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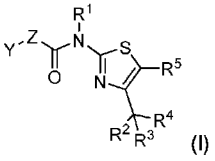
(54) Title: AMIDE SUBSTITUTED THIAZOLES AS PROTEIN SECRETION INHIBITORS

(57) Abstract: Provided herein are thiazole carboxamide protein secretin inhibitors, such as inhibitors of Sec61, methods for their preparation, related pharmaceutical compositions, and methods for using the same. For example, provided herein are compounds of Formula (I): and pharmaceutically acceptable salts and compositions including the same. The compounds disclosed herein may be used, for example, in the treatment of diseases including inflammation and/or cancer.



(I)

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AMIDE SUBSTITUTED THIAZOLES AS PROTEIN SECRETION INHIBITORS

STATEMENT OF GOVERNMENT SUPPORT

[0001] This invention was made with government support under grant no. K12 GM081266 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Field of the Invention

[0002] The present disclosure relates to protein secretion inhibitors, including methods of making and using the same.

Description of Related Technology

[0003] Protein translocation into the endoplasmic reticulum ("ER") constitutes the first step of protein secretion. ER protein import is essential in all eukaryotic cells and is particularly important in fast-growing tumour cells. Thus, the process of protein secretion can serve as a target both for potential cancer drugs and for bacterial virulence factors. *See* Kalies and Römisch, Traffic, 16(10):1027-1038 (2015).

[0004] Protein transport to the ER is initiated in the cytosol when N-terminal hydrophobic signal peptides protrude from the ribosome. Binding of signal recognition particle ("SRP") to the signal sequence allows targeting of the ribosome–nascent chain–SRP complex to the ER membrane where contact of SRP with its receptor triggers handing over of the signal peptide to Sec61. Sec61 is an ER membrane protein translocator (aka translocon) that is doughnut-shaped with 3 major subunits (heterotrimeric). It includes a "plug," which blocks transport into or out of the ER. The plug is displaced when the hydrophobic region of a nascent polypeptide interacts with the "seam" region of Sec61, allowing translocation of the polypeptide into the ER lumen. In mammals, only short proteins (<160 amino acids) can enter the ER posttranslationally, and proteins smaller than 120 amino acids are obliged to use this pathway. Some of the translocation competence is maintained by the binding of calmodulin to the signal sequence. Upon arrival at the Sec61 channel, the signal peptide or signal anchor intercalates between transmembrane domains ("TMDs") 2 and 7 of Sec61α, which form the lateral portion of the gate, allowing the channel to open for soluble secretory proteins. As the Sec61 channel consists of 10 TMDs (Sec61α) surrounded by a hydrophobic clamp formed by Sec61γ, channel opening is dependent on conformational changes that involve practically all TMDs.

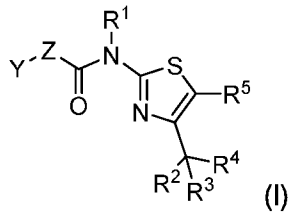
[0005] Inhibition of protein transport across the ER membrane has the potential to treat or prevent diseases, such as the growth of cancer cells and inflammation. Known secretion inhibitors, which range from broad-spectrum to highly substrate-specific, can interfere with virtually any stage of this multistep process, and even with transport of endocytosed antigens into the cytosol for cross-presentation. These inhibitors interact with the signal peptide,

chaperones, or the Sec61 channel to block substrate binding or to prevent the conformational changes needed for protein import into the ER. Examples of protein secretin inhibitors include, calmodulin inhibitors (e.g., E6 Berbamine and Ophiobolin A), Lanthanum, sterols, cyclodepsipeptides (e.g., HUN-7293, CAM741, NFI028, Cotrainsin, Apratoxin A, Decatransin, Valinomycin), CADA, Mycolactone, Eeyarestatin I ("ESI"), and Exotoxin A. However, the above secretion inhibitors suffer from one or more of the following: lack selectivity for the Sec61 channel, challenging manufacture due to structural complexity, and molecular weight limited administration, bio-availability and distribution.

[0006] Thus, a need exits for new small molecule inhibitors of protein secretion.

SUMMARY

[0007] In one aspect the disclosure provies a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzoimidazolyl, pyrrolopyridinyl, benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, dihydroindenyl, thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiopheneyl, dihydrothienopyridinyl, tetrahydrocycloheptathiopheneyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, C_{5-7}cycloalkyl, C_{3-7}heterocycloalkyl, or C_{5-7}cycloalkenyl;

Z is C_{0-2}alkylene and

when Z is C_{1-2}alkylene, then (a) one carbon can be substituted with one or two substituents selected from C_{1-6}alkyl, unsubstituted C_{0-3}alkylene-aryl, $NR^1C(O)C_{1-3}$alkyl, NR^1C_{1-3}alkyl, and OH, with the proviso that the carbon is not substituted with two OH, or (b) one carbon and its two substituents form a 3- to 6-membered ring;

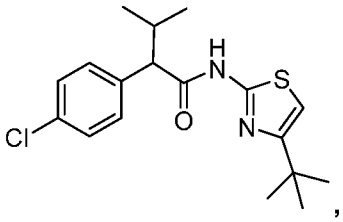
R^1 is H or C_{1-3}alkyl;

R^2 and R^3 are each independently unsubstituted C_{1-3}alkyl or halo, or R^2 and R^3, together with the carbon to which they are attached, form a 3- to 6-membered ring;

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-3}alkylene-OH, C_{0-3}alkylene-C_{1-6}alkoxyl, C_{1-3}alkylene-$C(O)OC_{1-4}$alkyl, or halo; and

R^5 is H, halo, CN, or $C(=O)OC_{1-3}$alkyl;

with the proviso that the compound of Formula (I) is not: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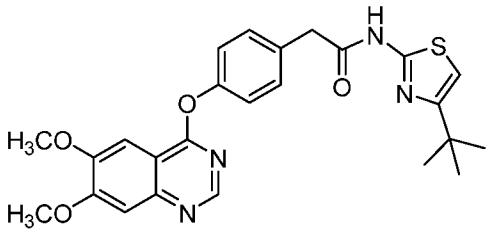
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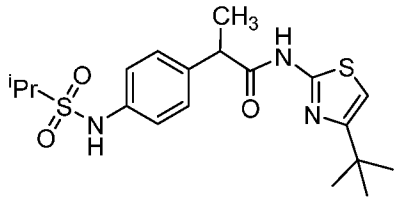
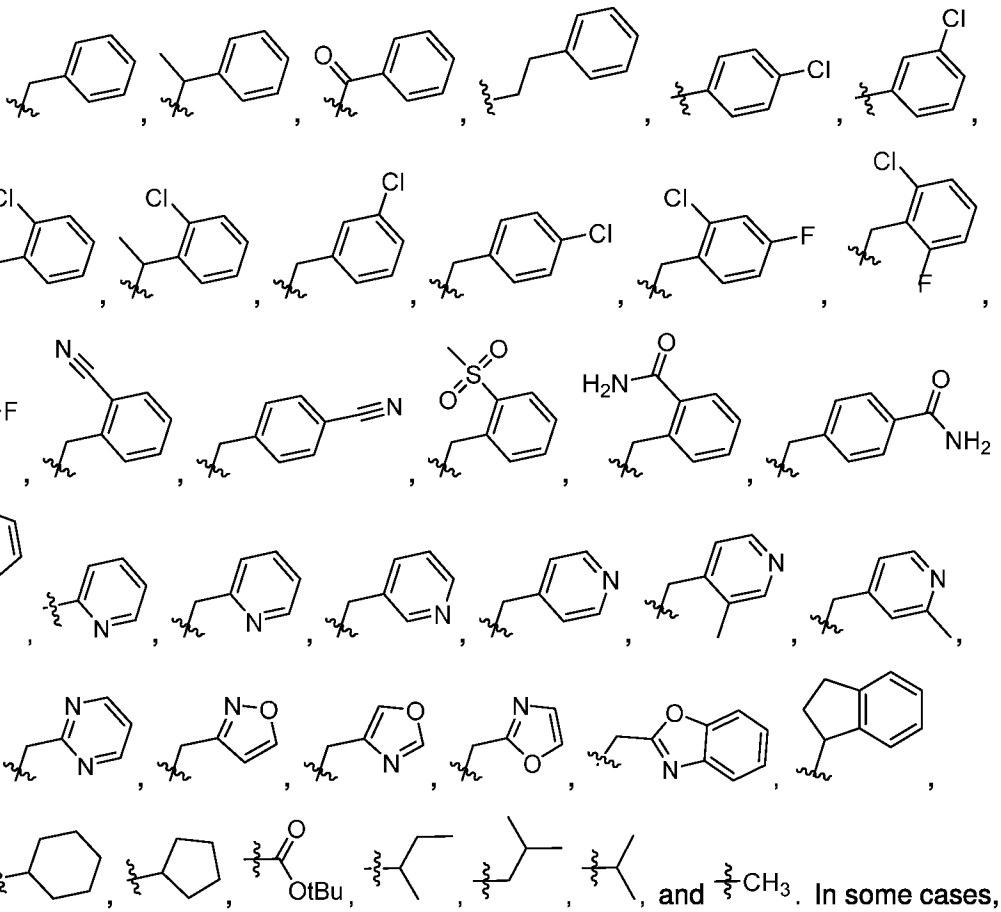
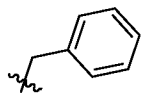
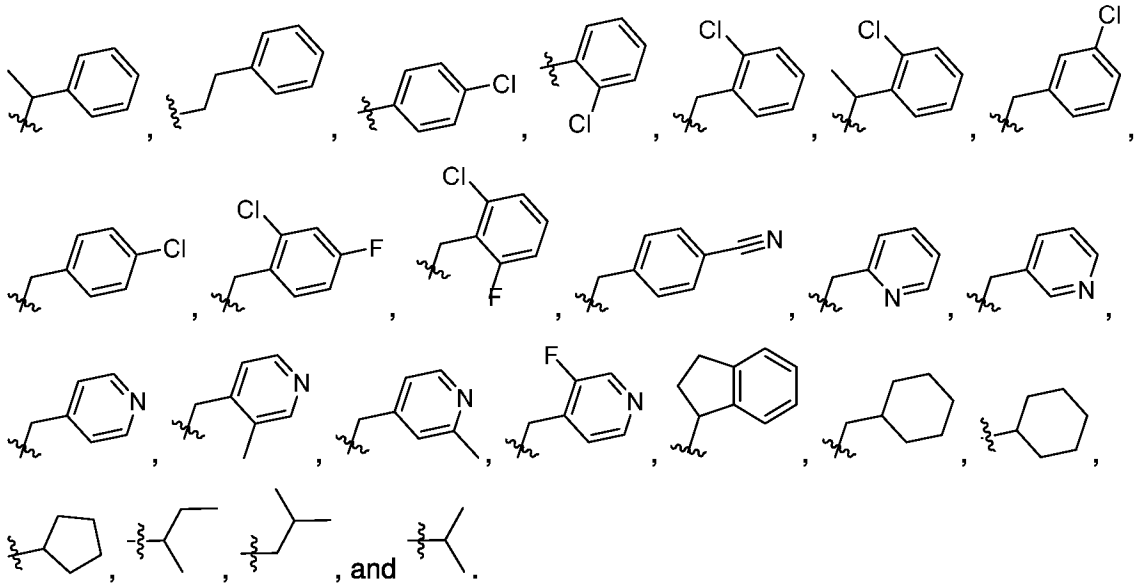

.

[0008] In some embodiments, Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzodimidzolyl, or pyrrolopyridinyl. In some cases, the ring nitrogen of Y is unsubstituted. In various embodiments, the ring nitrogen of Y is substituted with $C_{1\text{-}6}$alkyl, $C(O)OC_{1\text{-}6}$alkyl, $C_{0\text{-}3}$alkylene-aryl, $C_{1\text{-}3}$alkylene-heteroaryl, $C_{3\text{-}6}$cycloalkyl, or $C_{1\text{-}3}$alkylene-amide. In various cases, the nitrogen ring atom of Y is substituted with methyl, isopropyl, isobutyl, sec-butyl, phenyl, indene, pyridinyl, pyrmidinyl, isooxazolyl, oxazolyl, benzooxazolyl, cyclohexyl, or cyclopentyl. In some embodiments, the ring nitrogen is substituted with a moiety selected from the group consisting of:



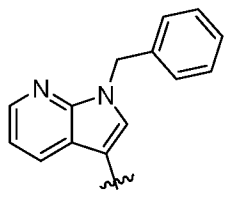
and . In some cases,

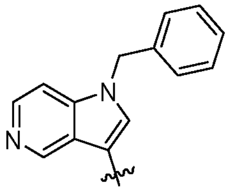
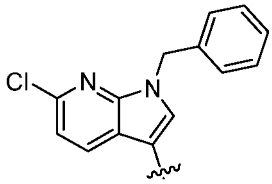
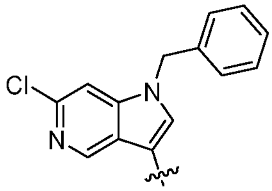
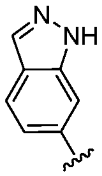
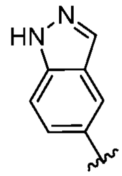
the ring nitrogen is substituted with a moiety selected from the group consisting of:  ,

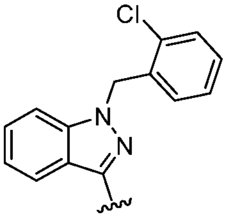
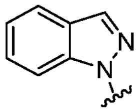
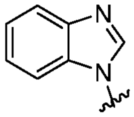
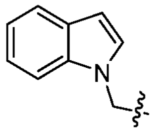
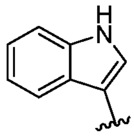
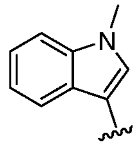


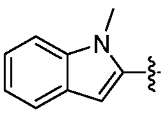
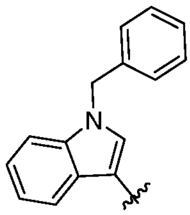
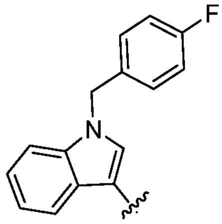
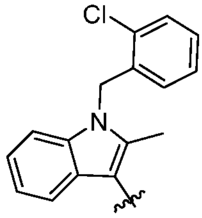
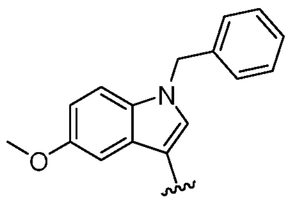
, and .

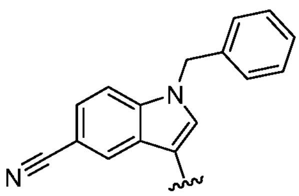
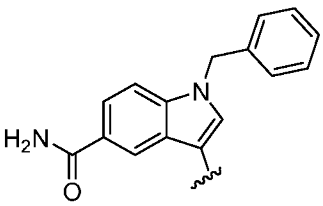
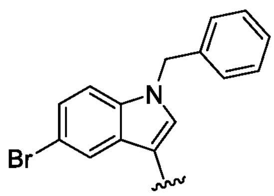
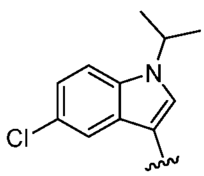
[0009] In various cases, Y comprises benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, or tetrahydrobenzooxazepinyl. In some cases, Y comprises phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, or dihydroindenyl. In some embodiments, Y comprises thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiophenyl, dihydrothienopyridinyl, or tetrahydrocycloheptathiopheneyl. In some embodiments, Y comprises dihydrothienopyridinyl and the ring nitrogen atom is unsubstituted or substituted with acetyl, $C(O)OC_{1-6}$alkyl, or C_{0-3}alkylene-aryl. In some cases, Y comprises triazolyl, thiadiazolyl, pyridinyl or pyridazinyl. In some embodiments, Y comprises C_{5-7}cycloalkyl, C_{3-7}heterocycloalkyl, or C_{5-7}cycloalkenyl. In various cases, Y comprises cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, morpholine, piperidine, oxazepaneyl, cyclopentenyl or cyclohexenyl. In some embodiments, Y is unsubstituted at all ring carbon atoms. In various cases, Y is substituted at one or more ring carbon atom with a substituent selected from halo, CN, C_{1-6}alkyl, C_{2-12}alkynyl, C_{1-3}alkoxyl, amido, sulfonyl, C_{3-8}cycloalkyl, C_{5-7}cycloalkenyl, C_{0-3}alkylene-heterocycloalkyl, C_{0-3}alkylene-aryl, and C_{0-3}alkylene-heteroaryl. In some embodiemtns, the ring carbon substituent is chloro.

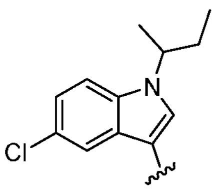
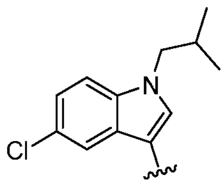
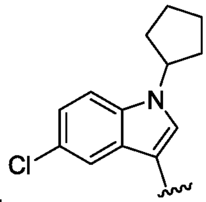
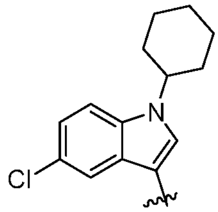
[0010] In some embodiments, Y is selected from the group consisting of:  ,

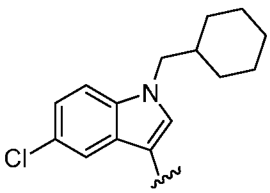
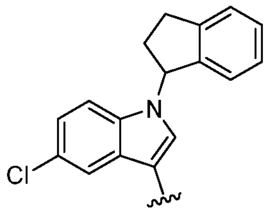
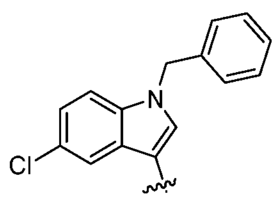
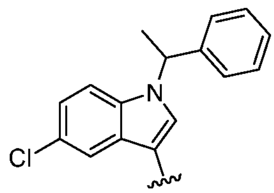
 ,  ,  ,  ,  ,

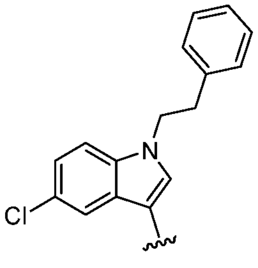
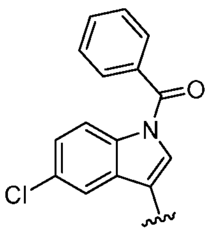
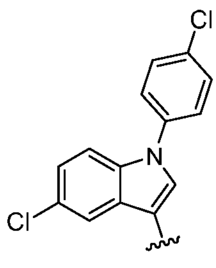
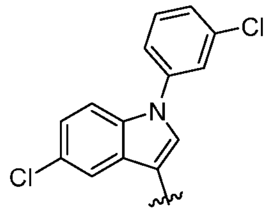
 ,  ,  ,  ,  ,  ,

