	Yellow solid	448.1 [M+H] ⁺ , (1.677 min)	1	δ (DMSO- <i>d</i> ₆): 9.23 (d, <i>J</i> = 1.76 Hz, 1 H) 9.09 (d, <i>J</i> = 3.08 Hz, 1 H) 8.48 (dd, <i>J</i> = 8.36, 2.20 Hz, 1 H) 8.39 (s, 1 H) 7.94 (d, <i>J</i> = 8.36 Hz, 1 H) 7.84 (d, <i>J</i> = 3.08 Hz, 1 H) 6.78 (m, 1 H) 5.12 (s, 2 H) 4.08 (s, 3 H) 3.50 (br d, <i>J</i> = 11.66 Hz, 1 H) 3.37 (br dd, <i>J</i> = 9.24, 5.06 Hz, 2 H) 3.25 (br d, <i>J</i> = 11.88 Hz, 1 H) 2.40 (m, 1 H) 2.11 (m, 1 H)
39		398.22 [M+H] ⁺ , (2.28 min)	5	δ (DMSO- <i>d</i> ₆): 8.34 - 8.36 (m, 2 H) 8.15 - 8.17 (m, 2 H) 8.10 (d, <i>J</i> = 4 Hz, 1 H) 7.93 - 7.97 (m, 1 H) 7.14 (d, <i>J</i> = 3.6 Hz, 1 H) 4.98 (s, 2 H) 3.05 (t, <i>J</i> = 6.4 Hz, 2 H) 2.96 (t, <i>J</i> = 6.4 Hz, 2 H)
40		320.18 [M+H] ⁺ , (1.68 min)	5	δ (DMSO- <i>d</i> ₆): 8.66 (s, 1H) 8.42 (s, 1H) 8.17 (d, <i>J</i> = 3.6 Hz, 1 H) 7.45 (d, <i>J</i> = 3.6 Hz, 1H) 5.02 (s, 2H) 4.32 (q, <i>J</i> = 16.4 Hz, 2 H) 4.02 (s, 3H)

41		387.9 [M+H] ⁺ , (2.659 min)	8	δ (DMSO- <i>d</i> ₆): 8.63 (s,1H) 8.53 (s, 2H) 8.16 (d, J = 4 Hz, 1 H) 7.42 (d, J = 4 Hz, 1H) 5.03 (s, 2H) 4.34 (s, 2H) 4.07 (s, 3H)
42		334.05 [M+H] ⁺ , (1.90 min)	6	δ (DMSO- <i>d</i> ₆): 8.68 (s, 1H), 8.40 (s, 1H), 8.06 (d, J = 4 Hz, 1 H), 7.13 (d, J = 4 Hz, 1H), 4.99 (s, 2H) 4.02 (s, 3H), 3.88 (s, 2H), 2.29 (s, 3H)
43		384.46 [M+H] ⁺ , (2.25 min)	5	δ (DMSO- <i>d</i> ₆): 8.35 (d, J=8,4 Hz, 1 H), 8.16 - 8.22 (m, 3 H) 8.11 (d, J=4 Hz, 1 H) 7.95 - 7.97 (m, 1 H), 7.17 (br s, 1 H) 4.99 (s, 2 H) 4.03 (d, J=2.8 Hz, 2 H)
44		331.1 [M+H] ⁺ , (1.326 min)	10	δ (DMSO- <i>d</i> ₆): 9.22 (t, J = 2.8 Hz, 1H), 8.73-8.67 (m, 3H), 8.21 (d, J = 3.6 Hz, 1H), 7.75-7.72 (m, 1H), 7.48 (d, J = 4.0 Hz, 1H), 5.23 (s, 4H), 4.96 (s, 2H), 4.34-4.30 (m, 2H), 2.51 (s, 3H).
45		414.1 [M+H] ⁺ , (0.665 min)	9	δ (DMSO- <i>d</i> ₆): 9.22 (s, 1H), 8.61 (s, 4H), 8.14 (d, J = 3.6 Hz, 1H), 7.43 (d, J = 4.0 Hz, 1H), 4.99 (s, 2H), 4.31-4.28 (m, 4H), 1.41-1.37 (m, 2H), 1.23-1.21 (m, 2H).
46		361.3 [M+H] ⁺ , (2.166 min)	9	δ (MeOD): 9.01 (d, J = 3.2 Hz, 1H), 8.16 (d, J = 3.6 Hz,1H), 7.97 (d, J = 2.8 Hz,1H), 7.43 (d, J = 4.0 Hz,1H), 4.45 (s, 2H), 4.11 (s, 3H), 2.66 (s, 3H)
47		375.1 [M+H] ⁺ , (2.325 min)	7	δ (DMSO- <i>d</i> ₆): 9.53 (d, J = 4.4 Hz, 2H), 8.96 (d, J = 2.8 Hz, 1H), 8.23 (d, J = 4.0 Hz, 1H), 7.73 (d, J = 3.2 Hz, 1H), 7.52 (d, J = 4.0 Hz, 1H), 4.94 (s, 2H), 4.41 (s, 2H), 4.02 (s, 3H), 2.56-2.54 (m, 3H), 2.44 (s, 3H).
48		385.1 [M+H] ⁺ , (0.599 min)	9	δ (DMSO- <i>d</i> ₆): 9.38 (t, J = 1.6 Hz, 1H), 8.82 (t, J = 8.4 Hz, 4H), 8.17 (s, 1H), 7.93 (t, J = 8.4 Hz, 1H), 7.48 (d, J = 3.6 Hz, 1H), 5.06 (s, 2H), 4.31 (d, J = 5.2 Hz, 2H)
49		360.0 [M+H] ⁺ , (0.770 min)	9	δ (DMSO- <i>d</i> ₆): 8.61 (s, 2H), 8.21 (d, J = 3.6 Hz, 1H), 7.91-7.89 (m, 1H), 7.70-7.67 (m, 1H), 7.45 (d, J = 3.6 Hz, 1H), 7.33 (s, 1H), 4.95 (s, 1H), 4.34-4.31 (m, 2H), 3.97 (s, 3H), 2.47 (s, 3H)
50		374.1 [M+H] ⁺ , (0.704 min)	9	δ (DMSO- <i>d</i> ₆): 8.72 (s, 3H), 8.29 (d, J = 8.0 Hz, 1H), 8.16 (d, J = 4.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 3.6 Hz, 1H), 5.15 (s, 2H), 4.32 (s, 2H).
51		402.1 [M+H] ⁺ , (0.710 min)	9	δ (DMSO- <i>d</i> ₆): 9.63 (s, 2H), 8.62 (s, 2H), 8.18 (d, J = 3.6 Hz, 1H), 7.53 (d, J = 3.6 Hz, 1H), 5.02 (s, 2H), 4.42 (s, 2H), 4.06 (s, 3H), 2.54 (s, 3H).

52	Yellow solid	442.0 [M+H] ⁺ , (2.730 min)	1	δ (DMSO- <i>d</i> ₆): 8.35 (d, J=7.92 Hz, 1 H) 8.13 - 8.19 (m, 3 H) 7.96 (ddd, J=8.25, 6.38, 1.87 Hz, 1 H) 7.36 (dd, J=3.96, 1.32 Hz, 1 H) 5.00 (s, 2 H) 3.02 - 3.15 (m, 4 H) 2.25 - 2.36 (m, 2 H)
53	Yellow solid	425.0 [M+H] ⁺ , (2.662 min)	1	δ (DMSO- <i>d</i> ₆): 8.39 - 8.26 (m, 3H), 8.21 - 8.11 (m, 2H), 7.99 - 7.93 (m, 1H), 5.01 (br s, 2H), 3.70 (quin, J = 7.7 Hz, 1H), 3.57 - 3.45 (m, 1H), 3.28 - 3.07 (m, 3H), 2.35 (br dd, J = 4.6, 12.2 Hz, 1H), 2.09 - 1.99 (m, 1H)
54	Yellow solid	440.0 [M+H] ⁺ , (1.901 min)	1	δ (DMSO- <i>d</i> ₆): 9.77 - 9.33 (m, 2H), 9.11 (d, J = 3.1 Hz, 1H), 9.03 (s, 1H), 8.07 (br s, 1H), 7.84 (d, J = 3.1 Hz, 1H), 6.80 (t, J = 54.1 Hz, 1H), 5.07 (s, 2H), 4.45 - 4.38 (m, 2H), 4.29 - 4.22 (m, 2H), 4.09 (s, 3H)
55	Yellow solid	447.1 [M+H] ⁺ , (1.825 min)	1	δ (DMSO- <i>d</i> ₆): 9.10 (d, J=3.08 Hz, 1 H) 8.38 (s, 1 H) 8.09 (d, J=8.36 Hz, 2 H) 7.84 (d, J=3.08 Hz, 1 H) 7.73 (d, J=8.36 Hz, 2 H) 6.82 (t, J=54.03 Hz, 1 H) 5.13 (s, 2 H) 4.08 (s, 3 H) 3.33 (m, 2 H) 3.24 (s, 3 H) 2.25 (m, 1 H) 2.14 (m, 1 H)
56	Yellow solid	442.0 [M+H] ⁺ , (2.061 min)	1	δ (DMSO- <i>d</i> ₆): 10.17 - 10.07 (m, 1H), 9.78 - 9.69 (m, 1H), 9.12 (dd, J = 3.1, 5.4 Hz, 2H), 7.84 (d, J = 3.1 Hz, 1H), 6.79 (t, J = 54.1 Hz, 1H), 5.10 (s, 2H), 4.68 - 4.60 (m, 4H), 4.09 (s, 3H)
57	Yellow solid	434.0 [M+H] ⁺ , (2.716 min)	1	δ (DMSO- <i>d</i> ₆): 8.44 (br s, 1 H) 8.35 (d, J=8.36 Hz, 1 H) 8.13 (m, 4 H) 7.94 (ddd, J=8.25, 6.49, 1.76 Hz, 1 H) 7.76 (d, J=8.58 Hz, 2 H) 5.09 (s, 2 H) 3.38 (m, 5 H) 2.32 (m, 1 H) 2.20 (m, 1 H)
58	White solid	454.0 [M+H] ⁺ , (1.923 min)	1	δ (DMSO- <i>d</i> ₆): 9.48 - 9.18 (m, 2H), 9.11 (d, J = 3.1 Hz, 1H), 8.93 (s, 1H), 7.83 (d, J = 3.1 Hz, 1H), 7.21 (s, 1H), 6.80 (t, J = 54.1 Hz, 1H), 5.05 (s, 2H), 4.09 (s, 3H), 3.64 - 3.44 (m, 4H), 2.46 - 2.29 (m, 2H)
59	Yellow solid	468.1 [M+H] ⁺ , (1.956 min)	1	δ (DMSO- <i>d</i> ₆): 9.11 (d, J=3.08 Hz, 1 H) 8.67 - 9.01 (m, 2 H) 7.83 (d, J=3.08 Hz, 1 H) 6.62 - 6.95 (m, 2 H) 5.03 (s, 2 H) 4.08 (s, 3 H) 3.30 (br s, 3 H) 3.09 - 3.24 (m, 2 H) 2.26 - 2.41 (m, 2 H) 1.93 (br d, J=13.20 Hz, 2 H)
60	Yellow solid	422.1 [M+H] ⁺ , (2.129 min)	1	δ (DMSO- <i>d</i> ₆): 9.24 (dd, J=4.40, 1.54 Hz, 1 H) 8.71 (d, J=8.14 Hz, 1 H) 8.35 (s, 1 H) 8.10 (d, J=3.96 Hz, 1 H) 7.87 (s, 1 H) 7.83 (dd, J=8.58, 4.40 Hz, 1 H) 7.24 (d, J=3.96 Hz, 1 H) 6.83 (t, J=54.91 Hz, 1 H) 4.93 (s, 2 H) 3.10 - 3.28 (m, 5 H) 2.13 - 2.28 (m, 2 H)
61	Yellow solid	453.1 [M+H] ⁺ , (2.455 min)	2	δ (DMSO- <i>d</i> ₆): 9.09 (d, J=3.08 Hz, 1 H) 8.35 (br s, 1 H) 8.12 (d, J=3.96 Hz, 1 H) 7.82 (d, J=3.08 Hz, 1 H) 7.28 (d, J=3.74 Hz, 1 H) 6.82 (t, J=54.14 Hz, 1 H) 5.03 (s, 2 H) 4.07 (s, 3 H) 3.17 - 3.39 (m, 5 H) 2.17 - 2.34 (m, 2 H)
62	Yellow solid	430.1 [M+H] ⁺ ,	1	δ (DMSO- <i>d</i> ₆): 8.39 (s, 1H), 8.12 (d, J = 4.0 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.60 (dd, J = 2.8, 9.1

		(1.965 min)		Hz, 1H), 7.28 (d, $J = 2.6$ Hz, 1H), 7.17 (d, $J = 4.0$ Hz, 1H), 4.91 - 4.78 (m, 2H), 3.95 (s, 3H), 3.04 (br d, $J = 6.8$ Hz, 4H), 2.41 (s, 3H), 2.15 - 2.02 (m, 2H), 1.86 (br d, $J = 13.0$ Hz, 2H)
63	Yellow solid	436.1 [M+H] ⁺ , (2.161 min)	1	δ (DMSO- d_6): 9.24 (dd, $J = 1.5, 4.2$ Hz, 1H), 8.71 (d, $J = 8.1$ Hz, 1H), 8.06 (d, $J = 4.0$ Hz, 1H), 7.87 (s, 1H), 7.83 (dd, $J = 4.2, 8.6$ Hz, 1H), 7.12 (d, $J = 3.7$ Hz, 1H), 7.01 - 6.61 (m, 1H), 5.64 (s, 1H), 5.03 - 4.68 (m, 2H), 2.95 - 2.81 (m, 2H), 2.81 - 2.65 (m, 2H), 1.92 - 1.79 (m, 2H), 1.77 - 1.68 (m, 2H)
64	Yellow solid	468.1 [M+H] ⁺ , (2.090 min)	1	δ (DMSO- d_6): 9.46 - 9.20 (m, 2H), 9.11 (d, $J = 3.1$ Hz, 1H), 8.98 (s, 1H), 7.83 (d, $J = 2.9$ Hz, 1H), 6.77 (t, $J = 54.1$ Hz, 1H), 5.04 (s, 2H), 4.09 (s, 3H), 3.82 (br d, $J = 12.3$ Hz, 1H), 3.61 (br d, $J = 12.1$ Hz, 1H), 3.56 - 3.43 (m, 2H), 3.25 (s, 3H), 2.65 - 2.56 (m, 1H), 2.48 - 2.44 (m, 1H)
65	Yellow solid	448.1 [M+H] ⁺ , (1.968 min)	1	δ (DMSO- d_6): 9.10 (d, $J = 3.06$ Hz, 1 H) 8.97 (d, $J = 1.96$ Hz, 1 H) 8.34 (s, 1 H) 8.17 (dd, $J = 8.31, 2.20$ Hz, 1 H) 8.01 (d, $J = 8.31$ Hz, 1 H) 7.85 (d, $J = 3.06$ Hz, 1 H) 6.76 (t, $J = 54.16$ Hz, 1 H) 5.26 (s, 2 H) 4.09 (s, 3 H) 3.24 (m, 5 H) 2.19 (m, 2 H)
66	Yellow solid	454.1 [M+H] ⁺ , (2.097 min)	1	δ (DMSO- d_6): 9.89 - 9.77 (m, 1H), 9.56 - 9.41 (m, 1H), 9.11 (d, $J = 3.1$ Hz, 1H), 9.06 (s, 1H), 7.83 (d, $J = 3.1$ Hz, 1H), 6.78 (t, $J = 54.1$ Hz, 1H), 5.07 (s, 2H), 4.42 (br d, $J = 4.8$ Hz, 4H), 4.09 (s, 3H), 3.38 (br s, 3H)
67	Yellow solid	482.1 [M+H] ⁺ , (2.160 min)	1	δ (DMSO- d_6): 9.09 (d, $J = 2.88$ Hz, 1 H) 8.89 (s, 1 H) 8.36 (s, 1 H) 7.82 (d, $J = 2.88$ Hz, 1 H) 6.75 (t, $J = 54.09$ Hz, 1 H) 5.01 (s, 2 H) 4.07 (s, 3 H) 3.15 (s, 3 H) 2.89 - 3.04 (m, 4 H) 2.03 - 2.21 (m, 4 H)
68	White solid	456.1 [M+H] ⁺ , (2.051 min)	1	δ (DMSO- d_6): 9.57 (br s, 2H), 9.12 (d, $J = 3.1$ Hz, 1H), 9.06 (d, $J = 3.1$ Hz, 1H), 7.84 (d, $J = 3.1$ Hz, 1H), 6.79 (t, $J = 54.0$ Hz, 1H), 5.07 (s, 2H), 4.09 (s, 3H), 4.07 - 3.96 (m, 1H), 3.95 - 3.78 (m, 1H), 3.74 - 3.64 (m, 1H), 3.57 - 3.45 (m, 1H), 2.81 - 2.58 (m, 2H)
69	Yellow solid	481.1 [M+H] ⁺ , (2.597 min)	2	δ (DMSO- d_6): 9.10 (d, $J = 3.1$ Hz, 1H), 8.23 (s, 1H), 8.08 (d, $J = 4.0$ Hz, 1H), 7.82 (d, $J = 2.9$ Hz, 1H), 7.17 (d, $J = 3.7$ Hz, 1H), 7.03 - 6.64 (m, 1H), 5.02 (s, 2H), 4.07 (s, 3H), 2.69 (br d, $J = 10.6$ Hz, 2H), 2.48 - 2.42 (m, 2H), 2.29 (s, 3H), 2.03 (dt, $J = 3.6, 12.6$ Hz, 2H), 1.80 (br d, $J = 12.8$ Hz, 2H)
70	Yellow solid	416.1 [M+H] ⁺ , (1.951 min)	1	δ (DMSO- d_6): 8.36 (s, 1 H) 8.14 (d, $J = 3.96$ Hz, 1 H) 7.79 (d, $J = 9.24$ Hz, 1 H) 7.58 (dd, $J = 9.13, 2.75$ Hz, 1 H) 7.27 (t, $J = 3.85$ Hz, 2 H) 4.85 (s, 2 H) 3.94 (s, 3 H) 3.18 - 3.36 (m, 5 H) 2.41 (s, 3 H) 2.17 - 2.32 (m, 2 H)
71	Yellow solid	416.1 [M+H] ⁺ , (1.951 min)	2	δ (DMSO- d_6): 8.84 (d, $J = 2.76$ Hz, 1 H) 8.27 (s, 1 H) 8.10 (d, $J = 4.02$ Hz, 1 H) 7.64 (d, $J = 2.76$ Hz, 1 H) 7.40 (s, 1 H) 7.21 (d, $J = 4.02$ Hz, 1 H) 4.80 (s,

		(3.362 min)		2 H) 3.99 (s, 3 H) 3.19 (br s, 1 H) 3.13 (m, 2 H) 3.01 (m, 2 H) 2.32 (s, 3 H) 2.15 (m, 2 H)
72	Yellow solid	444.1 [M+H] ⁺ , (1.981 min)	1	δ (DMSO-d ₆): 8.10 (d, J = 4.0 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.59 (dd, J = 2.8, 9.1 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 7.17 (d, J = 4.0 Hz, 1H), 4.84 (s, 2H), 3.95 (s, 3H), 2.72 (br d, J = 11.0 Hz, 2H), 2.41 (s, 3H), 2.31 (s, 3H), 2.04 (dt, J = 4.1, 12.6 Hz, 2H), 1.81 (br d, J = 12.5 Hz, 2H)
73	Yellow solid	425.1 [M+H] ⁺ , (2.613 min)	1	δ (DMSO-d ₆): 8.41 (s, 1 H) 8.11 (d, J=3.96 Hz, 1 H) 8.05 (dd, J=10.12, 1.98 Hz, 1 H) 7.98 (s, 1 H) 7.17 (d, J=3.96 Hz, 1 H) 4.89 (s, 2 H) 3.17 (s, 1 H) 3.01 (m, 4 H) 2.46 (s, 3 H) 2.04 (m, 2 H) 1.84 (br d, J=12.54 Hz, 2 H)
74	Yellow solid	431.1 [M+H] ⁺ , (1.747 min)	1	δ (DMSO-d ₆): 8.83 (s, 1H), 7.79 (br d, J = 9.2 Hz, 1H), 7.59 (br d, J = 7.5 Hz, 1H), 7.27 (br s, 1H), 6.45 - 6.14 (m, 1H), 4.85 (br s, 2H), 3.95 (s, 3H), 2.95 - 2.82 (m, 4H), 2.35 (s, 3H), 2.02 (br s, 2H), 1.66 (br d, J = 12.3 Hz, 2H)
75	Yellow solid	445.1 [M+H] ⁺ , (1.768 min)	1	δ (DMSO-d ₆): 8.83 (s, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.59 (dd, J = 2.9, 9.2 Hz, 1H), 7.27 (d, J = 2.9 Hz, 1H), 6.23 (s, 1H), 4.84 (s, 2H), 3.95 (s, 3H), 2.64 (br d, J = 11.0 Hz, 2H), 2.34 (s, 3H), 2.32 - 2.26 (m, 2H), 2.21 (s, 3H), 2.13 (dt, J = 4.2, 12.8 Hz, 2H), 1.71 (br d, J = 12.1 Hz, 2H)
76	Yellow solid	207.6 [M+H]/2 ⁺ , (2.145 min)	1	δ (DMSO-d ₆): 8.11 (d, J=3.88 Hz, 1 H) 7.80 (d, J=9.13 Hz, 1 H) 7.59 (dd, J=9.19, 2.69 Hz, 1 H) 7.28 (d, J=2.63 Hz, 1 H) 7.11 (d, J=3.63 Hz, 1 H) 4.84 (s, 2 H) 3.95 (s, 3 H) 3.01 (br d, J=12.26 Hz, 3 H) 2.59 (br t, J=11.51 Hz, 2 H) 2.41 (s, 3 H) 1.90 (br d, J=11.88 Hz, 2 H) 1.50 (qd, J=12.07, 3.94 Hz, 2 H)
77	Yellow solid	430.1 [M+H] ⁺ , (3.535 min)	2	δ (DMSO-d ₆): 8.35 (s, 1 H) 8.14 - 8.21 (m, 1 H) 7.78 (d, J=9.02 Hz, 1 H) 7.58 (dd, J=9.13, 2.75 Hz, 1 H) 7.28 - 7.36 (m, 1 H) 7.25 (d, J=2.64 Hz, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 3.36 - 3.50 (m, 2 H) 3.07 - 3.15 (m, 5 H) 2.09 - 2.46 (m, 5 H)
78	Yellow solid	417.1 [M+H] ⁺ , (1.866 min)	1	δ (DMSO-d ₆): 8.89 (s, 1H), 8.32 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.66 - 7.54 (m, 1H), 7.27 (d, J = 2.4 Hz, 1H), 4.87 (s, 2H), 3.95 (s, 3H), 3.36 - 3.13 (m, 5H), 2.42 - 2.29 (m, 4H), 2.23 - 2.10 (m, 1H)
79	Yellow solid	431.1 [M+H] ⁺ , (1.925 min)	1	δ (DMSO-d ₆): 8.85 (s, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.27 (d, J = 2.6 Hz, 1H), 6.55 (s, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 2.94 - 2.83 (m, 3H), 2.63 - 2.55 (m, 1H), 2.45 - 2.38 (m, 1H), 2.36 (s, 3H), 2.31 (s, 3H), 2.15 - 2.06 (m, 1H)
80	Yellow solid	448.1 [M+H] ⁺ ,	1	δ (DMSO-d ₆): 8.42 (s, 1H), 8.11 (br d, J = 3.3 Hz, 1H), 7.94 (br t, J = 9.0 Hz, 1H), 7.70 (br d, J = 9.0 Hz, 1H), 7.17 (br d, J = 3.1 Hz, 1H), 4.73