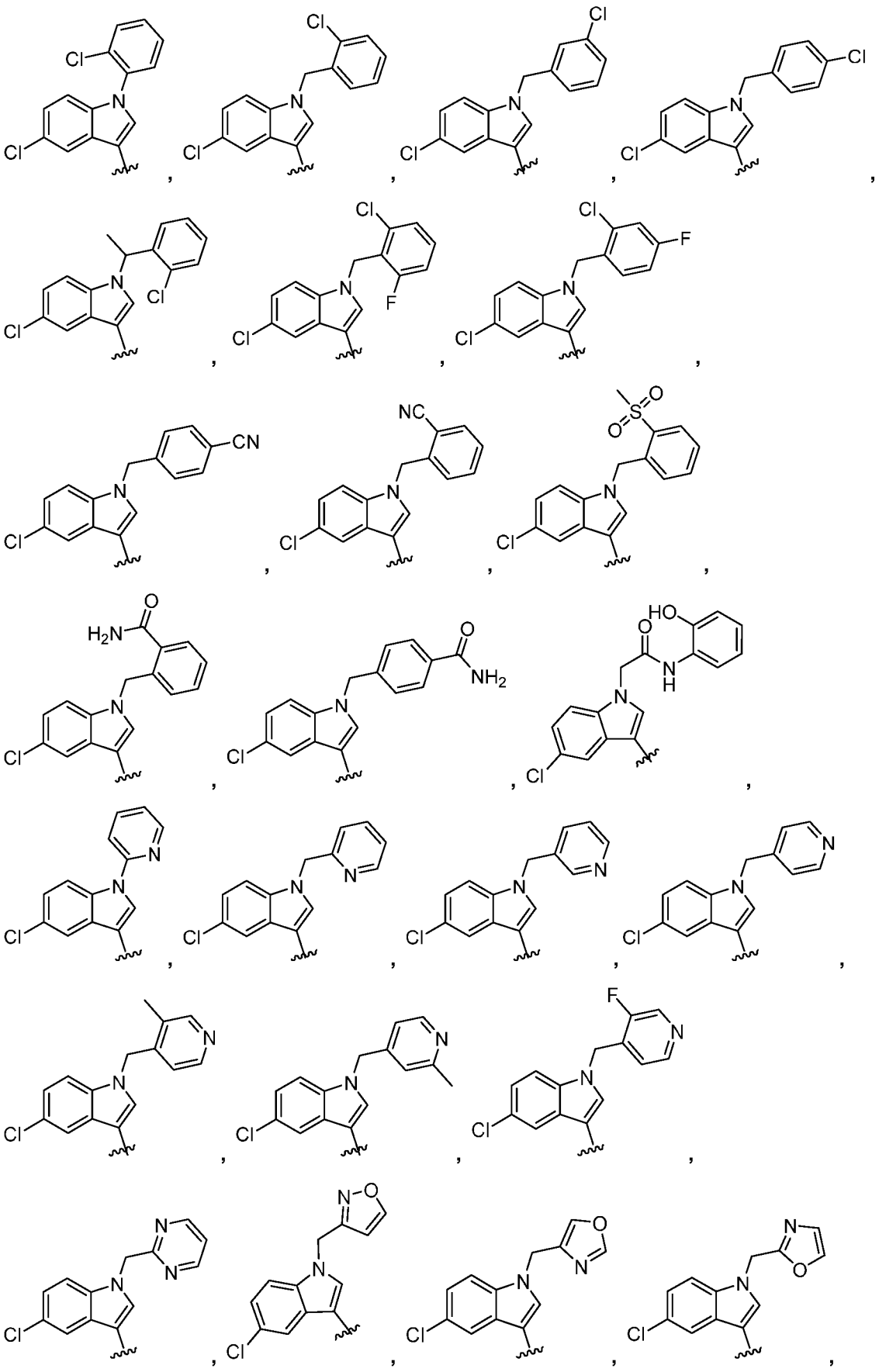
 ,  ,  ,  ,  ,

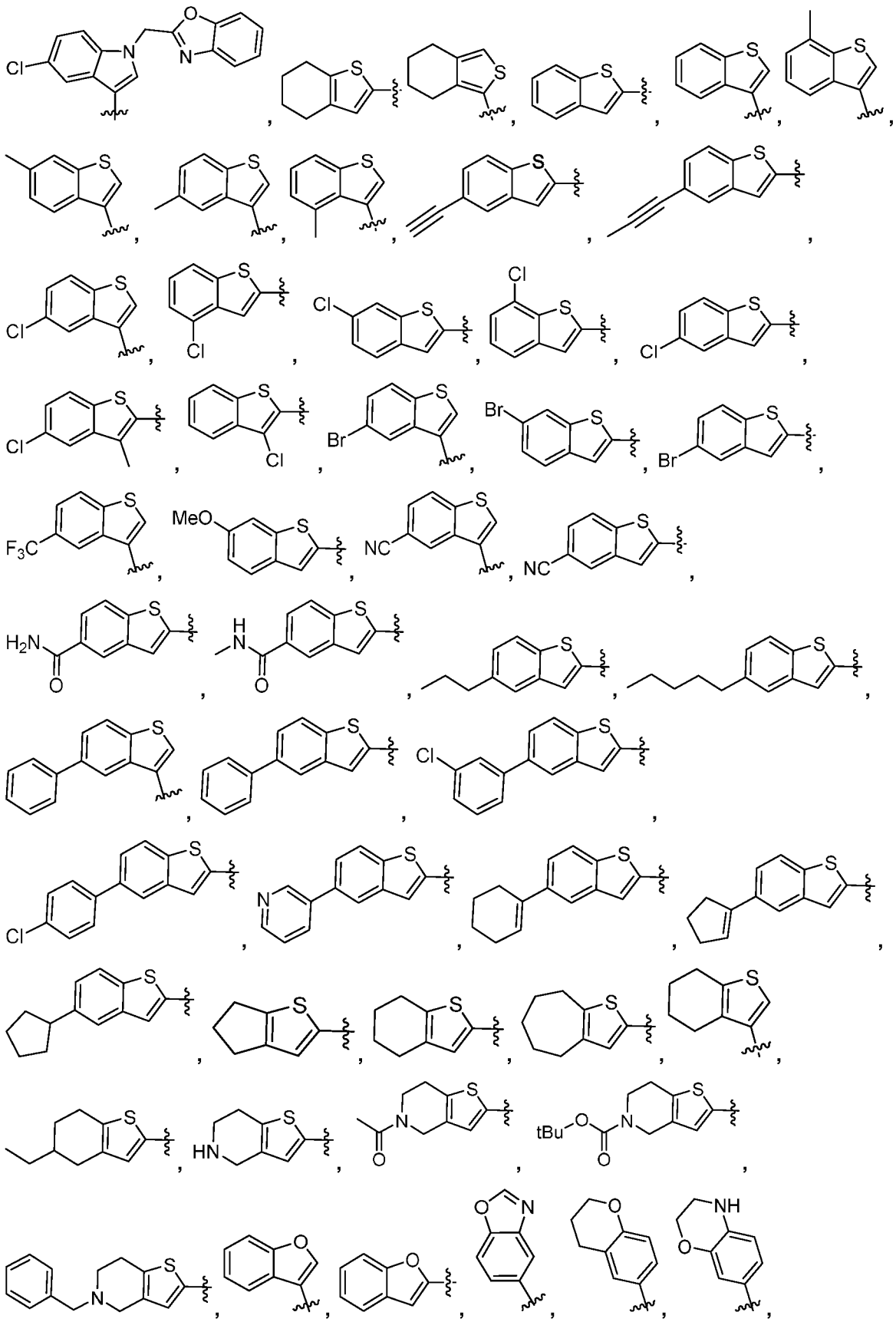
 ,  ,  ,  ,

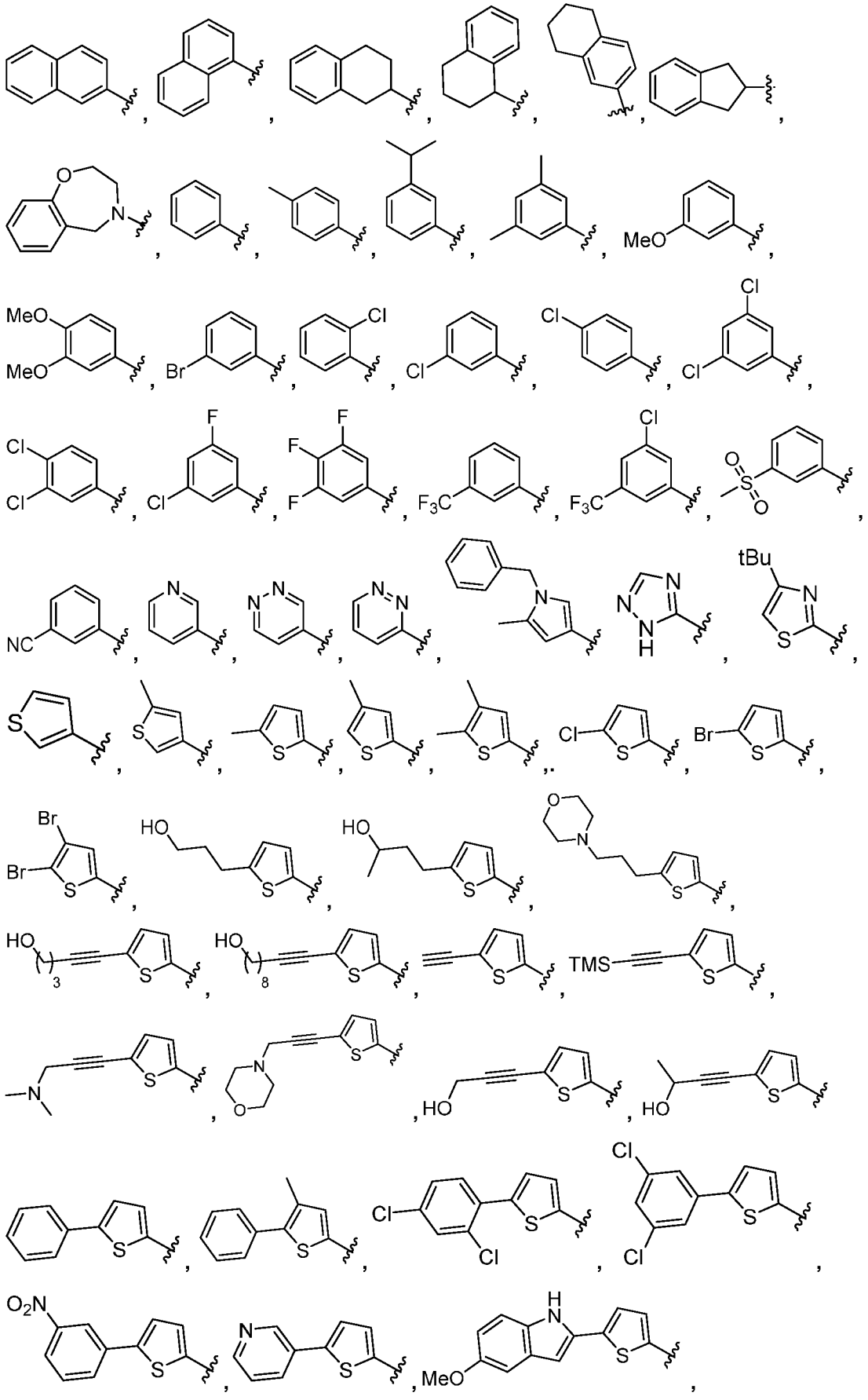
 ,  ,  ,  ,

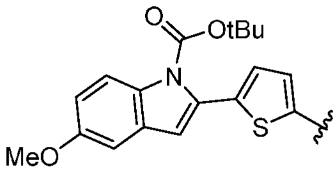
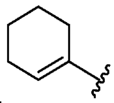
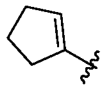
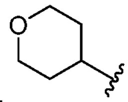
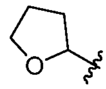
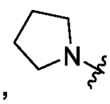
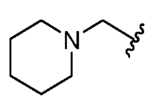
 ,  ,  ,  ,

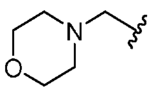
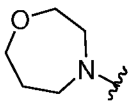
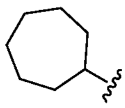
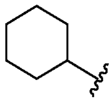
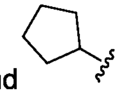
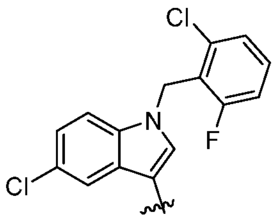
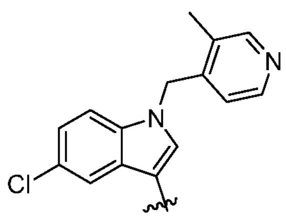
 ,  ,  ,  ,

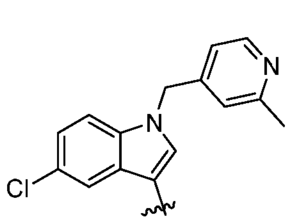
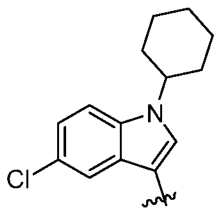
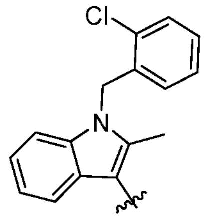
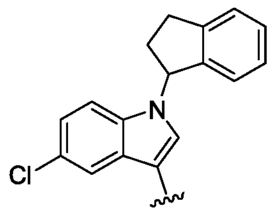


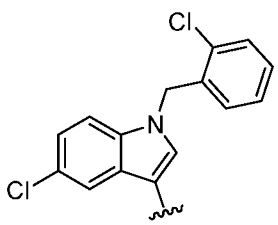
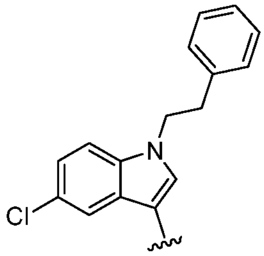
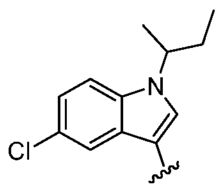
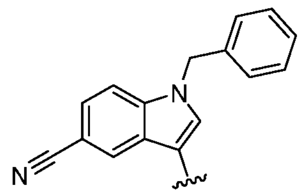


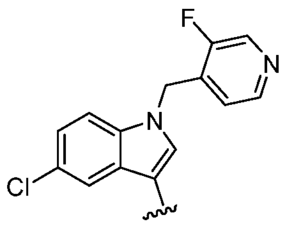
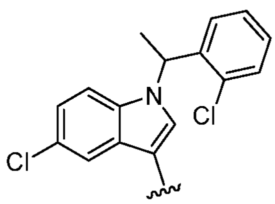
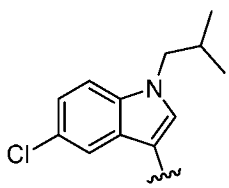
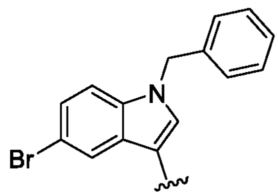


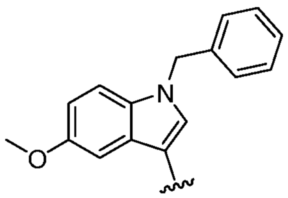
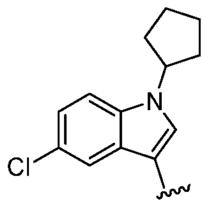
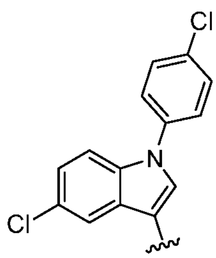
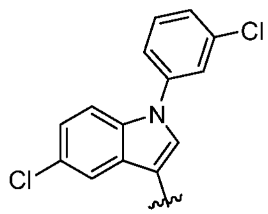
 ,,  ,  ,.  ,  ,  ,  ,

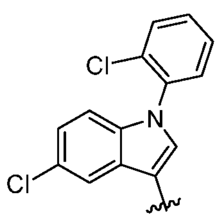
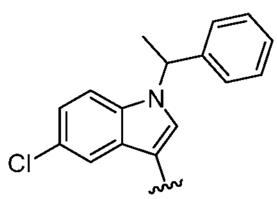
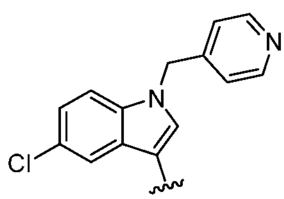
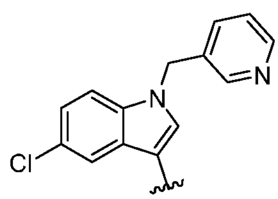
 ,  ,  ,  , and  . In various embodiments, Y is selected from the group consisting of:  ,  ,

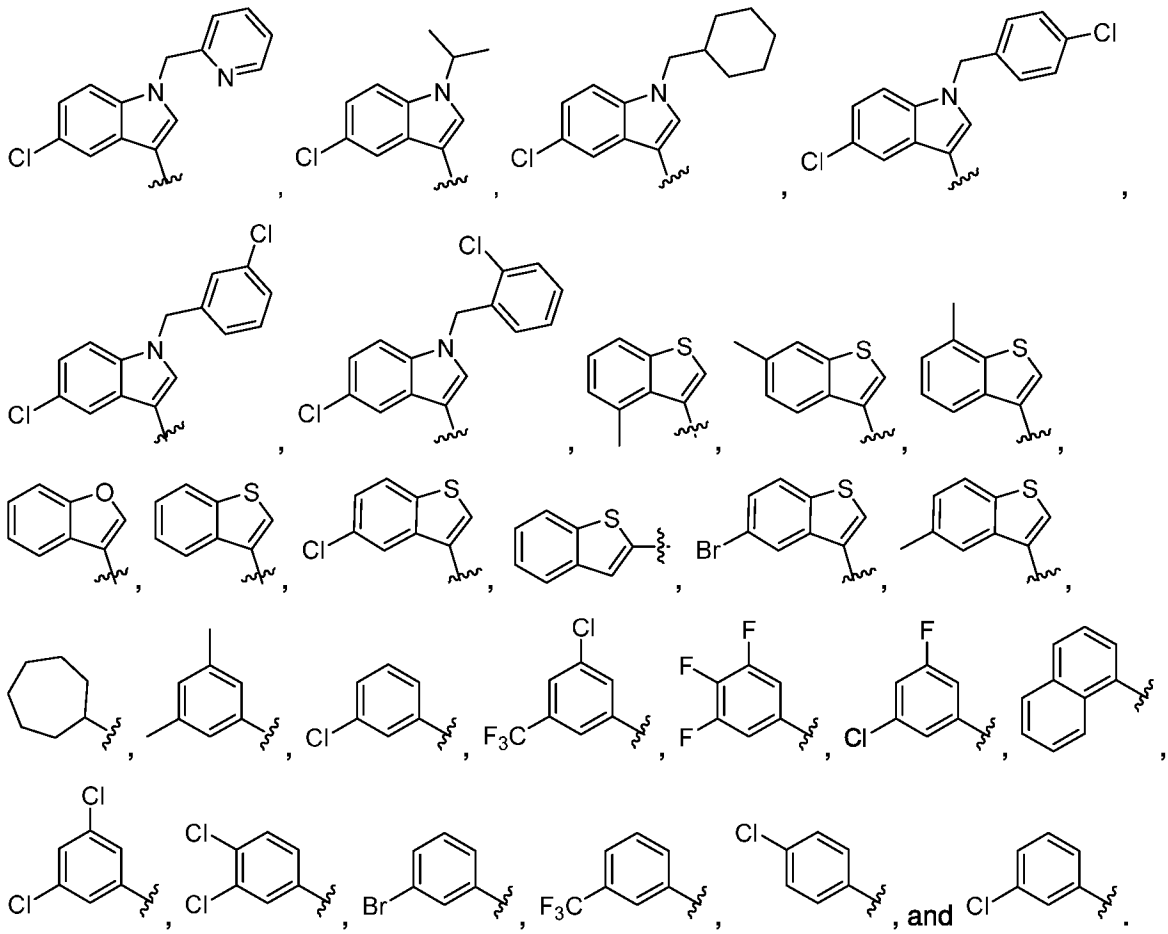
 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,

 ,  ,  ,  ,



[0011] In some embodiments, Z is C_0alkylene. In some cases, Z is C_{1-2}alkylene. In some various embodiments, Z is CH_2. In various embodiments, Z is CH_2CH_2. In some cases, Z is substituted with one substituent. In various cases, Z is substituted with two substituents. In some embodiments, at least one of the one or two substituents is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, isobutyl, phenyl, benzyl, hydroxyl, methylamido, and methylamino. In various embodiments, the two substituents together with the carbon atom to which they are attached form a cyclopropyl or cyclopentyl group.

[0012] In some embodiments, R^1 is H.

[0013] In some cases, R^2 and R^3 are each CH_3. In various cases, R^2 and R^3, together with the carbon to which they are attached from a cyclopropyl group. In some embodiments, R^4 is methyl, ethyl, or propyl. In some cases, R^4 is methyl. In various embodiments, R^4 is methoxy, ethoxy, isopropoxy, methoxyethyl, ethanolyl, $CH_2C(O)OEt$, or 2-propenyl. In various cases, R^2, R^3, and R^4 are each fluoro.

[0014] In some embodiments, R^5 is H. In various embodiments, R^5 is halo, CN, or $C(=O)OC_{1-3}$alkyl.

[0015] In some embodiments, Z is CH_2 or C_0alkylene, R^1 is H, and each of R^2, R^3, and R^4 is CH_3. In some cases, the disclosure provides a compound as recited in Table A or Table B,

below, or a pharmaceutically acceptable salt thereof. In various embodiments, the disclosure provides a compound as recited in Table C or D, below, or a pharmaceutically acceptable salt thereof.

[0016] Another aspect of the disclosure provides a pharmaceutical composition comprising the compound described herein and a pharmaceutically acceptable excipient.

[0017] Yet another aspect of the disclosure provides a method of inhibiting protein secretion in a cell comprising contacting the cell with a compound or pharmaceutical composition described herein in an amount effective to inhibit secretion. In some embodiments, the contacting is *in vivo*. In various embodiments, the contacting comprises administering the compound or the composition to a subject.

[0018] Yet another aspect of the disclosure provides a method for treating inflammation in a subject comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutical formulation disclosed herein

[0019] Still another aspect of the disclosure provides a method for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of a compound or pharmaceutical formulation disclosed herein.

[0020] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description, taken in conjunction with the drawings. The description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] Figure 1 shows at (a) CT8, a macrocyclic Sec61 modualtor; at (b) a schematic for the cellular high-throughput screening assay described in the Examples section; at (c) the protocol used for the screening described in the Examples; at (d) two compounds that were found to selectively inhibit VCAMss-GLuc secretion (compounds 1a and 1b).

[0022] Figure 2 depicts at (a) compound 1a, which was used to elucidate structure-activity relationships (SAR); at (b) the IC_{50} values of 8 analogs of compound 1a; at (c) dose-response curves for compounds 2 and 3; at (d) inhibition of full-length VCAM expression by compound 2 but not 3.

[0023] Figure 3 depicts at (a) inhibition of various signal sequence-GLuc reporters with compound 2; (b) HER3 and HER2 expression with compound 2.

[0024] Figure 4 depicts at (a) the effect of compound 2 on R66I Sec61α affinity probe; and (b) a western blot analysis of the binding of compound 2 versus CT7 to Sec61α.

[0025] Figure 5 depicts at (a) compounds 10-(*R*) and 10-(*S*); (b) the ability of compounds 10-

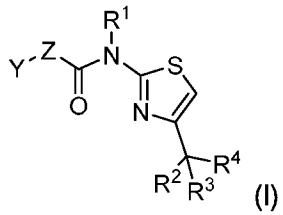
(*R*) and 10-(*S*) to inhibit the expression of Gaussia luciferase C-terminally fused to the indicated signal sequence; (c) the ability of compounds 10-(*R*) and 10-(*S*) to inhibit the expression of Gaussia luciferase C-terminally fused to the full-length secretory protein; (d) the effect of compounds 10-(*R*) and 10-(*S*) on the expression of full-length VCAM; and (e) the effect of compounds 10-(*R*) and 10-(*S*) on the expression of endogenous HGF secretion.

[0026] Further aspects and advantages will be apparent to those of ordinary skill in the art from a review of the following detailed description. While the compounds and methods disclosed herein are susceptible of embodiments in various forms, the description hereafter includes specific embodiments with the understanding that the disclosure is illustrative, and is not intended to limit the invention to the specific embodiments described herein.

DETAILED DESCRIPTION

[0027] Provided herein are compounds that inhibit protein secretion. The compounds described herein can be used to treat or prevent diseases associated with excessive protein secretion, such as inflammation and cancer, improving the quality of life for afflicted individuals.

[0028] The compounds described herein have a structure of Formula (I)



(I)

wherein the substituents are described in detail below.

[0029] Without being bound by any particular theory, the compounds described herein inhibit protein secretion by binding to and disabling components of the translocon, including but not limited to Sec61, and in some cases, disrupting in a sequence specific fashion interactions between the nascent signaling sequence of translated proteins with components of the translocon including but not limited to Sec61.

[0030] The compounds described herein can advantagouely inhibit the secretion of TNFα with an IC_{50} of up to 5 μM, or up to 3μM, or up to 1 μM. In various cases, the compounds disclosed herein can inhibit the secretion of VCAM with an IC_{50} of up to 5 μM, or up to 3μM, or up to 1 μM. In some cases, the compounds disclosed herein can inhibit the secretion of PRL with an IC_{50} of up to 5 μM, or up to 3μM, or up to 1 μM. In various cases, the compounds disclosed herein can inhibit the secretion of PD-1 with an IC_{50} of up to 5 μM, or up to 3μM, or up to 1 μM.

Chemical Definitions

[0031] As used herein, the term "alkyl" refers to straight chained and branched saturated

hydrocarbon groups containing one to thirty carbon atoms, for example, one to twenty carbon atoms, or one to ten carbon atoms. The term C_n means the alkyl group has "n" carbon atoms. For example, C_4 alkyl refers to an alkyl group that has 4 carbon atoms. C_{1-7}alkyl refers to an alkyl group having a number of carbon atoms encompassing the entire range (i.e., 1 to 7 carbon atoms), as well as all subgroups (*e.g.*, 1-6, 2-7, 1-5, 3-6, 1, 2, 3, 4, 5, 6, and 7 carbon atoms). Nonlimiting examples of alkyl groups include, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl (2-methylpropyl), *t*-butyl (1,1-dimethylethyl), 3,3-dimethylpentyl, and 2-ethylhexyl. Unless otherwise indicated, an alkyl group can be an unsubstituted alkyl group or a substituted alkyl group.

[0032] As used herein, the term "alkylene" refers to a bivalent saturated aliphatic radical. The term C_n means the alkylene group has "n" carbon atoms. For example, C_{1-6}alkylene refers to an alkylene group having a number of carbon atoms encompassing the entire range, as well as all subgroups, as previously described for "alkyl" groups.

[0033] As used herein, the term "alkenyl" is defined identically as "alkyl" except for containing at least one carbon-carbon double bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkenyl group has "n" carbon atoms. For example, C_4 alkenyl refers to an alkenyl group that has 4 carbon atoms. C_{2-7}alkenyl refers to an alkenyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (*e.g.*, 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, and butenyl. Unless otherwise indicated, an alkenyl group can be an unsubstituted alkenyl group or a substituted alkenyl group.

[0034] As used herein, the term "alkynyl" is defined identically as "alkyl" except for containing at least one carbon-carbon triple bond, and having two to thirty carbon atoms, for example, two to twenty carbon atoms, or two to ten carbon atoms. The term C_n means the alkynyl group has "n" carbon atoms. For example, C_4 alkynyl refers to an alkynyl group that has 4 carbon atoms. C_{2-7}alkynyl refers to an alkynyl group having a number of carbon atoms encompassing the entire range (i.e., 2 to 7 carbon atoms), as well as all subgroups (*e.g.*, 2-6, 2-5, 3-6, 2, 3, 4, 5, 6, and 7 carbon atoms). Specifically contemplated alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, and butynyl. Unless otherwise indicated, an alkynyl group can be an unsubstituted alkynyl group or a substituted alkynyl group.

[0035] As used herein, the term "cycloalkyl" refers to an aliphatic cyclic hydrocarbon group containing three to eight carbon atoms (*e.g.*, 3, 4, 5, 6, 7, or 8 carbon atoms). The term C_n means the cycloalkyl group has "n" carbon atoms. For example, C_5 cycloalkyl refers to a cycloalkyl group that has 5 carbon atoms in the ring. C_{5-8} cycloalkyl refers to cycloalkyl groups having a number of carbon atoms encompassing the entire range (i.e., 5 to 8 carbon atoms), as

well as all subgroups (*e.g.*, 5-6, 6-8, 7-8, 5-7, 5, 6, 7, and 8 carbon atoms). Nonlimiting examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Unless otherwise indicated, a cycloalkyl group can be an unsubstituted cycloalkyl group or a substituted cycloalkyl group.

[0036] As used herein, the term "cycloalkenyl" is defined similarly to "cycloalkyl" except for containing at least one carbon-carbon double bond, but is not aromatic. The term C_n means the cycloalkenyl group has "n" carbon atoms. For example, C_5 cycloalkenyl refers to a cycloalkenyl group that has 5 carbon atoms in the ring. C_{5-8} cycloalkenyl refers to cycloalkenyl groups having a number of carbon atoms encompassing the entire range (i.e., 5 to 8 carbon atoms), as well as all subgroups (*e.g.*, 5-6, 6-8, 7-8, 5-7, 5, 6, 7, and 8 carbon atoms). Nonlimiting examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Unless otherwise indicated, a cycloalkenyl group can be an unsubstituted cycloalkenyl group or a substituted cycloalkenyl group.

[0037] As used herein, the term "heterocycloalkyl" is defined similarly as cycloalkyl, except the ring contains one to three heteroatoms independently selected from oxygen, nitrogen, or sulfur. Nonlimiting examples of heterocycloalkyl groups include piperdine, tetrahydrofuran, tetrahydropyran, dihydrofuran, morpholine, oxazepaneyl, and the like. Cycloalkyl and heterocycloalkyl groups can be saturated or partially unsaturated ring systems optionally substituted with, for example, one to three groups, independently selected alkyl, alkyleneOH, $C(O)NH_2$, NH_2, oxo (=O), aryl, haloalkyl, halo, and OH. Heterocycloalkyl groups optionally can be further N-substituted as described herein.

[0038] As used herein, the term "aryl" refers to monocyclic or polycyclic (*e.g.*, fused bicyclic and fused tricyclic) carbocyclic aromatic ring systems. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, tetrahydronaphthyl, phenanthrenyl, biphenylenyl, indanyl, indenyl, anthracenyl, fluorenyl, tetralinyl. Unless otherwise indicated, an aryl group can be an unsubstituted aryl group or a substituted aryl group.

[0039] As used herein, the term "heteroaryl" refers to monocyclic or polycyclic (*e.g.*, fused bicyclic and fused tricyclic) aromatic ring systems, wherein one to four-ring atoms are selected from oxygen, nitrogen, or sulfur, and the remaining ring atoms are carbon, said ring system being joined to the remainder of the molecule by any of the ring atoms. Nonlimiting examples of heteroaryl groups include, but are not limited to, pyridyl, pyridazinyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, tetrazolyl, oxazolyl, isooxazolyl, thiadiazolyl, oxadiazolyl, furanyl, thienyl, quinolinyl, isoquinolinyl, benzoxazolyl, benzimidazolyl, benzofuranyl, benzothiazolyl, triazinyl, triazolyl, purinyl, pyrazinyl, purinyl, indolinyl, phthalzinyl, indazolyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, naphthyridinyl, pyridopyridinyl, indolyl, 3H-

indolyl, pteridinyl, and quinooxalinyl. Unless otherwise indicated, a heteroaryl group can be an unsubstituted heteroaryl group or a substituted heteroaryl group.

[0040] As used herein, the term "hydroxy" or "hydroxyl" as used herein refers to the "—OH" group.

[0041] As used herein, the term "alkoxy" or "alkoxyl" refers to a "—O-alkyl" group.

[0042] As used herein, the term "halo" is defined as fluoro, chloro, bromo, and iodo.

[0043] As used herein, the term "carboxy" or "carboxyl" refers to a "–COOH" group.

[0044] As used herein, the term "amino" refers to a —NH_2 or —NH— group, wherein any hydrogen can be replaced with an alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl group.

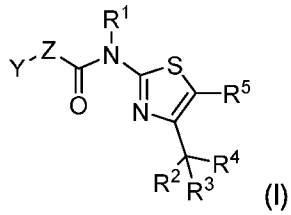
[0045] As used herein, the term "amido" refers to a group comprising a —NHC(=O)— or —C(=O) NH— group, wherein the hydrogen in each Formula can be replaced with an alkyl, cycloalkyl, aryl, heteroaryl, or heterocycloalkyl group.

[0046] As used herein, the term "sulfonyl" refers to a  group.

[0047] A "substituted" functional group (e.g., a substituted alkyl, alkyleneyl, cycloalkyl, aryl, or heteroaryl) is a functional group having at least one hydrogen radical that is substituted with a non-hydrogen radical (i.e., a substitutent). Examples of non-hydrogen radicals (or substituents) include, but are not limited to, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, ether, aryl, heteroaryl, heterocycloalkyl, hydroxyl, oxy (or oxo), alkoxyl, ester, thioester, acyl, carboxyl, cyano, nitro, amino, sulfhydryl, and halo. When a substituted alkyl group includes more than one non-hydrogen radical, the substituents can be bound to the same carbon or two or more different carbon atoms.

Protein Secretin Inhibitors

[0048] In one aspect, the compounds of the disclosure have a structure of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzoimidazolyl, pyrrolopyridinyl, benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, phenyl, naphthalenyl,

tetrahydronaphthalenyl, indenyl, dihydroindenyl, thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiopheneyl, dihydrothienopyridinyl, tetrahydrocycloheptathiopheneyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, C_{5-7}cycloalkyl, C_{3-7}heterocycloalkyl, or C_{5-7}cycloalkenyl;

Z is C_{0-2}alkylene, and

when Z is C_{1-2}alkylene, then (a) one carbon can be substituted with one or two substituents selected from C_{1-6}alkyl, unsubstituted C_{0-3}alkylene-aryl, $NR^1C(O)C_{1-3}$alkyl, NR^1C_{1-3}alkyl, and OH, with the proviso that the carbon is not substituted with two OH, or (b) one carbon and its two substituents form a 3- to 6-membered ring;

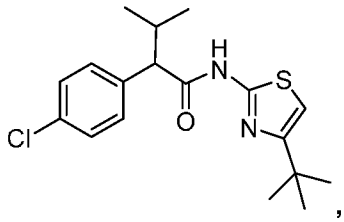
R^1 is H or C_{1-3}alkyl;

R^2 and R^3 are each independently unsubstituted C_{1-3}alkyl or halo, or R^2 and R^3, together with the carbon to which they are attached, form a 3- to 6-membered ring;

R^4 is unsubstituted C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-3}alkylene-OH, C_{0-3}alkylene-C_{1-6}alkoxyl, C_{1-3}alkylene-$C(O)OC_{1-4}$alkyl, or halo; and

R^5 is H, halo, CN, or $C(=O)OC_{1-3}$alkyl;

with the proviso that the compound of Formula (I) is not:



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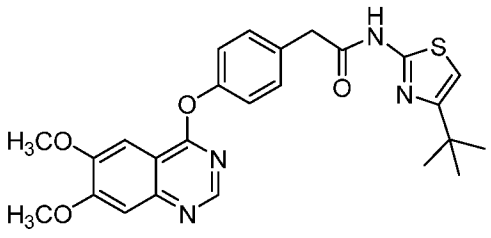

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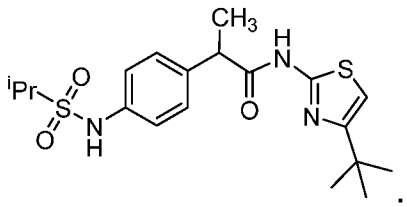
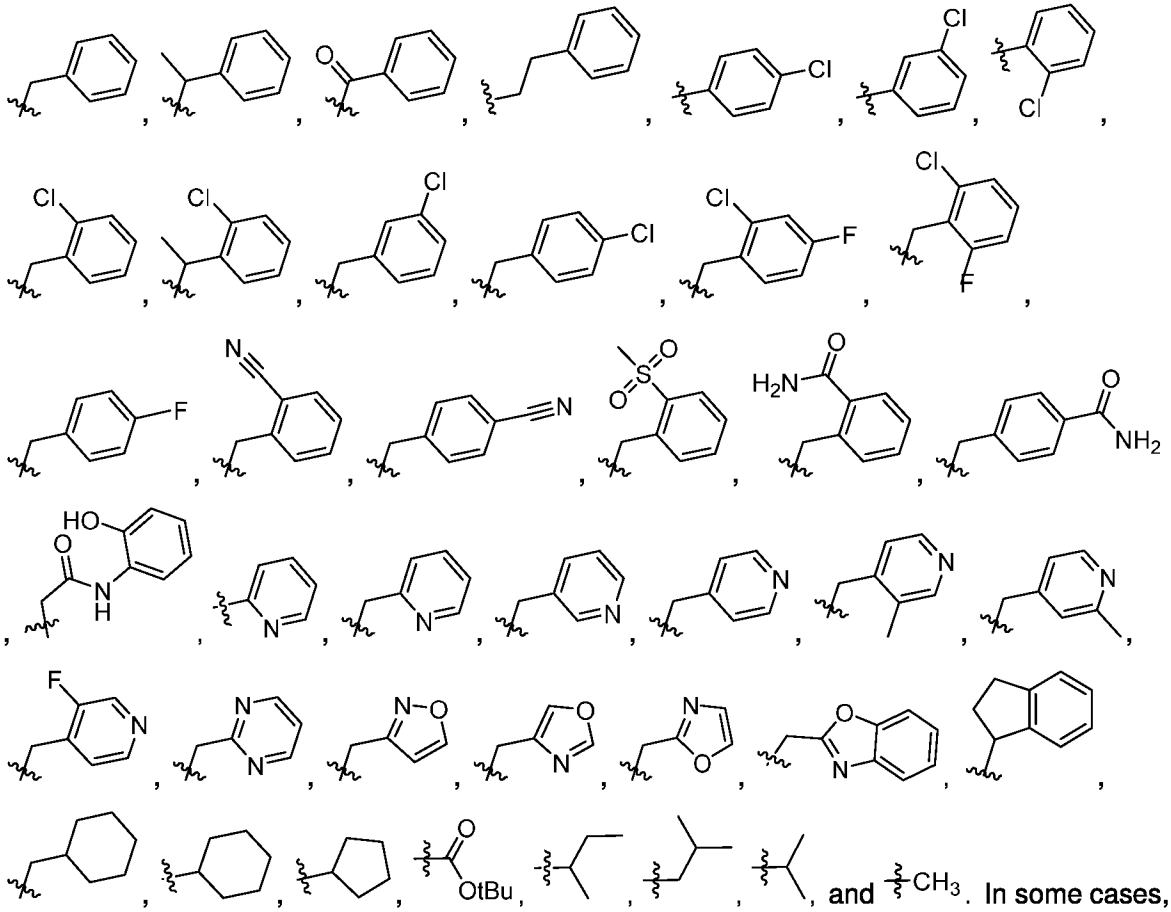


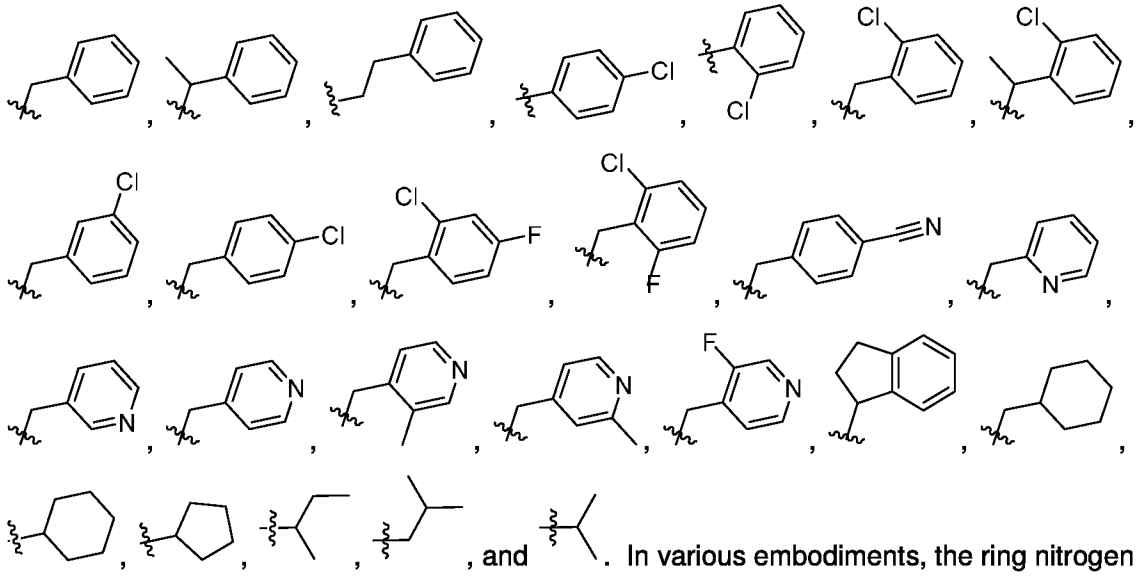
.

[0049] In some embodiments, Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzodimidzolyl, or pyrrolopyridinyl. In some cases, Y comprises indolyl. In embodiments where Y comprises a ring nitrogen, the ring nitrogen can be unsubstituted, substituted, or bonded to Z. In various embodiments, the ring nitrogen is bonded to Z. In some cases, the ring nitrogen atom is not bonded to Z and is unsubstituted. In various cases, the ring nitrogen atom not bonded to Z and is substituted. Suitable substituents include C_{1-6}alkyl, $C(O)OC_{1-6}$alkyl, C_{0-3}alkylene-aryl, C_{1-3}alkylene-heteroaryl, C_{3-6}cycloalkyl, and C_{1-3}alkylene-amide. In some cases the alkyl group of the C_{1-6}alkyl or $C(O)OC_{1-6}$alkyl substituent is methyl, isopropyl, isobutyl, or sec-butyl. In some embodiments, the aryl group of the C_{0-3}alkylene-aryl substituent is phenyl or indene. In various embodiments, the heteroaryl group of the C_{1-3}alkylene-

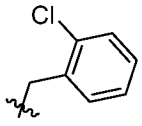
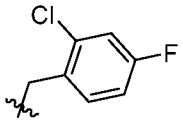
heteroaryl substituent is pyridinyl, pyrmidinyl, isooxazolyl, oxazolyl, or benzooxazolyl. In various cases, the C_{3-6}cycloalkyl group is cyclohexyl or cyclopentyl. For example, the ring nitrogen atom of Y can be substituted with a moiety selected from the group consisting of:



and . In some cases, the ring nitrogen atom of Y is substituted with a moiety selected from the group consisting of



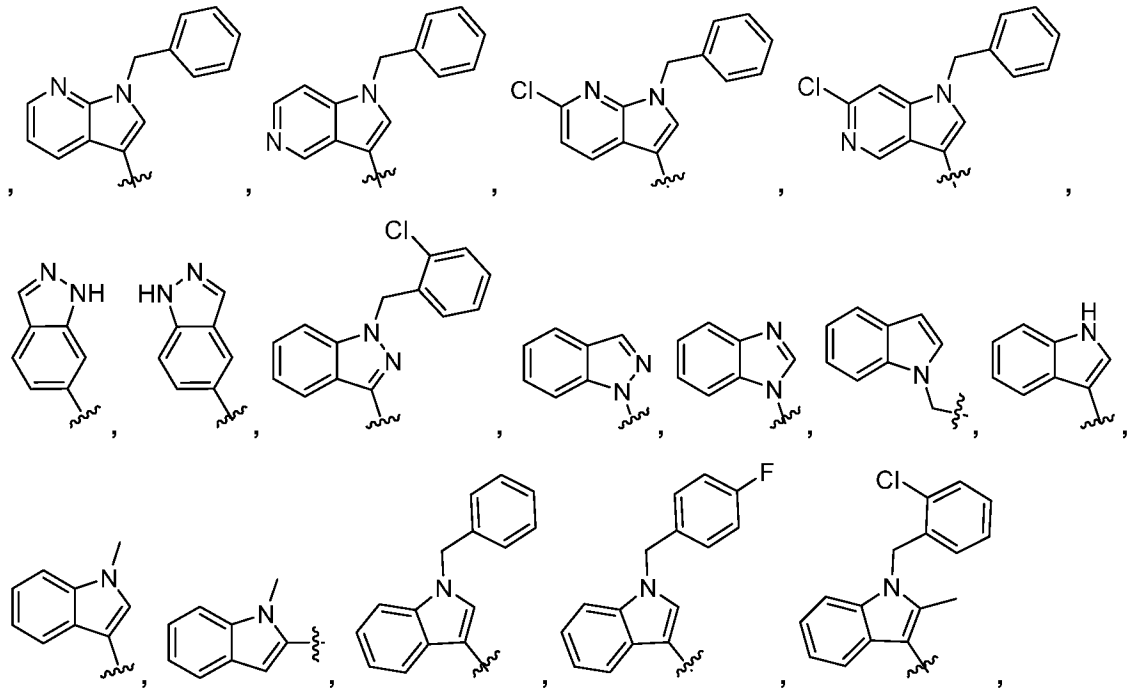
and . In various embodiments, the ring nitrogen

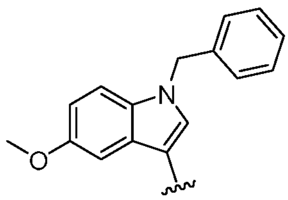
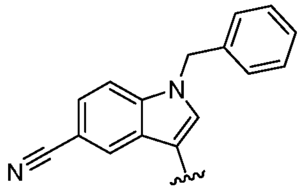
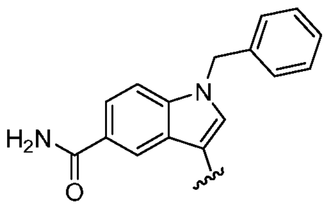
atom of Y is substituted with  or  .

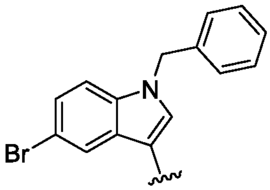
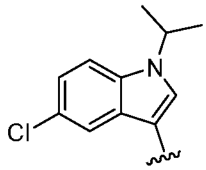
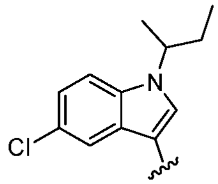
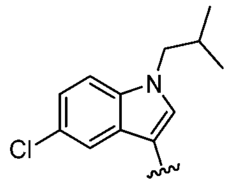
[0050] In some cases, Y comprises benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, or tetrahydrobenzooxazepinyl. For example, Y can comprise benzofuranyl. In various cases, Y comprises phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, or dihydroindenyl. For example, Y can comprise phenyl. In some cases, Y comprises thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiophenyl, dihydrothienopyridinyl, or tetrahydrocycloheptathiopheneyl. For example, Y can comprise thiophenyl or benzothiophenyl. In some embodiments when Y comprises dihydrothienopyridinyl, the ring nitrogen atom is unsubstituted or substituted with acetyl, $C(O)OC_{1-6}$alkyl, or C_{0-3}alkylene-aryl. In various embodiments, Y comprises triazolyl, thiadiazolyl, pyridinyl or pyridazinyl. In some cases, Y comprises C_{5-7}cycloalkyl (e.g., cyclopentyl, cyclohexyl, or cycloheptyl), C_{3-7}heterocycloalkyl (e.g., tetrahydrofuranyl, tetrahydropyranyl, morpholine, piperidine, or oxazepaneyl), or C_{5-7}cycloalkenyl (e.g., cyclopentenyl or cyclohexenyl).