		(2.162 min)		(s, 2H), 4.00 (s, 3H), 3.08 (br d, J = 5.9 Hz, 5H), 2.28 (s, 3H), 2.18 - 2.04 (m, 2H), 1.88 (br d, J = 13.0 Hz, 2H)
81	Yellow solid	468.1 [M+H] ⁺ , (2.632 min)	1	δ (DMSO-d ₆): 8.39 (s, 2H), 8.24 (dd, J = 1.8, 8.8 Hz, 1H), 8.13 (d, J = 4.0 Hz, 1H), 8.06 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 4.0 Hz, 1H), 5.04 - 4.84 (m, 2H), 3.04 (br d, J = 7.0 Hz, 4H), 2.49 (s, 3H), 2.07 (td, J = 8.5, 13.4 Hz, 2H), 1.86 (br d, J = 12.8 Hz, 2H)
82	Yellow solid	428.1 [M+H] ⁺ , (2.140 min)	1	δ (DMSO-d ₆): 8.11 (d, J=3.96 Hz, 1 H) 7.79 (d, J=9.02 Hz, 1 H) 7.59 (dd, J=9.13, 2.53 Hz, 1 H) 7.27 (d, J=2.42 Hz, 1 H) 7.13 (d, J=3.74 Hz, 1 H) 4.84 (s, 2 H) 3.95 (s, 3 H) 2.83 (br d, J=11.44 Hz, 3 H) 2.41 (s, 3 H) 2.19 (s, 3 H) 1.97 (m, 4 H) 1.66 (m, 2 H)
83	White solid	444.0 [M+H] ⁺ , (2.228 min)	1	δ (DMSO-d ₆): 8.14 (d, J = 3.9 Hz, 1H), 7.84 (d, J = 9.0 Hz, 1H), 7.63 (dd, J = 2.8, 9.5 Hz, 1H), 7.30 (d, J = 2.7 Hz, 1H), 7.17 (d, J = 3.8 Hz, 1H), 4.88 (s, 2H), 4.23 (d, J = 7.1 Hz, 2H), 3.19 - 3.10 (m, 4H), 2.43 (s, 3H), 2.33 (br d, J = 1.7 Hz, 1H), 2.26 (br s, 4H), 1.42 (t, J = 6.9 Hz, 3H)
84	Yellow solid	452.1 [M+H] ⁺ , (2.633 min)	1	δ (DMSO-d ₆): 8.38 (s, 1 H) 8.35 (d, J=7.92 Hz, 1 H) 8.11 (d, J=3.96 Hz, 1 H) 7.87 (d, J=10.12 Hz, 1 H) 7.16 (d, J=3.96 Hz, 1 H) 4.87 (s, 2 H) 3.06 (br d, J=7.26 Hz, 4 H) 2.42 (s, 3 H) 2.09 (m, 2 H) 1.87 (br d, J=12.98 Hz, 2 H)
85	Yellow solid	444.1 [M+H] ⁺ , (2.233 min)	1	(DMSO-d ₆) δ ppm 8.16 (d, J=3.91 Hz, 1 H) 7.80 (d, J=9.17 Hz, 1 H) 7.60 (dd, J=9.11, 2.75 Hz, 1 H) 7.28 (d, J=2.81 Hz, 1 H) 7.25 (d, J=3.79 Hz, 1 H) 4.85 (s, 1 H) 4.82 (s, 1 H) 3.96 (s, 3 H) 3.02 (s, 3 H) 2.80 (m, 4 H) 2.68 (m, 1 H) 2.37 (s, 3 H) 2.33 (m, 1 H) 1.99 (m, 2 H) 1.90 (m, 2 H)
86	Yellow solid	444.1 [M+H] ⁺ , (2.169 min)	1	δ (DMSO-d ₆): 8.12 (d, J=3.96 Hz, 1 H) 7.79 (d, J=9.02 Hz, 1 H) 7.58 (dd, J=9.24, 2.64 Hz, 1 H) 7.25 (dd, J=7.15, 3.19 Hz, 2 H) 4.83 (s, 2 H) 3.94 (s, 3 H) 3.10 (s, 3 H) 2.90 (br d, J=1.98 Hz, 2 H) 2.63 - 2.73 (m, 2 H) 2.38 (s, 3 H) 2.15 - 2.31 (m, 5 H)
87	Yellow solid	430.0 [M+H] ⁺ , (1.980 min)	1	δ (DMSO-d ₆): 10.15 - 10.61 (m, 1 H) 8.15 - 8.24 (m, 1 H) 7.80 (d, J=9.17 Hz, 1 H) 7.60 (dd, J=9.11, 2.63 Hz, 1 H) 7.24 - 7.39 (m, 2 H) 6.68 - 6.96 (m, 1 H) 4.87 (s, 2 H) 3.95 (s, 3 H) 3.67 - 3.88 (m, 3 H) 3.36 (br d, J=4.89 Hz, 1 H) 2.89 - 3.00 (m, 3 H) 2.56 - 2.70 (m, 1 H) 2.35 - 2.44 (m, 4 H)
88	Yellow solid	458.1 [M+H] ⁺ , (2.256 min)	1	¹ H NMR (400 MHz, DMSO-d ₆) δ ppm 8.15 (d, J=3.91 Hz, 1 H) 7.79 (d, J=9.17 Hz, 1 H) 7.59 (dd, J=9.17, 2.69 Hz, 1 H) 7.26 (dd, J=6.66, 3.36 Hz, 2 H) 4.84 (s, 2 H) 3.95 (s, 3 H) 3.01 (s, 3 H) 2.54 (m, 2 H) 2.36 (s, 3 H) 2.29 (m, 2 H) 2.18 (s, 3 H) 2.02 (m, 4 H)

89	Yellow solid	430.1 [M+H] ⁺ , (1.640 min)	1	δ (DMSO- <i>d</i> ₆): 8.06 (d, <i>J</i> =4.00 Hz, 1 H) 8.79 (d, <i>J</i> =16.40 Hz, 1 H) 7.38 (dd, <i>J</i> =8.00 Hz, 1 H) 7.13 (m, 1 H) 5.57 (s, 1 H) 4.56 (s, 2 H) 4.03 (s, 3 H) 2.86 (m, 2 H) 2.73 (m, 2 H) 2.24 (s, 3 H) 1.83 (m, 2 H) 1.68 (br d, <i>J</i> =12.40 Hz, 2 H)
90	White solid	467.0 [M+H] ⁺ , (3.058 min)	2	δ (DMSO- <i>d</i> ₆): 8.84 (s, 1H), 8.38 (d, <i>J</i> = 7.7 Hz, 1H), 8.18 (s, 1H), 7.90 (d, <i>J</i> = 10.1 Hz, 1H), 6.24 (br s, 1H), 4.89 (s, 2H), 2.73 - 2.61 (m, 3H), 2.38 (s, 3H), 2.36 - 2.31 (m, 2H), 2.25 (s, 3H), 2.18 - 2.11 (m, 2H), 1.73 (br d, <i>J</i> = 12.9 Hz, 2H), 1.24 (s, 1H)
91	Yellow solid	444.1 [M+H] ⁺ , (2.704 min)	1	δ (DMSO- <i>d</i> ₆): 8.06 (d, <i>J</i> =3.88 Hz, 1 H) 7.80 (t, <i>J</i> =8.19 Hz, 1 H) 7.36 (d, <i>J</i> =8.50 Hz, 1 H) 7.13 (m, 2 H) 5.61 (s, 1 H) 4.57 (s, 2 H) 4.04 (s, 3 H) 2.57 (m, 2 H) 2.32 (m, 2 H) 2.24 (s, 3 H) 2.20 (s, 3 H) 1.98 (td, <i>J</i> =12.51, 3.75 Hz, 2 H) 1.77 (br d, <i>J</i> =12.38 Hz, 2 H)
92	Yellow solid	476.1 [M+H] ⁺ , (2.901 min)	2	δ (DMSO- <i>d</i> ₆): 8.08 (d, <i>J</i> =3.96 Hz, 1 H) 7.79 (d, <i>J</i> =9.24 Hz, 1 H) 7.59 (dd, <i>J</i> =9.24, 2.86 Hz, 1 H) 7.27 (d, <i>J</i> =2.64 Hz, 1 H) 7.18 (d, <i>J</i> =3.96 Hz, 1 H) 5.66 (s, 1 H) 4.84 (s, 2 H) 4.60 (t, <i>J</i> =4.95 Hz, 1 H) 4.48 (t, <i>J</i> =4.95 Hz, 1 H) 3.94 (s, 3 H) 2.64 - 2.75 (m, 3 H) 2.61 (t, <i>J</i> =4.95 Hz, 1 H) 2.40 - 2.48 (m, 5 H) 1.97 (td, <i>J</i> =12.32, 3.96 Hz, 2 H) 1.77 (br d, <i>J</i> =12.10 Hz, 2 H)
93	Yellow solid	472.1 [M+H] ⁺ , (3.235 min)	2	δ (DMSO- <i>d</i> ₆): 8.08 (d, <i>J</i> =3.74 Hz, 1 H) 7.79 (d, <i>J</i> =9.02 Hz, 1 H) 7.59 (dd, <i>J</i> =9.24, 2.64 Hz, 1 H) 7.27 (d, <i>J</i> =2.64 Hz, 1 H) 7.16 (d, <i>J</i> =3.74 Hz, 1 H) 5.59 (s, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 2.70 (dt, <i>J</i> =12.98, 6.49 Hz, 1 H) 2.55 (br s, 4 H) 2.41 (s, 3 H) 1.86 - 1.99 (m, 2 H) 1.77 (br d, <i>J</i> =11.66 Hz, 2 H) 0.98 (d, <i>J</i> =6.38 Hz, 6 H)
94	Yellow solid	488.1 [M+H] ⁺ , (2.841 min)	2	δ (DMSO- <i>d</i> ₆): 8.08 (d, <i>J</i> =3.88 Hz, 1 H) 7.79 (d, <i>J</i> =9.13 Hz, 1 H) 7.59 (dd, <i>J</i> =9.26, 2.75 Hz, 1 H) 7.27 (d, <i>J</i> =2.75 Hz, 1 H) 7.17 (d, <i>J</i> =3.88 Hz, 1 H) 5.62 (s, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 3.44 (t, <i>J</i> =5.88 Hz, 2 H) 3.23 (s, 3 H) 2.66 (br d, <i>J</i> =11.13 Hz, 2 H) 2.47 - 2.49 (m, 2 H) 2.36 - 2.45 (m, 5 H) 1.95 (td, <i>J</i> =12.51, 4.13 Hz, 2 H) 1.75 (br d, <i>J</i> =12.13 Hz, 2 H)
95	Yellow solid	416.1 [M+H] ⁺ , (1.900 min)	1	δ (DMSO- <i>d</i> ₆): 8.19 (m, 1 H) 8.12 (d, <i>J</i> =3.74 Hz, 1 H) 7.79 (d, <i>J</i> =9.24 Hz, 1 H) 7.58 (dd, <i>J</i> =9.13, 2.75 Hz, 1 H) 7.27 (d, <i>J</i> =2.86 Hz, 1 H) 7.20 (d, <i>J</i> =3.74 Hz, 1 H) 4.84 (d, <i>J</i> =1.98 Hz, 2 H) 4.72 (dd, <i>J</i> =9.90, 2.42 Hz, 1 H) 3.94 (s, 3 H) 3.87 (br d, <i>J</i> =10.78 Hz, 1 H) 3.62 (td, <i>J</i> =10.56, 3.96 Hz, 1 H) 3.10 (dd, <i>J</i> =12.21, 2.53 Hz, 1 H) 2.73 (m, 2 H) 2.59 (dd, <i>J</i> =12.21, 10.01 Hz, 1 H) 2.38 (s, 3 H)
96	Yellow solid	430.1 [M+H] ⁺ ,	2	δ (DMSO- <i>d</i> ₆): 8.14 (br s, 1 H) 7.78 (br d, <i>J</i> =9.02 Hz, 1 H) 7.58 (br d, <i>J</i> =8.80 Hz, 1 H) 7.25 (br d,

		(3.142 min)		$J=7.70$ Hz, 2 H) 4.84 (br s, 3 H) 3.90 (br s, 4 H) 3.69 (br t, $J=10.78$ Hz, 1 H) 3.00 (br d, $J=10.56$ Hz, 1 H) 2.65 (br d, $J=11.44$ Hz, 1 H) 2.37 (s, 3 H) 2.23 (s, 3 H) 2.04 (m, 2 H)
97	Yellow solid	484.2 [M+H] ⁺ , (1.974 min)	1	δ (DMSO- d_6): 8.24 (s, 1 H) 8.09 (d, $J=4.00$ Hz, 1 H) 7.79 (d, $J=9.13$ Hz, 1 H) 7.58 (dd, $J=9.13$, 2.75 Hz, 1 H) 7.26 (d, $J=2.75$ Hz, 1 H) 7.18 (d, $J=3.88$ Hz, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 2.89 (br d, $J=11.01$ Hz, 2 H) 2.52 - 2.57 (m, 2 H) 2.41 (s, 3 H) 2.35 (br d, $J=6.50$ Hz, 2 H) 2.05 (td, $J=12.66$, 3.81 Hz, 2 H) 1.81 (br d, $J=12.38$ Hz, 2 H) 0.83 - 0.94 (m, 1 H) 0.45 - 0.52 (m, 2 H) 0.13 (q, $J=4.92$ Hz, 2 H)
98	Yellow solid	470.1 [M+H] ⁺ , (3.212 min)	2	δ (DMSO- d_6): 8.07 (d, $J=3.96$ Hz, 1 H) 7.79 (d, $J=9.02$ Hz, 1 H) 7.59 (dd, $J=9.13$, 2.75 Hz, 1 H) 7.27 (d, $J=2.64$ Hz, 1 H) 7.15 (d, $J=3.96$ Hz, 1 H) 5.68 (s, 1 H) 4.83 (s, 2 H) 3.94 (s, 3 H) 2.69 - 2.78 (m, 2 H) 2.55 - 2.62 (m, 2 H) 2.40 (s, 3 H) 1.83 - 1.95 (m, 2 H) 1.71 - 1.79 (m, 2 H) 1.64 (dt, $J=6.38$, 2.97 Hz, 1 H) 0.38 - 0.45 (m, 2 H) 0.27 - 0.33 (m, 2 H)
99	Yellow solid	484.2 [M+H] ⁺ (1.965 min)	1	δ (DMSO- d_6): 8.07 (d, $J=3.88$ Hz, 1 H) 7.79 (d, $J=9.13$ Hz, 1 H) 7.58 (dd, $J=9.13$, 2.63 Hz, 1 H) 7.27 (d, $J=2.63$ Hz, 1 H) 7.16 (d, $J=3.75$ Hz, 1 H) 5.63 (s, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 2.72 (br t, $J=7.57$ Hz, 1 H) 2.57 (br d, $J=10.38$ Hz, 2 H) 2.41 (s, 3 H) 2.13 (br t, $J=10.63$ Hz, 2 H) 1.88 - 2.00 (m, 4 H) 1.76 (br d, $J=11.38$ Hz, 4 H) 1.58 - 1.67 (m, 2 H)
100	Yellow solid	486.1 [M+H] ⁺ , (2.693 min)	2	δ (DMSO- d_6): 8.09 (d, $J=3.96$ Hz, 1 H) 7.79 (d, $J=9.02$ Hz, 1 H) 7.59 (dd, $J=9.13$, 2.53 Hz, 1 H) 7.27 (d, $J=2.64$ Hz, 1 H) 7.18 (d, $J=3.96$ Hz, 1 H) 5.70 (s, 1 H) 4.84 (s, 2 H) 4.50 - 4.58 (m, 2 H) 4.43 (t, $J=6.05$ Hz, 2 H) 3.94 (s, 3 H) 3.44 (br s, 1 H) 2.51 - 2.55 (m, 2 H) 2.41 (s, 3 H) 2.19 (br t, $J=10.56$ Hz, 2 H) 1.93 - 2.05 (m, 2 H) 1.78 (br d, $J=12.54$ Hz, 2 H)
101	Yellow solid	416.1 [M+H] ⁺ , (1.767 min)	1	δ (DMSO- d_6): 8.12 (br d, $J = 3.5$ Hz, 1H), 7.79 (br d, $J = 9.2$ Hz, 1H), 7.59 (br d, $J = 7.5$ Hz, 1H), 7.27 (br s, 1H), 7.24 (br d, $J = 3.3$ Hz, 1H), 4.91 - 4.78 (m, 2H), 4.15 (br d, $J = 7.0$ Hz, 1H), 3.95 (s, 3H), 3.83 (br d, $J = 9.9$ Hz, 1H), 3.74 (br d, $J = 11.0$ Hz, 1H), 3.51 - 3.42 (m, 1H), 3.30 - 3.17 (m, 2H), 2.85 (br s, 2H), 2.41 (s, 3H)
102	Yellow solid	430.1 [M+H] ⁺ , (1.996 min)	1	δ (DMSO- d_6): 8.13 (d, $J = 4.0$ Hz, 1H), 7.79 (d, $J = 9.2$ Hz, 1H), 7.61 - 7.55 (m, 1H), 7.31 - 7.23 (m, 2H), 4.91 - 4.74 (m, 2H), 3.95 (s, 3H), 3.83 (br d, $J = 11.0$ Hz, 1H), 3.79 - 3.71 (m, 1H), 3.68 - 3.57 (m, 1H), 3.56 - 3.49 (m, 1H), 3.34 - 3.29 (m, 1H), 2.82 (br d, $J = 11.9$ Hz, 1H), 2.36 (s, 3H), 2.34 - 2.26 (m, 1H), 2.10 (s, 3H)

103	Yellow solid	462.1 [M+H] ⁺ , (2.174 min)	1	δ (DMSO- <i>d</i> ₆): 8.08 (d, <i>J</i> = 3.7 Hz, 1H), 7.94 (t, <i>J</i> = 9.0 Hz, 1H), 7.71 (d, <i>J</i> = 9.5 Hz, 1H), 7.16 (d, <i>J</i> = 4.0 Hz, 1H), 5.63 (s, 1H), 4.73 (s, 2H), 4.00 (s, 3H), 2.56 (br d, <i>J</i> = 10.8 Hz, 2H), 2.37 - 2.26 (m, 5H), 2.19 (s, 3H), 2.05 - 1.91 (m, 2H), 1.77 (br d, <i>J</i> = 12.5 Hz, 2H)
104	Yellow solid	482.1 [M+H] ⁺ , (2.505 min)	1	δ (DMSO- <i>d</i> ₆): 8.40 (s, 1H), 8.24 (dd, <i>J</i> = 1.8, 8.8 Hz, 1H), 8.14 - 8.02 (m, 2H), 7.18 (d, <i>J</i> = 4.0 Hz, 1H), 5.65 (s, 1H), 4.92 (s, 2H), 2.57 (br d, <i>J</i> = 10.8 Hz, 2H), 2.49 (br s, 3H), 2.33 (br t, <i>J</i> = 10.8 Hz, 2H), 2.20 (s, 3H), 2.05 - 1.93 (m, 2H), 1.77 (br d, <i>J</i> = 12.3 Hz, 2H)
105	White solid	474.1 [M+H] ⁺ , (2.685 min)	2	δ (DMSO- <i>d</i> ₆): 8.08 (d, <i>J</i> = 3.9 Hz, 1H), 7.25 (s, 1H), 7.20 (s, 1H), 7.16 (d, <i>J</i> = 3.8 Hz, 1H), 5.68 (s, 1H), 4.82 (s, 2H), 3.95 (d, <i>J</i> = 3.8 Hz, 6H), 2.63 - 2.60 (m, 2H), 2.40 (s, 3H), 2.24 (s, 3H), 2.06 - 1.91 (m, 4H), 1.78 (br d, <i>J</i> = 12.3 Hz, 2H)
106	Yellow solid	433.1 [M+H] ⁺ , (1.990 min)	1	δ (DMSO- <i>d</i> ₆): 8.74 (d, <i>J</i> = 4.62 Hz, 1 H) 8.17 (d, <i>J</i> = 8.80 Hz, 1 H) 8.11 (d, <i>J</i> = 4.18 Hz, 1 H) 8.07 (d, <i>J</i> = 2.20 Hz, 1 H) 7.70 (dd, <i>J</i> = 9.02, 2.20 Hz, 1 H) 7.46 (d, <i>J</i> = 4.84 Hz, 1 H) 7.18 (d, <i>J</i> = 3.96 Hz, 1 H) 5.65 (s, 1 H) 4.97 (s, 2 H) 2.55 (m, 2 H) 2.31 (br t, <i>J</i> = 11.00 Hz, 2 H) 2.19 (s, 3 H) 1.97 (td, <i>J</i> = 12.38, 3.85 Hz, 2 H) 1.75 (br d, <i>J</i> = 11.22 Hz, 2 H)
107	Brown solid	459.1 [M+H] ⁺ , (1.722 min)	1	δ (DMSO- <i>d</i> ₆): 8.57 (d, <i>J</i> = 4.9 Hz, 1H), 7.70 (d, <i>J</i> = 3.9 Hz, 1H), 7.39 (d, <i>J</i> = 11.0 Hz, 2H), 7.25 (d, <i>J</i> = 4.9 Hz, 1H), 7.04 (d, <i>J</i> = 4.0 Hz, 1H), 4.39 (s, 2H), 4.05 (s, 6H), 2.76 (br d, <i>J</i> = 11.0 Hz, 2H), 2.45 (br t, <i>J</i> = 10.8 Hz, 2H), 2.37 (s, 3H), 2.26 - 2.13 (m, 3H), 1.93 (br d, <i>J</i> = 12.6 Hz, 2H)
108	Yellow solid	466.1 [M+H] ⁺ , (2.450 min)	1	δ (DMSO- <i>d</i> ₆): 8.35 (d, <i>J</i> = 7.92 Hz, 1 H) 8.08 (d, <i>J</i> = 3.96 Hz, 1 H) 7.88 (d, <i>J</i> = 10.34 Hz, 1 H) 7.16 (d, <i>J</i> = 3.96 Hz, 1 H) 5.63 (s, 1 H) 4.87 (s, 2 H) 2.54 (br d, <i>J</i> = 11.22 Hz, 2 H) 2.43 (s, 3 H) 2.30 (m, 2 H) 2.18 (s, 3 H) 1.96 (m, 2 H) 1.75 (br d, <i>J</i> = 12.32 Hz, 2 H)
109	Yellow solid	448.0 [M+H] ⁺ , (3.137 min)	2	δ (DMSO- <i>d</i> ₆): 9.08 (d, <i>J</i> = 2.42 Hz, 1 H) 8.58 (d, <i>J</i> = 1.54 Hz, 1 H) 8.06 (d, <i>J</i> = 3.96 Hz, 1 H) 7.46 (s, 1 H) 7.14 (d, <i>J</i> = 3.96 Hz, 1 H) 5.61 (s, 1 H) 4.81 (s, 2 H) 2.54 (m, 2 H) 2.32 (m, 5 H) 2.18 (s, 3 H) 1.96 (td, <i>J</i> = 12.60, 3.85 Hz, 2 H) 1.75 (br d, <i>J</i> = 12.54 Hz, 2 H)
110	Yellow solid	444.2 [M+H] ⁺ , (2.092 min)	1	δ (DMSO- <i>d</i> ₆): 8.83 (d, <i>J</i> = 2.64 Hz, 1 H) 8.06 (d, <i>J</i> = 3.96 Hz, 1 H) 7.63 (d, <i>J</i> = 2.86 Hz, 1 H) 7.39 (s, 1 H) 7.14 (d, <i>J</i> = 3.96 Hz, 1 H) 5.61 (s, 1 H) 4.79 (s, 2 H) 3.99 (s, 3 H) 2.54 (br d, <i>J</i> = 10.78 Hz, 2 H) 2.32 (m, 5 H) 2.18 (s, 3 H) 1.96 (td, <i>J</i> = 12.49, 3.85 Hz, 2 H) 1.75 (br d, <i>J</i> = 12.10 Hz, 2 H)
111	Pink solid	429.1 [M+H] ⁺ ,	1	δ (DMSO- <i>d</i> ₆) 8.57 (d, <i>J</i> = 4.84 Hz, 1 H) 8.11 (d, <i>J</i> = 3.96 Hz, 1 H) 7.93 (d, <i>J</i> = 9.24 Hz, 1 H) 7.45