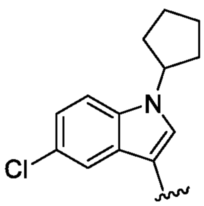
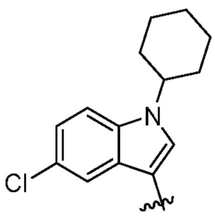
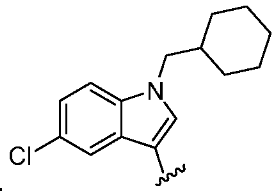
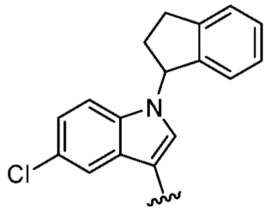
[0051] In any of the embodiments, Y can be substituted at one or more ring carbon atoms. Suitable substituents include halo, CN, C_{1-6}alkyl, C_{2-12}alkynyl, C_{1-3}alkoxyl, amido, sulfonyl, C_{3-8}cycloalkyl, C_{5-7}cycloalkenyl, C_{0-3}alkylene-heterocycloalkyl, C_{0-3}alkylene-aryl, and C_{0-3}alkylene heteroaryl. In some embodiments, Y is substituted at a ring carbon atom with chlorine.

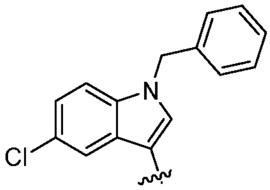
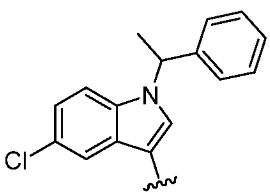
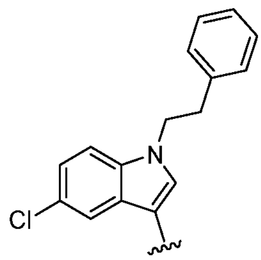
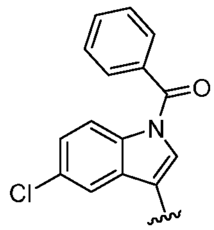
[0052] In some cases, Y is selected from the group consisting of:

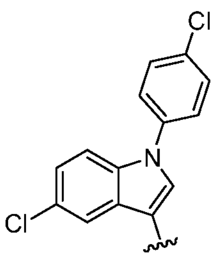
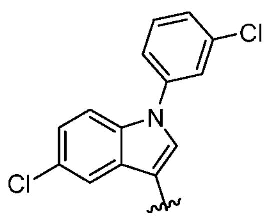
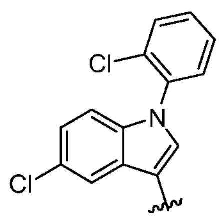
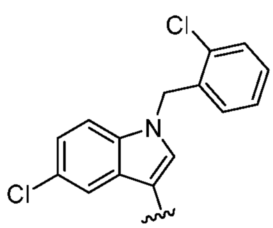


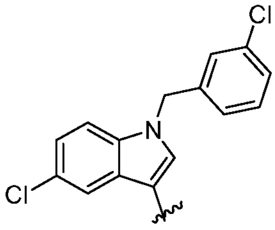
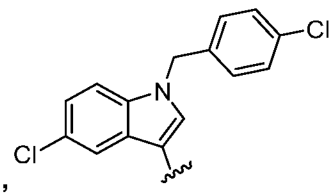
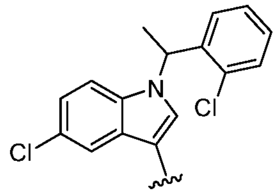
 ,  ,  ,

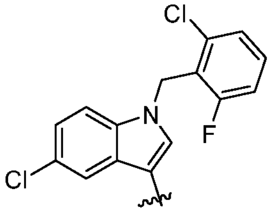
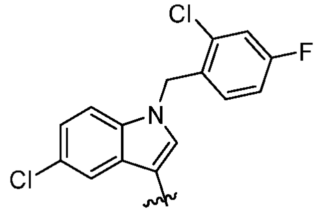
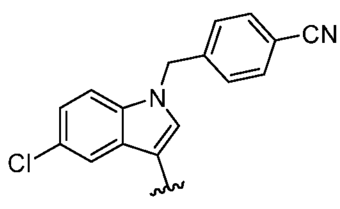
 ,  ,  ,  ,

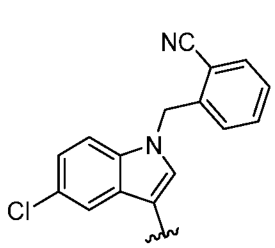
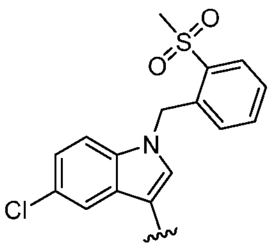
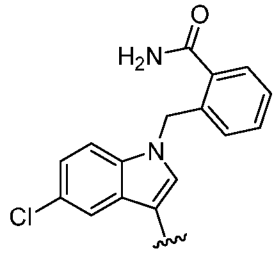
 ,  ,  ,  ,

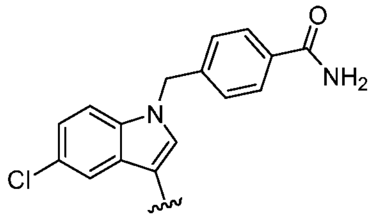
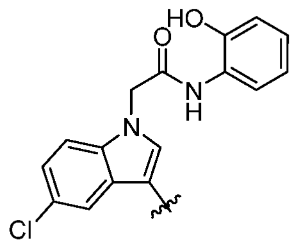
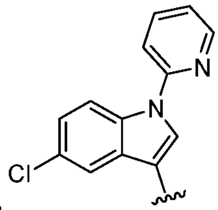
 ,  ,  ,  ,

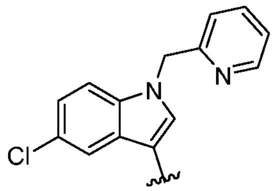
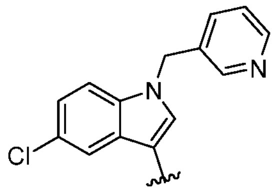
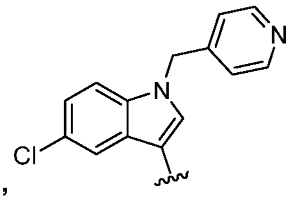
 ,  ,  ,  ,

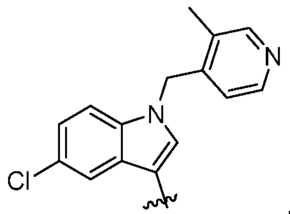
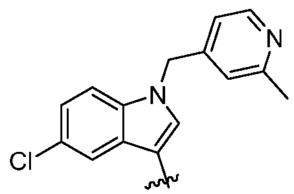
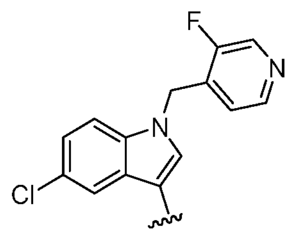
 ,  ,  ,

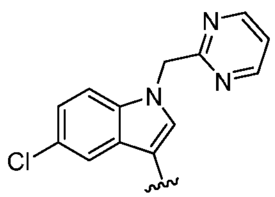
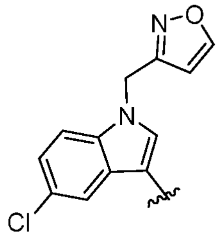
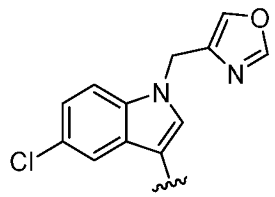
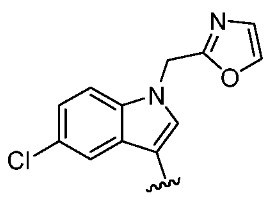
 ,  ,  ,

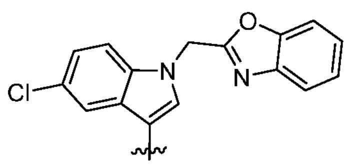
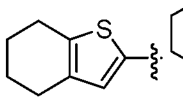
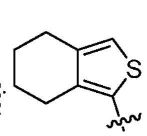
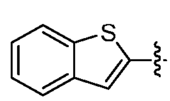
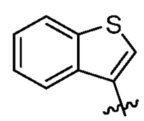
 ,  ,  ,

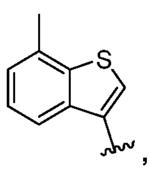
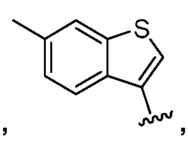
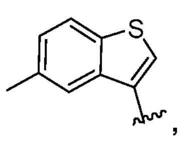
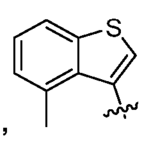
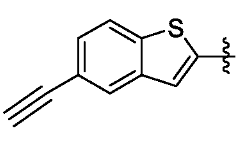
 ,  ,  ,

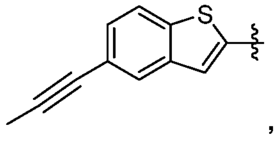
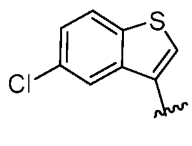
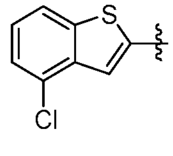
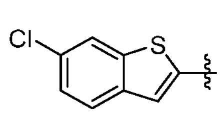
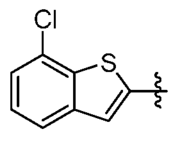
 ,  ,  ,

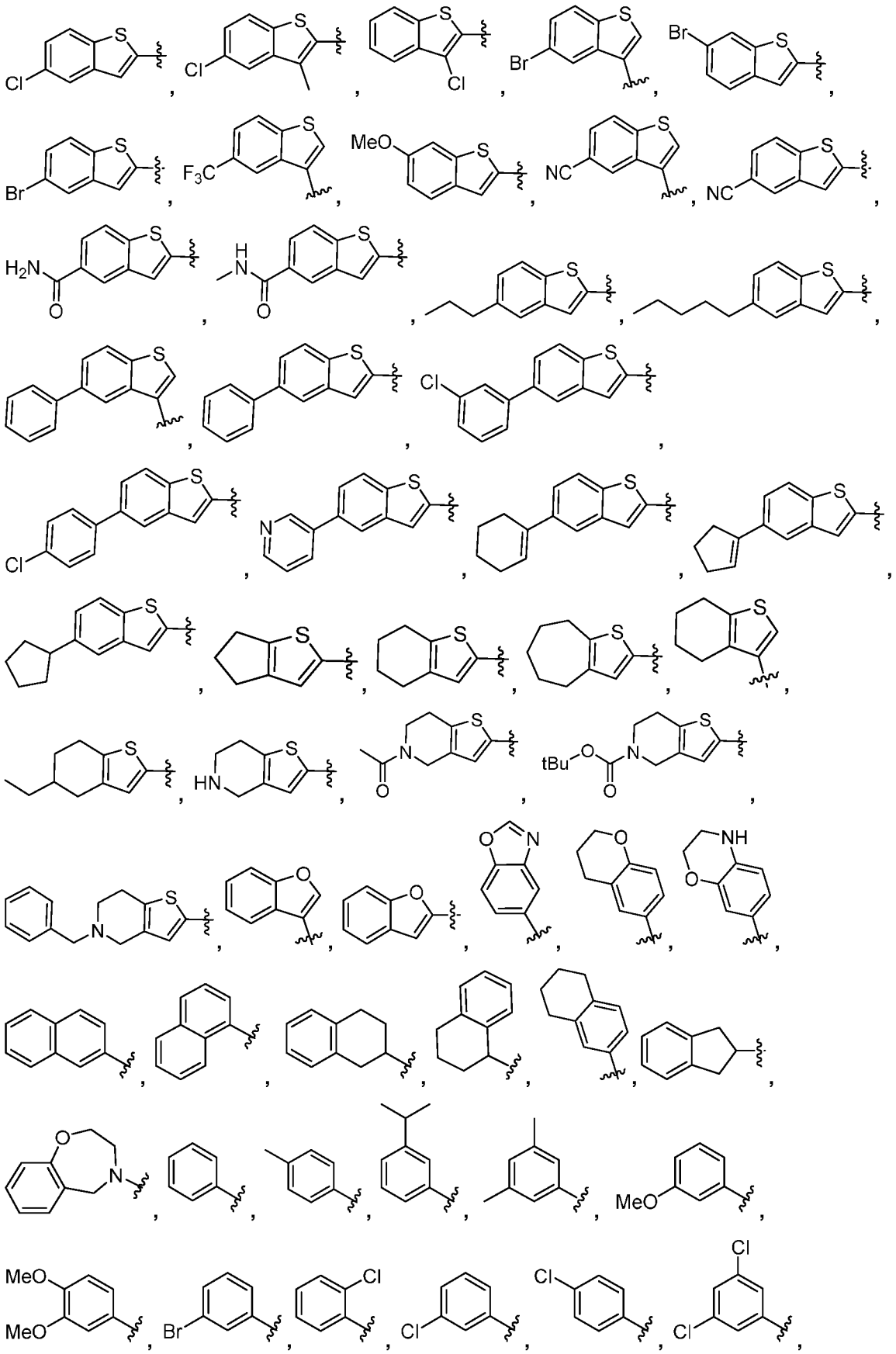
 ,  ,  ,

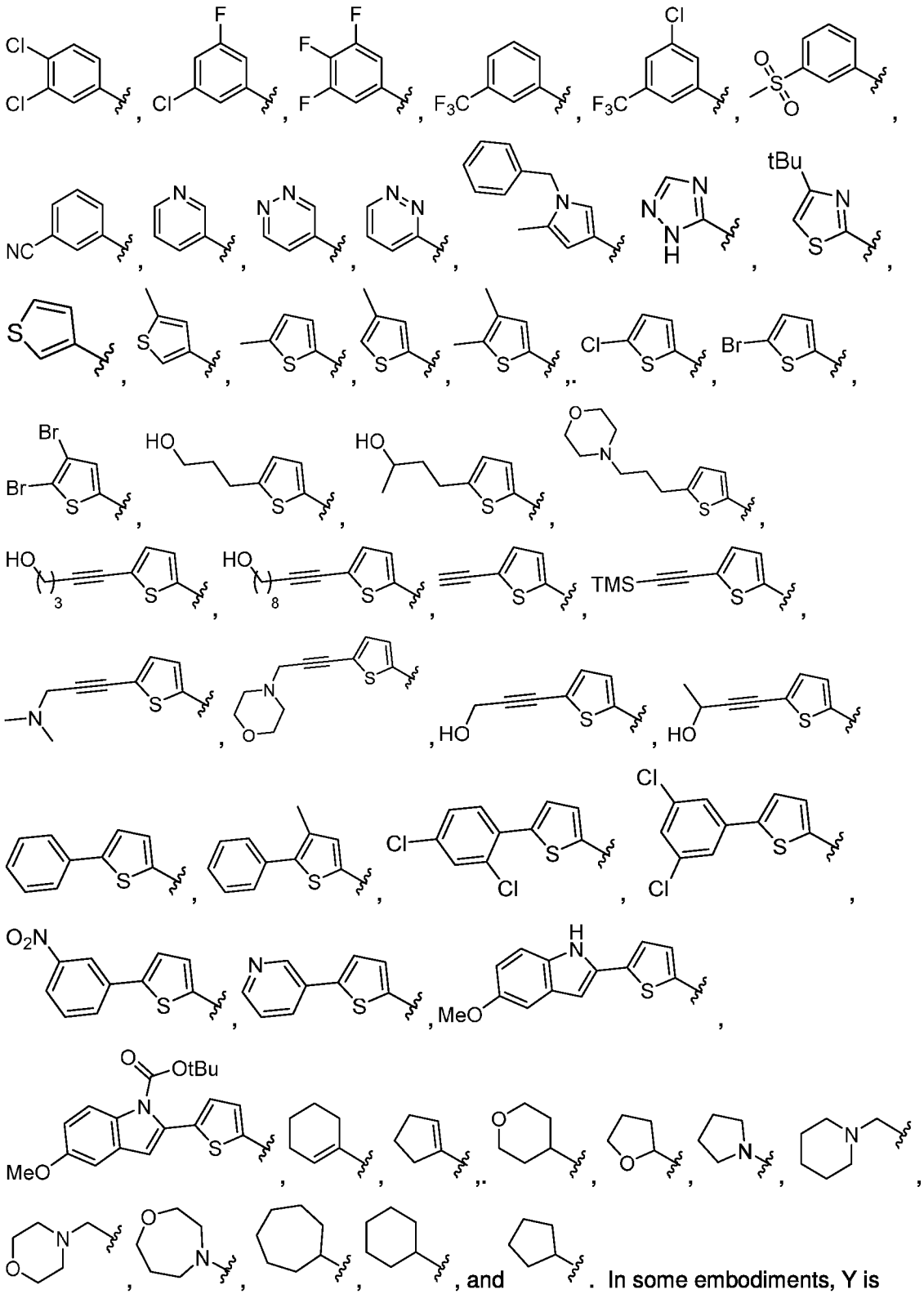
 ,  ,  ,  ,

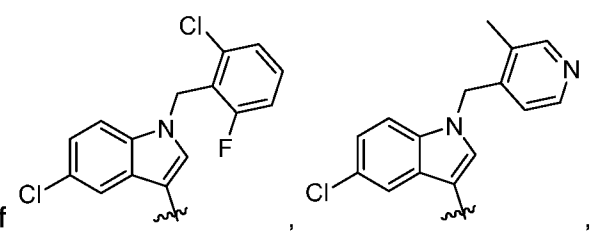
 ,  ,  ,  ,  ,

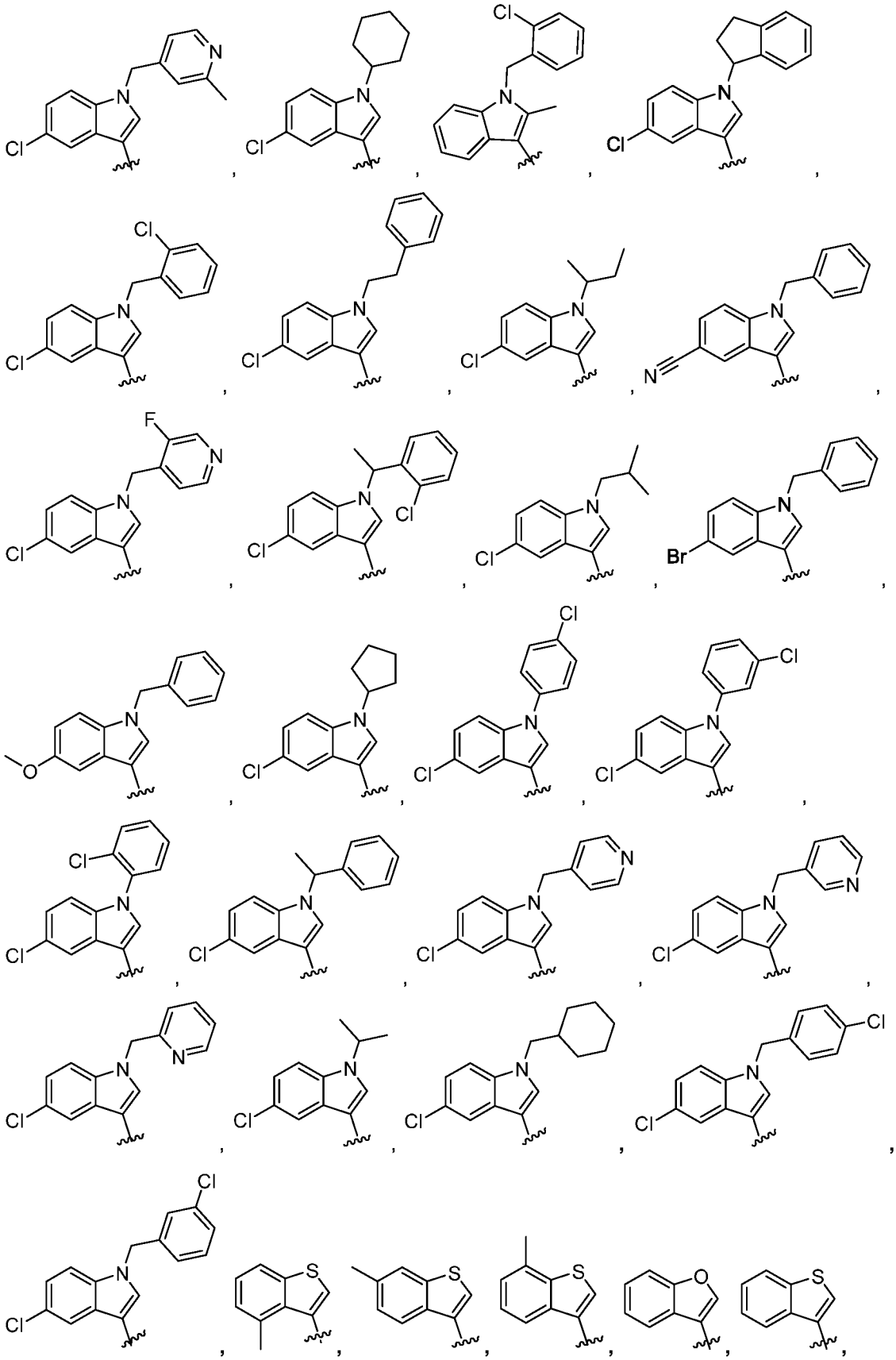
 ,  ,  ,  ,  ,

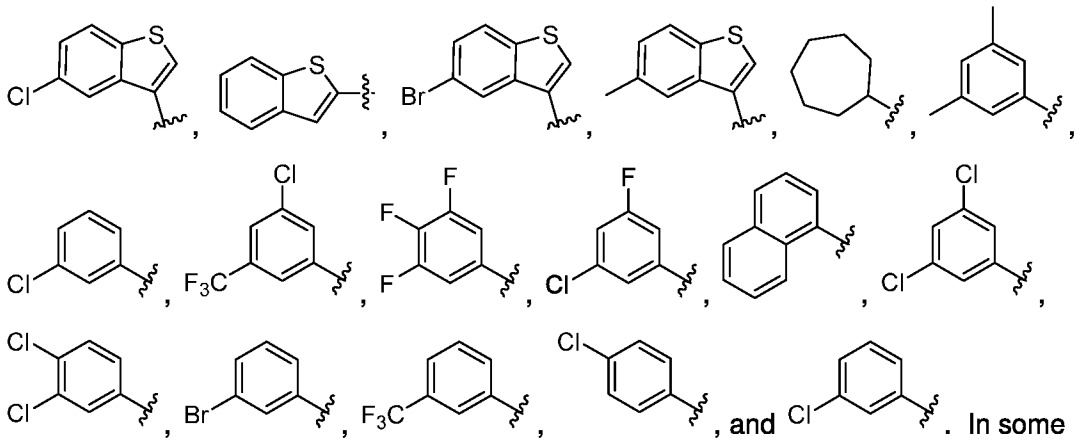
 ,  ,  ,  ,  ,

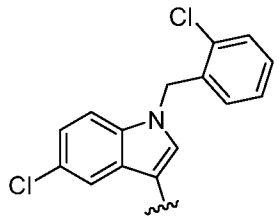


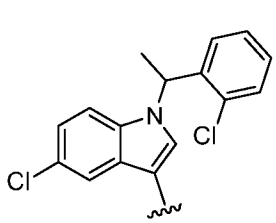
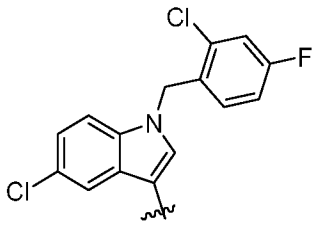


selected from the group consisting of  .





cases, Y is selected from the group consisting of  ,

 , and  .