		(1.717 min)		(dd, J=9.13, 2.75 Hz, 1 H) 7.41 (d, J=4.84 Hz, 1 H) 7.32 (d, J=2.64 Hz, 1 H) 7.17 (d, J=3.96 Hz, 1 H) 5.67 (s, 1 H) 4.90 (s, 2 H) 3.93 (s, 3 H) 2.56 (br d, J=10.78 Hz, 2 H) 2.31 (br t, J=10.67 Hz, 2 H) 2.19 (s, 3 H) 1.96 (td, J=12.65, 3.74 Hz, 2 H) 1.75 (br d, J=12.54 Hz, 2 H)
112	Yellow solid	458.1 [M+H] ⁺ , (2.029 min)	1	δ (DMSO-d ₆): 8.11 (d, J = 3.7 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.60 (dd, J = 2.8, 9.1 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.12 (d, J = 4.0 Hz, 1H), 5.88 (d, J = 4.6 Hz, 1H), 4.84 (s, 2H), 4.63 (t, J = 5.5 Hz, 1H), 3.95 (s, 3H), 2.75 (br t, J = 12.0 Hz, 2H), 2.39 (s, 3H), 2.11 (s, 3H), 1.87 - 1.63 (m, 3H), 1.54 - 1.24 (m, 4H)
113	White solid	443.1 [M+H] ⁺ , (1.783 min)	1	δ (DMSO-d ₆): 8.11 (d, J = 4.0 Hz, 1H), 7.83 (d, J = 9.2 Hz, 1H), 7.48 - 7.34 (m, 2H), 7.28 (d, J = 2.6 Hz, 1H), 7.17 (d, J = 4.0 Hz, 1H), 5.66 (s, 1H), 4.86 (s, 2H), 3.90 (s, 3H), 2.58 (br s, 2H), 2.55 (s, 3H), 2.32 (br t, J = 10.7 Hz, 2H), 2.20 (s, 3H), 1.97 (dt, J = 4.1, 12.5 Hz, 2H), 1.75 (br d, J = 12.3 Hz, 2H)
114	Yellow solid	466.1 [M+H] ⁺ , (3.189 min)	2	δ (DMSO-d ₆): 8.09 (d, J=4.00 Hz, 1 H) 8.06 (dd, J=10.13, 2.13 Hz, 1 H) 8.00 (d, J=1.13 Hz, 1 H) 7.17 (d, J=3.88 Hz, 1 H) 5.64 (s, 1 H) 4.89 (s, 2 H) 2.56 (m, 2 H) 2.47 (s, 3 H) 2.32 (m, 2 H) 2.20 (s, 3 H) 1.98 (td, J=12.60, 3.94 Hz, 2 H) 1.77 (br d, J=12.26 Hz, 2 H)
115	Yellow solid	433.0 [M+H] ⁺ , (2.994 min)	2	δ (DMSO-d ₆): 8.74 (d, J=4.75 Hz, 1 H) 8.11 (d, J=2.88 Hz, 2 H) 8.05 (d, J=9.01 Hz, 1 H) 7.83 (dd, J=9.01, 2.25 Hz, 1 H) 7.50 (d, J=4.88 Hz, 1 H) 7.18 (d, J=3.88 Hz, 1 H) 5.65 (s, 1 H) 4.97 (s, 2 H) 2.57 (br d, J=11.13 Hz, 2 H) 2.32 (br t, J=11.13 Hz, 2 H) 2.20 (s, 3 H) 1.97 (m, 2 H) 1.75 (br d, J=12.13 Hz, 2 H)
116	Yellow solid	429.1 [M+H] ⁺ , (2.749 min)	2	δ (DMSO-d ₆): 8.62 (d, J=4.88 Hz, 1 H) 8.11 (d, J=3.88 Hz, 1 H) 8.03 (d, J=9.13 Hz, 1 H) 7.38 (d, J=2.50 Hz, 1 H) 7.29 (m, 2 H) 7.17 (d, J=4.00 Hz, 1 H) 5.65 (s, 1 H) 4.90 (s, 2 H) 3.93 (s, 3 H) 2.56 (br d, J=12.13 Hz, 2 H) 2.31 (m, 2 H) 2.20 (s, 3 H) 1.97 (td, J=12.48, 3.81 Hz, 2 H) 1.75 (br d, J=12.51 Hz, 2 H)
117	Pink solid	403.1 [M+H] ⁺ , (2.260 min)	1	δ (DMSO-d ₆): 8.10 (d, J=4.18 Hz, 1 H) 7.81 (d, J=1.54 Hz, 1 H) 7.69 (d, J=1.32 Hz, 1 H) 7.19 (d, J=3.96 Hz, 1 H) 7.07 (s, 1 H) 5.70 (s, 1 H) 5.10 (s, 2 H) 2.58 (br d, J=10.34 Hz, 2 H) 2.50 (s, 3 H) 2.34 (br t, J=10.78 Hz, 2 H) 2.21 (s, 3 H) 1.97 (td, J=12.65, 4.18 Hz, 2 H) 1.75 (br d, J=12.32 Hz, 2 H)
118	White solid	458.1 [M+H] ⁺ , (3.110 min)	2	δ (DMSO-d ₆): 8.07 (d, J = 3.9 Hz, 1H), 7.78 (d, J = 9.0 Hz, 1H), 7.57 (dd, J = 2.6, 9.2 Hz, 1H), 7.25 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 3.9 Hz, 1H), 5.68 (s, 1H), 4.82 (s, 2H), 4.20 (q, J = 7.0 Hz,

				2H), 2.58 (br d, $J = 11.4$ Hz, 2H), 2.40 (s, 3H), 2.35 (br t, $J = 10.8$ Hz, 2H), 2.21 (s, 3H), 1.98 (dt, $J = 4.0, 12.5$ Hz, 2H), 1.77 (br d, $J = 12.3$ Hz, 2H), 1.41 (t, $J = 6.9$ Hz, 3H)
119	Yellow solid	414.1 [M+H] ⁺ , 1.439 min)	1	δ (DMSO- d_6): 9.01 - 9.07 (m, 1 H) 8.53 (br d, $J=8.58$ Hz, 1 H) 8.11 (d, $J=3.74$ Hz, 1 H) 7.58 (dd, $J=8.25, 4.29$ Hz, 1 H) 7.50 (s, 1 H) 7.17 (d, $J=3.52$ Hz, 1 H) 5.65 (s, 1 H) 4.95 (s, 2 H) 2.63 (s, 3 H) 2.55 (br d, $J=8.14$ Hz, 2 H) 2.26 - 2.36 (m, 2 H) 2.19 (s, 3 H) 1.92 - 2.00 (m, 2 H) 1.74 (br d, $J=11.88$ Hz, 2 H)
120	Yellow solid	444.1 [M+H] ⁺ , (3.240 min)	2	δ (DMSO- d_6): 8.06 (d, $J=3.91$ Hz, 1 H) 7.79 (d, $J=9.17$ Hz, 1 H) 7.59 (dd, $J=9.23, 2.26$ Hz, 1 H) 7.27 (br s, 2 H) 5.61 (s, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 2.54 (s, 1 H) 2.29 - 2.44 (m, 6 H) 2.21 (s, 3 H) 1.72 - 1.81 (m, 2 H) 1.62 - 1.70 (m, 1 H) 1.45 - 1.55 (m, 1 H)
121	Yellow solid	453.1 [M+H] ⁺ , (3.309 min)	2	δ (DMSO- d_6): 8.23 (d, $J = 4.0$ Hz, 1H), 7.80 (d, $J = 9.0$ Hz, 1H), 7.60 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.48 (d, $J = 4.0$ Hz, 1H), 7.27 (d, $J = 2.6$ Hz, 1H), 4.87 (s, 2H), 3.95 (s, 3H), 2.88 (br d, $J = 11.9$ Hz, 2H), 2.37 (s, 3H), 2.32 (br d, $J = 11.9$ Hz, 2H), 2.28 - 2.20 (m, 5H), 2.13 - 2.01 (m, 2H)
122	White solid	468.2 [M+H] ⁺ , (2.456 min)	1	δ (DMSO- d_6): 8.41 - 8.27 (m, 2H), 8.21 - 8.05 (m, 3H), 8.00 - 7.90 (m, 1H), 7.17 (d, $J = 3.7$ Hz, 1H), 4.99 (d, $J = 2.2$ Hz, 2H), 3.09 (br s, 2H), 2.64 - 2.55 (m, 1H), 2.39 - 2.31 (m, 1H), 2.22 (s, 2H), 2.15 - 2.05 (m, 1H), 2.04 - 1.94 (m, 1H), 1.89 (br d, $J = 12.3$ Hz, 1H), 1.77 (br d, $J = 12.5$ Hz, 1H)
123	Yellow solid	458.1 [M+H] ⁺ , (2.057 min)	1	δ (DMSO- d_6): 8.10 (d, $J=3.91$ Hz, 1 H) 7.80 (d, $J=9.17$ Hz, 1 H) 7.59 (dd, $J=9.11, 2.75$ Hz, 1 H) 7.28 (d, $J=2.45$ Hz, 1 H) 7.12 (d, $J=3.91$ Hz, 1 H) 5.47 (s, 1 H) 4.83 (s, 2 H) 3.95 (s, 3 H) 2.57 (m, 4 H) 2.39 (s, 3 H) 2.19 (s, 3 H) 2.02 (m, 2 H) 1.80 (br d, $J=13.33$ Hz, 1 H) 0.64 (br d, $J=5.75$ Hz, 3 H)
124	Yellow solid	512.1 [M+H] ⁺ , (3.587 min)	2	δ (DMSO- d_6): 8.09 (d, $J=3.96$ Hz, 1 H) 7.79 (d, $J=9.24$ Hz, 1 H) 7.59 (dd, $J=9.13, 2.75$ Hz, 1 H) 7.27 (d, $J=2.86$ Hz, 1 H) 7.20 (d, $J=3.74$ Hz, 1 H) 5.74 (s, 1 H) 4.84 (s, 2 H) 3.94 (s, 3 H) 3.20 (q, $J=10.34$ Hz, 2 H) 2.70 - 2.82 (m, 4 H) 2.41 (s, 3 H) 1.93 - 2.05 (m, 2 H) 1.75 (br d, $J=11.88$ Hz, 2 H)
125	Yellow solid	414.1 [M+H] ⁺ , (2.713 min)	2	δ (DMSO- d_6): 8.05 - 8.15 (m, 2 H) 7.91 - 7.99 (m, 1 H) 7.80 - 7.89 (m, 1 H) 7.67 (t, $J=7.59$ Hz, 1 H) 7.16 (d, $J=3.74$ Hz, 1 H) 5.63 (s, 1 H) 4.85 (s, 2 H) 2.55 (br d, $J=11.00$ Hz, 2 H) 2.43 (s, 3 H) 2.31 (br t, $J=10.89$ Hz, 2 H) 2.18 (s, 3 H) 1.97 (td, $J=12.32, 3.52$ Hz, 2 H) 1.76 (br d, $J=12.54$ Hz, 2 H)

126	Yellow solid	444.1 [M+H] ⁺ , (1.950 min)	1	δ (DMSO- <i>d</i> ₆): 8.09 (d, <i>J</i> = 4.0 Hz, 1H), 7.80 (d, <i>J</i> = 9.0 Hz, 1H), 7.63 - 7.55 (m, 1H), 7.28 (d, <i>J</i> = 2.6 Hz, 1H), 7.13 (d, <i>J</i> = 3.7 Hz, 1H), 5.04 (d, <i>J</i> = 6.2 Hz, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 3.52 - 3.40 (m, 1H), 2.99 - 2.88 (m, 1H), 2.78 (br d, <i>J</i> = 12.3 Hz, 1H), 2.71 - 2.57 (m, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 2.01 - 1.86 (m, 2H), 1.84 - 1.58 (m, 2H)
127	Yellow solid	444.3 [M+H] ⁺ , (1.806 min)	1	δ (DMSO- <i>d</i> ₆): 8.09 (d, <i>J</i> = 3.9 Hz, 1H), 7.80 (d, <i>J</i> = 9.1 Hz, 1H), 7.66 - 7.52 (m, 1H), 7.28 (d, <i>J</i> = 2.5 Hz, 1H), 7.13 (d, <i>J</i> = 3.8 Hz, 1H), 5.04 (d, <i>J</i> = 6.1 Hz, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 3.57 - 3.38 (m, 1H), 2.99 - 2.90 (m, 1H), 2.78 (br d, <i>J</i> = 11.3 Hz, 1H), 2.69 - 2.57 (m, 1H), 2.44 (s, 3H), 2.21 (s, 3H), 1.98 - 1.85 (m, 2H), 1.84 - 1.63 (m, 2H)
128	Yellow solid	472.1 [M+H] ⁺ , (2.339 min)	1	δ (DMSO- <i>d</i> ₆): 8.61 (s, 1H), 8.05 (br d, <i>J</i> = 3.6 Hz, 1H), 7.15 (br d, <i>J</i> = 3.5 Hz, 1H), 5.64 (s, 1H), 4.98 (s, 2H), 4.07 (s, 3H), 2.56 (br d, <i>J</i> = 10.8 Hz, 2H), 2.32 (br t, <i>J</i> = 10.7 Hz, 2H), 2.20 (s, 3H), 2.04 - 1.90 (m, 2H), 1.76 (br d, <i>J</i> = 12.9 Hz, 2H)
129	Yellow solid	402.1 [M+H] ⁺ , (2.577 min)	2	δ (DMSO- <i>d</i> ₆): 8.14 (d, <i>J</i> = 4.0 Hz, 1H), 7.79 (d, <i>J</i> = 9.2 Hz, 1H), 7.59 (dd, <i>J</i> = 2.8, 9.1 Hz, 1H), 7.42 (d, <i>J</i> = 4.0 Hz, 1H), 7.27 (d, <i>J</i> = 2.6 Hz, 1H), 6.92 - 6.45 (m, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 3.85 (br d, <i>J</i> = 8.6 Hz, 2H), 3.61 (br d, <i>J</i> = 8.6 Hz, 2H), 2.42 (s, 3H)
130	Yellow solid	416.1 [M+H] ⁺ , (2.752 min)	2	δ (DMSO- <i>d</i> ₆): 8.13 (d, <i>J</i> = 4.0 Hz, 1H), 7.80 (d, <i>J</i> = 9.2 Hz, 1H), 7.60 (dd, <i>J</i> = 2.9, 9.2 Hz, 1H), 7.38 (d, <i>J</i> = 4.0 Hz, 1H), 7.28 (d, <i>J</i> = 2.6 Hz, 1H), 6.65 (s, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 3.62 (br d, <i>J</i> = 7.3 Hz, 2H), 3.42 (br s, 2H), 2.42 (s, 3H), 2.40 (s, 3H), 2.08 (s, 1H)
131	Yellow solid	444.1 [M+H] ⁺ , (2.047 min)	1	δ (DMSO- <i>d</i> ₆): 8.18 (s, 1H), 8.11 (br d, <i>J</i> = 3.7 Hz, 1H), 7.80 (d, <i>J</i> = 9.0 Hz, 1H), 7.60 (dd, <i>J</i> = 2.3, 9.1 Hz, 1H), 7.35 (br d, <i>J</i> = 3.7 Hz, 1H), 7.28 (br d, <i>J</i> = 1.8 Hz, 1H), 6.70 - 6.32 (m, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 3.50 (br d, <i>J</i> = 7.1 Hz, 2H), 3.25 (br d, <i>J</i> = 7.2 Hz, 2H), 2.43 (s, 3H), 2.39 (br d, <i>J</i> = 6.2 Hz, 1H), 0.92 (br d, <i>J</i> = 6.0 Hz, 6H)
132	Yellow solid	404.1 [M+H] ⁺ , (1.902 min)	1	δ (DMSO- <i>d</i> ₆): 8.10 (d, <i>J</i> = 4.0 Hz, 1H), 7.79 (d, <i>J</i> = 9.2 Hz, 1H), 7.62 - 7.55 (m, 1H), 7.27 (d, <i>J</i> = 2.6 Hz, 1H), 7.16 (d, <i>J</i> = 3.7 Hz, 1H), 5.95 (br d, <i>J</i> = 1.5 Hz, 1H), 4.93 (t, <i>J</i> = 6.1 Hz, 1H), 4.85 (d, <i>J</i> = 0.9 Hz, 2H), 3.95 (s, 3H), 2.71 (d, <i>J</i> = 6.2 Hz, 2H), 2.42 (s, 3H), 2.33 (s, 3H)
133	Yellow solid	416.2 [M+H] ⁺ , (1.511 min)	1	δ (DMSO- <i>d</i> ₆): 8.79 (d, <i>J</i> = 2.86 Hz, 1 H) 8.31 (s, 1 H) 8.14 (d, <i>J</i> = 3.96 Hz, 1 H) 7.67 (d, <i>J</i> = 3.08 Hz, 1 H) 7.48 (s, 1 H) 7.28 (d, <i>J</i> = 3.74 Hz, 1 H) 4.93 (s, 2 H) 3.96 (s, 3 H) 3.19 - 3.33 (m, 5 H) 2.60 (s, 3 H) 2.17 - 2.30 (m, 2 H)

134	Yellow solid	466.1 [M+H] ⁺ , (3.041 min)	2	δ (CHLOROFORM-d): 8.39 (s, 1H), 8.29 (s, 1H), 8.20 (s, 1H), 8.03 - 7.97 (m, 2H), 4.75 (br s, 1H), 4.67 (s, 2H), 4.13 (s, 1H), 3.67 (dd, J = 1.9, 10.5 Hz, 1H), 3.50 (br d, J = 9.7 Hz, 1H), 3.31 - 3.20 (m, 2H), 2.75 (s, 3H), 2.16 - 1.99 (m, 2H)
135	Yellow solid	508.2 [M+H] ⁺ (2.732 min)	1	δ (CHLOROFORM-d): 8.39 (s, 1H), 8.20 (s, 1H), 8.04 - 7.95 (m, 2H), 4.67 (s, 3H), 4.09 - 3.91 (m, 1H), 3.80 - 3.63 (m, 1H), 3.48 (br d, J = 10.8 Hz, 1H), 3.39 - 3.24 (m, 1H), 2.76 (s, 3H), 2.73 - 2.61 (m, 2H), 2.29 - 2.16 (m, 1H), 2.02 (br d, J = 9.5 Hz, 1H), 1.17 (br t, J = 7.0 Hz, 6H)
136	White solid	424.0 [M+H] ⁺ , (3.010 min)	2	δ (DMSO-d ₆): 9.57 (br d, J = 3.1 Hz, 2H), 8.37 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 3.9 Hz, 1H), 7.89 (d, J = 10.1 Hz, 1H), 7.63 (d, J = 3.9 Hz, 2H), 4.92 (s, 2H), 4.32 - 4.29 (m, 2H), 4.26 - 4.22 (m, 2H), 2.44 (s, 3H)
137	White solid	438.0 [M+H] ⁺ , (3.204 min)	2	δ (DMSO-d ₆): 8.35 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 4.0 Hz, 1H), 7.88 (d, J = 10.3 Hz, 1H), 7.36 (d, J = 3.9 Hz, 1H), 6.56 (s, 1H), 4.88 (s, 2H), 3.55 (br d, J = 7.7 Hz, 2H), 3.28 (br d, J = 7.8 Hz, 2H), 2.44 (s, 3H), 2.35 (s, 3H)
138	White solid	466.0 [M+H] ⁺ , (2.752 min)	1	δ (DMSO-d ₆): 8.37 (d, J = 7.7 Hz, 1H), 8.11 (d, J = 4.0 Hz, 1H), 7.90 (d, J = 10.1 Hz, 1H), 7.35 (d, J = 4.0 Hz, 1H), 6.53 (s, 1H), 4.89 (s, 2H), 3.49 (br d, J = 7.7 Hz, 2H), 3.24 (br d, J = 7.5 Hz, 2H), 2.45 (s, 3H), 2.41 - 2.36 (m, 1H), 0.91 (d, J = 6.2 Hz, 6H)
139	Yellow solid	456.1 [M+H] ⁺ , (1.999 min)	1	δ (DMSO-d ₆): 8.32 (s, 1 H) 8.10 (d, J=3.96 Hz, 1 H) 7.80 (d, J=9.24 Hz, 1 H) 7.60 (dd, J=9.13, 2.75 Hz, 1 H) 7.27 (dd, J=8.36, 3.30 Hz, 2 H) 4.86 (s, 2 H) 3.95 (s, 3 H) 3.46 (m, 3 H) 2.70 (dd, J=9.90, 3.30 Hz, 1 H) 2.51 (s, 3 H) 2.42 (s, 3 H) 2.22 (m, 1 H) 2.11 (m, 1 H) 1.89 (br d, J=10.78 Hz, 1 H) 1.74 (br d, J=10.56 Hz, 1 H)
140	Yellow solid	457.1 [M+H] ⁺ , (2.452 min)	2	δ (400 MHz, DMSO-d ₆): 8.20 (d, J = 1.7 Hz, 2H), 8.15 (d, J = 4.0 Hz, 1H), 8.09 (d, J = 1.5 Hz, 1H), 7.58 (s, 1H), 7.21 (d, J = 3.9 Hz, 1H), 5.88 - 5.54 (m, 1H), 5.31 (s, 2H), 2.61 (br d, J = 10.9 Hz, 2H), 2.37 (br t, J = 10.8 Hz, 2H), 2.23 (s, 3H), 1.99 (dt, J = 4.3, 12.7 Hz, 2H), 1.77 (br d, J = 11.7 Hz, 2H)
141	Yellow solid	470.2 [M+H] ⁺ , (2.008 min)	1	δ (DMSO-d ₆) δ ppm 8.24 (s, 1 H) 8.09 (d, J=3.91 Hz, 1 H) 7.80 (d, J=9.17 Hz, 1 H) 7.60 (dd, J=9.11, 2.75 Hz, 1 H) 7.28 (d, J=2.69 Hz, 1 H) 7.13 (d, J=3.91 Hz, 1 H) 5.91 (m, 1 H) 4.84 (s, 2 H) 3.95 (s, 3 H) 2.48 (br s, 3 H) 2.41 (s, 3 H) 2.30 (m, 5 H) 2.03 (br d, J=13.94 Hz, 5 H)
142	White solid	460.1 [M+H] ⁺ , (2.784 min)	2	δ (DMSO-d ₆): 8.09 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 9.3 Hz, 1H), 7.59 (dd, J = 2.7, 9.2 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.19 (d, J = 3.8 Hz, 1H), 6.14 (d, J = 5.5 Hz, 1H), 4.85 (s, 2H), 4.74 (t, J =

				6.1 Hz, 1H), 3.95 (s, 3H), 3.79 (br d, $J = 10.9$ Hz, 1H), 3.52 - 3.43 (m, 2H), 2.82 (br d, $J = 10.9$ Hz, 1H), 2.58 (br d, $J = 10.9$ Hz, 1H), 2.41 (s, 3H), 2.19 (s, 3H), 2.03 - 1.93 (m, 1H), 1.88 (br t, $J = 10.4$ Hz, 1H)
143	Yellow solid	460.1 [M+H] ⁺ (2.771 min)	2	δ (DMSO- d_6): 8.11 (d, $J = 3.9$ Hz, 1H), 7.80 (d, $J = 9.3$ Hz, 1H), 7.60 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.28 (d, $J = 2.6$ Hz, 1H), 7.16 (d, $J = 3.9$ Hz, 1H), 6.06 (br d, $J = 4.9$ Hz, 1H), 4.89 (br t, $J = 4.6$ Hz, 1H), 4.84 (s, 2H), 3.95 (s, 3H), 3.84 (br d, $J = 9.9$ Hz, 1H), 3.61 (dt, $J = 3.1, 5.1$ Hz, 1H), 3.56 - 3.48 (m, 1H), 2.62 - 2.53 (m, 2H), 2.39 (s, 3H), 2.13 (s, 3H), 1.95 - 1.87 (m, 1H), 1.73 (br t, $J = 10.6$ Hz, 1H)
144	Yellow solid	445.1 [M+H] ⁺ (2.706 min)	2	δ (DMSO- d_6): 9.05 (s, 1 H) 8.09 (d, $J = 3.88$ Hz, 1 H) 7.21 (s, 1 H) 7.17 (d, $J = 3.88$ Hz, 1 H) 5.64 (s, 1 H) 4.88 (s, 2 H) 4.01 (s, 3 H) 2.56 (br d, $J = 10.63$ Hz, 2 H) 2.44 (s, 3 H) 2.32 (br t, $J = 10.82$ Hz, 2 H) 2.20 (s, 3 H) 1.97 (td, $J = 12.41, 3.81$ Hz, 2 H) 1.76 (br d, $J = 12.51$ Hz, 2 H)
145	Yellow solid	444.1 [M+H] ⁺ , (1.619 min)	1	δ (DMSO- d_6): 8.79 (d, $J = 3.08$ Hz, 1 H) 8.20 (s, 1 H) 8.09 (d, $J = 3.96$ Hz, 1 H) 7.68 (d, $J = 3.08$ Hz, 1 H) 7.48 (s, 1 H) 7.17 (d, $J = 3.96$ Hz, 1 H) 4.91 (s, 2 H) 3.96 (s, 3 H) 2.59 - 2.65 (m, 5 H) 2.38 (br t, $J = 11.11$ Hz, 2 H) 2.24 (s, 3 H) 1.93 - 2.03 (m, 2 H) 1.76 (br d, $J = 12.54$ Hz, 2 H)
146	Yellow solid	418.1 [M+H] ⁺ , (1.911 min)	1	δ (DMSO- d_6): 8.09 (d, $J = 4.0$ Hz, 1H), 7.79 (d, $J = 9.0$ Hz, 1H), 7.62 - 7.54 (m, 1H), 7.27 (d, $J = 2.6$ Hz, 1H), 7.18 (d, $J = 3.7$ Hz, 1H), 5.81 (br d, $J = 4.4$ Hz, 1H), 4.98 - 4.89 (m, 1H), 4.85 (s, 2H), 3.95 (s, 3H), 2.54 (br d, $J = 7.0$ Hz, 1H), 2.50 - 2.45 (m, 1H), 2.42 (s, 3H), 2.23 (s, 6H)
147	White solid	481.1 [M+H] ⁺ , (2.141 min)	1	δ (DMSO- d_6): 8.35 (s, 1H), 8.14 - 8.08 (m, 2H), 8.06 - 7.97 (m, 1H), 7.58 (s, 1H), 7.18 (d, $J = 4.0$ Hz, 1H), 5.66 (s, 1H), 4.98 (s, 2H), 2.64 (s, 3H), 2.56 (br d, $J = 11.0$ Hz, 2H), 2.30 (br t, $J = 10.7$ Hz, 2H), 2.19 (s, 3H), 2.03 - 1.91 (m, 2H), 1.75 (br d, $J = 11.9$ Hz, 2H)
148	Yellow solid	470.1 [M+H] ⁺ , (2.199 min)	1	δ (DMSO- d_6): 8.27 (m, 1 H) 8.08 (d, $J = 3.74$ Hz, 1 H) 7.78 (d, $J = 9.24$ Hz, 1 H) 7.58 (dd, $J = 9.13, 2.75$ Hz, 2 H) 7.25 (dd, $J = 10.12, 3.30$ Hz, 2 H) 4.82 (s, 2 H) 4.70 (s, 1 H) 3.94 (s, 3 H) 3.06 (dt, $J = 10.23, 6.44$ Hz, 1 H) 2.89 (m, 1 H) 2.75 (m, 1 H) 2.64 (dt, $J = 10.29, 6.41$ Hz, 1 H) 2.38 (s, 3 H) 2.12 (m, 1 H) 1.91 (dt, $J = 12.82, 6.68$ Hz, 1 H) 1.73 (m, 3 H) 1.47 (td, $J = 11.94, 6.93$ Hz, 2 H) 1.33 (m, 1 H)
149	White solid	460.1 [M+H] ⁺ , (2.769 min)	2	δ (DMSO- d_6): 8.11 (d, $J = 3.9$ Hz, 1H), 7.80 (d, $J = 9.1$ Hz, 1H), 7.60 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.28 (d, $J = 2.8$ Hz, 1H), 7.16 (d, $J = 3.9$ Hz, 1H), 6.06 (d, $J = 5.1$ Hz, 1H), 4.89 (t, $J = 4.9$ Hz, 1H),

				4.84 (s, 2H), 3.95 (s, 3H), 3.83 (br d, $J=9.3$ Hz, 1H), 3.61 (ddd, $J=1.8, 4.8, 10.0$ Hz, 1H), 3.52 (dt, $J=2.1, 11.2$ Hz, 1H), 2.61 - 2.52 (m, 2H), 2.39 (s, 3H), 2.12 (s, 3H), 1.95 - 1.85 (m, 1H), 1.76 - 1.67 (m, 1H)
150	White solid	460.1 [M+H] ⁺ , (2.781 min)	2	δ (DMSO- d_6): 8.09 (d, $J=3.9$ Hz, 1H), 7.80 (d, $J=9.1$ Hz, 1H), 7.59 (dd, $J=2.8, 9.1$ Hz, 1H), 7.28 (d, $J=2.6$ Hz, 1H), 7.19 (d, $J=3.9$ Hz, 1H), 6.15 (d, $J=5.5$ Hz, 1H), 4.85 (s, 2H), 4.74 (t, $J=6.1$ Hz, 1H), 3.95 (s, 3H), 3.79 (br d, $J=10.1$ Hz, 1H), 3.53 - 3.43 (m, 2H), 2.82 (br d, $J=11.0$ Hz, 1H), 2.57 (br d, $J=11.1$ Hz, 1H), 2.41 (s, 3H), 2.18 (s, 3H), 1.97 (dt, $J=3.1, 11.0$ Hz, 1H), 1.87 (br t, $J=10.5$ Hz, 1H)
151	Yellow solid	444.0 [M+H] ⁺ , (1.695 min)	1	δ (DMSO- d_6): 8.22 - 8.07 (m, 2H), 7.49 (s, 1H), 7.24 (d, $J=9.0$ Hz, 1H), 7.18 (d, $J=4.0$ Hz, 1H), 5.63 (s, 1H), 4.75 (s, 2H), 4.01 (s, 3H), 2.60 - 2.53 (m, 5H), 2.36 - 2.26 (m, 2H), 2.19 (s, 3H), 2.03 - 1.90 (m, 2H), 1.75 (br d, $J=12.1$ Hz, 2H)
152	Yellow solid	460.0 [M+H] ⁺ , (1.775 min)	1	δ (DMSO- d_6): 8.10 (d, $J=3.9$ Hz, 1H), 7.80 (d, $J=9.2$ Hz, 1H), 7.63 - 7.55 (m, 1H), 7.28 (d, $J=2.6$ Hz, 1H), 7.19 (d, $J=3.8$ Hz, 1H), 5.83 (d, $J=4.2$ Hz, 1H), 5.06 - 4.95 (m, 1H), 4.85 (s, 2H), 3.95 (s, 3H), 3.58 (t, $J=4.6$ Hz, 4H), 2.64 - 2.52 (m, 4H), 2.49 - 2.43 (m, 2H), 2.42 (s, 3H)
153	Yellow solid	482.0 [M+H] ⁺ , (2.559 min)	1	δ (DMSO- d_6): 9.39 (d, $J=1.98$ Hz, 1 H) 8.80 (s, 1 H) 8.24 (s, 1 H) 8.09 (m, 1 H) 7.57 (s, 1 H) 7.16 (m, 1 H) 4.86 (m, 2 H) 3.13 (m, 1 H) 2.60 (br d, $J=11.22$ Hz, 1 H) 2.37 (m, 5 H) 2.22 (s, 3 H) 1.98 (m, 2 H) 1.77 (br d, $J=12.10$ Hz, 2 H)
154	Light purple solid	482.1 [M+H] ⁺ , (2.82 min)	2	δ (DMSO- d_6): 9.36 (d, $J=2.3$ Hz, 1H), 8.81 (d, $J=1.1$ Hz, 1H), 8.11 (d, $J=4.0$ Hz, 1H), 7.69 (s, 1H), 7.18 (d, $J=4.0$ Hz, 1H), 5.66 (s, 1H), 5.02 (s, 2H), 2.70 (s, 3H), 2.59 - 2.53 (m, 2H), 2.31 (br t, $J=10.8$ Hz, 2H), 2.19 (s, 3H), 1.97 (dt, $J=3.9, 12.5$ Hz, 2H), 1.75 (br d, $J=12.3$ Hz, 2H)
155	Yellow solid	472.1 [M+H] ⁺ , (2.386 min)	1	δ (DMSO- d_6): 8.62 (s, 1H), 8.05 (d, $J=4.0$ Hz, 1H), 7.16 (d, $J=4.0$ Hz, 1H), 5.63 (s, 1H), 4.99 (s, 2H), 4.07 (s, 3H), 2.57 (br s, 1H), 2.40 - 2.25 (m, 3H), 2.20 (s, 3H), 1.97 (dt, $J=4.2, 12.4$ Hz, 2H), 1.76 (br d, $J=11.7$ Hz, 2H)
156	Yellow solid	433.1 [M+H] ⁺ , (2.361 min)	2	δ (DMSO- d_6): 9.26 (d, $J=3.1$ Hz, 1H), 8.57 - 8.40 (m, 1H), 8.10 (d, $J=4.0$ Hz, 1H), 7.18 (d, $J=4.0$ Hz, 1H), 5.66 (s, 1H), 4.91 (s, 2H), 2.60 - 2.54 (m, 2H), 2.49 (br s, 3H), 2.33 (br t, $J=10.6$ Hz, 2H), 2.20 (s, 3H), 2.02 - 1.94 (m, 2H), 1.77 (br d, $J=11.9$ Hz, 2H)
157	Yellow solid	416.2 [M+H] ⁺ , (2.076 min)	1	δ (DMSO- d_6): 8.14 (d, $J=3.96$ Hz, 1 H) 7.79 (d, $J=9.24$ Hz, 1 H) 7.59 (dd, $J=9.24, 2.64$ Hz, 1 H) 7.27 (d, $J=2.86$ Hz, 1 H) 7.22 (d, $J=3.74$ Hz, 1 H) 4.85 (d, $J=1.32$ Hz, 2 H) 4.77 (dd, $J=9.90, 2.20$

				Hz, 1 H) 3.94 (m, 4 H) 3.66 (td, J=10.95, 3.41 Hz, 1 H) 3.18 (dd, J=12.21, 2.09 Hz, 1 H) 2.79 (m, 2 H) 2.67 (dd, J=12.10, 10.12 Hz, 1 H) 2.38 (s, 3 H)
158	Yellow solid	416.1 [M+H] ⁺ , (2.084 min)	1	δ (DMSO- <i>d</i> ₆): 8.14 (d, J=3.96 Hz, 1 H) 7.79 (d, J=9.24 Hz, 1 H) 7.59 (dd, J=9.13, 2.75 Hz, 1 H) 7.27 (d, J=2.64 Hz, 1 H) 7.22 (d, J=3.74 Hz, 1 H) 4.85 (d, J=1.10 Hz, 2 H) 4.78 (dd, J=10.01, 2.31 Hz, 1 H) 3.94 (m, 4 H) 3.67 (td, J=11.06, 3.19 Hz, 1 H) 3.19 (dd, J=12.32, 2.20 Hz, 1 H) 2.81 (m, 2 H) 2.68 (dd, J=12.32, 10.12 Hz, 1 H) 2.38 (s, 3 H)
159	Yellow solid	456.1 [M+H] ⁺ , (2.010 min)	1	δ (DMSO- <i>d</i> ₆): 8.07 (d, J=4.00 Hz, 1 H) 7.79 (d, J=9.13 Hz, 1 H) 7.59 (dd, J=9.19, 2.69 Hz, 1 H) 7.27 (d, J=2.63 Hz, 1 H) 7.20 (d, J=3.88 Hz, 1 H) 6.02 (s, 1 H) 4.85 (s, 2 H) 3.94 (s, 3 H) 3.12 (m, 2 H) 2.46 (br dd, J=9.26, 3.50 Hz, 1 H) 2.42 (s, 3 H) 2.37 (br s, 1 H) 2.31 (s, 3 H) 2.01 (m, 2 H) 1.71 (m, 1 H) 1.60 (br d, J=10.26 Hz, 1 H)
160	Yellow solid	456.1 [M+H] ⁺ , (1.999 min)	1	δ (DMSO- <i>d</i> ₆): 8.07 (d, J=3.88 Hz, 1 H) 7.79 (d, J=9.13 Hz, 1 H) 7.59 (dd, J=9.07, 2.69 Hz, 1 H) 7.27 (d, J=2.63 Hz, 1 H) 7.21 (d, J=4.00 Hz, 1 H) 6.03 (s, 1 H) 4.85 (s, 2 H) 3.94 (s, 3 H) 3.14 (m, 2 H) 2.46 (br s, 1 H) 2.42 (s, 3 H) 2.38 (br s, 1 H) 2.31 (s, 3 H) 2.02 (m, 2 H) 1.72 (br d, J=9.51 Hz, 1 H) 1.60 (br d, J=9.63 Hz, 1 H)
161	Yellow solid	444.1 [M+H] ⁺ , (1.886 min)	1	δ (DMSO- <i>d</i> ₆): 8.07 (d, J=3.74 Hz, 1 H) 8.00 (d, J=9.02 Hz, 1 H) 7.26 (m, 2 H) 7.16 (d, J=3.74 Hz, 1 H) 5.63 (s, 1 H) 4.82 (s, 2 H) 3.93 (s, 3 H) 2.56 (br d, J=10.78 Hz, 2 H) 2.40 (s, 3 H) 2.32 (br t, J=10.78 Hz, 2 H) 2.19 (s, 3 H) 1.98 (m, 2 H) 1.76 (br d, J=12.10 Hz, 2 H)
162	Yellow solid	442.1 [M+H] ⁺ , (1.919 min)	1	δ (DMSO- <i>d</i> ₆): 9.48 (m, 1 H) 8.83 (br d, J=2.20 Hz, 1 H) 8.14 (d, J=3.96 Hz, 1 H) 7.93 (d, J=9.02 Hz, 1 H) 7.70 (dd, J=9.24, 2.64 Hz, 1 H) 7.34 (m, 2 H) 4.95 (s, 2 H) 4.05 (br s, 1 H) 3.98 (s, 3 H) 3.68 (br s, 1 H) 3.03 (br t, J=9.79 Hz, 1 H) 2.68 (br s, 1 H) 2.50 (br s, 3 H) 2.43 (m, 1 H) 2.07 (dd, J=14.75, 2.86 Hz, 1 H) 1.84 (m, 2 H)
163	Yellow solid	456.1 [M+H] ⁺ , (2.895 min)	1	δ (400 MHz, DMSO- <i>d</i> ₆) 8.30 (s, 1H), 8.10 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.60 (dd, J = 2.7, 9.2 Hz, 1H), 7.29 (t, J = 3.5 Hz, 2H), 6.14 - 5.73 (m, 1H), 4.86 (s, 2H), 3.95 (s, 3H), 2.95 (br d, J = 13.7 Hz, 1H), 2.87 - 2.61 (m, 5H), 2.42 (s, 3H), 2.16 - 2.04 (m, 1H), 1.87 (br s, 1H), 1.50 - 1.22 (m, 3H)
164	Yellow solid	486.1 [M+H] ⁺ , (3.093 min)	2	δ (DMSO- <i>d</i> ₆): 8.10 (d, J = 4.0 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.62 - 7.54 (m, 1H), 7.30 - 7.22 (m, 2H), 6.83 (s, 1H), 4.85 (s, 2H), 3.95 (s, 3H), 3.93 - 3.86 (m, 2H), 3.82 - 3.76 (m, 2H), 2.80 (br

				s, 2H), 2.59 - 2.52 (m, 2H), 2.50 (s, 3H), 2.42 (s, 3H), 1.73 (d, J = 14.7 Hz, 2H)
165	Yellow solid	214.6 [M+H] ⁺ /2 ⁺ , (2.112 min)	1	δ (DMSO-d ₆): 8.23 (s, 1 H) 8.16 (d, J=3.88 Hz, 1 H) 7.80 (d, J=9.13 Hz, 1 H) 7.60 (dd, J=9.19, 2.69 Hz, 1 H) 7.29 (dd, J=6.69, 3.31 Hz, 2 H) 4.87 (s, 2 H) 3.95 (m, 4 H) 3.85 (d, J=6.88 Hz, 1 H) 3.77 (s, 1 H) 3.23 (d, J=10.01 Hz, 1 H) 3.09 (d, J=9.76 Hz, 1 H) 2.41 (s, 3 H) 2.12 (m, 1 H) 1.92 (d, J=9.51 Hz, 1 H)
166	Yellow solid	428.1 [M+H] ⁺ , (2.852 min)	2	δ (DMSO-d ₆): 8.14 (d, J = 3.7 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.59 (dd, J = 2.8, 9.1 Hz, 1H), 7.27 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 3.7 Hz, 1H), 5.07 (s, 1H), 4.84 (s, 2H), 4.66 (s, 1H), 3.95 (s, 3H), 3.72 (s, 2H), 2.88 (s, 2H), 2.39 (s, 3H), 1.81 - 1.36 (m, 2H)
167	Yellow solid	484.1 [M+H] ⁺ , (2.505 min)	1	δ (DMSO-d ₆): 8.25 (d, J = 4.2 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.63 - 7.56 (m, 1H), 7.51 (d, J = 4.0 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 4.97 - 4.79 (m, 2H), 3.95 (s, 3H), 3.80 (br d, J = 11.2 Hz, 1H), 3.72 - 3.56 (m, 2H), 3.18 (br d, J = 13.0 Hz, 1H), 2.81 - 2.66 (m, 2H), 2.36 (s, 3H)
168	Yellow solid	484.1 [M+H] ⁺ , (2.511 min)	1	δ (DMSO-d ₆): 8.25 (d, J = 4.0 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.64 - 7.56 (m, 1H), 7.51 (d, J = 4.0 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 4.96 - 4.78 (m, 2H), 3.95 (s, 3H), 3.80 (br d, J = 10.8 Hz, 1H), 3.73 - 3.57 (m, 2H), 3.18 (br d, J = 13.2 Hz, 1H), 2.87 - 2.60 (m, 2H), 2.36 (s, 3H)
169	Yellow solid	430.1 [M+H] ⁺ , (2.196 min)	1	δ (DMSO-d ₆): 8.11 (d, J=3.96 Hz, 1 H) 7.79 (d, J=9.24 Hz, 1 H) 7.59 (dd, J=9.13, 2.75 Hz, 1 H) 7.27 (d, J=2.64 Hz, 1 H) 7.20 (d, J=3.96 Hz, 1 H) 4.85 (s, 2 H) 3.95 (s, 3 H) 3.60 (m, 2 H) 3.10 (d, J=12.54 Hz, 1 H) 2.86 (d, J=12.76 Hz, 1 H) 2.68 (m, 2 H) 2.41 (s, 3 H) 1.49 (s, 3 H)
170	Yellow solid	430.1 [M+H] ⁺ , (2.182 min)	1	δ (DMSO-d ₆): 8.11 (d, J=3.74 Hz, 1 H) 7.79 (d, J=9.02 Hz, 1 H) 7.59 (dd, J=9.24, 2.64 Hz, 1 H) 7.24 (m, 2 H) 4.85 (s, 2 H) 3.94 (s, 3 H) 3.60 (m, 2 H) 3.09 (d, J=12.76 Hz, 1 H) 2.85 (d, J=12.54 Hz, 1 H) 2.67 (m, 2 H) 2.41 (s, 3 H) 1.49 (s, 3 H)
171	White solid	465.8 [M+H] ⁺ , (2.345 min)	1	δ (DMSO-d ₆): 8.15 (d, J = 4.0 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.60 (dd, J = 2.8, 9.1 Hz, 1H), 7.28 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 3.6 Hz, 1H), 4.97 (dd, J = 3.0, 9.8 Hz, 1H), 4.86 (d, J = 0.9 Hz, 2H), 4.22 - 4.12 (m, 2H), 3.95 (s, 3H), 3.47 - 3.36 (m, 2H), 3.23 - 2.99 (m, 2H), 2.78 (dd, J = 9.9, 13.6 Hz, 1H), 2.39 (s, 3H)
172	White solid	465.8 [M+H] ⁺ , 2.345 min)	1	δ (DMSO-d ₆): 8.15 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 9.1 Hz, 1H), 7.60 (dd, J = 2.8, 9.1 Hz, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.21 (d, J = 3.8 Hz, 1H), 4.97 (dd, J = 2.9, 9.7 Hz, 1H), 4.86 (s, 2H), 4.23 - 4.11 (m, 2H), 3.95 (s, 3H), 3.48 - 3.35 (m, 2H),