[0053] In some embodiments Z is C_0alkylene, or absent. In some cases, Z is C_{1-2}alkylene, and the alkylene is unsubstituted (e.g., -CH_2- or -CH_2CH_2-). In various cases, Z is C_1alkylene and is substituted with one or two groups. In some embodiments, Z is C_2alkylene, and one carbon atom of the alkylene is substituted with one or two groups. When Z is C_2alkylene, one carbon atom of the alkylene is unsubstituted. Suitable substituents for Z include, for example, C_{1-6}alkyl, C_{0-3}alkylene-aryl (e.g., unsubstituted C_{0-3}alkylene-aryl), $NR^1C(O)C_{1-3}$alkyl, NR^1C_{1-3}alkyl, and OH. For example, Z can be substituted with one or two substituents selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, isobutyl, phenyl, benzyl, hydroxyl, methylamido, and methylamino. In some cases, two substituents of Z, together with the carbon atom to which they are attached, form a C_{3-6}cycloalkyl group (e.g., cyclopropyl or cyclopentyl).

[0054] In some embodiments, R^1 is H. In various embodiments, R^1 is C_{1-3}alkyl. For example, R^1 can be methyl.

[0055] In various cases, R^2 and R^3 are each independently unsubstituted C_{1-3}alkyl or halo. For example, each of R^2 and R^3 can be methyl. In some embodiments, R^2 and R^3, together with the carbon to which they are attached, form a 3- to 6-membered ring, such as a cyclopropyl group. In various embodiments, R^4 can be C_{1-6}alkyl, such as methyl, ethyl, or propyl. In some cases, R^4 can be C_{2-6}alkenyl, such as 2-propenyl. In some embodiments, R^4 can be C_{0-}

$_3$alkylene-OH, C_{0-3}alkylene-C_{1-6}alkoxyl, such as methoxy, ethoxy, isopropoxy, methoxyethyl, and ethanolyl. In various cases, R^4 can be C_{1-3}alkylene-C(O)OC_{1-4}alkyl, such as $CH_2C(O)OEt$. In some cases, R^4 can be halo. In some embodiments, R^2, R^3, and R^4 are each methyl. In some cases, R^2, R^3, and R^4 are each fluoro.

[0056] In some embodiments, R^5 is H. In some cases, R^5 is halo (e.g., Cl). In various embodiments, R^5 is CN or C(=O)OC_{1-3}alkyl (e.g., $C(=O)OCH_3$).

[0057] Examples of the compounds of Formula (I) are shown in Tables A and B, below, as compounds A1-A189 and B1-B51. Additional compounds of the disclosure are shown in Tables C and D, below, as compounds C1-C9 and D1-D11. In some embodiments, the compounds of the disclosure include A24, A35, A33b, A2, A23, A8, A55, A186, A15, A56, A47, A41. In various embodiments, the compounds of the disclosure include A33b, A35, A24, A2, A23, A8, A55.

[0058] The chemical structures having one or more stereocenters depicted with dashed and bold bonds (i.e., ····· and ——) are meant to indicate absolute stereochemistry of the stereocenter(s) present in the chemical structure. Bonds symbolized by a simple line do not indicate a stereo-preference. Unless otherwise indicated to the contrary, chemical structures that include one or more stereocenters which are illustrated herein without indicating absolute or relative stereochemistry, encompass all possible stereoisomeric forms of the compound (e.g., diastereomers, enantiomers) and mixtures thereof. Structures with a single bold or dashed line, and at least one additional simple line, encompass a single enantiomeric series of all possible diastereomers.

Synthesis of Protein Secretin Inhibitors

[0059] The compounds provided herein can be synthesized using conventional techniques readily available starting materials known to those skilled in the art. In general, the compounds provided herein are conveniently obtained via standard organic chemistry synthesis methods.

Synthesis of Final Compounds

[0060] In some embodiments, the compounds provided herein can be synthesized by coupling a desired carboxylic acid-derivatized Y group, (e.g., Y-COOH when Z is C_0-alkylene), or Y-Z group (e.g., Y-Z-COOH when Z is C_{1-2}-alkylene), with the desired 4-substituted-2-thiazolamine using standard coupling chemistry between the carboxylic acid and amine, as exemplified by **Route 1** in the Examples section.

[0061] In various embodiments, the compounds provided herein can be synthesized by coupling a desired carboxylic acid chloride-derivatized Y group, (e.g., Y-C=OCl when Z is C_0-alkylene), or Y-Z group (e.g., Y-Z-C=OCl when Z is C_{1-2}-alkylene), with the desired 4-substituted-2-thiazolamine using standard coupling chemistry between the carboxylic acid chloride and amine, as exemplified by **Route 2** in the Examples section.

[0062] In some cases, the substituted-benzothiophene carboxamide compounds provided herein can be synthesized using a palladium cross-coupling reaction between a desired bromo-benzothiophene carboxamide starting material and a desired bromo-functionalized group, as exemplified by **Route 3** in the Examples section.

[0063] In various cases, the alkyne-substituted-benzothiophene carboxamide compounds provided herein can be synthesized using a Sonogashira coupling reaction between a desired bromo-benzothiophene carboxamide starting material and a desired alkyne starting material, as exemplified by **Route 4** and **Route 5** in the Examples section.

[0064] In some embodiments, the alkyl-substituted-benzothiophene carboxamide compounds provided herein can be synthesized by reducing a desired alkyne-substituted-benzothiophene carboxamide starting material using standared reduction chemistry, as exemplified by **Route 6** in the Examples section.

[0065] In various embodiments, the substituted-benzothiophene carboxamide compounds provided herein can be synthesized using a Suzuki coupling reagtion between a desired bromo-benzothiophene carboxamide starting material and a desired organoboron starting material, as exemplified by **Route7** in the Examples section.

[0066] In some cases, the cyano-substituted-benzothiophene carboxamide compounds provided herein can be synthesized using zinc-catalyzed cyanation of the desired bromo-substituted benzothiophene carboxamide compound, as exemplified by **Route 8** in the Examples section.

[0067] In various cases, the amido-substituted-benzothiophene carboxamide compounds provided herein can be synthesized by reducing a desired cyano-substituted-benzothiophene carboxamide starting material, a exemplified by **Route 9** in the Examples section.

[0068] In some embodiments, the cycloalkyl-substituted-benzothiophene carboxamide compounds provided herein can be synthesized by reducing a desired cycloalkenyl-substituted-benzothiophene carboxamide starting material, as exemplified by **Route 10** in the Examples section.

[0069] In various embodiments, the carboxamide compounds provided herein having an alkene-substituted thiazole group can be prepared by oxidizing a desired compound having an alcohol-substituted thiazole group to a carbonyl, and then conducting a Wittig reaction with an appropriate Wittig reagent, as exemplified by **Route 11** in the Examples section.

[0070] In some cases, the the carboxamide compounds provided here having an alkyl-substituted thiazole group can be prepared by reducing a a desired compound having an alkenyl-substituted thiazole, as exemplified by **Route 12** in the Examples section.

[0071] In various cases, the carboxamide compounds provided herein having a hydroxyalkyl-

substituted thiazole group can be prepared by coupling together a desired carboxylic acid-functionalized Y group with a desired alkylester-substituted-2-thiazolamine using standard coupling chemistry between the carboxylic acid and the amine, and then reducing the ester using standard reduction techniques, as exemplified by **Route 13** in the Examples section

[0072] In various embodiments, the carboxamide compounds provided herein having a alkoxyalkyl-substituted thiazole group can be prepared by methylation of a desired hydroxyalkyl-substituted-2-thiazolamine using standard methylation chemistry, as exemplified by **Route 14** in the Examples section.

[0073] In some embodiments, the carboxamide compounds provided herein having alkyl-substitution at the amido nitrogen atom can be prepared by alkylating a desired carboxamide starting material with an unsubstituted amido nitrogen atom using standard alkylation chemistry (e.g. NaH, MeI), as exemplified by **Route 15** in the Examples section.

[0074] In some cases, the benzamide-substituted carboxamide compounds provided herein can be prepared by the base-catalyzed conversion of a desired nitrile-substituted starting material, as exemplified by **Route 16** and **Route 17** in the Examples section.

[0075] In various cases, the carboxamide compounds provided herein are prepared as a mixture of enantiomers. Chiral separation of the enantiomers can occur using a chiral HPLC column, as exemplified by **Route 18** in the Examples section.

[0076] In some cases, an enantiopure compound can be synthesized de novo using a desired chiral starting material, as exemplified by **Route 19** in the Examples section

Synthesis of Intermediates

[0077] The intermediates used to prepare the compounds described herein also can be prepared by standard methods known to those skilled in the art, as described in the Examples, section below.

Methods of Use

[0078] The compounds disclosed herein (e.g., the compounds of Formula (I) and the compounds listed in Tables A, B, C, and D, and pharmaceutically acceptable salts of the foregoing) can inhibit protein secretion of a protein of interest. The compounds disclosed herein can interfere with the Sec61 protein secretion machinery of a cell. In some cases, a compound as disclosed herein inhibits secretion of one or more of TNFα, VCAM, PRL, and PD-1, or each of TNFα, VCAM, PRL, and PD-1. Protein secretion activity can be assessed in a manner as described in the Examples section below.

[0079] As used herein, the term "inhibitor" is meant to describe a compound that blocks or reduces an activity of a pharmacological target (for example, a compound that inhibits Sec61 function in the protein secretion pathway). An inhibitor can act with competitive, uncompetitive,

or noncompetitive inhibition. An inhibitor can bind reversibly or irreversibly, and therefore, the term includes compounds that are suicide substrates of a protein or enzyme. An inhibitor can modify one or more sites on or near the active site of the protein, or it can cause a conformational change elsewhere on the enzyme. The term inhibitor is used more broadly herein than scientific literature so as to also encompass other classes of pharmacologically or therapeutically useful agents, such as agonists, antagonists, stimulants, co-factors, and the like.

[0080] Thus, provided herein are methods of inhibiting protein secretion in a cell. In these methods, a cell is contacted with a compound described herein (e.g., a compound of Formula (I) or a compound listed in Tables A, B, C, or D, and pharmaceutically acceptable salts of the foregoing), or pharmaceutical formulation thereof, in an amount effective to inhibit secretion of the protein of interest. In some embodiments, the cell is contacted *in vitro*. In various embodiments, the cell is contacted *in vivo*. In various embodiments, the contacting includes administering the compound or pharmaceutical formulation to a subject.

[0081] The biological consequences of Sec61 inhibition are numerous. For example, Sec61 inhibition has been suggested for the treatment or prevention of inflammation and/or cancer in a subject. Therefore, pharmaceutical formulations for Sec61 specific compounds, provide a means of administering a drug to a subject and treating these conditions. As used herein, the terms "treat," "treating," "treatment," and the like refer to eliminating, reducing, or ameliorating a disease or condition, and/or symptoms associated therewith. Although not precluded, treating a disease or condition does not require that the disease, condition, or symptoms associated therewith be completely eliminated. As used herein, the terms "treat," "treating," "treatment," and the like may include "prophylactic treatment," which refers to reducing the probability of redeveloping a disease or condition, or of a recurrence of a previously-controlled disease or condition, in a subject who does not have, but is at risk of or is susceptible to, redeveloping a disease or condition or a recurrence of the disease or condition. The term "treat" and synonyms contemplate administering a therapeutically effective amount of a compound of the invention to an individual in need of such treatment. Within the meaning of the invention, "treatment" also includes relapse prophylaxis or phase prophylaxis, as well as the treatment of acute or chronic signs, symptoms and/or malfunctions. The treatment can be orientated symptomatically, for example, to suppress symptoms. It can be effected over a short period, be oriented over a medium term, or can be a long-term treatment, for example within the context of a maintenance therapy. As used herein, the terms “patient” and “subject” may be used interchangeably and mean animals, such as dogs, cats, cows, horses, and sheep (i.e., non-human animals) and humans. Particular patients are mammals (e.g., humans). The term patient includes males and females.

[0082] Inhibition of Sec61-mediated secretion of inflammatory proteins (e.g., TNFα) can disrupt inflammation signaling. Thus, provided herein is a method of treating inflammation in a

subject by administering to the subject a therapeutically effective amount of a compound described herein, (i.e., a compound of Formula (I) or a compound listed in Tables A, B, C, or D), or a pharmaceutically acceptable salt thereof.

[0083] Further, the viability of cancer cells relies upon increased protein secretion into the ER for survival. Therefore, non-selective or partially selective inhibition of Sec61 mediated protein secretion may inhibit tumor growth. Alternatively, in the immune-oncology setting, selective secretion inhibitors of known secreted immune checkpoints proteins (e.g., PD-1, TIM-3, LAG3, etc.) can result in activation of the immune system to against various cancers. Accordingly, also provided herein is a method of treating cancer in a subject by administering to the subject a therapeutically effective amount of a compound described herein, (e.g., a compound of Formula (I), a compound listed in Tables A, B, C, or D), or a pharmaceutically acceptable salt thereof. Specifically contemplated cancers that can be treated using the compounds and compositions described herein include, but are not limited to multiple myeloma, prostate, lung, bladder, and colorectal cancers.

[0084] Further guidance for using compounds and compositions described herein (e.g., a compound of Formula (I), a compound listed in Table A, B, C, or D, or a pharmaceutically acceptable salt thereof) for inhibiting protein secretion can be found in the Examples section, below.

Pharmaceutical Formulations and Administration

[0085] The methods provided herein include the manufacture and use of pharmaceutical compositions, which include one or more of the compounds provided herein. Also included are the pharmaceutical compositions themselves. Pharmaceutical compositions typically include a pharmaceutically acceptable carrier. Thus, provided herein are pharmaceutical formulations that include a compound described herein (e.g., a compound of Formula (I), a compound listed in Table A, B, C, or D, or a pharmaceutically acceptable salt thereof), as previously described herein, and one or more pharmaceutically acceptable carriers.

[0086] The phrase "pharmaceutically acceptable" is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0087] The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. As used herein the language "pharmaceutically acceptable carrier" includes buffer, sterile water for injection, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Each carrier

must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch, potato starch, and substituted or unsubstituted β-cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions provided herein are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

[0088] The term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts of a compound provided herein. These salts can be prepared *in situ* during the final isolation and purification of a compound provided herein, or by separately reacting the compound in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66: 1-19.)

[0089] In some embodiments, a compound provided herein may contain one or more acidic functional groups and, thus, is capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound provided herein. These salts can likewise be prepared *in situ* during the final isolation and purification of the compound, or by separately reacting the purified compound in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., supra).

[0090] Wetting agents, emulsifiers, and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

[0091] Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, and the like; (2) oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

[0092] A pharmaceutical composition may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include tonicity-adjusting agents, such as sugars and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

[0093] In some cases, in order to prolong the effect of one or more compounds provided herein, it is desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. For example, delayed absorption of a parenterally administered compound can be accomplished by dissolving or suspending the compound in an oil vehicle.

[0094] Compositions prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compositions are to be administered orally, they may be formulated as tablets, capsules, granules, powders, or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eye drops or eye ointments. These formulations can be prepared by conventional means in conjunction with the methods described herein, and, if desired, the active ingredient may be mixed with any conventional additive or excipient, such as a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, or a coating agent.

[0095] Formulations suitable for oral administration may be in the form of capsules (e.g., gelatin capsules), cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, troches, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert matrix, such as gelatin and glycerin, or sucrose and

acacia) and/or as mouthwashes, and the like, each containing a predetermined amount of a compound provided herein as an active ingredient. A composition may also be administered as a bolus, electuary, or paste. Oral compositions generally include an inert diluent or an edible carrier.

[0096] Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of an oral composition. In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient can be mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cyclodextrins, lactose, sucrose, saccharin, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, microcrystalline cellulose, gum tragacanth, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato, corn, or tapioca starch, alginic acid, Primogel, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, Sterotes, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; (10) a glidant, such as colloidal silicon dioxide; (11) coloring agents; and (12) a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

[0097] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of a powdered compound moistened with an inert liquid diluent.

[0098] Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, microspheres, and/or nanoparticles. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents

in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

[0099] Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

[00100] Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

[00101] Suspensions, in addition to the active compound(s) may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00102] Pharmaceutical compositions suitable for parenteral administration can include one or more compounds provided herein in combination with one or more pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00103] Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions provided herein include water for injection (e.g., sterile water for injection), bacteriostatic water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol such as liquid polyethylene glycol, and the like), sterile buffer (such as citrate buffer), and suitable mixtures thereof, vegetable oils, such as olive oil, injectable organic esters, such as ethyl oleate, and Cremophor EL™ (BASF, Parsippany, NJ). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of

surfactants.

[00104] The composition should be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

[00105] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle, which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the methods of preparation are freeze-drying (lyophilization), which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00106] Injectable depot forms can be made by forming microencapsule or nanoencapsule matrices of a compound provided herein in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes,microemulsions or nanoemulsions, which are compatible with body tissue.

[00107] For administration by inhalation, the compounds can be delivered in the form of an aerosol spray from a pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer. Such methods include those described in U.S. Patent No. 6,468,798. Additionally, intranasal delivery can be accomplished, as described in, inter alia, Hamajima et al., *Clin. Immunol. Immunopathol.*, 88(2), 205-10 (1998). Liposomes (e.g., as described in U.S. Patent No. 6,472,375, which is incorporated herein by reference in its entirety), microencapsulation and nanoencapsulation can also be used. Biodegradable targetable microparticle delivery systems or biodegradable targetable nanoparticle delivery systems can also be used (e.g., as described in U.S. Patent No. 6,471,996, which is incorporated herein by reference in its entirety).

[00108] Systemic administration of a therapeutic compound as described herein can also be by transmucosal or transdermal means. Dosage forms for the topical or transdermal administration of a compound provided herein include powders, sprays, ointments, pastes,

creams, lotions, gels, solutions, patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00109] The ointments, pastes, creams, and gels may contain, in addition to one or more compounds provided herein, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

[00110] Powders and sprays can contain, in addition to a compound provided herein, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00111] A compound provided herein can be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation, or solid particles containing a compound or composition provided herein. A nonaqueous (e.g., fluorocarbon propellant) suspension could be used. In some embodiments, sonic nebulizers are used because they minimize exposing the agent to shear, which can result in degradation of the compound.

[00112] Ordinarily, an aqueous aerosol can be made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular composition, but typically include nonionic surfactants (TWEEN® (polysorbates), PLURONIC® (poloxamers), sorbitan esters, lecithin, CREMOPHOR® (polyethoxylates)), pharmaceutically acceptable co-solvents such as polyethylene glycol, innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00113] Transdermal patches have the added advantage of providing controlled delivery of a compound provided herein to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[00114] The pharmaceutical compositions can also be prepared in the form of suppositories or retention enemas for rectal and/or vaginal delivery. Formulations presented as a suppository can be prepared by mixing one or more compounds provided herein with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, glycerides, polyethylene glycol, a suppository wax or a salicylate, which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent. Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

[00115] In one embodiment, the therapeutic compounds are prepared with carriers that will protect the therapeutic compounds against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Such formulations can be prepared using standard techniques, or obtained commercially, e.g., from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to selected cells with monoclonal antibodies to cellular antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811, which is incorporated herein by reference in its entirety.

[00116] As described above, the preparations of one or more compounds provided herein may be given orally, parenterally, topically, or rectally. They are, of course, given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, infusion; topically by lotion or ointment; and rectally by suppositories. In some embodiments, administration is oral.

[00117] The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection, and infusion.

[00118] The phrases "systemic administration", "administered systemically", "peripheral administration", and "administered peripherally" as used herein mean the administration of a ligand, drug, or other material via route other than directly into the central nervous system, such that it enters the patient's system and thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

[00119] A compound provided herein may be administered to humans and other animals for

therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracistemally, and topically, as by powders, ointments or drops, including buccally and sublingually. Regardless of the route of administration selected, a compound provided herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions provided herein, is formulated into a pharmaceutically acceptable dosage form by conventional methods known to those of skill in the art. In another embodiment, the pharmaceutical composition is an oral solution or a parenteral solution. Another embodiment is a freeze-dried preparation that can be reconstituted prior to administration. As a solid, this formulation may also include tablets, capsules or powders.

[00120] Actual dosage levels of the active ingredients in the pharmaceutical compositions provided herein may be varied so as to obtain "therapeutically effective amount," which is an amount of the active ingredient effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

[00121] The concentration of a compound provided herein in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. In some embodiments, the compositions provided herein can be provided in an aqueous solution containing about 0.1-10% w/v of a compound disclosed herein, among other substances, for parenteral administration. Typical dose ranges can include from about 0.01 to about 50 mg/kg of body weight per day, given in 1-4 divided doses. Each divided dose may contain the same or different compounds. The dosage will be a therapeutically effective amount depending on several factors including the overall health of a patient, and the formulation and route of administration of the selected compound(s).

[00122] Dosage forms or compositions containing a compound as described herein in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, in one embodiment 0.1-95%, in another embodiment 75-85%. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses. The amount of active ingredient which can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

[00123] The pharmaceutical composition may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is also noted that the

dose of the compound can be varied over time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular patient, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00124] The precise time of administration and/or amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the patient and adjusting the dosage and/or timing.

[00125] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[00126] Also provided herein is a conjoint therapy wherein one or more other therapeutic agents, or pharmaceuticaly active compounds/agents, are administered with a compound or a pharmaceutical composition comprising a compound provided herein. The additional pharmaceutically active compounds/agents may be small molecules or can be macromolecules such as proteins, antibodies, peptibodies, DNA, RNA or fragments of such macromolecules. Such conjoint treatment may be achieved by way of the simultaneous, sequential, or separate dosing of the individual components of the treatment.

[00127] In jurisdictions that forbid the patenting of methods that are practiced on the human body, the meaning of "administering" of a composition to a human subject shall be restricted to prescribing a controlled substance that a human subject will self-administer by any technique (*e.g.*, orally, inhalation, topical application, injection, insertion, etc.). The broadest reasonable interpretation that is consistent with laws or regulations defining patentable subject matter is intended. In jurisdictions that do not forbid the patenting of methods that are practiced on the human body, the "administering" of compositions includes both methods practiced on the human body and also the foregoing activities.

Combination Therapy

[00128] Also contemplated are methods of administering a compound as disclosed herein in

combination with a second therapeutic agent.

[00129] For example, when treating a cancer with the Sec61 protein section inhibitor as disclosed herein, a chemotherapeutic agent can be administered in combination. Contemplated chemotherapeutics for use in combination therapies as disclosed herein include aspirin, sulindac, curcumin, alkylating agents including: nitrogen mustards, such as mechlor-ethamine, cyclophosphamide, ifosfamide, melphalan and chlorambucil; nitrosoureas, such as carmustine (BCNU), lomustine (CCNU), and semustine (methyl-CCNU); ethylenimines/methylmelamine such as thriethylenemelamine (TEM), triethylene, thiophosphoramide (thiotepa), hexamethylmelamine (HMM, altretamine); alkyl sulfonates such as busulfan; triazines such as dacarbazine (DTIC); antimetabolites including folic acid analogs such as methotrexate and trimetrexate, pyrimidine analogs such as 5-fluorouracil, fluorodeoxyuridine, gemcitabine, cytosine arabinoside (AraC, cytarabine), 5-azacytidine, 2,2´-difluorodeoxycytidine, purine analogs such as 6-mercaptopurine, 6-thioguanine, azathioprine, 2'-deoxycoformycin (pentostatin), erythrohydroxynonyladenine (EHNA), fludarabine phosphate, and 2-chlorodeoxyadenosine (cladribine, 2-CdA); natural products including antimitotic drugs such as paclitaxel, vinca alkaloids including vinblastine (VLB), vincristine, and vinorelbine, taxotere, estramustine, and estramustine phosphate; epipodophylotoxins such as etoposide and teniposide; antibiotics such as actimomycin D, daunomycin (rubidomycin), doxorubicin, mitoxantrone, idarubicin, bleomycins, plicamycin (mithramycin), mitomycinC, and actinomycin; and enzymes such as L-asparaginase.

[00130] When treating an inflammatory disease, an anti-inflammatory agent can be administerd in combination. Contemplated anti-inflammatory agents for use in combination therapies as disclosed herein include a corticosteroid, a TNF blocker, IL-1 RA, azathioprine, cyclophosphamide, sulfasalazine, and yclo-oxygenase 2 inhibitors, such as Celecoxib, Nepafenac, Ibuprofen (Dolgesic), Indomethacin, Sulindac, Xanthohumol, Meclofenamate Sodium, Meloxicam, Rofecoxib, Bromfenac Sodium, Ibuprofen Lysine, Ketorolac (Ketorolac tromethamine), Diclofenac Sodium, Etodolac, Ketoprofen, Naproxen Sodium, Piroxicam, Acemetacin, Phenacetin, Tolfenamic Acid, Nimesulide, Flunixin Meglumin, Aspirin, Bufexamac, Niflumic acid, Licofelone, Oxaprozin, Lornoxicam, Lumiracoxib, Zaltoprofen, Ampiroxicam, Valdecoxib, Nabumetone, Mefenamic Acid, Carprofen, Amfenac Sodium monohydrate, Curcumin, Asaraldehyde and Suprofen.

[00131] In some embodiments, the second therapeutic agent is a proteasome inhibitor. Examples of proteasome inhibitors include, but are not limited to carfilzomib and bortezomib.

Other Embodiments

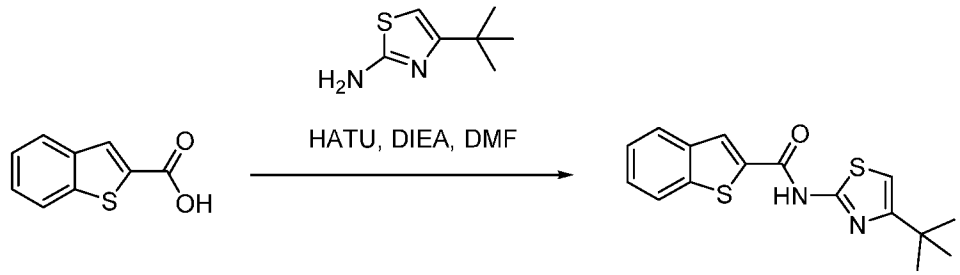
[00132] It is to be understood that while the disclosure is read in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the disclosure, which is defined by the scope of the appended claims. Other aspects,

advantages, and modifications are within the scope of the following claims.

EXAMPLES

[00133] The following examples are provided for illustration and are not intended to limit the scope of the invention.

Route 1: Synthesis of Compounds Via Coupling of Amino and Carboxylic Acid Starting Materials



[00134] To a solution of benzo[*b*]thiophene-2-carboxylic acid (274 mg, 1.54 mmol) and 4-(*tert*-butyl)thiazol-2-amine (200 mg, 1.28 mmol) in DMF (0.84 mL) was added HATU (585 mg, 1.54 mmol) followed by DIEA (791 uL, 4.90 mmol). The mixture was heated to 80 °C for 3 h then cooled to ambient temperature, diluted with ethyl acetate (5 mL) and brine (5 mL), and extracted with ethyl acetate (1X5 mL). The organics were combined, washed with brine (2X5 mL), dried with sodium sulfate, filtered, and concentrated. Flash chromatography (0-60% hexanes/ethyl acetate) provided *N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-benzothiophene-2-carboxamide (397 mg, 98% yield) as an off-white solid. (A145) ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 8.63 (s, 1H), 8.38 – 7.81 (m, 2H), 7.71 – 7.29 (m, 2H), 6.85 (s, 1H), 3.33 (s, 3H), 1.31 (s, 9H). LCMS for $C_{16}H_{16}N_2O_2S$, found 317 $[M+H]^+$.

[00135] The following compounds were synthesized in a similar manner:

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A166	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)-1-benzothiophene-2-carboxamide	385	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.10 (s, 1H), 8.62 (s, 1H), 8.39 (s, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.76 (d, *J* = 10.4 Hz, 1H), 6.79 (s, 1H), 1.27 (s, 8H).
A61	2-(1-benzyl-5-chloro-1H-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	438	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.24 (s, 1H), 7.64 (s, 1H), 7.54 – 7.33 (m, 2H), 7.33 – 7.13 (m, 4H), 7.07 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.68 (s, 1H), 5.36 (s, 2H), 3.78 (s, 2H), 1.22 (s, 9H).
A146	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide	321	^{1}H NMR (400 MHz, DMSO-d6) δ 12.44 (s, 1H), 7.96 (s, 1H), 6.77 (s, 1H), 2.77 (t, *J* = 6.6 Hz, 2H), 2.58 (t, *J* = 6.5 Hz, 2H), 1.90 – 1.53 (m, 4H), 1.29 (s, 9H).
A159	2-(1H-1,3-benzodiazol-1-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	315	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H), 8.19 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.02 (m, 2H), 6.73 (s, 1H), 5.23 (s, 2H), 1.23 (s, 9H).

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A76	2-(5-chloro-1-benzothiophen-3-yl)-*N*-[4-(2-methylbutan-2-yl)-1,3-thiazol-2-yl]acetamide	379	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.36 (s, 1H), 8.07 – 7.86 (m, 2H), 7.70 (s, 1H), 7.47 – 7.23 (m, 1H), 6.69 (s, 1H), 3.99 (s, 2H), 1.58 (q, *J* = 7.5 Hz, 2H), 1.17 (s, 9H), 0.60 (t, *J* = 7.4 Hz, 3H).
A66	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-yl)-3-phenylpropanamide	455	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.30 (s, 1H), 8.10 (s, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 7.85 (s, 1H), 7.46 – 7.31 (m, 1H), 7.31 – 7.14 (m, 3H), 7.14 – 6.99 (m, 1H), 6.68 (s, 1H), 4.69 – 4.50 (m, 1H), 3.56 – 3.38 (m, 1H), 3.13 (dd, *J* = 14.0, 6.8 Hz, 1H), 1.17 (s, 6H).
A168	5-bromo-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-benzothiophene-2-carboxamide	395	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.54 (s, 1H), 8.22 (d, *J* = 1.9 Hz, 1H), 8.03 (d, *J* = 11.6 Hz, 1H), 7.62 (d, *J* = 11.5 Hz, 1H), 6.82 (s, 1H), 1.27 (s, 9H).
A161	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-chloro-1-benzothiophene-2-carboxamide	351	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 8.55 (s, 1H), 8.11-8.06 (m, 2H), 7.51 (d, *J* = 12.2 Hz, 1H), 6.82 (s, 1H), 1.27 (s, 9H).
A67	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{1-[(4-fluorophenyl)methyl]-1H-indol-3-yl}acetamide	422	^{1}H NMR (400 MHz,) δ 12.27 (s, 1H), 7.60 (d, *J* = 8.9 Hz, 2H), 7.51 – 7.31 (m, 2H), 7.27 (dd, *J* = 9.6, 6.0 Hz, 1H), 7.20 – 6.88 (m, 2H), 6.70 (s, 1H), 5.38 (s, 2H), 3.84 (s, 4H), 1.25 (s, 9H).
A115	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(4-chlorophenyl)acetamide	309	1H NMR (500 MHz, DMSO-d6) δ 12.32 (s, 1H), 7.41 – 7.37 (m, 2H), 7.36 – 7.32 (m, 2H), 6.72 (s, 1H), 3.74 (s, 2H), 1.25 (s, 9H).
A91	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3,4,5-trifluorophenyl)acetamide	329	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 7.24 (dd, *J* = 8.9, 6.8 Hz, 2H), 6.70 (s, 1H), 3.74 (s, 2H), 1.21 (s, 9H).
A104	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-(3-chlorophenyl)cyclopentane-1-carboxamide	363	^{1}H NMR (500 MHz, DMSO-d6) δ 11.71 (s, 1H), 7.47 (s, 1H), 7.44 – 7.19 (m, 3H), 6.71 (s, 1H), 2.75 – 2.58 (m, 2H), 1.94 (dt, *J* = 14.8, 7.1 Hz, 2H), 1.81 – 1.53 (m, 4H), 1.21 (s, 9H).
A134	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1H-indazole-6-carboxamide	301	1H NMR (400 MHz, DMSO-d6) δ 13.51 (s, 1H), 12.64 (s, 1H), 8.36 (s, 1H), 8.19 (s, 1H), 7.88 (d, *J* = 8.7 Hz, 1H), 7.79 (d, *J* = 9.2 Hz, 1H), 6.82 (s, 1H), 1.31 (s, 9H).
A100	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3,4-dichlorophenyl)acetamide	343	^{1}H NMR (500 MHz,) δ 12.33 (s, 1H), 7.69 – 7.45 (m, 2H), 7.31 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.74 (s, 1H), 3.78 (s, 2H), 1.25 (s, 9H).
A132	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3,4-dihydro-2H-1-benzopyran-6-carboxamide	317	1H NMR (400 MHz, DMSO-d6) δ 12.26 (s, 1H), 7.93 (s, 1H), 7.84 (d, *J* = 11.4 Hz, 1H), 6.82 (d, *J* = 8.7 Hz, 1H), 6.76 (s, 1H), 4.41 – 4.13 (m, 2H), 2.80 (t, *J* = 7.0 Hz, 2H), 1.95 (dt, *J* = 14.1, 7.1 Hz, 2H), 1.29, (s, 9H).
A71	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-	379	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.12 – 7.92 (m, 2H), 7.72 (s, 1H), 7.37 (d, *J* = 10.6 Hz, 1H), 6.71 (s, 1H), 4.33 (q, *J* = 7.5 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H), 1.21 (s, 9H).

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	yl)propanamide		
A143	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4,5-dimethylthiophene-2-carboxamide	295	1H NMR (400 MHz, DMSO-d6) δ 12.42 (s, 1H), 8.01 (s, 1H), 6.77 (s, 1H), 2.36 (s, 3H), 2.12 (s, 3H), 1.29 (s, 9H).
A131	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-methylthiophene-3-carboxamide	281	1H NMR (400 MHz, DMSO-d6) δ 12.30 (s, 1H), 8.38 (s, 1H), 7.41 (s, 1H), 6.78 (s, 1H), 2.47 (d, *J* = 1.2 Hz, 3H), 1.29 (s, 9H).
A125b	(2S)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)oxolane-2-carboxamide	255	
A124	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)oxane-4-carboxamide	269	
A133	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5,6,7,8-tetrahydronaphthalene-2-carboxamide	315	
A135	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1H-indazole-5-carboxamide	301	
A136	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1,3-benzoxazole-5-carboxamide	302	
A137	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3,4-dihydro-2H-1,4-benzoxazine-7-carboxamide	318	
A123	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2,3-dihydro-1H-indene-2-carboxamide	301	
A122	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1,2,3,4-tetrahydronaphthalene-2-carboxamide	315	
A121	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)cyclopent-1-ene-1-carboxamide	251	
A120	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)cyclohex-1-ene-1-carboxamide	265	
A119	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)oxolane-3-carboxamide	255	
A138	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)pyridazine-4-carboxamide	263	
A139	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)pyridazine-	263	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	3-carboxamide		
A140	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1H-1,2,4-triazole-5-carboxamide	252	
C1	*N*-(4-ethyl-1,3-thiazol-2-yl)-5-methylthiophene-3-carboxamide	253	
C2	*N*-(4-cyclopropyl-1,3-thiazol-2-yl)-5-methylthiophene-3-carboxamide	265	
C3	5-methyl-*N*-[4-(propan-2-yl)-1,3-thiazol-2-yl]thiophene-3-carboxamide	267	
A141	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-methylthiophene-2-carboxamide	281	
A142	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4-methylthiophene-2-carboxamide	281	
A144	5-methyl-*N*-[4-(trifluoromethyl)-1,3-thiazol-2-yl]thiophene-2-carboxamide	293	
A147	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-cyanobenzamide	286	
A148	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-(propan-2-yl)benzamide	303	
A149	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-(pyrrolidin-1-yl)benzamide	330	
A150	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-(morpholin-4-ylmethyl)benzamide	360	
A151	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-methoxybenzamide	291	
A118	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-cyclohexylacetamide	281	
A117	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(2-chlorophenyl)acetamide	309	
A116	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-chlorophenyl)acetamid	309	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	e		
A152	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4,5,6,7-tetrahydro-2-benzothiophene-1-carboxamide	321	
A153	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-benzothiophene-3-carboxamide	317	
A114	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide	315	
A113	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-methyl-2-phenylpropanamide	303	
A112b	(2R)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-phenylpropanamide	289	
A112a	(2S)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-phenylpropanamide	289	
A111	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-cyanophenyl)acetamide	300	
A110	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[3-(trifluoromethyl)phenyl]acetamide	343	
A109	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-methoxyphenyl)acetamide	305	
A108	2-(3-bromophenyl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	353	
A107	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-phenylpropanamide	289	
A190	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-chloro-4-methoxybenzamide	325	
A106	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-phenylacetamide	275	
A105	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-chlorophenyl)-2-methylpropanamide	337	
A103	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-(3-chlorophenyl)cyclopropane-1-carboxamide	335	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A102	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3,5-dichlorophenyl)acetamide	343	
A101	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3,4-dichlorophenyl)-2-methylpropanamide	371	
A99	2-(1-benzothiophen-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	331	
C4	4-*tert*-butyl-*N*-(5-methylthiophen-3-yl)-1,3-thiazole-2-carboxamide	281	
A98a	(2*R*)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-phenylbutanamide	303	
A97	ethyl 3-{2-[2-(3,5-dichlorophenyl)acetamido]-1,3-thiazol-4-yl}-3-methylbutanoate	415	
A95	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-cyclopentylacetamide	267	
A94	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(naphthalen-2-yl)acetamide	325	
A93	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(naphthalen-1-yl)acetamide	325	
A92	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-chloro-5-fluorophenyl)acetamide	327	
A90	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(pyridin-3-yl)acetamide	276	
A89	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[3-chloro-5-(trifluoromethyl)phenyl]acetamide	377	
A88	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-methanesulfonylphenyl)acetamide	353	
A87a	(2*R*)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3-chlorophenyl)-2-hydroxyacetamide	325	
A86	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-	309	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	cyclohexyl-2-methylpropanamide		
A85	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(3,5-dimethylphenyl)acetamide	303	
A84	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(oxan-4-yl)acetamide	283	
A155	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(morpholin-4-yl)acetamide	284	
A156	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(piperidin-1-yl)acetamide	282	
A157	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1H-indol-1-yl)acetamide	314	
A158	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1H-indazol-1-yl)acetamide	315	
C5	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(cyclohexyloxy)acetamide	297	
A160	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2,3,4,5-tetrahydro-1,4-benzoxazepine-4-carboxamide	332	
A83	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-yl)acetamide	365	
A82	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1H-indol-3-yl)acetamide	314	
A81	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-cycloheptylacetamide	295	
A80	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-methyl-1-benzothiophen-3-yl)acetamide	345	
A79	2-(5-bromo-1-benzothiophen-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	409	
A78	2-(1-benzothiophen-2-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	331	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A77	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1H-indazol-6-yl)acetamide	315	
A162	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-chloro-3-methyl-1-benzothiophene-2-carboxamide	365	
A163	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-6-chloro-1-benzothiophene-2-carboxamide	351	
A164	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4-chloro-1-benzothiophene-2-carboxamide	351	
A165	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-chloro-1-benzothiophene-2-carboxamide	351	
A167	*N*-(4-(*tert*-butyl)thiazol-2-yl)-7-chlorobenzo[b]thiophene-2-carboxamide	351	
C6	*N*-(4-benzyl-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-yl)acetamide	399	
A68	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1-methyl-1H-indol-3-yl)acetamide	328	
A65	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-yl)-4-methylpentanamide	421	
A64	3-(1-benzothiophen-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)propanamide	345	
A63	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(1,2,3,4-tetrahydronaphthalen-1-yl)acetamide	329	
A62	2-(1-benzofuran-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	315	
C7	2-(1-benzothiophen-3-yl)-*N*-[(4-*tert*-butyl-1,3-thiazol-2-yl)methyl]acetamide	345	
A180	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-	301	1H NMR (400MHz, DMSO-d6) δ 12.82 (br s, 1H), 8.10 (br s, 1H), 7.84 (d, J=7.7 Hz, 1H),