				3.17 - 2.99 (m, 2H), 2.77 (ddd, $J = 3.0, 10.2, 13.3$ Hz, 1H), 2.39 (s, 3H)
173	Yellow solid	427.8 [M+H] ⁺ , (2.050 min)	1	δ (DMSO- d_6): 8.15 (d, $J = 4.0$ Hz, 1H), 7.80 (d, $J = 9.2$ Hz, 1H), 7.60 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.28 (t, $J = 3.2$ Hz, 2H), 4.87 (s, 2H), 3.98 - 3.89 (m, 4H), 3.83 (d, $J = 6.8$ Hz, 1H), 3.72 (s, 1H), 3.20 (d, $J = 9.9$ Hz, 1H), 3.06 (d, $J = 9.9$ Hz, 1H), 2.41 (s, 3H), 2.16 - 2.03 (m, 1H), 1.89 (d, $J = 9.5$ Hz, 1H)
174	Yellow solid	442.2 [M+H] ⁺ , (3.004 min)	1	δ (DMSO- d_6): 8.23 - 8.08 (m, 1H), 7.89 - 7.74 (m, 1H), 7.66 - 7.51 (m, 1H), 7.38 - 7.18 (m, 2H), 4.85 (br d, $J = 6.2$ Hz, 2H), 4.10 (br t, $J = 6.7$ Hz, 1H), 3.94 (br d, $J = 6.2$ Hz, 3H), 3.81 (br t, $J = 6.4$ Hz, 1H), 3.54 (br s, 1H), 3.20 - 3.13 (m, 1H), 2.76 - 2.65 (m, 1H), 2.43 - 2.35 (m, 6H), 2.32 - 2.23 (m, 1H), 1.92 - 1.83 (m, 1H)
175	Yellow solid	446.2 [M+H] ⁺ , (2.792 min)	1	δ (DMSO- d_6): 8.15 (d, $J = 3.7$ Hz, 1H), 7.95 (t, $J = 9.1$ Hz, 1H), 7.72 (dd, $J = 1.5, 9.2$ Hz, 1H), 7.28 (d, $J = 3.7$ Hz, 1H), 4.75 (s, 2H), 4.00 (s, 3H), 3.95 (dd, $J = 1.5, 7.0$ Hz, 1H), 3.83 (d, $J = 6.8$ Hz, 1H), 3.72 (s, 1H), 3.21 (d, $J = 9.9$ Hz, 1H), 3.07 (d, $J = 9.9$ Hz, 1H), 2.29 (s, 3H), 2.10 (dd, $J = 1.4, 9.4$ Hz, 1H), 1.89 (d, $J = 9.2$ Hz, 1H)
176	Yellow solid	460.1 [M+H] ⁺ , (2.989 min)	1	δ (DMSO- d_6): 8.15 (d, $J = 3.9$ Hz, 1H), 8.03 - 7.88 (m, 1H), 7.71 (br d, $J = 9.1$ Hz, 1H), 7.30 (d, $J = 3.9$ Hz, 1H), 4.75 (s, 2H), 4.10 (d, $J = 7.5$ Hz, 1H), 4.00 (s, 3H), 3.81 (dd, $J = 1.5, 7.4$ Hz, 1H), 3.54 (br s, 1H), 3.17 (d, $J = 9.6$ Hz, 1H), 2.71 (br d, $J = 9.5$ Hz, 1H), 2.39 (s, 2H), 2.32 - 2.24 (m, 4H), 1.88 (br d, $J = 9.6$ Hz, 1H)
177	White solid	427.9 [M+H] ⁺ , (2.045 min)	1	δ (DMSO- d_6): 8.21 (s, 1H), 8.14 (d, $J = 3.7$ Hz, 1H), 7.80 (d, $J = 9.0$ Hz, 1H), 7.59 (dd, $J = 2.8, 9.1$ Hz, 1H), 7.27 (d, $J = 2.6$ Hz, 1H), 7.15 (d, $J = 3.5$ Hz, 1H), 5.05 (s, 1H), 4.84 (s, 2H), 4.65 (s, 1H), 3.95 (s, 3H), 3.67 (s, 1H), 2.85 (s, 2H), 2.39 (s, 3H), 1.73 - 1.49 (m, 2H)
178	Yellow solid	441.9 [M+H] ⁺ , (2.009 min)	1	δ (DMSO- d_6): 8.15 (d, $J = 3.96$ Hz, 1 H) 7.79 (d, $J = 9.24$ Hz, 1 H) 7.59 (dd, $J = 9.13, 2.75$ Hz, 1 H) 7.28 (dd, $J = 12.87, 3.19$ Hz, 2 H) 4.85 (s, 2 H) 4.09 (d, $J = 7.48$ Hz, 1 H) 3.94 (s, 3 H) 3.80 (dd, $J = 7.48, 1.54$ Hz, 1 H) 3.54 (s, 1 H) 3.17 (d, $J = 9.46$ Hz, 1 H) 2.70 (d, $J = 9.90$ Hz, 1 H) 2.39 (s, 6 H) 2.28 (br d, $J = 8.14$ Hz, 1 H) 1.87 (d, $J = 9.24$ Hz, 1 H)
179	Yellow solid	446.2 [M+H] ⁺ , (2.792 min)	1	δ (DMSO- d_6): 8.15 (d, $J = 3.7$ Hz, 1H), 7.95 (t, $J = 9.1$ Hz, 1H), 7.72 (dd, $J = 1.5, 9.2$ Hz, 1H), 7.28 (d, $J = 3.7$ Hz, 1H), 4.75 (s, 2H), 4.00 (s, 3H), 3.95 (dd, $J = 1.5, 7.0$ Hz, 1H), 3.83 (d, $J = 6.8$ Hz, 1H), 3.72 (s, 1H), 3.21 (d, $J = 9.9$ Hz, 1H), 3.07 (d, $J = 9.9$ Hz, 1H), 2.29 (s, 3H), 2.10 (dd, $J = 1.4, 9.4$ Hz, 1H), 1.89 (d, $J = 9.2$ Hz, 1H)

180	Yellow oil	464.1 [M+H] ⁺ , (2.504 min)	1	δ (DMSO- <i>d</i> ₆): 8.16 (d, <i>J</i> = 4.0 Hz, 1H), 7.95 (d, <i>J</i> = 9.1 Hz, 1H), 7.81 (dd, <i>J</i> = 2.6, 9.1 Hz, 1H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.53 (t, <i>J</i> = 73.4 Hz, 1H), 7.30 (d, <i>J</i> = 3.9 Hz, 1H), 4.90 (s, 2H), 3.95 (dd, <i>J</i> = 1.4, 6.8 Hz, 1H), 3.83 (d, <i>J</i> = 6.9 Hz, 1H), 3.73 (s, 1H), 3.21 (d, <i>J</i> = 9.9 Hz, 1H), 3.07 (d, <i>J</i> = 9.4 Hz, 1H), 2.44 (s, 3H), 2.10 (br d, <i>J</i> = 7.9 Hz, 1H), 1.90 (d, <i>J</i> = 9.5 Hz, 1H)
181	Yellow oil	478.1 [M+H] ⁺ , (2.523 min)	1	δ (DMSO- <i>d</i> ₆): 7.90 (dd, <i>J</i> = 2.4, 6.4 Hz, 2H), 7.74 (d, <i>J</i> = 2.4 Hz, 1H), 7.63 (dd, <i>J</i> = 2.4, 9.1 Hz, 1H), 7.13 (d, <i>J</i> = 3.9 Hz, 1H), 6.66 (t, <i>J</i> = 73.0 Hz, 1H), 4.72 (s, 2H), 4.32 (d, <i>J</i> = 7.9 Hz, 1H), 3.95 (d, <i>J</i> = 7.9 Hz, 1H), 3.61 (s, 1H), 3.32 (d, <i>J</i> = 9.9 Hz, 1H), 2.91 (d, <i>J</i> = 9.8 Hz, 1H), 2.62 (s, 3H), 2.55 (s, 3H), 2.36 (br d, <i>J</i> = 9.3 Hz, 1H), 2.05 (d, <i>J</i> = 10.0 Hz, 1H)
182	Yellow solid	460.1 [M+H] ⁺ , (2.989 min)	1	δ (DMSO- <i>d</i> ₆): 8.15 (d, <i>J</i> = 3.9 Hz, 1H), 8.03 - 7.88 (m, 1H), 7.71 (br d, <i>J</i> = 9.1 Hz, 1H), 7.30 (d, <i>J</i> = 3.9 Hz, 1H), 4.75 (s, 2H), 4.10 (d, <i>J</i> = 7.5 Hz, 1H), 4.00 (s, 3H), 3.81 (dd, <i>J</i> = 1.5, 7.4 Hz, 1H), 3.54 (br s, 1H), 3.17 (d, <i>J</i> = 9.6 Hz, 1H), 2.71 (br d, <i>J</i> = 9.5 Hz, 1H), 2.39 (s, 2H), 2.32 - 2.24 (m, 4H), 1.88 (br d, <i>J</i> = 9.6 Hz, 1H)
183	Yellow solid	482.1 [M+H] ⁺ , (2.816 min)	1	δ (DMSO- <i>d</i> ₆): 8.16 (d, <i>J</i> = 3.74 Hz, 1 H) 8.00 (m, 3 H) 7.29 (d, <i>J</i> = 3.96 Hz, 1 H) 4.91 (s, 2 H) 3.94 (dd, <i>J</i> = 6.71, 1.43 Hz, 1 H) 3.82 (d, <i>J</i> = 6.82 Hz, 1 H) 3.72 (s, 1 H) 3.20 (br d, <i>J</i> = 9.90 Hz, 2 H) 3.06 (d, <i>J</i> = 9.68 Hz, 1 H) 2.45 (s, 3 H) 2.09 (br d, <i>J</i> = 8.14 Hz, 1 H) 1.88 (d, <i>J</i> = 9.46 Hz, 1 H)
184	Yellow solid	496.1 [M+H] ⁺ , (2.862 min)	1	δ (DMSO- <i>d</i> ₆): 8.16 (d, <i>J</i> = 3.96 Hz, 1 H) 8.00 (m, 3 H) 7.31 (d, <i>J</i> = 3.96 Hz, 1 H) 4.90 (s, 2 H) 4.09 (d, <i>J</i> = 7.26 Hz, 1 H) 3.80 (dd, <i>J</i> = 7.37, 1.43 Hz, 1 H) 3.54 (s, 1 H) 3.17 (d, <i>J</i> = 9.68 Hz, 1 H) 2.70 (d, <i>J</i> = 9.46 Hz, 1 H) 2.44 (s, 3 H) 2.39 (s, 3 H) 2.28 (br d, <i>J</i> = 8.36 Hz, 1 H) 1.87 (d, <i>J</i> = 9.46 Hz, 1 H)
185	Yellow solid	466.1 [M+H] ⁺ , (2.820 min)	1	δ (DMSO- <i>d</i> ₆): 9.39 (d, <i>J</i> = 1.98 Hz, 1 H) 8.81 (s, 1 H) 8.15 (d, <i>J</i> = 3.96 Hz, 1 H) 7.57 (s, 1 H) 7.28 (d, <i>J</i> = 3.74 Hz, 1 H) 4.87 (s, 2 H) 3.93 (dd, <i>J</i> = 6.82, 1.32 Hz, 1 H) 3.82 (d, <i>J</i> = 7.04 Hz, 1 H) 3.71 (s, 1 H) 3.20 (br d, <i>J</i> = 9.90 Hz, 2 H) 3.06 (br d, <i>J</i> = 9.68 Hz, 1 H) 2.37 (s, 3 H) 2.09 (br d, <i>J</i> = 7.92 Hz, 1 H) 1.88 (d, <i>J</i> = 9.46 Hz, 1 H)
186	Yellow solid	479.9 [M+H] ⁺ , (3.606 min)	2	δ (DMSO- <i>d</i> ₆): 9.39 (d, <i>J</i> = 1.76 Hz, 1 H) 8.80 (s, 1 H) 8.14 (d, <i>J</i> = 3.96 Hz, 1 H) 7.56 (s, 1 H) 7.29 (d, <i>J</i> = 3.96 Hz, 1 H) 4.87 (s, 2 H) 4.09 (d, <i>J</i> = 7.48 Hz, 1 H) 3.80 (dd, <i>J</i> = 7.37, 1.21 Hz, 1 H) 3.53 (s, 1 H) 3.17 (d, <i>J</i> = 9.68 Hz, 1 H) 2.70 (d, <i>J</i> = 9.68 Hz, 1 H) 2.37 (d, <i>J</i> = 9.90 Hz, 6 H) 2.27 (br d, <i>J</i> = 8.36 Hz, 1 H) 1.86 (d, <i>J</i> = 9.46 Hz, 1 H)
187	Yellow solid	460.1 [M+H] ⁺ ,	1	δ (DMSO- <i>d</i> ₆): 8.10 (d, <i>J</i> = 3.74 Hz, 1 H) 7.94 (t, <i>J</i> = 9.13 Hz, 1 H) 7.71 (dd, <i>J</i> = 9.24, 1.32 Hz, 1 H)

		(2.308 min)		7.12 (d, $J=3.96$ Hz, 1 H) 4.72 (s, 2 H) 4.14 (d, $J=7.48$ Hz, 1 H) 3.99 (m, 4 H) 2.92 (d, $J=12.98$ Hz, 1 H) 2.69 (m, 3 H) 2.44 (br s, 1 H) 2.27 (s, 3 H) 2.20 (d, $J=10.78$ Hz, 1 H) 2.01 (m, 1 H)
188	Yellow solid	460.1 [M+H] ⁺ , (2.310 min)	1	δ (DMSO- d_6): 8.10 (d, $J=3.96$ Hz, 1 H) 7.94 (t, $J=9.13$ Hz, 1 H) 7.71 (dd, $J=9.24, 1.54$ Hz, 1 H) 7.12 (d, $J=3.96$ Hz, 1 H) 4.72 (s, 2 H) 4.14 (d, $J=7.48$ Hz, 1 H) 3.99 (m, 4 H) 2.91 (d, $J=12.98$ Hz, 1 H) 2.68 (m, 3 H) 2.43 (br d, $J=2.20$ Hz, 1 H) 2.27 (s, 3 H) 2.20 (d, $J=11.00$ Hz, 1 H) 2.01 (m, 1 H)
189	Yellow solid	474.1 [M+H] ⁺ , (2.163 min)	1	δ (DMSO- d_6): 8.11 (d, $J=3.96$ Hz, 1 H) 7.94 (t, $J=9.13$ Hz, 1 H) 7.71 (d, $J=9.24$ Hz, 1 H) 7.17 (d, $J=3.96$ Hz, 1 H) 4.73 (s, 2 H) 4.00 (m, 4 H) 3.90 (m, 1 H) 2.82 (m, 2 H) 2.60 (br d, $J=3.74$ Hz, 1 H) 2.40 (br d, $J=7.04$ Hz, 1 H) 2.28 (m, 7 H) 1.96 (m, 2 H)
190	Yellow solid	474.1 [M+H] ⁺ , (2.164 min)	1	δ (DMSO- d_6): 8.11 (d, $J=3.96$ Hz, 1 H) 7.94 (t, $J=9.13$ Hz, 1 H) 7.71 (dd, $J=9.24, 1.54$ Hz, 1 H) 7.17 (d, $J=3.96$ Hz, 1 H) 4.73 (s, 2 H) 4.00 (m, 4 H) 3.90 (m, 1 H) 2.82 (br d, $J=10.34$ Hz, 2 H) 2.60 (br d, $J=3.96$ Hz, 1 H) 2.42 (br d, $J=10.56$ Hz, 1 H) 2.28 (m, 7 H) 1.95 (m, 2 H)

Table 4

Example 2: In vitro enzymatic assay on HDAC6, 1 and 3***Materials and Methods***

[0660] Inhibition of HDAC enzymes was performed in 384-well plate format using

5 human full-length recombinant HDAC1, HDAC3 (in complex with NcoR2) and HDAC6, isolated from a baculovirus expression system in Sf9 cells (BPS Bioscience). Reaction buffer for enzymatic reaction contained 50 mM Tris/HCl pH 7.5, 137 mM NaCl, 2.7 mM KCl, 5 mM GSH and 0.003% BSA in aqueous solution. Compounds (dissolved in 100% DMSO) or DMSO (vehicle) were diluted in assay buffer at 3x final assay concentration

10 and then added to assay plates. SAHA (10 μ M) was used as a positive control. 3x final assay concentration of recombinant enzymes (final assay concentration is 3.3 nM for HDAC1 and HDAC3 and 0.33 nM for HDAC6) were preincubated for 10 minutes with test compounds at room temperature. Afterwards, 3x final assay concentration of an acetylated fluorogenic peptide (Ac-Gly-Ala-Lys(Ac))-AMC, Bachem; final assay

15 concentration is 10 μ M for HDAC1, HDAC3 and HDAC6) was added to assay plate,

allowing deacetylase reactions to incubate for 60 minutes at room temperature. The developer reagent containing 5 μM SAHA and 50 μM trypsin was added to stop the deacetylase reaction and generate AMC-fluorescence. 15 minutes after addition of developer reagent, endpoint measurements were taken using CLARIOstar (BMG Labtech) plate reader (excitation/emission: 360/450). Fluorescence signals were normalized for each plate : reaction HDAC-substrate in presence of DMSO was set to 100% while reaction HDAC-substrate in presence of 10 μM SAHA was set to 0%. IC50-values were calculated from normalized measurements using a 4 parameter nonlinear regression model with 0% bottom and 100% top constraints. From experimental pIC50, Ki values were computed using the Cheng-Prusoff equation and leveraging the experimentally determined Km of each enzyme for this substrate (59.35 μM, 16.98 μM and 7.59 μM for HDAC1, HDAC3 and HDAC6, respectively).

$$Ki = \frac{IC50}{1 + \frac{[S]}{Km}}$$

Cheng-Prusoff equation where IC50 is the experimentally determined concentration of compound to inhibit the enzyme by 50%, [S] the concentration of substrate in the assay (10 μM in this case) and Km the experimentally determined Km of each enzyme for this fluorogenic peptide.

Results

[0661] The results of this assay are presented on Table 5 below, wherein “+” means: 1000 nM < Ki ≤ 10000 nM, “++” means: 500 nM < Ki ≤ 1000 nM, “+++” means: 100 nM < Ki ≤ 500 nM, “++++” means: Ki < 100 nM, and “-” means Ki > 10000 nM.

Cpd #	HDAC6 biochem Ki	HDAC1 biochem Ki	HDAC3 biochem Ki
35	++	+	+
72	++++	+++	++
90	+++	++	++
91	+++	++	++

92	+++	++	++
93	+++	++	++
94	+++	++	++
95	++++	++	++
96	+++	++	+
97	++++	+++	++
98	+++	++	++
99	+++	++	++
100	+++	++	+
101	+++	++	+
102	+++	++	+
103	++++	+++	++
104	++++	+++	++
105	+++	++	++
106	+++	++	++
107	+++	++	++
108	++++	+++	++
109	++++	++	++
110	+++	++	++
111	+++	++	++
112	+++	++	+
113	+++	++	++
114	++++	+++	++
115	+++	++	++
116	+++	++	++
117	++++	+++	++
118	++++	+++	++
119	+++	++	++
120	+++	++	+
121	++++	+++	++
122	++++	+++	++
123	+++	++	++
124	+++	++	+
125	++++	+++	++
126	+++	++	++
127	+++	++	++
128	+++	++	++
129	+++	++	++
130	+++	++	++
131	+++	++	++
132	+++	++	++
133	+++	++	++
134	+++	++	+
135	+++	++	+

136	++++	++	NT
137	++++	+++	NT
138	+++	++	NT
139	+++	++	NT
140	+++	++	NT
141	+++	++	NT
142	+++	++	NT
143	+++	++	NT
144	+++	++	NT
145	+++	++	++
146	+++	+	NT
147	++++	+++	NT
148	+++	+	NT
149	+++	++	NT
150	+++	++	NT
151	++	++	+
152	+++	++	NT
153	+++	++	NT
154	+++	++	NT
155	+++	++	NT
156	++++	++	NT
157	+++	++	++
158	+++	++	++
159	+++	++	NT
160	+++	++	NT
161	+++	++	NT
162	+++	++	NT
163	+++	++	NT
164	++++	++	++
165	+++	+++	++
166	++++	+++	++
167	+++	+	+
168	+++	++	+
169	+++	++	++
170	+++	++	+
171	+++	++	+
172	+++	++	+
173	+++	++	++
174	+++	++	++
175	+++	++	++
176	+++	++	++
177	+++	++	++
178	++++	++	++
179	++++	+++	+++

180	+++	++	++
181	+++	++	++
182	++++	+++	+++
183	+++	+++	++
184	++++	++	++
185	+++	+++	+++
186	++++	++	++
187	+++	++	++
188	++++	++	++
189	++++	++	++
190	++++	+++	+++

Table 5

[0662] The results clearly evidence that the compounds of formula (I) inhibit fluorogenic substrate conversion by HDAC6, but not by HDAC1 and HDAC3. Thus, this assay provides direct evidence that the compounds of formula (I) specifically inhibit HDAC6 over class 1 HDAC1 and HDAC3 and may therefore be used in the treatment and/or prevention of HDAC6-associated diseases, with no or reduced toxicity due to inhibition of other HDAC proteins.

[0663] Taken together, the aforementioned results demonstrate that the compounds of formula (I) act as specific HDAC6 inhibitors.

Example 3: Cellular target engagement assay - NanoBRET

Materials and Methods

[0664] NanoBRET target engagement was performed against the catalytic domain 2 (CD2) of HDAC6, with minor modifications of kit manufacturer protocol (Promega). Expression of exogenous NanoLuc-HDAC6(CD2) fusion and in HEK293T was achieved following transient transfection with FuGENE HD Transfection Reagent (Promega). The intracellular target engagement assay on HDAC6(CD2) was performed in a 384-well plate format with 8,000 cells per well and a tracer concentration of 0.125 µM or 0.600 µM for HDAC6(CD2). Compounds (dissolved in 100% DMSO) or DMSO (vehicle) were added either manually by diluting them in culture medium at 8x final assay concentration and then adding 5 µL to assay plate or in an automated way by adding 160 nL compound to 5 µL OptiMEM without phenol red (Gibco) using the Echo650 (Labcyte). Tracer

solution was added to the cells before seeding 35 µL cell/tracer mixture in the assay plate. The final reaction volume was 40 µL, final DMSO concentration was 1.4% (manual compound addition) or 1.25% (automated compound addition). Assay plates were incubated at 37 °C in a humidified atmosphere containing 5% CO₂ for 2 hours. The

5 NanoBRET Nano-glo Substrate/Inhibitor was prepared by diluting NanoBRET Nano-Glo Substrate (1:332) and Extracellular Inhibitor (1:1000) in assay medium (Promega). The NanoBRET TE Nano-glo Substrate/Inhibitor was added to cells and measurement of NanoBRET donor and acceptor signal (460-80 and 647-75, respectively) was performed at room temperature with either the EnVision Xcite (PerkinElmer) or the CLARIOstar

10 (BMG Labtech) plate reader 1-2 minutes after NanoLuc substrate addition. BRET ratios were calculated from acceptor/donor signal ratio (mBRET = acceptor/donor*1000) and normalized for each plate. Percentage inhibition was calculated by setting the mBRET obtained with cells without tracer to 100%, while the mBRET obtained with uninhibited cells with tracer was set to 0%. IC₅₀-values were calculated from the percentage inhibition

15 with the log(inhibitor) vs. response – Variable slope (four parameters) nonlinear regression in GraphPad Prism software.

Results

[0665] The results of Cellular target engagement assay (BRET) assay are presented on **Table 6** below. In the column **HEK293T hHDAC6-CD2 nanoBRET activity “+”**

20 means: 1000 nM < IC₅₀ ≤ 10000 nM, “++” means: 500 nM < IC₅₀ ≤ 1000 nM, “+++” means: 100 nM < IC₅₀ ≤ 500 nM and “++++” means: IC₅₀ < 100 nM.

Cpd#	HEK293T hHDAC6-CD2 nanoBRET activity
1	++++
2	++++
3	++++
4	++++
5	+++
6	+++

7 [enantiomer 1]	++++
8 [enantiomer 2]	++++
9	++
10	++++
11	+++
12	+++
13	+++
14	++++
15	+++
16	++++
17	++++
18	++++
19	+++
21	++
22	+++
23	+++
24	++
25	++
26	++++
27	+++
28	+++
29	+++
30	+++
31	++++
32	+++
33	+++
34	++++

35	++
36	++++
37	++++
38	+++
39	+++
40	++
41	+++
42	+
43	++++
44	++
45	++
46	+++
47	+++
48	+++
49	+
50	++
51	+
52	++++
53	+
54	++++
55	+++
56	+++
57	++++
58	++++
59	++++
60	+
61	++++

62	++++
63	+
64	++++
65	-
66	++++
67	++++
68	++++
69	++++
70	++++
71	++++
72	++++
73	++++
74	++++
75	++++
76	++++
77	++++
78	++++
79	+++
80	++++
81	++++
82	+++
83	++++
84	++++
85	+++
86	+++
87	+++
88	+++

89	+++
90	++++
91	+++
92	+++
93	++++
94	++++
95	++++
96	+++
97	+++
98	++
99	+++
100	+++
101	+
102	++
103	+++
104	++++
105	+++
106	+++
107	++
108	++++
109	+++
110	+++
111	+++
112	+++
113	+++
114	++++
115	+++

116	++++
117	+++
118	+++
119	+++
120	+++
121	++++
122	++++
123	+++
124	+
125	++++
126	+++
127	+++
128	++++
129	++++
130	+++
131	+++
132	++++
133	++
134	+++
135	+++
136	++++
137	++++
138	++++
139	++++
140	++++
141	++++
142	+++

143	+++
144	++++
145	+++
146	+++
147	++++
148	+++
149	++
150	+
151	+
152	+++
153	+++
154	+++
155	++++
156	++++
157	+++
158	+++
159	++++
160	++++

Table 6

[0666] The results clearly evidence that the compounds of formula (I), effectively inhibit the interaction between HDAC6 catalytic domain 2 and its substrate, thereby inhibiting its deacetylation activity. Thus, this assay shows that the compounds of formula (I) may
5 be used in the treatment and/or prevention of HDAC6 associated diseases.

Example 4: Acetylated α -tubulin measurement *in vitro****Materials and Methods***

HeLa cells were cultured in ADMEM medium (Gibco) supplemented with 1% FBS. 2,000 cells were plated per well in a 384-well plate (Perkin Elmer) and incubated at 37 °C overnight in a humidified atmosphere containing 5% CO₂. Compounds (dissolved in 100% DMSO) or DMSO (vehicle) were added to the cells using the Echo650 (Labcyte) with a final DMSO concentration of 0,1%. Trichostatin A (TSA) was used as a positive control. Cells were incubated with compounds at 37 °C in a humidified atmosphere containing 5% CO₂ for 6 hours. Levels of acetylated tubulin (Lys40) and histone H3 (Lys9) were assessed by immunocytochemistry using target-specific antibodies. Cells were fixed using a 2-step protocol: 10min incubation at RT with 2% PFA (4% PFA solution directly added to the culture medium in a 1:1 ratio), followed by medium/PFA aspiration and another 10min incubation with fresh 4% PFA solution. After 3 wash steps with PBS, cells were permeabilized with 0.5% Triton in PBS at RT for 10 minutes followed by 2 washes with PBS. To avoid non-specific antibody staining, cells were blocked with 3% BSA (in PBS) at room temperature for 1 hour. Then, cells were incubated with primary antibodies anti-acetylated tubulin (mouse monoclonal antibody, acetylated tubulin Lys40, clone 6-11B, Sigma) and anti- α -tubulin (rabbit monoclonal, abcam) diluted in 1 % BSA for 1h at RT. Cells were washed 2 times with PBS and labelled with secondary antibodies, goat anti-mouse conjugated with Alexa 647 (Thermofisher) and goat anti-rabbit conjugated with Alexa 555 (Thermofisher), diluted in 1% BSA to a final concentration of 1:1,000 at room temperature for 1 hour. Simultaneously, nuclei were stained with 1:15,000 Hoechst (Thermofisher). Finally, cells were washed 2 times with PBS and immunostained with Alexa 488-conjugated anti-histone H3 (acetyl K9) antibody (abcam) for 3h at RT. Cells were washed 2 times with PBS and they were imaged with the Opera Phenix (PerkinELmer) using 10x objective and spinning disc confocality. 3 focal planes are captured in a single field of view per well. For imaging analysis, the Columbus analysis software (PerkinElmer) was used. In each cell, the intensity levels of acetylated tubulin were normalized to the intensity levels of total tubulin. The intensity levels of acetylated histone were not normalized. The changes in

acetylated tubulin or acetylated histone were normalized for each plate using GraphPad Prism software: tubulin acetylation and histone acetylation in vehicle (DMSO)-treated cells were set to 0% while tubulin acetylation and histone acetylation in TSA-treated cells were set to 100%. EC50 values were calculated using the log(inhibitor) vs. response –
5 Variable slope (four parameters) nonlinear regression in GraphPad Prism software.

Results

The results of acetylated α -tubulin level assay are presented on **Table 7** below. In the column **HeLa Tubulin Acetylation** “+” means: $1000\text{ nM} < IC_{50} \leq 3333\text{ nM}$, “++” means: $500\text{ nM} < IC_{50} \leq 1000\text{ nM}$, “+++” means: $100\text{ nM} < IC_{50} \leq 500\text{ nM}$, “++++” means: $IC_{50} < 100\text{ nM}$, and “-” means: $IC_{50} > 3333\text{ nM}$.
10

Cpd#	HeLa Tubulin Acetylation	HeLa Histone Acetylation
1	+++	+
2	+++	+
6	++	-
7	+++	+
8	+++	+
9	+	-
10	+++	+
11	+++	+
12	+++	-
13	+++	-
14	++++	+++
16	++++	++++
17	++++	+++
18	++++	+++
19	++	-

26	++++	+++
27	+++	+++
28	+++	+
29	+++	+
30	+++	+
31	++++	+++
34	+++	+
35	+	-
36	+++	+
37	++++	+++
40	+++	-
43	+++	-
44	+++	+
45	+++	-
46	+++	NT
48	++++	-
49	+++	-
50	++++	+
51	-	-
52	++++	+++
54	++++	++++
55	+++	+++
57	+++	+++
58	++++	+++
59	+++	+++
61	++++	+++
62	++++	++++

64	++++	+
66	+++	+
67	+++	++
68	+++	++
69	++++	+++
71	++++	+++
72	+++	+
73	++++	++++
74	++++	+++
75	+++	++
76	+++	+
77	+++	+
78	+++	+++
80	++++	+++
81	++++	++++
83	++++	+++
84	++++	+++
85	+++	+
87	+++	+
89	++++	+++
90	+++	+++
93	+++	++
94	+++	+
95	+++	-
96	+++	-
104	++++	+++
108	+++	++

110	+++	++
112	+++	-
113	+++	+
114	+++	++
116	+++	+
117	++	+
121	+++	-
122	++++	+++
123	+	-
125	+++	++
128	+++	++
129	++++	+++
136	++++	+++
137	++	+
139	++++	++
140	++++	+++
141	++++	+++
142	+++	-
143	+++	-
144	++++	+++
145	+++	+
146	++	-
147	+++	++
148	+++	-
153	+++	++
154	+++	+
155	+++	++

156	++++	+++
158	+++	-
159	++++	++
160	++++	++
161	+++	+
162	++++	+++
163	+++	-
164	+++	-
165	++++	++
167	-	-
168	+	-
169	+++	-
170	++	-
171	++	-
172	++	-
173	++++	++
174	++++	+
175	++++	++
176	++++	+
177	++++	+
178	++++	+
179	++++	++
180	++++	++
181	++++	+
182	++++	+
183	++++	+++
184	++++	++

185	++++	+
186	++++	+
187	++++	+
188	++++	++
189	++++	+
190	++++	+

Table 7

[0667] The results clearly evidence that the compounds of formula (I), increase acetylated α -tubulin over total α -tubulin ratio in HeLa cells, indicating HDAC6 inhibition, HDAC6 being the only HDAC enzyme enabling α -tubulin deacetylation.

5 Thus, this assay shows that the compounds of formula (I) may be used in the treatment and/or prevention of HDAC6-associated diseases.

Example 5: Brain penetration *in vivo*

Materials and Methods

[0668] An appropriate amount of test article was accurately weighed and mixed with an appropriate volume of vehicle to get a clear solution or a uniform suspension. Where

10 needed, vortexing or sonication in a water bath was applied to aid dissolution. Animals were dosed within four hours after the formulation was prepared. The Example compounds (Example 1, 10, 30 and 28) were dosed via oral gavage to CD-1 mouse at a 10 mg/kg dose. Two groups of 3 animals were dosed to assess plasma and brain levels

15 respectively. Blood (about 0.025 mL) was collected in one group at the 1 h time point via saphenous vein puncture, transferred into pre-chilled commercial EDTA-K2 tubes, and placed on wet ice until centrifugation. Blood samples were processed for plasma by centrifugation at approximately 4°C, 3200 g for 10 min. Plasma was collected and transferred into pre-labeled 96 well plate or polypropylene tubes, quick frozen over dry

20 ice and kept at -60°C or lower until LC-MS/MS analysis. Brain was collected from another group of mice after sacrifice, and subsequently homogenized. The brain homogenate samples for PK analysis were mixed with MeOH/15 mM PBS (1:2, v:v) with

a dilution factor of 11 (1 g tissue:10 mL buffer). After terminal homogenization, 800 µL homogenate was stored at approximately -80°C freezer until bioanalysis was performed. An LC-MS/MS method for the quantitative determination of test compound in biological matrix was developed. A calibration curve with at least 6 non-zero calibration standards was applied for the method including LLOQ. A set of QCs consisting of low, middle, and high concentrations was applied for the method. Brain samples were diluted with plasma first and then together with plasma samples quantified against the plasma calibration curve. The brain over plasma ratio was determined by dividing the mean brain concentration of 3 animals over the mean plasma concentration of 3 other animals at the 1 h time point post dosing with the test article.

Results

[0669] The brain penetration results for Example compounds 1, 10, 28 and 30 are presented on **Table 8** below versus **Ricolinostat** as reported in “Gu X. et al. Histone deacetylase 6 inhibitors with blood-brain barrier penetration as a potential strategy for CNS-Disorders therapy. Eur J Med Chem. 2022 Feb 5; 229:114090”.

	Ricolinostat	Ex. 1	Ex.10	Ex. 30	Ex. 28	Ex. 165
Total Brain over total plasma (1 h)	0.07	0.85	1.0	0.45	0.74	0.34

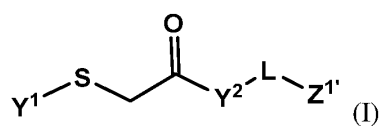
Table 8

[0670] The results clearly evidence that the compounds of formula (I) have improved total brain over total plasma ratios compared to **Ricolinostat**. Thus, this assay shows that the compounds of formula (I) have potential to cross the blood-brain barrier, and hence could be used in the treatment and/or prevention of HDAC6-associated diseases in the central nervous system.

CLAIMS

1. Compound for use in the treatment and/or the prevention of an HDAC6-associated disease;

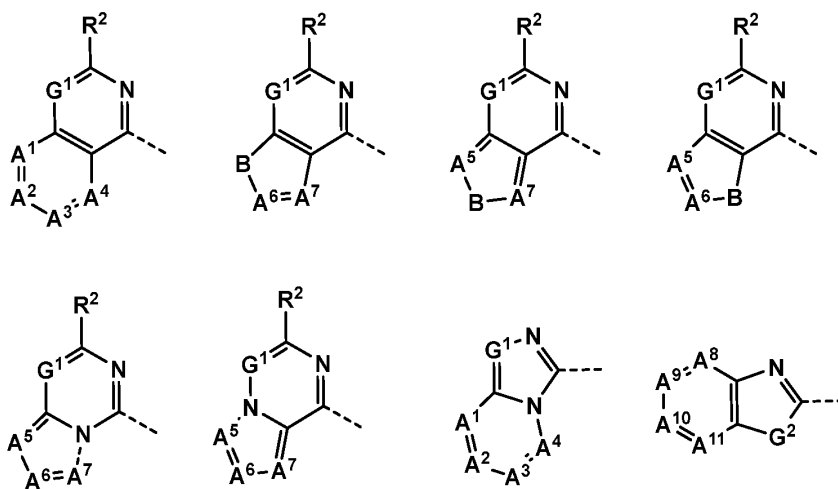
5 wherein said compound is a compound of formula (I)

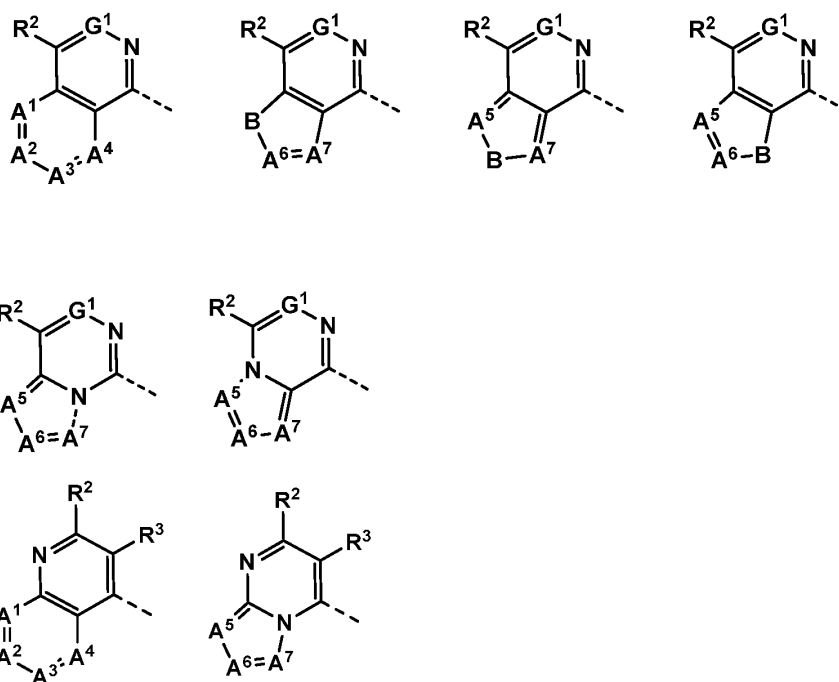


or a pharmaceutically acceptable salt and/or solvate thereof;

wherein

10 - Y^1 is a 9- or 10-membered bicyclic heteroaryl selected from the following formulae





wherein

A^1 , A^2 , A^3 , A^4 , A^5 , A^6 and A^7 are each independently selected from C- R^7 and N;

5 A^8 , A^9 , A^{10} and A^{11} are each independently selected from C- R^7 and N, provided that at least one of A^8 , A^9 , A^{10} or A^{11} is N;

G^1 is selected from C- R^3 and N;

G^2 is selected from O and N- R^4 ;

B is selected from O, S and N- R^5 ,

10 provided that when A^5 , A^6 and A^7 are C- R^7 , then B is not S; and

R^2 is selected from hydrogen, halogen, cyano, amino, hydroxy, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-OR^{15}$, $-(C_1-C_6)$ alkylene- OR^{15} , $-O-(C_2-C_6)$ alkylene- OR^{15} , $-NR^{16}(C_2-C_6)$ alkylene- OR^{15} , $-NR^{17}R^{18}$, $-(C_1-C_6)$ alkylene- $NR^{17}R^{18}$, $-O-(C_2-C_6)$ alkylene- $NR^{17}R^{18}$, $-NR^{16}-(C_2-C_6)$ alkylene- $NR^{17}R^{18}$, $-(C_1-C_6)$ alkylene- $SO_2-NR^{17}R^{18}$, $-NR^{16}-SO_2-R^{15}$, $-(C_1-C_6)$ alkylene- $NR^{16}-SO_2-R^{15}$, $-O-(C_2-C_6)$ alkylene- $NR^{16}-SO_2-R^{15}$,

15

-NR¹⁶-(C₂-C₆) alkylene-NR¹⁷-SO₂-R¹⁵, -C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -O-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -C(O)-R¹⁵, -C(O)OR¹⁵,
 5 -(C₁-C₆) alkylene-C(O)OR¹⁵, -O-(C₁-C₆) alkylene-C(O)OR¹⁵, and -NR¹⁶-(C₁-C₆) alkylene-C(O)OR¹⁵;

R³ is selected from hydrogen, halogen, cyano, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -OR¹⁵,
 10 -(C₁-C₆) alkylene-OR¹⁵, -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-SO₂-NR¹⁷R¹⁸, -NR¹⁶-SO₂-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷-SO₂-R¹⁵, -C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -O-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -C(O)-R¹⁵, -C(O)OR¹⁵,
 15 -(C₁-C₆) alkylene-C(O)OR¹⁵, -O-(C₁-C₆) alkylene-C(O)OR¹⁵, and -NR¹⁶-(C₁-C₆) alkylene-C(O)OR¹⁵;

20 R⁴ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -(C₁-C₆) alkylene-OR¹⁵, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-C(O)OR¹⁵, and -(C₁-C₆) alkylene-OC(O)-R¹⁵;

25 R⁵ is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -(C₁-C₆) alkylene-OR¹⁵, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵,
 30 -(C₁-C₆) alkylene-C(O)OR¹⁵, and -(C₁-C₆) alkylene-OC(O)-R¹⁵;

R⁷ is selected from hydrogen, halogen, amino, hydroxy, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -OR¹⁵, -(C₁-C₆) alkylene-OR¹⁵, -O-(C₂-C₆) alkylene-OR¹⁵, -NR¹⁶(C₂-C₆) alkylene-OR¹⁵,
 5 -NR¹⁷R¹⁸, -(C₁-C₆) alkylene-NR¹⁷R¹⁸, -O-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷R¹⁸, -SO-R¹⁵, -SO₂-R¹⁵, -SO₂NR¹⁷R¹⁸, -(C₁-C₆) alkylene-SO₂-NR¹⁷R¹⁸, -NR¹⁶-SO₂-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶-SO₂-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷-SO₂-R¹⁵, -C(O)-NR¹⁷R¹⁸, -(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -O-(C₁-C₆) alkylene-C(O)-
 10 NR¹⁷R¹⁸, -NR¹⁶-(C₁-C₆) alkylene-C(O)-NR¹⁷R¹⁸, -NR¹⁶C(O)-R¹⁵, -(C₁-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -O-(C₂-C₆) alkylene-NR¹⁶C(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-NR¹⁷C(O)-R¹⁵, -C(O)-R¹⁵, -C(O)-OR¹⁵, -(C₁-C₆) alkylene-C(O)-OR¹⁵, -O-(C₁-C₆) alkylene-C(O)-OR¹⁵, -NR¹⁶-(C₁-C₆) alkylene-C(O)-OR¹⁵, -OC(O)-R¹⁵, -(C₁-C₆) alkylene-OC(O)-R¹⁵,
 15 -O-(C₂-C₆) alkylene-OC(O)-R¹⁵, -NR¹⁶-(C₂-C₆) alkylene-OC(O)-R¹⁵, and -NR¹⁶-C(O)-OR¹⁵;

wherein

each of said -(C₁-C₆) alkyl or -(C₁-C₆) alkylene in **R**², **R**³, **R**⁴, **R**⁵ or **R**⁷ is optionally substituted with at least one group selected from halogen, cyano,
 20 hydroxy, oxo, amino, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂;

each of said -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl or heteroaryl in **R**², **R**³, **R**⁴, **R**⁵ or **R**⁷ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, amino, -(C₁-C₆) alkyl,
 25 -CH₂-O-(C₁-C₆) alkyl, -CH₂-NH-(C₁-C₆) alkyl, -CH₂-N-((C₁-C₆) alkyl)₂, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂;

R¹⁵, **R**¹⁶, **R**¹⁷ and **R**¹⁸ are each independently selected from hydrogen, -(C₁-C₆) haloalkyl, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl,
 30 -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-heteroaryl, and

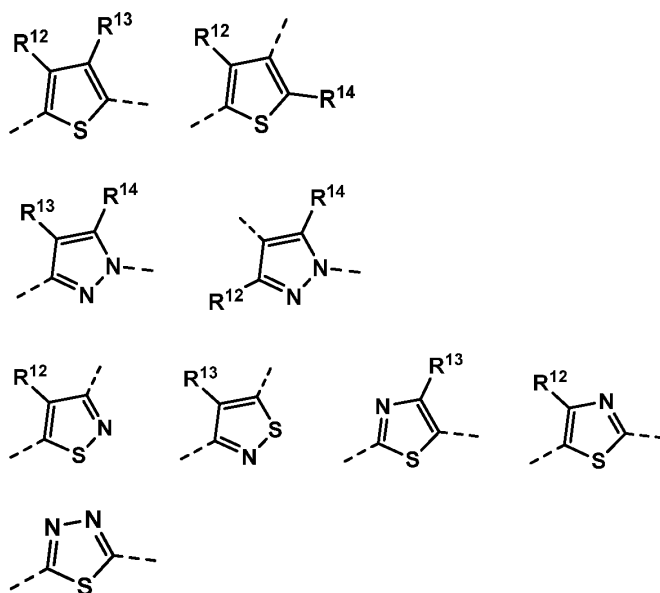
-(C₁-C₆) alkylene-aryl; and/or two groups selected from **R**¹⁵, **R**¹⁶, **R**¹⁷ and **R**¹⁸ form together a cycle selected from -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, and heteroaryl;