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	benzofuran-2-carboxamide		7.72 (d, J=8.4 Hz, 1H), 7.52 (br t, J=7.7 Hz, 1H), 7.37 (t, J=7.5 Hz, 1H), 6.85 (br s, 1H), 1.31 (s, 9H).
A181	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-methyl-1H-indole-2-carboxamide	314	1H NMR (400MHz, DMSO-d6) δ 12.56 (s, 1H), 7.68 (d, J=7.9 Hz, 1H), 7.64 (s, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.34 (t, J=7.7 Hz, 1H), 7.14 (t, J=7.4 Hz, 1H), 6.82 (s, 1H), 4.05 (s, 3H), 1.31 (s, 9H).
A191	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-(trifluoromethyl)-4,5,6,7-tetrahydro-1-benzothiophene-2-carboxamide	389	1H NMR (400MHz, DMSO-d6) δ 12.53 (s, 1H), 8.02 (s, 1H), 6.79 (s, 1H), 3.04 - 2.74 (m, 4H), 2.69 - 2.57 (m, 1H), 2.16 (br d, J=13.1 Hz, 1H), 1.70 (dq, J=5.6, 12.1 Hz, 1H), 1.29 (s, 9H).
A60	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(7-methyl-1-benzothiophen-3-yl)acetamide	345	1H NMR (400MHz, DCM-d1) δ 9.91 (br s, 1H), 7.63 (d, J=8.0 Hz, 1H), 7.53 (s, 1H), 7.36 (t, J=7.6 Hz, 1H), 7.22 (d, J=7.2 Hz, 1H), 6.54 (s, 1H), 4.08 (s, 2H), 2.58 (s, 3H), 1.25 (s, 9H).
A59	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(6-methyl-1-benzothiophen-3-yl)acetamide	345	1H NMR (400MHz, DMSO-d6) δ 12.41 (s, 1H), 7.79 - 7.73 (m, 2H), 7.51 (s, 1H), 7.24 (d, J=8.2 Hz, 1H), 6.73 (s, 1H), 3.99 (s, 2H), 2.42 (s, 3H), 1.26 (s, 9H).
A57	2-(1-benzyl-5-chloro-1H-indol-3-yl)-*N*-[4-(1-methylcyclopropyl)-1,3-thiazol-2-yl]acetamide	436	
A56	2-(1-benzyl-5-chloro-1H-indol-3-yl)-*N*-[4-(2-methylbutan-2-yl)-1,3-thiazol-2-yl]acetamide	452	
A55	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-chlorophenyl)methyl]-1*H*-indol-3-yl}acetamide	472	
A54	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(3-chlorophenyl)methyl]-1*H*-indol-3-yl}acetamide	472	
A53	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(4-chlorophenyl)methyl]-1*H*-indol-3-yl}acetamide	472	
A52	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(cyclohexylmethyl)-1*H*-indol-3-yl]acetamide	444	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A51	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(propan-2-yl)-1*H*-indol-3-yl]acetamide	390	
A50	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(pyridin-2-ylmethyl)-1*H*-indol-3-yl]acetamide	439	
A49	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(pyridin-3-ylmethyl)-1*H*-indol-3-yl]acetamide	439	
A48	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(pyridin-4-ylmethyl)-1*H*-indol-3-yl]acetamide	439	
A47	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(1-phenylethyl)-1*H*-indol-3-yl]acetamide	452	
A46	2-(1-benzoyl-5-chloro-1H-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	452	
C8	2-(5-chloro-1-benzothiophen-3-yl)-*N*-[4-(2,2-dimethylpropyl)-1,3-thiazol-2-yl]acetamide	379	1H NMR (400MHz, DMSO-d6) δ 12.36 (s, 1H), 7.80 (d, J=7.9 Hz, 1H), 7.54 (s, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.11 (d, J=7.3 Hz, 1H), 6.74 (s, 1H), 4.23 (s, 2H), 2.64 (s, 3H), 1.27 (s, 9H).
A184	*N*-(4-*tert*-butyl-5-chloro-1,3-thiazol-2-yl)-2-(5-chloro-1-benzothiophen-3-yl)acetamide	399	1H NMR (400MHz, DMSO-d6) δ 12.39 (s, 1H), 8.04 (d, J=8.6 Hz, 1H), 8.00 (d, J=1.9 Hz, 1H), 7.74 (s, 1H), 7.41 (dd, J=2.0, 8.6 Hz, 1H), 6.75 (s, 1H), 4.03 (s, 2H), 2.49 - 2.48 (m, 2H), 0.91 (s, 9H).
A58	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(4-methyl-1-benzothiophen-3-yl)acetamide	345	1H NMR (400MHz, DMSO-d6) δ 12.60 (s, 1H), 8.04 (d, J=8.5 Hz, 1H), 7.97 (d, J=1.9 Hz, 1H), 7.74 (s, 1H), 7.42 (dd, J=2.0, 8.6 Hz, 1H), 4.04 (s, 2H), 1.37 (s, 9H).
A43	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(2-chlorophenyl)-1*H*-indol-3-yl]acetamide	458	
A42	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(3-chlorophenyl)-1*H*-indol-3-yl]acetamide	458	
A41	*N*-(4-*tert*-butyl-1,3-	458	

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	thiazol-2-yl)-2-[5-chloro-1-(4-chlorophenyl)-1*H*-indol-3-yl]acetamide		
A40	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(pyridin-2-yl)-1*H*-indol-3-yl]acetamide	425	
A39	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-cyclopentyl-1*H*-indol-3-yl)acetamide	416	
A36	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(2-methylpropyl)-1*H*-indol-3-yl]acetamide	404	
A35	2-{5-chloro-1-[(2-chlorophenyl)methyl]-1H-indol-3-yl}-*N*-[4-(2-methylbutan-2-yl)-1,3-thiazol-2-yl]acetamide	486	
A34	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{1-[(2-chlorophenyl)methyl]-1H-indazol-3-yl}acetamide	439	
A33	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[1-(2-chlorophenyl)ethyl]-1*H*-indol-3-yl}acetamide	486	
A187	1-benzyl-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1*H*-indole-2-carboxamide	390	
A188	1-benzyl-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1H-indole-3-carboxamide	390	
A27	2-[1-(butan-2-yl)-5-chloro-*1H*-indol-3-yl]-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	404	
A20	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(2,3-dihydro-1*H*-inden-1-yl)-1*H*-indol-3-yl]acetamide	464	
A15	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{1-[(2-chlorophenyl)methyl]-2-methyl-1*H*-indol-3-	452	

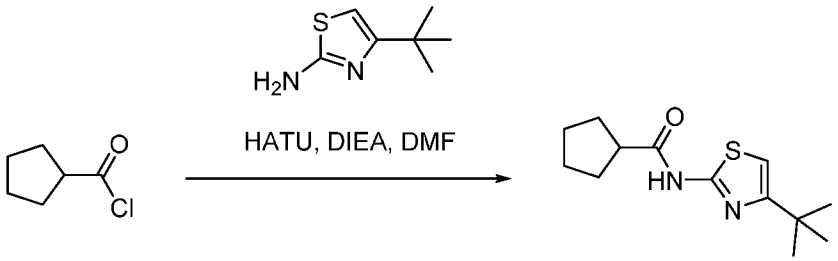
No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	yl}acetamide		
A192	2-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-*N*,5-*N*-dimethyl-1-benzothiophene-2,5-dicarboxamide	388	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.99 (s, 1H), 8.67 (s, 1H), 8.14 (br d, *J*=8.2 Hz, 1H), 8.03 (s, 1H), 7.53 (br d, *J*=8.4 Hz, 1H), 6.86 (s, 1H), 3.02 (br s, 3H), 2.96 (br s, 3H), 1.31 (s, 9H).
A186	2-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-*N*-methyl-1-benzothiophene-2,5-dicarboxamide	374	. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.98 (br s, 1H), 8.67 (br s, 1H), 8.61 (br d, *J*=4.3 Hz, 1H), 8.44 (s, 1H), 8.14 (br d, *J*=8.6 Hz, 1H), 7.94 (br d, *J*=8.4 Hz, 1H), 6.83 (br d, *J*=1.8 Hz, 1H), 2.83 (d, *J*=4.4 Hz, 3H), 1.31 (s, 9H).
A38	2-(1-benzyl-5-methoxy-1*H*-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	434	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.25 (s, 1H), 7.36 (s, 1H), 7.32 - 7.26 (m, 3H), 7.25 - 7.21 (m, 1H), 7.20 - 7.16 (m, 2H), 7.13 (d, *J*=2.4 Hz, 1H), 6.74 (dd, *J*=2.5, 8.8 Hz, 1H), 6.70 (s, 1H), 5.34 (s, 2H), 3.79 (s, 2H), 3.74 (s, 3H), 1.25 (s, 9H).
A37	2-(1-benzyl-5-bromo-1H-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	482	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.29 (s, 1H), 7.48 (s, 1H), 7.42 (d, *J*=8.8 Hz, 1H), 7.29 (d, *J*=7.5 Hz, 2H), 7.26 - 7.16 (m, 4H), 6.71 (s, 1H), 5.40 (s, 2H), 3.83 (s, 2H), 1.25 (s, 9H).
A31	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-cyanophenyl)methyl]-1H-indol-3-yl}acetamide	463	
A30	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(3-fluoropyridin-4-yl)methyl]-1*H*-indol-3-yl}acetamide	457	
A10	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(3-methylpyridin-4-yl)methyl]-1*H*-indol-3-yl}acetamide	453	
A26	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(2-phenylethyl)-1*H*-indol-3-yl]acetamide	452	
A25	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-methanesulfonylphenyl)methyl]-1*H*-indol-3-yl}acetamide	516	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.31 (s, 1H), 8.07 - 7.97 (m, 1H), 7.74 (d, *J*=1.8 Hz, 1H), 7.59 - 7.52 (m, 2H), 7.51 (s, 1H), 7.34 (d, *J*=8.8 Hz, 1H), 7.12 (dd, *J*=1.8, 8.8 Hz, 1H), 6.72 (s, 1H), 6.55 - 6.46 (m, 1H), 5.89 (s, 2H), 3.87 (s, 2H), 3.33 (s, 3H), 1.26 (s, 9H).
A2	2-{5-chloro-1-[(2-chlorophenyl)methyl]-1*H*-indol-3-yl}-*N*-[4-(2-ethoxypropan-2-yl)-1,3-thiazol-2-yl]acetamide	502	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.42 (s, 1H), 7.72 (d, *J*=1.9 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.44 (s, 1H), 7.42 (d, *J*=8.8 Hz, 1H), 7.32 (dt, *J*=1.4, 7.6 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.12 (dd, *J*=2.1, 8.8 Hz, 1H), 6.94 (s, 1H), 6.76 (d,

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
			J=6.6 Hz, 1H), 5.50 (s, 2H), 3.83 (s, 2H), 3.17 (q, *J*=7.0 Hz, 2H), 1.46 (s, 6H), 1.02 (t, *J*=7.0 Hz, 3H).
A24	2-{5-chloro-1-[(2-chlorophenyl)methyl]-1*H*-indol-3-yl}-*N*-{4-[2-(propan-2-yloxy)propan-2-yl]-1,3-thiazol-2-yl}acetamide	516	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.41 (s, 1H), 7.71 (d, *J*=1.9 Hz, 1H), 7.50 (d, *J*=7.8 Hz, 1H), 7.44 (s, 1H), 7.42 (d, *J*=8.8 Hz, 1H), 7.35 - 7.29 (m, 1H), 7.26 - 7.20 (m, 1H), 7.12 (dd, *J*=1.9, 8.8 Hz, 1H), 7.00 (s, 1H), 6.76 (d, *J*=7.2 Hz, 1H), 5.50 (s, 2H), 3.84 (s, 2H), 3.63 - 3.54 (m, 1H), 1.47 (s, 5H), 0.91 (d, *J*=6.2 Hz, 6H).
A23	2-{5-chloro-1-[(2-chlorophenyl)methyl]-1*H*-indol-3-yl}-*N*-[4-(2-methoxypropan-2-yl)-1,3-thiazol-2-yl]acetamide	488	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.41 (s, 1H), 7.72 (d, *J*=1.9 Hz, 1H), 7.51 (d, *J*=7.9 Hz, 1H), 7.44 (s, 1H), 7.42 (d, *J*=8.9 Hz, 1H), 7.32 (dt, *J*=1.2, 7.7 Hz, 1H), 7.26 - 7.21 (m, 1H), 7.13 (dd, *J*=2.1, 8.8 Hz, 1H), 6.97 (s, 1H), 6.76 (d, *J*=7.5 Hz, 1H), 5.50 (s, 2H), 3.84 (s, 2H), 2.96 (s, 3H), 1.45 (s, 6H).
A22	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(1,3-oxazol-2-ylmethyl)-1*H*-indol-3-yl]acetamide	429	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.30 (s, 1H), 8.05 (s, 1H), 7.69 (d, *J*=1.9 Hz, 1H), 7.53 - 7.39 (m, 2H), 7.30 - 7.06 (m, 1H), 6.72 (s, 1H), 5.61 (s, 2H), 3.81 (s, 3H), 1.25 (s, 9H).
A21	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(pyrimidin-2-ylmethyl)-1*H*-indol-3-yl]acetamide	440	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.29 (s, 1H), 8.74 (d, *J*=4.9 Hz, 2H), 7.68 (d, *J*=1.9 Hz, 1H), 7.47 (s, 1H), 7.41 (t, *J*=4.9 Hz, 1H), 7.34 (d, *J*=8.6 Hz, 1H), 7.08 (dd, *J*=2.0, 8.7 Hz, 1H), 6.72 (s, 1H), 5.61 (s, 2H), 3.82 (s, 2H), 1.25 (s, 9H).
C9	2-{5-chloro-1-[(2-chlorophenyl)methyl]-1*H*-indol-3-yl}-*N*-[4-(2,2-dimethylpropyl)-1,3-thiazol-2-yl]acetamide	486	
A19	2-{1-benzyl-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	405	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.29 (s, 1H), 8.26 (dd, *J*=1.1, 4.6 Hz, 1H), 8.02 (dd, *J*=1.4, 7.9 Hz, 1H), 7.52 (s, 1H), 7.33 - 7.21 (m, 5H), 7.11 (dd, *J*=4.7, 7.9 Hz, 1H), 6.71 (s, 1H), 5.46 (s, 2H), 3.85 (s, 2H), 1.25 (s, 9H).
A18	2-[1-(1,3-benzoxazol-2-ylmethyl)-5-chloro-1*H*-indol-3-yl]-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	479	. ^{1}H NMR (400MHz, CD3OD-d_4) δ = 7.68 - 7.62 (m, 2H), 7.57 - 7.53 (m, 1H), 7.50 - 7.43 (m, 2H), 7.41 - 7.31 (m, 2H), 7.16 (dd, *J*=1.9, 8.8 Hz, 1H), 6.63 (s, 1H), 5.70 (s, 2H), 3.89 (s, 2H), 1.28 (s, 9H).
A17	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(1,3-oxazol-4-ylmethyl)-1*H*-indol-3-yl]acetamide	429	
A16	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-[5-chloro-1-(1,2-oxazol-3-ylmethyl)-1*H*-indol-3-yl]acetamide	429	
A13	2-{1-benzyl-1*H*-	405	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.34 (s, 1H),

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
	pyrrolo[3,2-c]pyridin-3-yl}-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide		8.88 (s, 1H), 8.18 (d, *J*=5.7 Hz, 1H), 7.49 (s, 2H), 7.41 - 7.13 (m, 5H), 6.73 (s, 1H), 5.43 (s, 2H), 3.92 (s, 2H), 1.26 (s, 9H).
A12	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-(5-chloro-1-cyclohexyl-1*H*-indol-3-yl)acetamide	430	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.27 (s, 1H), 7.66 (d, *J*=1.9 Hz, 1H), 7.55 (d, *J*=8.8 Hz, 1H), 7.46 (s, 1H), 7.11 (dd, *J*=1.9, 8.8 Hz, 1H), 6.71 (s, 1H), 4.31 (br s, 1H), 3.81 (s, 2H), 1.95 (br d, *J*=11.1 Hz, 2H), 1.84 (br d, *J*=12.9 Hz, 2H), 1.76 - 1.65 (m, 3H), 1.49 (br d, *J*=12.9 Hz, 2H), 1.25 (s, 9H).
A11	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-methylpyridin-4-yl)methyl]-1*H*-indol-3-yl}acetamide	453	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.30 (s, 1H), 8.33 (d, *J*=5.1 Hz, 1H), 7.70 (d, *J*=1.9 Hz, 1H), 7.51 (s, 1H), 7.41 (d, *J*=8.6 Hz, 1H), 7.11 (dd, *J*=2.0, 8.7 Hz, 1H), 6.98 (s, 1H), 6.85 (d, *J*=4.7 Hz, 1H), 6.72 (s, 1H), 5.43 (s, 2H), 3.84 (s, 2H), 2.38 (s, 3H), 1.25 (s, 9H).
A9	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-chloro-6-fluorophenyl)methyl]-1*H*-indol-3-yl}acetamide	490	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.24 (s, 1H), 7.66 (d, *J*=1.8 Hz, 1H), 7.58 (d, *J*=8.9 Hz, 1H), 7.51 - 7.40 (m, 2H), 7.35 - 7.26 (m, 2H), 7.19 (dd, *J*=1.9, 8.8 Hz, 1H), 6.70 (s, 1H), 5.49 (s, 2H), 3.77 (s, 2H), 1.25 (s, 9H).
A8	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(2-chloro-4-fluorophenyl)methyl]-1*H*-indol-3-yl}acetamide	490	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.28 (s, 1H), 7.71 (d, *J*=1.8 Hz, 1H), 7.51 (dd, *J*=2.6, 8.6 Hz, 1H), 7.46 - 7.40 (m, 2H), 7.18 - 7.10 (m, 2H), 6.85 (dd, *J*=6.2, 8.6 Hz, 1H), 6.71 (s, 1H), 5.47 (s, 2H), 3.83 (s, 2H), 1.25 (s, 9H).
A189	1-benzyl-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-methyl-1*H*-pyrrole-3-carboxamide	354	^{1}H NMR (400MHz, DMSO-d_6) δ = 11.77 (s, 1H), 7.76 (d, *J*=1.8 Hz, 1H), 7.41 - 7.34 (m, 2H), 7.33 - 7.27 (m, 1H), 7.15 (d, *J*=7.3 Hz, 2H), 6.67 (s, 1H), 6.55 (s, 1H), 5.14 (s, 2H), 2.11 (s, 3H), 1.28 (s, 9H).
A7	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-{5-chloro-1-[(4-cyanophenyl)methyl]-1*H*-indol-3-yl}acetamide	463	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.30 (s, 1H), 7.78 (d, *J*=8.3 Hz, 1H), 7.70 (d, *J*=1.9 Hz, 1H), 7.53 (s, 1H), 7.43 (d, *J*=8.6 Hz, 1H), 7.31 (d, *J*=8.2 Hz, 2H), 7.11 (dd, *J*=2.0, 8.7 Hz, 1H), 6.72 (s, 1H), 5.53 (s, 2H), 3.84 (s, 2H), 1.26 (s, 9H).
A5	2-{1-benzyl-6-chloro-1*H*-pyrrolo[2,3-b]pyridin-3-yl}-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	439	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.30 (s, 1H), 8.07 (d, *J*=8.3 Hz, 1H), 7.54 (s, 1H), 7.35 - 7.22 (m, 5H), 7.19 (d, *J*=8.3 Hz, 1H), 6.71 (s, 1H), 5.41 (s, 2H), 3.85 (s, 2H), 1.25 (s, 9H).
A4	2-(1-benzyl-5-chloro-1*H*-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)propanamide	452	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.27 (s, 1H), 7.78 (d, *J*=1.9 Hz, 1H), 7.53 (s, 1H), 7.46 (d, *J*=8.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.21 (d, *J*=6.9 Hz, 2H), 7.33 (s, 1H), 7.10 (dd, *J*=2.0, 8.7 Hz, 1H), 6.72 (s, 1H), 5.41 (s, 2H), 1.52 (d, *J*=7.1 Hz, 3H), 1.25 (s, 9H).
A3	2-(1-benzyl-5-chloro-1*H*-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-phenylpropanamide	528	^{1}H NMR (400MHz, DMSO-d_6) δ = 12.23 (s, 1H), 7.85 (d, *J*=1.6 Hz, 1H), 7.56 (s, 1H), 7.41 (d, *J*=8.8 Hz, 1H), 7.31 - 7.05 (m, 12H), 6.69 (s, 1H), 5.39 (s, 2H), 4.40 (t, *J*=7.7 Hz, 1H), 3.44 (dd, *J*=8.3, 13.5 Hz, 1H), 3.13 (dd, *J*=7.4, 13.6

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
			Hz, 1H), 1.21 (s, 9H).
A1	2-{1-benzyl-6-chloro-1*H*-pyrrolo[3,2-c]pyridin-3-yl}-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	439	^{1}H NMR (400MHz, METHANOL-d_4) δ = 8.68 (s, 1H), 7.49 (s, 1H), 7.45 (s, 1H), 7.35 (br d, *J*=7.4 Hz, 3H), 7.24 (d, *J*=6.9 Hz, 2H), 6.66 (s, 1H), 5.41 (s, 2H), 3.97 (s, 2H), 1.31 (s, 9H).

Route 2: Synthesis of Compounds Via Coupling of Amino and Carboxylic Acid Chloride Starting Materials

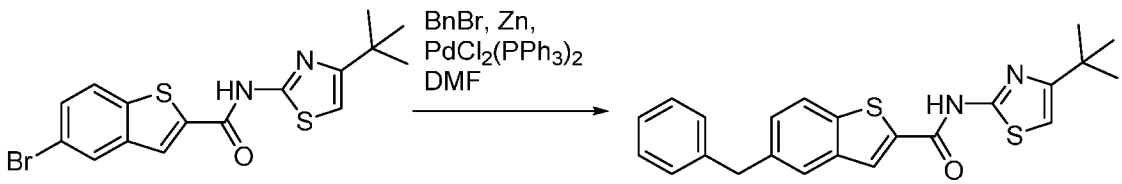


[00136] To a solution of 4-(*tert*-butyl)thiazol-2-amine (200 mg, 1.28 mmol), and DIEA (438 µL, 2.56 mmol) in THF (1.5 mL) was added cyclopentanecarbonyl chloride (172 µL, 1.41 mmol). After allowing to stand at ambient temperature for 1 h, the mixture was washed with 1 N NaOH (2X2 mL), brine (2X2 mL), dried with sodium sulfate, filtered, and concentrated. Flash chromatography (0-20% hexanes/ethyl acetate) provided *N*-(4-*tert*-butyl-1,3-thiazol-2-yl)cyclopentanecarboxamide (286 mg, 89% yield) (A127) as a colorless solid. LCMS for $C_{13}H_{20}N_2OS$, found 253 $[M+H]^+$.