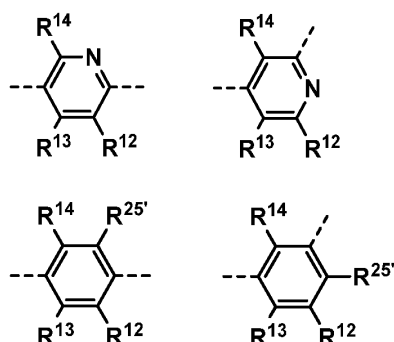
wherein

5 each of said -(C₁-C₆) alkyl or -(C₁-C₆) alkylene in **R**¹⁵, **R**¹⁶, **R**¹⁷ or **R**¹⁸ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, amino, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl and -N-((C₁-C₆) alkyl)₂;

10 each of said -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl or heteroaryl in **R**¹⁵, **R**¹⁶, **R**¹⁷ or **R**¹⁸ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, amino, -(C₁-C₆) alkyl, -CH₂-O-(C₁-C₆) alkyl, -CH₂-NH-(C₁-C₆) alkyl, -CH₂-N-((C₁-C₆) alkyl)₂, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl and -N-((C₁-C₆) alkyl)₂;

15 - **Y**² is a 5- or 6-membered heteroaryl or 6-membered aryl selected from the following formulae





wherein **R¹²**, **R¹³**, **R¹⁴** and **R^{25'}** are each independently selected from hydrogen, halogen, cyano, hydroxy, amino, -(C₁-C₆) alkyl, -(C₃-C₆) cycloalkyl, -CH₂-O-(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂;

wherein each of said -(C₁-C₆) alkyl in **R¹²**, **R¹³**, **R¹⁴** or **R^{25'}** is optionally substituted with at least one group selected from halogen, cyano, hydroxy, amino, -O-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂;

- **L** is -(**CR¹⁰R¹¹**)_n;

wherein

n is an integer selected from 0, 1, 2, 3 and 4;

R¹⁰ and **R¹¹** are independently selected from hydrogen, halogen, hydroxy, amino, -(C₁-C₃) alkyl, -(C₁-C₂) haloalkyl, -(C₁-C₂) hydroxyalkyl, -(C₁-C₂) aminoalkyl, -O-(C₁-C₄) alkyl, -NH-(C₁-C₃) alkyl, and -N-((C₁-C₃) alkyl)₂;

or **R¹⁰** and **R¹¹** form together with the carbon atom to which they are bond a (C₃-C₆) cycloalkyl;

- **Z^{1'}** is selected from -**NR^{23'}R^{24'}** and a -(C₃-C₇) heterocycloalkyl comprising at least one nitrogen atom;

wherein

each nitrogen atom of said (C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one group selected from -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl;

each carbon atom of said (C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one group selected from halogen, cyano, hydroxy, oxo, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl;

wherein each of said -(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl or -(C₃-C₇) heterocycloalkyl in **Z**^{1'} is optionally substituted with at least one halogen; and

wherein each of said aryl or heteroaryl in **Z**^{1'} is optionally substituted with at least one group selected from halogen, CN, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, and O-(C₃-C₇) cycloalkyl; and

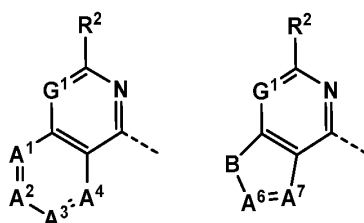
R^{23'} and **R**^{24'} are each independently selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-aryl;

wherein each of said -(C₁-C₆) alkyl, -(C₁-C₆) alkylene, -(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl in **R**^{23'} or **R**^{24'} is optionally substituted with at least one group selected from halogen, cyano, hydroxy, -O-(C₁-C₆) alkyl, -NH-(C₁-C₆) alkyl, and -N-((C₁-C₆) alkyl)₂; and

each of said aryl or heteroaryl in $R^{23'}$ or $R^{24'}$ is optionally substituted with at least one group selected from halogen, cyano, hydroxy, $-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl, $-NH-(C_1-C_6)$ alkyl, and $-N-((C_1-C_6) \text{ alkyl})_2$.

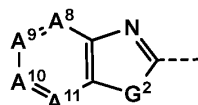
2. The compound for use according to claim 1, wherein Y^1 is a 9- or 10-membered bicyclic heteroaryl selected from:

the following formulae



wherein A^1-A^4 , A^6 , A^7 , G^1 and R^2 are independently as defined in claim 1; and

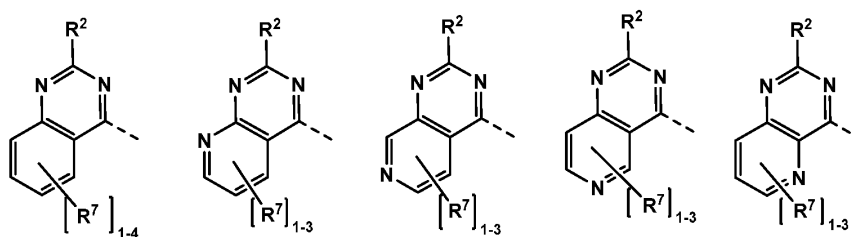
the following formula

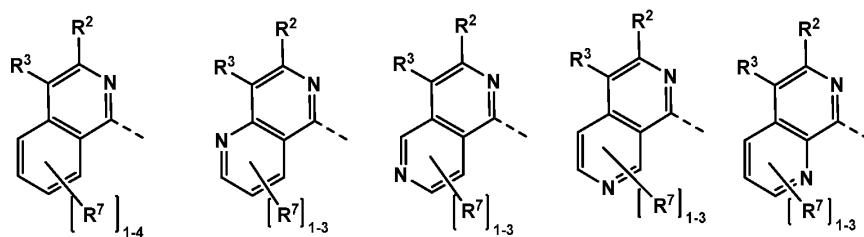


wherein A^8-A^{11} and G^2 are independently as defined in claim 1.

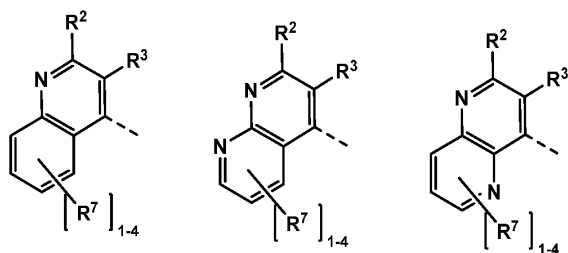
3. The compound for use according to claim 1, wherein Y^1 is selected from:

(i) a 10-membered bicyclic [6,6] heteroaryl selected from the following formulae



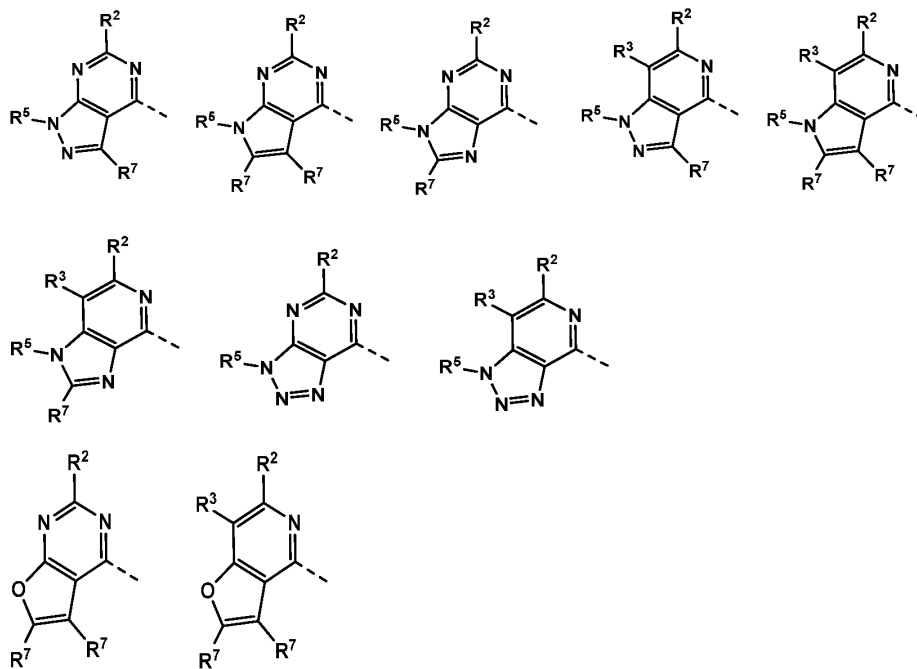


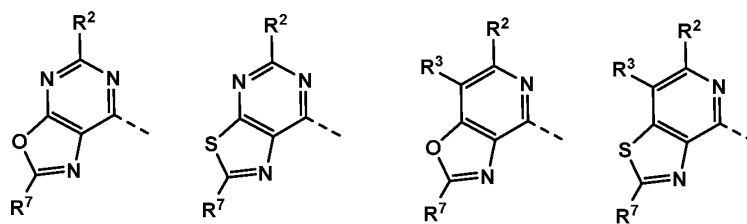
and the following formulae



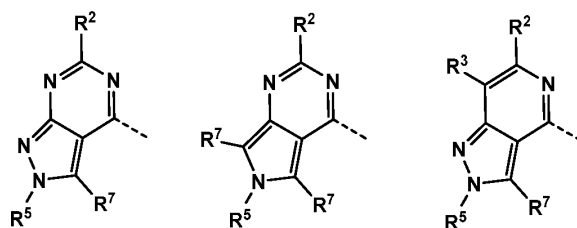
wherein **R**², **R**³ and **R**⁷ are independently as defined in claim 1;

- 5 (ii) a 9-membered bicyclic [6,5] heteroaryl selected from the following formulae

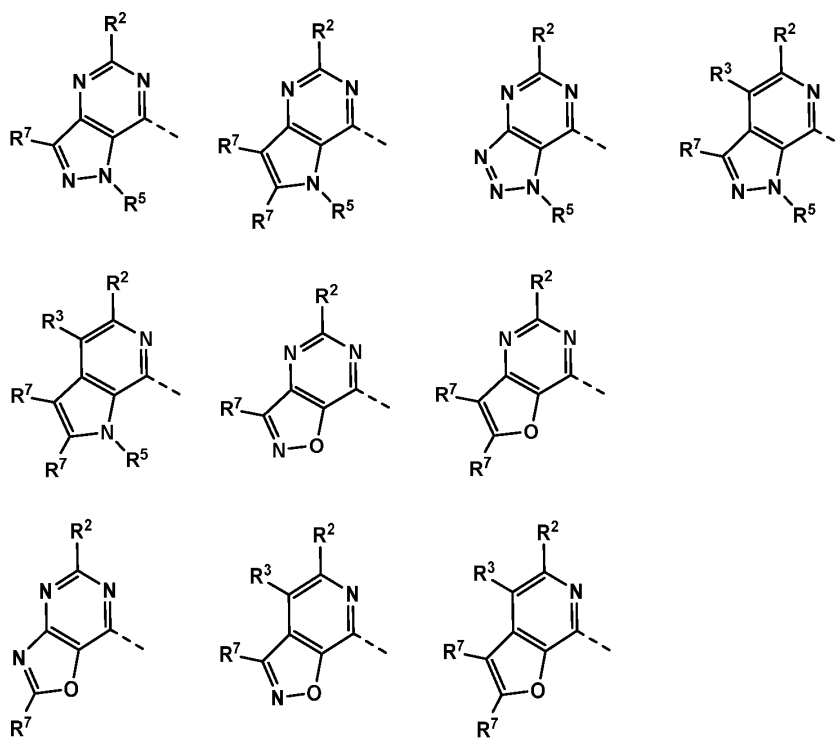




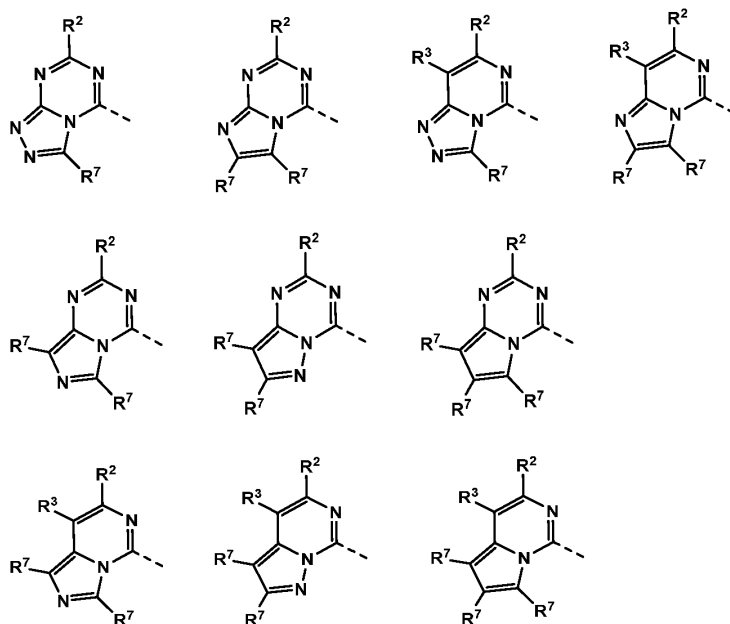
the following formulae



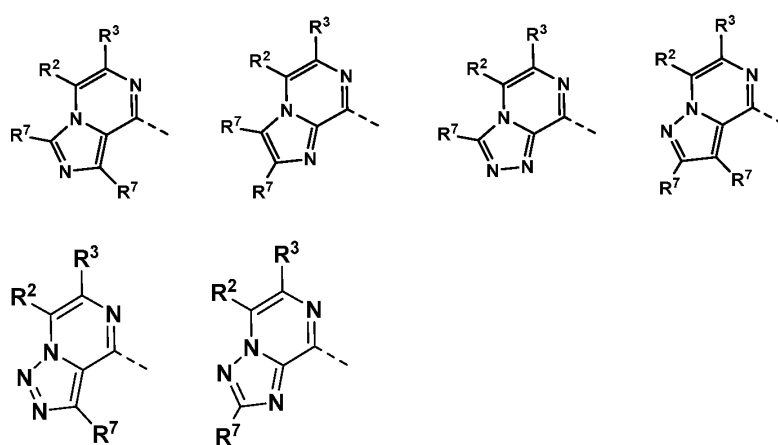
the following formulae



the following formulae

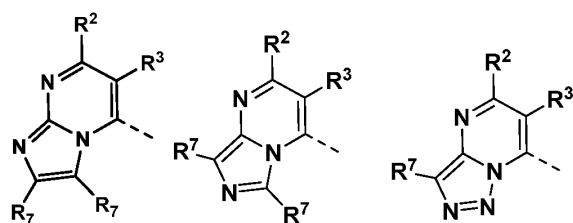


and the following formulae



wherein **R²**, **R³**, **R⁵** and **R⁷** are independently as defined in claim 1;

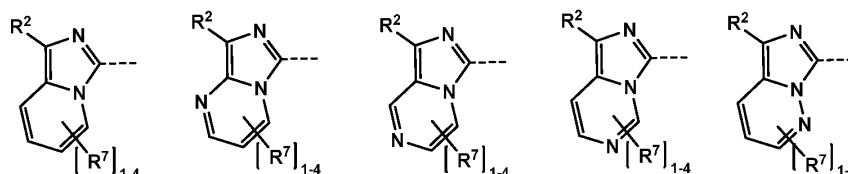
and the following formula



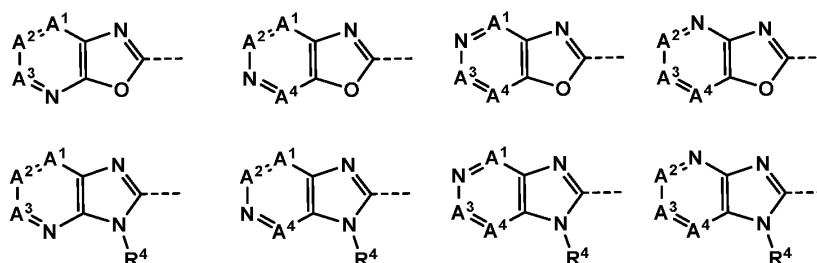
wherein **R**², **R**³ and **R**⁷ are independently as defined in claim 1; and

(iii) a 9-membered bicyclic [5,6] heteroaryl selected from:

the following formulae



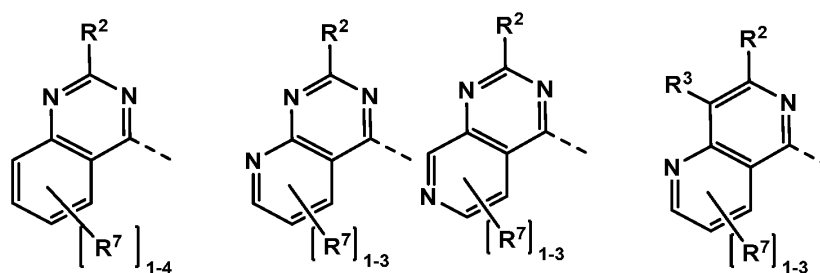
5 and the following formulae

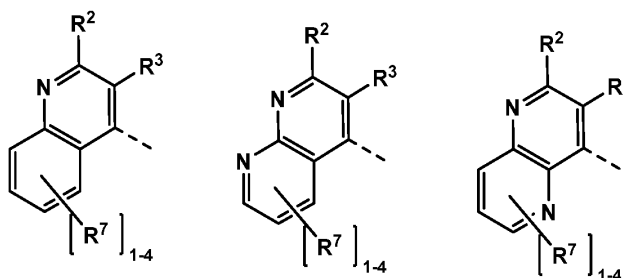


wherein **A**¹, **A**², **A**³, **A**⁴, **R**², **R**⁴ and **R**⁷ are independently as defined in claim 1.

4. The compound for use according to any one of claims 1 to 3, wherein **Y**¹ is selected from:

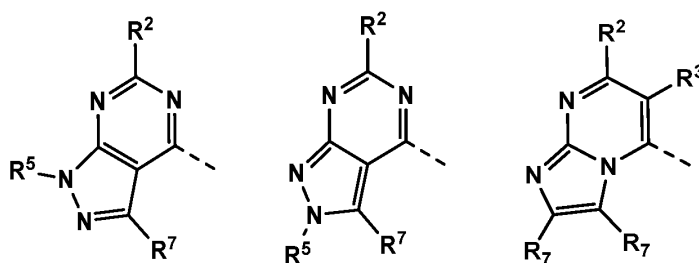
10 (i) a 10-membered bicyclic [6,6] heteroaryl selected from the following formulae





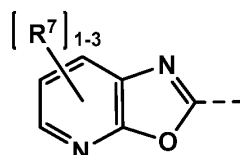
wherein **R**², **R**³ and **R**⁷ are independently as defined in claim 1;

(ii) a 9-membered bicyclic [6,5] heteroaryl selected from the following formulae



5 wherein **R**², **R**³, **R**⁵ and **R**⁷ are independently as defined in claim 1;

(iii) a 9-membered bicyclic [5,6] heteroaryl selected from the following formulae

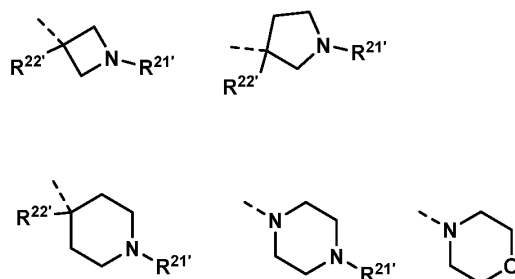


wherein **R**², **R**⁵ and **R**⁷ are independently as defined in claim 1;

preferably **Y**¹ is selected from 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl,
 10 5-(trifluoromethyl)oxazolo[5,4-*b*]pyridin-2-yl, 2-(trifluoromethyl)quinazolin-4-yl,
 1-(2-methoxyethyl)-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl,
 1-methyl-6-(trifluoromethyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl,
 2-(trifluoromethyl)pyrido[2,3-*d*]pyrimidin-4-yl, 2-(difluoromethyl)-6-
 methoxypyrido[2,3-*d*]pyrimidin-4-yl, 2-(trifluoromethyl)quinazolin-4-yl,
 15 6-methoxy-2-(trifluoromethyl)quinazolin-4-yl, 6-methoxy-2-methylquinazolin-4-
 yl, 2-methylpyrido[2,3-*d*]pyrimidin-4-yl, 2-cyclopropyl-6-(trifluoromethyl)-2*H*-
 pyrazolo[3,4-*d*]pyrimidin-4-yl, 6-methoxy-2-methylpyrido[2,3-*d*]pyrimidin-4-yl,

- 2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl, 6-methoxy-2-methyl-1,8-naphthyridin-4-yl, 7-(difluoromethyl)-1,6-naphthyridin-5-yl, 3-methoxy-7-methyl-1,6-naphthyridin-5-yl, 6-chloro-8-fluoro-2-methylquinazolin-4-yl, 2-methyl-6-(trifluoromethyl)quinazolin-4-yl, 6-ethoxy-2-methylquinazolin-4-yl, 6-chloro-7-fluoro-2-methylquinazolin-4-yl, 5-methoxy-2-methylquinazolin-4-yl, 6,7-dimethoxy-2-methylquinazolin-4-yl, 6,7-dimethoxyquinolin-4-yl, 3-chloro-7-methyl-1,6-naphthyridin-5-yl, 6-methoxyquinolin-4-yl, 6-methoxy-2-methylquinolin-4-yl, 6-chloro-8-fluoro-2-methylquinazolin-4-yl, 6-chloroquinolin-4-yl, 7-methoxyquinolin-4-yl, 6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl, 7-(trifluoromethyl)imidazo[1,2-a]pyrimidin-5-yl, 7-methylimidazo[1,2-a]pyrimidin-5-yl, 2-methyl-1,8-naphthyridin-4-yl, 6-methoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl, 2-methyl-6-(trifluoromethyl)quinolin-4-yl, 6-methoxy-2-methyl-1,5-naphthyridin-4-yl, (6-methoxy-2-methyl-1,5-naphthyridin-4-yl, 2-methyl-6-(trifluoromethyl)-1,8-naphthyridin-4-yl, 5-fluoro-6-methoxy-2-methylquinazolin-4-yl, 6-(difluoromethoxy)-2-methylquinazolin-4-yl, 2-methyl-6-(trifluoromethoxy)quinazolin-4-yl, and 7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl.
5. The compound for use according to any one of claims **1** to **4**, wherein **R**¹², **R**¹³, **R**¹⁴ or **R**^{25'} are each independently selected from hydrogen and (C₁-C₃) alkyl, preferably **R**¹², **R**¹³, **R**¹⁴ and **R**^{25'} are hydrogen.
6. The compound for use according to any one of claims **1** to **5**, wherein **R**¹⁰ and **R**¹¹ are independently selected from hydrogen and (C₁-C₃) alkyl, preferably **R**¹⁰ and **R**¹¹ are each hydrogen.

7. The compound for use according to any one of claims 1 to 6, wherein **Z**^{1'} is a -(C₃-C₇) heterocycloalkyl selected from the following formulae



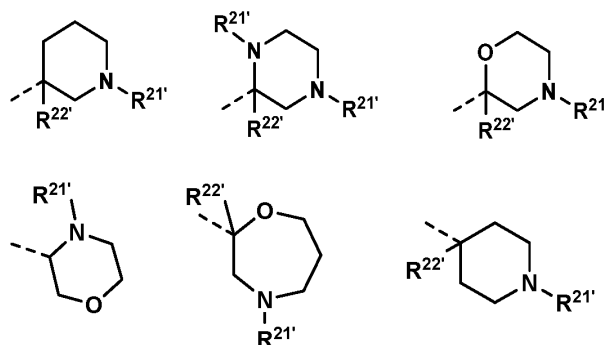
wherein

- 5 **R**^{21'} is selected from hydrogen, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, and -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl; and
- 10 **R**^{22'} is selected from hydrogen, halogen, cyano, hydroxy, oxo, -(C₁-C₆) alkyl, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, aryl, heteroaryl, -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl, -(C₁-C₆) alkylene-O-(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) heterocycloalkyl, -(C₁-C₆) alkylene-aryl, -(C₁-C₆) alkylene-heteroaryl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl;

wherein each of said -(C₁-C₆) alkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl or -(C₃-C₇) heterocycloalkyl in **R**^{21'} or **R**^{22'} is optionally substituted with at least one halogen; and

- 20 wherein each of said aryl or heteroaryl in **R**^{21'} or **R**^{22'} is optionally substituted with at least one group selected from halogen, CN, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl, and -O-(C₃-C₇) cycloalkyl.

8. The compound for use according to any one of claims 1 to 6, wherein $Z^{1'}$ is a $-(C_3-C_7)$ heterocycloalkyl of the following formula



5 wherein

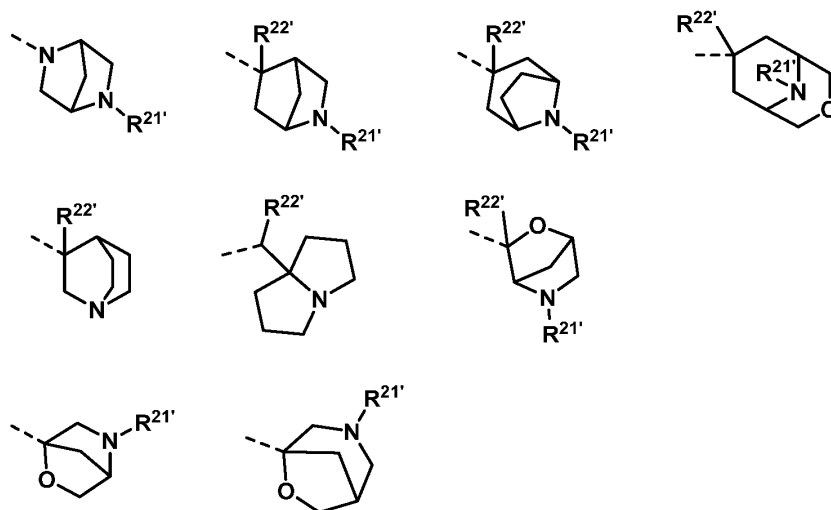
$R^{21'}$ is selected from hydrogen, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, and $-(C_1-C_6)$ alkylene-O- (C_3-C_7) cycloalkyl; and

$R^{22'}$ is selected from hydrogen, halogen, cyano, hydroxy, oxo, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- (C_1-C_6) alkyl, $-(C_1-C_6)$ alkylene-O- (C_3-C_7) cycloalkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, $-O-(C_1-C_6)$ alkyl and $-O-(C_3-C_7)$ cycloalkyl;

wherein each of said $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene- (C_3-C_7) cycloalkyl or $-(C_3-C_7)$ heterocycloalkyl in $R^{21'}$ is optionally substituted with at least one halogen; and

20 wherein each of said aryl or heteroaryl in $R^{21'}$ is optionally substituted with at least one group selected from halogen, CN, $-(C_1-C_6)$ alkyl, $-O-(C_1-C_6)$ alkyl and $O-(C_3-C_7)$ cycloalkyl.

9. The compound for use according to any one of claims 1 to 6, wherein Z^1 is a $-(C_3-C_7)$ heterocycloalkyl of the following formula



5 wherein

$R^{21'}$ is selected from hydrogen, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- $-(C_3-C_7)$ cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene- $-(C_3-C_7)$ heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, and $-(C_1-C_6)$ alkylene-O- $-(C_3-C_7)$ cycloalkyl; and

$R^{22'}$ is selected from hydrogen, halogen, cyano, hydroxy, oxo, $-(C_1-C_6)$ alkyl, $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- $-(C_3-C_7)$ cycloalkyl, $-(C_3-C_7)$ heterocycloalkyl, aryl, heteroaryl, $-(C_1-C_6)$ alkylene-O- $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene-O- $-(C_3-C_7)$ cycloalkyl, $-(C_1-C_6)$ alkylene- $-(C_3-C_7)$ heterocycloalkyl, $-(C_1-C_6)$ alkylene-aryl, $-(C_1-C_6)$ alkylene-heteroaryl, $-O-(C_1-C_6)$ alkyl and $-O-(C_3-C_7)$ cycloalkyl;

wherein each of said $-(C_1-C_6)$ alkyl, $-(C_1-C_6)$ alkylene- $-(C_3-C_7)$ cycloalkyl or $-(C_3-C_7)$ heterocycloalkyl in $R^{21'}$ is optionally substituted with at least one halogen; and

wherein each of said aryl or heteroaryl in **R**^{21'} is optionally substituted with at least one group selected from halogen, CN, -(C₁-C₆) alkyl, -O-(C₁-C₆) alkyl and O-(C₃-C₇) cycloalkyl.

10. The compound for use according to any one of claims **7** to **9**, wherein:

5 **R**^{21'} is selected from hydrogen, -(C₁-C₆) alkyl, -(C₁-C₆) alkyl substituted with at least one fluoro, -(C₃-C₇) cycloalkyl, -(C₁-C₆) alkylene-(C₃-C₇) cycloalkyl, -(C₃-C₇) heterocycloalkyl, and -(C₁-C₆) alkylene-O-(C₁-C₆) alkyl; preferably **R**^{21'} is selected from hydrogen, -(C₁-C₃) alkyl, -(C₃-C₅) cycloalkyl, -(C₁-C₃) alkylene-(C₃-C₅) cycloalkyl, oxetanyl, and -(C₁-C₃) alkylene-O-(C₁-C₃) alkyl; and

R^{22'} is selected from hydrogen, halogen, -(C₁-C₆) alkyl, -(C₁-C₆) alkyl substituted with at least one fluoro, cyano, hydroxy and -O-(C₁-C₆) alkyl; preferably **R**^{22'} is hydrogen, fluoro, trifluoromethyl, cyano, hydroxy and -O-(C₁-C₃) alkyl.

15 **11.** The compound for use according to any one of claims **1** to **6**, wherein **Z**^{1'} is selected from azetidin-3-yl, 1-methylazetidin-3-yl, 3-fluoroazetidin-3-yl, 3-hydroxyazetidin-3-yl, 3-methoxyazetidin-3-yl, 1-methylpiperidin-4-yl, 1-(2-methoxyethyl)azetidin-3-yl, pyrrolidin-3-yl, 3-fluoropyrrolidin-3-yl, 3-hydroxypyrrolidin-3-yl, 3-methoxypyrrolidin-3-yl, morpholinomethyl, **20** 3-methoxy-1-methylpyrrolidin-3-yl, piperidin-4-yl, 4-hydroxypiperidin-4-yl, 4-cyano-1-methylpiperidin-4-yl, 3-hydroxy-1-methylpyrrolidin-3-yl, 4-methoxypiperidin-4-yl, 4-hydroxy-1-isopropylpiperidin-4-yl, 1-hydroxy-2-(methylamino)ethyl, 1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-methylpiperidin-4-yl, 4-hydroxy-1,3-dimethylpiperidin-4-yl, **25** 1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl, 4-hydroxy-1-(2-methoxyethyl)piperidin-4-yl, 1-cyclobutyl-4-hydroxypiperidin-4-yl)thiophen-2-yl, 1-cyclopropyl-4-hydroxypiperidin-4-yl, piperazin-1-yl, 3-hydroxy-1-methylpiperidin-4-yl, 4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl, 4-methoxy-1-methylpiperidin-4-yl, 3-hydroxy-1-methylpiperidin-3-yl, morpholin-4-yl, **30** morpholin-2-yl, 4-methylmorpholin-2-yl, 4-methylmorpholin-3-yl, morpholin-3-

yl, 2-aminoethyl, aminomethyl, and N-(methylamino)-methyl, 3-hydroxy-1-methylazetidin-3-yl, 5-(hydroxy(1-methylpiperidin-4-yl)methyl, 3-hydroxy-1-isopropylazetidin-3-yl, 6-oxa-3-azabicyclo[3.2.1]octan-5-yl, 3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl, 3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl, 5
2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-3-yl, 6,6-difluoro-1,4-oxazepan-2-yl, 2-methylmorpholin-2-yl, 2-(trifluoromethyl)morpholin-2-yl, 2,5-diazabicyclo[2.2.1]heptan-2-yl, 5-isopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl, 7-hydroxy-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl, 5-hydroxy-2-
10 methyl-2-azabicyclo[2.2.1]heptan-5-yl, 3-hydroxyquinuclidin-3-yl, 5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl, 1-hydroxy-2-morpholinoethyl, 5-(hydroxy(4-methylmorpholin-2-yl)methyl, 5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl, and 2-(dimethylamino)-1-hydroxyethyl;
preferably **Z'** is selected from azetidin-3-yl, 1-methylazetidin-3-yl, 15 3-fluoroazetidin-3-yl, 3-hydroxyazetidin-3-yl, 3-methoxyazetidin-3-yl, 1-(2-methoxyethyl)azetidin-3-yl, pyrrolidin-3-yl, 3-fluoropyrrolidin-3-yl, 3-hydroxypyrrolidin-3-yl, 3-methoxypyrrolidin-3-yl, piperidin-4-yl, 4-hydroxypiperidin-4-yl, piperazin-1-yl, morpholin-4-yl, 2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl, 20 6-oxa-3-azabicyclo[3.2.1]octan-5-yl, and 3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl.

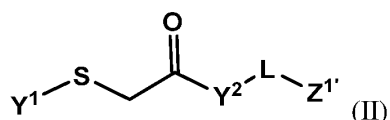
12. The compound for use according to claim **1**, wherein said compound is selected from

1	(<i>rac</i>)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
5	2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
39	1-(5-(2-aminoethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
40	1-(5-(aminomethyl)thiophen-2-yl)-2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone
41	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethanone

42	2-((1-methyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethanone
43	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethanone
44	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
45	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-cyclopropyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
46	1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
47	2-((6-methoxy-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one
48	1-(5-(aminomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3-d]pyrimidin-4-yl)thio)ethan-1-one
49	1-(5-(aminomethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethanone
50	1-(5-(aminomethyl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4-b]pyridin-2-yl)thio)ethan-1-one
51	2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)-1-(5-((methylamino)methyl)thiophen-2-yl)ethan-1-one

and pharmaceutically acceptable salts and/or solvates thereof.

13. **Pharmaceutical composition for use in the treatment and/or the prevention of an HDAC6-associated disease** comprising a compound as defined in any one of claims **1** to **12** and at least one pharmaceutically acceptable carrier.
- 5 14. The compound for use according to any one of claims **1** to **12** or the pharmaceutical composition for use according to claim **13**, wherein said HDAC6-associated disease is selected from inflammatory diseases, autoimmune diseases, proliferative diseases (such as cancers), neurodegenerative diseases (including neuromuscular diseases), pains, neuropathies (including neuromuscular diseases), psychiatric diseases, 10 neurodevelopmental disorders, sleep disorders, cardiovascular diseases, and metabolic or hormonal disorders.

15. Compound of formula (II)

or a pharmaceutically acceptable salt and/or solvate thereof;

wherein

5 **Y¹**, **Y²** and **L** are independently as defined in claim 1;

Z^{1'} is a -(C₃-C₇) heterocycloalkyl comprising at least one nitrogen atom, as defined in claim 1;

provided that the compound is *not* selected from:

10 1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one,

2-((1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one, and

pharmaceutically acceptable salts and/or solvates thereof.

16. The compound according to claim 13, wherein said compound is selected from

2	1-(5-(piperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
3	1-(5-(morpholinomethyl)thiophen-2-yl)-2-((2-(trifluoromethyl)pyrido[2,3- <i>d</i>]pyrimidin-4-yl)thio)ethan-1-one
4	1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((5-(trifluoromethyl)oxazolo[5,4- <i>b</i>]pyridin-2-yl)thio)ethan-1-one
6	2-((6-methoxy-2-(trifluoromethyl)quinazolin-4-yl)thio)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
7 and 8	(<i>R</i>)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
	(<i>S</i>)-1-(5-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
9	1-(1-(pyrrolidin-3-yl)-1 <i>H</i> -pyrazol-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one

10	1-(5-(azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
11	1-(5-(1-methylazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
12	1-(5-(1-(2-methoxyethyl)azetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
13	1-(5-(3-methoxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
14	1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
15	1-(6-(piperazin-1-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
16	1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
17	1-(2-(pyrrolidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
18	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
19	1-(4-(pyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
21	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-morpholinopyridin-3-yl)ethan-1-one
22	1-(6-(3-methoxypyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
23	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
24	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
25	1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
26	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
27	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(piperazin-1-yl)pyridin-3-yl)ethan-1-one
28	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
29	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-(2-methoxyethyl)-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one

30	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
31	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)ethan-1-one
32	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-fluoropyrrolidin-3-yl)pyridin-3-yl)ethan-1-one
33	1-(5-(3-fluoroazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
34	1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
35	1-(2-(pyrrolidin-3-yl)pyridin-4-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
36	1-(2-(azetidin-3-yl)thiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
37	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
38	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(6-(3-hydroxypyrrolidin-3-yl)pyridin-3-yl)ethan-1-one
52	1-(5-(3-fluoropyrrolidin-3-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
53	1-(3-(pyrrolidin-3-yl)isothiazol-5-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
54	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxyazetidin-3-yl)thiazol-5-yl)ethan-1-one
55	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(4-(3-hydroxypyrrolidin-3-yl)phenyl)ethan-1-one
56	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoroazetidin-3-yl)thiazol-5-yl)ethan-1-one
57	1-(4-(3-hydroxypyrrolidin-3-yl)phenyl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
58	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
59	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)ethan-1-one
60	2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
61	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
62	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
63	2-((7-(difluoromethyl)-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one

64	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-methoxypyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
65	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(3-hydroxypyrrolidin-3-yl)pyridin-2-yl)ethan-1-one
66	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-methoxyazetidin-3-yl)thiazol-5-yl)ethan-1-one
67	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(4-methoxypiperidin-4-yl)thiazol-5-yl)ethan-1-one
68	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(2-(3-fluoropyrrolidin-3-yl)thiazol-5-yl)ethan-1-one
69	2-((2-(difluoromethyl)-6-methoxypyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
70	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
71	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one
72	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
73	2-((6-chloro-8-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
74	1-(2-(4-hydroxypiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
75	1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
76	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(piperidin-4-yl)thiophen-2-yl)ethan-1-one
77	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(3-methoxypyrrolidin-3-yl)thiophen-2-yl)ethan-1-one
78	1-(2-(3-hydroxypyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
79	1-(2-(3-hydroxy-1-methylpyrrolidin-3-yl)thiazol-5-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
80	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
81	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
82	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
83	2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
84	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
85	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methoxypiperidin-4-yl)thiophen-2-yl)ethan-1-one
86	1-(5-(3-methoxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

87	1-(5-(3-hydroxy-1-methylpyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
88	1-(5-(4-methoxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
89	1-(5-(4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((5-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
90	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(2-(4-hydroxy-1-methylpiperidin-4-yl)thiazol-5-yl)ethan-1-one
91	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((5-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
92	1-(5-(1-(2-fluoroethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
93	1-(5-(4-hydroxy-1-isopropylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
94	1-(5-(4-hydroxy-1-(2-methoxyethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
95	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
96	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
97	1-(5-(1-(cyclopropylmethyl)-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
98	1-(5-(1-cyclopropyl-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
99	1-(5-(1-cyclobutyl-4-hydroxypiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
100	1-(5-(4-hydroxy-1-(oxetan-3-yl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
101	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-3-yl)thiophen-2-yl)ethan-1-one
102	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-methylmorpholin-3-yl)thiophen-2-yl)ethan-1-one
103	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
104	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
105	2-((6,7-dimethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
106	2-((7-chloroquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
107	2-((6,7-dimethoxyquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
108	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
109	2-((3-chloro-7-methyl-1,6-naphthyridin-5-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one

110	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((3-methoxy-7-methyl-1,6-naphthyridin-5-yl)thio)ethan-1-one
111	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxyquinolin-4-yl)thio)ethan-1-one
112	1-(5-(hydroxy(1-methylpiperidin-4-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
113	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinolin-4-yl)thio)ethan-1-one
114	2-((6-chloro-8-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
115	2-((6-chloroquinolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
116	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methoxyquinolin-4-yl)thio)ethan-1-one
117	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methylimidazo[1,2-a]pyrimidin-5-yl)thio)ethan-1-one
118	2-((6-ethoxy-2-methylquinazolin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
119	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
120	1-(5-(3-hydroxy-1-methylpiperidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
121	4-(5-(2-((6-methoxy-2-methylquinazolin-4-yl)thio)acetyl)thiophen-2-yl)-1-methylpiperidine-4-carbonitrile
122	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
123	1-(5-((3R,4S)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((3S,4R)-4-hydroxy-1,3-dimethylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
124	1-(5-(4-hydroxy-1-(2,2,2-trifluoroethyl)piperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
125	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methylquinazolin-4-yl)thio)ethan-1-one
126 or 127	1-(5-((3R,4S)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
126 or 127	1-(5-((3S,4R)-3-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
128	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((1-methyl-6-(trifluoromethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
129	1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
130	1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

131	1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
133	1-(5-(3-hydroxypyrrolidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
134	1-(2-(2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
135	1-(2-(5-isopropyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)thiazol-5-yl)-2-((2-methyl-6-(trifluoromethyl)quinazolin-4-yl)thio)ethan-1-one
136	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxyazetidin-3-yl)thiophen-2-yl)ethan-1-one
137	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-methylazetidin-3-yl)thiophen-2-yl)ethan-1-one
138	2-((6-chloro-7-fluoro-2-methylquinazolin-4-yl)thio)-1-(5-(3-hydroxy-1-isopropylazetidin-3-yl)thiophen-2-yl)ethan-1-one
139	1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
140	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-(trifluoromethyl)imidazo[1,2-a]pyrimidin-5-yl)thio)ethan-1-one
141	1-(5-(3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150	1-(5-((S)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150	1-(5-((R)-hydroxy((R)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
144	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methylpyrido[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
145	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,8-naphthyridin-4-yl)thio)ethan-1-one
147	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)quinolin-4-yl)thio)ethan-1-one
148	1-(5-(hydroxy(tetrahydro-1H-pyrrolizin-7a(5H)-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
142 or 143 or 149 or 150	1-(5-((R)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

142 or 143 or 149 or 150	1-(5-((S)-hydroxy((S)-4-methylmorpholin-2-yl)methyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
151	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((6-methoxy-2-methyl-1,5-naphthyridin-4-yl)thio)ethan-1-one
152	1-(5-(1-hydroxy-2-morpholinoethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
153	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
154	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-1,8-naphthyridin-4-yl)thio)ethan-1-one
155	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethyl)-2H-pyrazolo[3,4-d]pyrimidin-4-yl)thio)ethan-1-one
156	2-((6-fluoro-2-methylpyrido[2,3-d]pyrimidin-4-yl)thio)-1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)ethan-1-one
157 or 158	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
157 or 158	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(morpholin-2-yl)thiophen-2-yl)ethan-1-one
159 or 160	1-(5-((1R,4R,5R)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
159 or 160	1-(5-((1S,4S,5S)-5-hydroxy-2-methyl-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
161	1-(5-(4-hydroxy-1-methylpiperidin-4-yl)thiophen-2-yl)-2-((7-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
162	1-(5-((1S,4S,5S)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one and 1-(5-((1R,4R,5R)-5-hydroxy-2-azabicyclo[2.2.1]heptan-5-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
163	1-(5-(3-hydroxyquinuclidin-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
164	1-(5-((1R,5S,7s)-7-hydroxy-9-methyl-3-oxa-9-azabicyclo[3.3.1]nonan-7-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
165	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
166	1-(5-((1S,3S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

167 or 168	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethan-1-one
167 or 168	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-(trifluoromethyl)morpholin-2-yl)thiophen-2-yl)ethan-1-one
169 or 170	(S)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
169 or 170	(R)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-(2-methylmorpholin-2-yl)thiophen-2-yl)ethan-1-one
171 or 172	(S)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
171 or 172	(R)-1-(5-(6,6-difluoro-1,4-oxazepan-2-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
173	1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
174	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
175	1-(5-((1S,4S)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
176	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,4S)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
177	1-(5-((1R,3R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-3-yl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
178	2-((6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
179	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
180	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)ethan-1-one
181	2-((6-(difluoromethoxy)-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
182	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)ethan-1-one
183	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
184	1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((2-methyl-6-(trifluoromethoxy)quinazolin-4-yl)thio)ethan-1-one
185	1-(5-((1R,4R)-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one

186	1-(5-((1R,4R)-5-methyl-2-oxa-5-azabicyclo[2.2.1]heptan-1-yl)thiophen-2-yl)-2-((7-methyl-3-(trifluoromethyl)-1,6-naphthyridin-5-yl)thio)ethan-1-one
187 or 188	1-(5-((1R,5S)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
187 or 188	1-(5-((1S,5R)-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)-2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
189 or 190	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1R,5S)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one
189 or 190	2-((5-fluoro-6-methoxy-2-methylquinazolin-4-yl)thio)-1-(5-((1S,5R)-3-methyl-6-oxa-3-azabicyclo[3.2.1]octan-5-yl)thiophen-2-yl)ethan-1-one

and pharmaceutically acceptable salts and/or solvates thereof.

17. **Process for manufacturing** a compound according to claim 13 or claim 14, wherein said process comprises the following steps: (i) reacting an amine-containing alkyl chain or heterocycloalkyl with a halo-heterocycle; then (ii) reacting a heterocycle or halo-heterocycle with first an acetylating reagent, and, where appropriate, subsequently a halogenating reagent, to form a halo-ketone; then (iii) reacting a halo-ketone with a thiol and, where appropriate, (iv) removing of at least one protective group.

18. Compound selected from

132	1-(5-(1-hydroxy-2-(methylamino)ethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one
146	1-(5-(2-(dimethylamino)-1-hydroxyethyl)thiophen-2-yl)-2-((6-methoxy-2-methylquinazolin-4-yl)thio)ethan-1-one

and pharmaceutically acceptable salts and/or solvates thereof.