[00137] The following compounds were synthesized in a similar manner:

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A126	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)cyclohexanecarboxamide	267	
A128	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-2-chlorobenzamide	295	
A129	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-3-chlorobenzamide	295	
A130	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-4-chlorobenzamide	295	

Route 3: Synthesis of 5-Substituted-Benzothiophene Carboxamide Compounds via Pd-Catalyzed Cross-Coupling



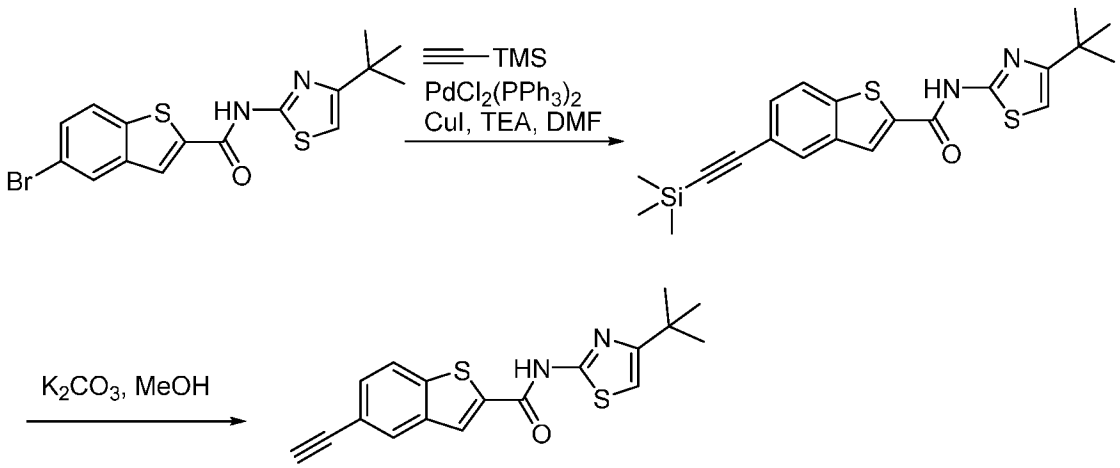
[00138] To a sealed vial with a stir bar and zinc metal (282 mg, 4.31 mmol) in DMF (1 mL) under argon was added TMS-Cl (0.090 mL, 0.71 mmol) and the reaction was then heated to 50

°C for 15 min. The reaction was allowed to cool to ambient temperature, and the solvent was removed. The zinc residue was washed with dry DMF (2X1 mL), and after two washes, the supernatant was clear. To the activated zinc, benzyl bromide (346 mg, 2.02 mmol) in DMF (2 mL) was added at once, and the mixture was stirred and heated at 55 °C for 15 minutes. A separate solution of 5-bromo-*N*-(4-(*tert*-butyl)thiazol-2-yl)benzo[b]thiophene-2-carboxamide (400 mg, 1.01 mmol) and bis(triphenylphosphine) palladium(II) dichloride (21.3 mg, 0.003 mmol) in DMF (1 mL) was sealed, and sparged with argon for 5 minutes. The organozinc was transferred under argon to the mixture of aryl iodide and catalyst, and heated to 55 °C for 1 hr. The reaction was then allowed to cool to ambient temperature, diluted with 3 ml of water, extracted with EtOAc (1X2 mL) and washed with brine (3X3 mL). The organics were combined and dried over sodium sulfate, filtered, and concentrated. The residue was first purified by flash column chromatography (0-40% ethyl acetate in hexane) followed by prep-HPLC (Mobile Phase A: H_2O, B: 0.1% formic acid in ACN; flow rate: 20 ml/min; gradient:10-95%. Column: Phenomenex Gemini (5 micron C18 110A, 150×21.20 mm 5 micron size) to afford 5-benzyl-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-1-benzothiophene-2-carboxamide (A193) as a white solid (300 mg, 73%). ^{1}H NMR (400MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.56 (br s, 1H), 7.97 (br d, *J* = 8.3 Hz, 1H), 7.84 (s, 1H), 7.39 (br d, *J* = 8.2 Hz, 1H), 7.33 - 7.26 (m, 4H), 7.23 - 7.15 (m, 1H), 6.85 (s, 1H), 4.09 (s, 2H), 1.41 - 1.22 (s, 9H). LCMS for $C_{23}H_{22}N_2OS_2$, found 407.2 [M+H$^+$].

[00139] The following compound was synthesized in a similar manner:

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A179	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-pentyl-1-benzothiophene-2-carboxamide	387	1H NMR (400MHz, ACETONITRILE-d3) δ 10.23 (br s, 1H), 8.10 (s, 1H), 7.87 (d, J=8.4 Hz, 1H), 7.77 (s, 1H), 7.37 (dd, J=1.6, 8.4 Hz, 1H), 6.69 (s, 1H), 2.77 - 2.72 (m, 2H), 1.68 (td, J=7.4, 14.9 Hz, 2H), 1.38 - 1.32 (m, 4H), 1.32 (s, 9H), 0.90 (t, J=6.8 Hz, 3H).

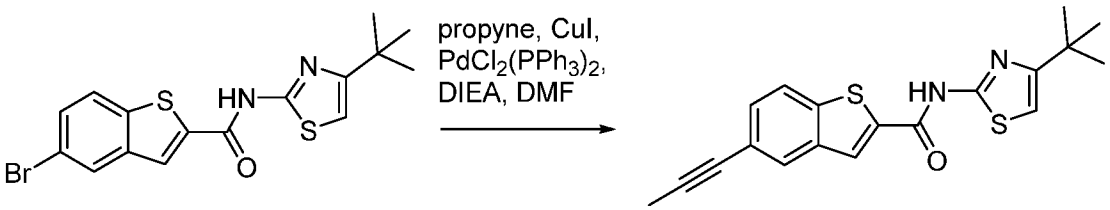
Route 4: Synthesis of Alkyne-Substituted Benzothiophene Carboxamide Compounds using a Sonogashira Coupling Reaction with a Protected Alkyne Starting Material



[00140] 5-Bromo-*N*-(4-(*tert*-butyl)thiazol-2-yl)benzo[b]thiophene-2-carboxamide (400 mg, 1.01 mmol) was dissolved in DMF (2 mL). The solution was purged with argon. To this reaction mixture was added ethynyltrimethylsilane (119 mg, 1.21 mmol), $PdCl_2(PPh_3)_2$ (35.5 mg, 50.6 µmol), copper iodide (19.3 mg, 101µmol) and triethylamine (19.3 mg, 0.10 mmol) was added. The reaction mixture was heated at 60 °C overnight under argon. After the completion of the reaction it was diluted with ethyl acetate, washed with water, brine (3X10 mL), dried over sodium sulfate, filtered, and concentrated. The residue was purified by FCC (0-40% ethyl acetate in hexane) to yield product. (350 mg, 84 %). LCMS for $C_{21}H_{24}N_2OS_2Si$, found $[M+H^+]$.

[00141] To a stirred solution of *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-((trimethylsilyl)ethynyl)benzo[b]thiophene-2-carboxamide (350 mg, 848 µmol) in methanol, potassium carbonate (1.17 g, 8.48 mmol) was added and the reaction mixture was stirred overnight at ambient temperature. After the completion the reaction mixture was diluted with water and partitioned with hexane. The aqueous layer was extracted with hexane (3X20 mL), which were combined, washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified over silica gel (0-30% ethyl acetate in hexane) to provide *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-ethynylbenzo[b]thiophene-2-carboxamide (A182) (115 mg, 40%). 1H NMR (400MHz, DMSO-d_6) δ = 13.00 (br s, 1H), 8.62 (br s, 1H), 8.15 (s, 1H), 8.11 (br d, J=8.0 Hz, 1H), 7.56 (br d, J=8.2 Hz, 1H), 6.86 (br s, 1H), 4.28 (s, 1H), 1.31 (s, 9H). LCMS for $C_{18}H_{16}N_2OS_2$, found 341.2 $[M+H^+]$.

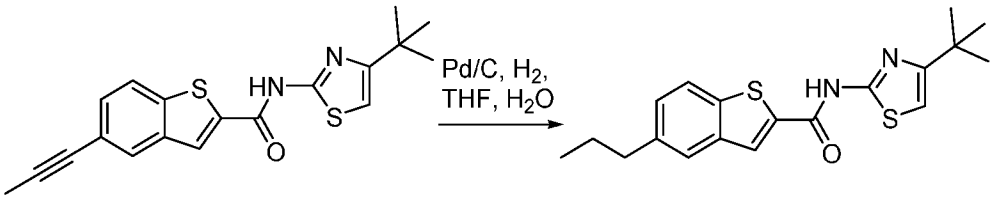
Route 5: Synthesis of Alkyne-Substituted Benzothiophene Carboxamide Compounds using a Sonogashira Coupling Reaction



[00142] To 1 mL of DMF under argon 4% propyne in DMF (40.5 mg, 1.01 mmol) was added. To this reaction mixture was added $PdCl_2(PPh_3)_2$ (35.5 mg, 50.6 µmol), copper iodide (19.3 mg, 101 µmol), DIEA (262 mg, 2.02 mmol) and 5-bromo-*N*-(4-(*tert*-butyl)thiazol-2-yl)benzo[b]thiophene-2-carboxamide (40.5 mg, 1.01 mmol) was added. The reaction mixture was heated at 60 °C for 2 hours under argon. 1 ml of 4% propyne in DMF (40.5 mg, 1.01 mmol) was added and stirred overnight. After completion of the reaction, the mixture was cooled to ambient temperature, diluted with ether and the organics were washed with brine (3×10 mL). The organics were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified over silica gel (0-40% ethyl acetate in hexane), which was further purified by prep-HPLC (Mobile Phase A: H_2O, B: 0.1% formic acid in ACN; flow rate: 20 ml/min; Gradient:10-95%. Column: Phenomenex Gemini (5 micron C18 110A, 150×21.20 mm 5 micron size) to provide *N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-(prop-1-yn-1-yl)-1-benzothiophene-2-carboxamide

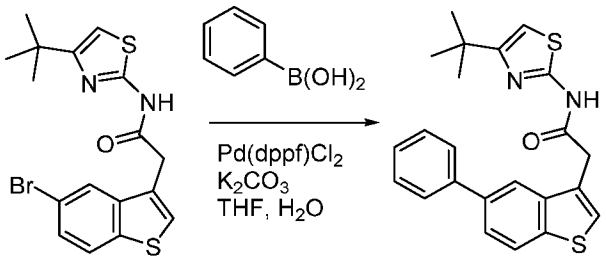
(A183) (60 mg, 17%). ^{1}H NMR (400MHz, DMSO-d_6) δ 12.97 (br s, 1H), 8.55 (br s, 1H), 8.09 - 7.98 (m, 2H), 7.47 (dd, J=1.2, 8.5 Hz, 1H), 6.82 (br d, J=4.4 Hz, 1H), 2.08 (s, 3H), 1.30 (s, 9H). LCMS for $C_{19}H_{18}N_2OS_2$, found 355.3 [M+H$^+$].

Route 6: Synthesis of Alkyl-Substituted Benzothiophene Carboxamide Compounds via Reduction



[00143] A solution of *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(prop-1-yn-1-yl)benzo[b]thiophene-2-carboxamide (45 mg, 127 µmol) and Pd/C (0.675 mg, 6.35 µmol) in 1:1 THF:water was stirred under hydrogen for 4 hours. After the completion of the reaction, the mixture was filtered through celite and concentrated. The residue was further purified by Prep-HPLC (Mobile Phase A: H_2O, B: 0.1% formic acid in ACN; Flow rate: 20 ml/min; Gradient:10-95%. Column: Phenomenex Gemini (5 micron C18 110A, 150×21.20 mm 5 micron size) to obtain *N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-propyl-1-benzothiophene-2-carboxamide (A185) (18 mg, 39.6 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (br s, 1H), 8.54 (br s, 1H), 7.96 (d, J = 8.3 Hz, 1H), 7.77 (s, 1H), 7.37 (dd, J = 1.2, 8.3 Hz, 1H), 6.83 (br s, 1H), 2.70 (t, J = 7.6 Hz, 2H), 1.66 (qd, J = 7.4, 14.9 Hz, 2H), 1.31 (s, 9H), 0.92 (t, J = 7.3 Hz, 3H). LCMS for $C_{19}H_{22}N_2OS_2$, found 359.3.

Route 7: Synthesis of Substituted-Benzothiophene Carboxamide Compounds Via Suzuki Coupling



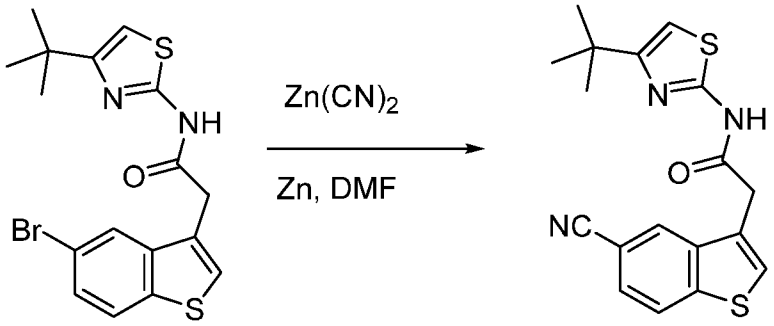
[00144] To 2-(5-bromobenzo[b]thiophen-3-yl)-*N*-(4-(*tert*-butyl)thiazol-2-yl)acetamide (20.0 mg, 0.049 mmol) in THF (0.2 mL) and water (0.1 mL) was added phenylboronic acid (9.0 mg, 0.074 mmol), potassium carbonate (24 mg, 0.147 mmol), and Pd(dppf)Cl_2 (11 mg, 0.015 mmol). The reaction mixture was heated to 80 °C for 2 h then purified directly by FCC (0-40% hexanes/ethyl acetate) to provide *N*-(4-(*tert*-butyl)thiazol-2-yl)-2-(5-phenylbenzo[b]thiophen-3-yl)acetamide (A75) (17 mg, 42 mmol) as an off-white solid. MS(EI) for $C_{23}H_{22}N_2OS_2$, found 407 [M+H]$^+$.

[00145] The following compounds were synthesized in a similar manner:

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)

A172	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(2-chlorophenyl)benzo[b]thiophene-2-carboxamide	427	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.63 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 1.7 Hz, 1H), 7.73 – 7.31 (m, 5H), 6.82 (s, 1H), 1.27 (s, 9H).
A169	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-phenyl-1-benzothiophene-2-carboxamide	393	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.95 (s, 1H), 8.64 (s, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.90 – 7.68 (m, 3H), 7.58 – 7.44 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 6.82 (s, 1H), 1.28 (s, 9H).
A174	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(4-chlorophenyl)benzo[b]thiophene-2-carboxamide	427	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 2H), 8.64 (s, 1H), 8.23 (d, *J* = 1.8 Hz, 1H), 8.13 (s, 1H), 7.85 – 7.67 (m, 3H), 7.67 – 7.44 (m, 2H), 6.82 (s, 1H), 1.28 (s, 9H).
A176	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(cyclohex-1-en-1-yl)benzo[b]thiophene-2-carboxamide	397	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.88 (s, 1H), 8.55 (s, 1H), 7.95 (d, *J* = 9.4 Hz, 1H), 7.87 (s, 1H), 7.57 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.81 (s, 1H), 6.23 (s, 1H), 2.44 – 2.39 (m, 2H), 2.33 – 2.10 (m, 2H), 1.91 – 1.68 (m, 2H), 1.68 – 1.49 (m, 2H), 1.27 (s, 9H).
A175	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(pyridin-3-yl)benzo[b]thiophene-2-carboxamide	394	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.98 (s, 1H), 8.98 (s, 1H), 8.62 (d, *J* = 30.7 Hz, 1H), 8.62 – 8.45 (m, 1H), 8.31 (s, 1H), 8.18 (s, 1H), 7.85 (d, *J* = 9.5 Hz, 1H), 7.50 (dd, *J* = 8.0, 5.7 Hz, 1H), 6.82 (s, 1H), 1.29 (s, 6H).
A173	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(3-chlorophenyl)benzo[b]thiophene-2-carboxamide	427	^{1}H NMR (400 MHz, DMSO-d_6) δ 12.97 (s, 1H), 8.64 (s, 1H), 8.27 (s, 1H), 8.14 (d, *J* = 9.1 Hz, 1H), 7.81 (s, 2H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.32 (m, 2H), 6.83 (s, 1H), 1.28 (s, 9H).
A177	*N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(cyclopent-1-en-1-yl)benzo[b]thiophene-2-carboxamide	383	1H NMR (400 MHz, DMSO-d6) δ 12.89 (s, 1H), 8.55 (s, 1H), 7.97 (d, J = 11.5 Hz, 1H), 7.86 (s, 1H), 7.69 (d, J = 9.8 Hz, 1H), 6.82 (s, 1H), 6.37 (s, 1H), 2.90 – 2.62 (m, 2H), 2.54 – 2.48 (m, 2H), 2.14 – 1.76 (m, 2H), 1.27 (s, 9H).

Route 8: Synthesis of Cyano-Substituted Benzothiophene Carboxamide Compounds

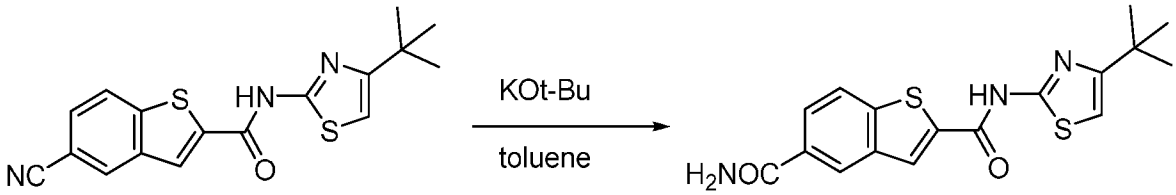


[00146] To 2-(5-bromobenzo[b]thiophen-3-yl)-*N*-(4-(*tert*-butyl)thiazol-2-yl)acetamide (20.0 mg, 0.049 mmol) in DMF (0.2 mL) was added zinc cyanide (8.7 mg, 0.074 mmol), Pd(dppf)Cl_2 (11 mg, 0.015 mmol) and zinc dust (2.9 mg, 0.045 mmol). The reaction mixture was heated to 80 °C for 2 h then purified directly by FCC (0-40% hexanes/ethyl acetate) to provide *N*-(4-(*tert*-butyl)thiazol-2-yl)-2-(5-cyanobenzo[b]thiophen-3-yl)acetamide (A74) (8.0 mg, 46%) as an off-white solid. MS(EI) for $C_{18}H_{17}N_3OS_2$, found 356 $[M+H]^+$.

[00147] The following compounds were synthesized in a similar manner from the corresponding aryl chloride starting material:

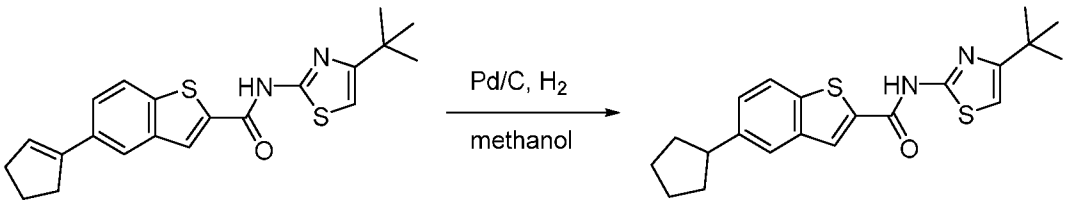
No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A170	*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)-5-cyano-1-benzothiophene-2-carboxamide	342	^{1}H NMR (400 MHz, DMSO-d_6) δ 13.05 (s, 1H), 8.68 (s, 1H), 8.57 (s, 1H), 8.29 (d, *J* = 10.7 Hz, 1H), 7.83 (d, *J* = 11.1 Hz, 1H), 6.85 (s, 1H), 1.27 (s, 9H).
A28	2-(1-benzyl-5-cyano-1H-indol-3-yl)-*N*-(4-*tert*-butyl-1,3-thiazol-2-yl)acetamide	429	

Route 9: Synthesis of Amido-Substituted Benzothiophene Carboxamide Compounds via Reduction



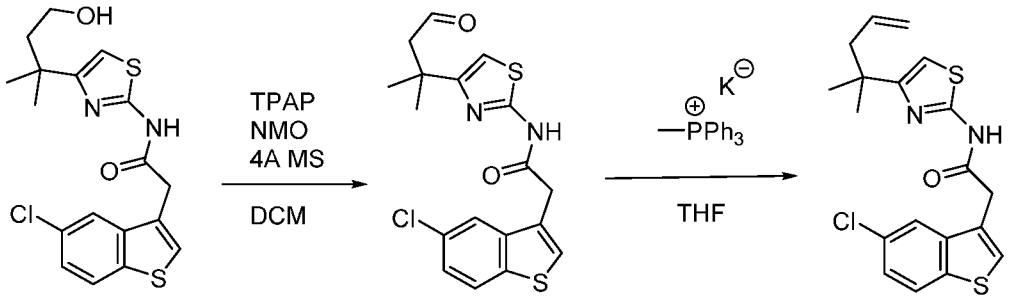
[00148] To *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-cyanobenzo[b]thiophene-2-carboxamide (20 mg, 0.059 mmol) was added toluene (100 uL), followed by potassium *tert*-butoxide (20 mg, 0.176 mmol). After stirring for 72 h the mixture was diluted with citric acid (conc., aq), extracted with DCM (3X), dried with sodium sulfate, filtered, and concentrated. FCC (0-100% hexanes/ethyl acetate) provided N^2-(4-(*tert*-butyl)thiazol-2-yl)benzo[b]thiophene-2,5-dicarboxamide (A171) (6 mg, 28%) as a colorless solid. MS(EI) for $C_{17}H_{17}N_3O_2S_2$, found 360 $[M+H]^+$.

Route 10: Synthesis of Cycloalkyl-Substituted Benzothiophene Carboxamide Compounds via Reduction



[00149] To *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-(cyclopent-1-en-1-yl)benzo[b]thiophene-2-carboxamide (20 mg, 0.052 mmol) was added methanol (3 mL) and Pd/C (10%, 20 mg). A hydrogen atmosphere was established (balloon) and the mixture was stirred at ambient temperature for 1 h then filtered and concentrated to provide *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-cyclopentylbenzo[b]thiophene-2-carboxamide (A178) (20 mg, quant.) as a colorless solid. MS(EI) for $C_{21}H_{24}N_2OS_2$, found 385 $[M+H]^+$.

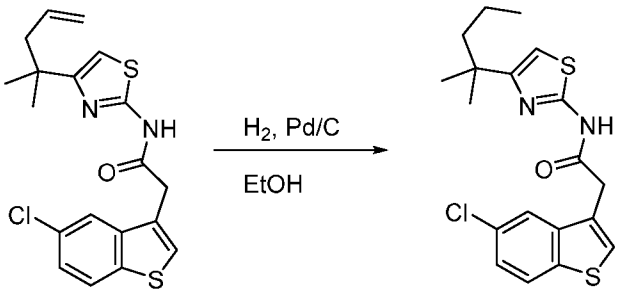
Route 11: Synthesis of Carboxamide Compounds with Alkenyl Substitution at the Thiazole Group



[00150] To 2-(5-chlorobenzo[b]thiophen-3-yl)-*N*-(4-(4-hydroxy-2-methylbutan-2-yl)thiazol-2-yl)acetamide (250 mg, 0.635 mmol) in DCM (2.5 mL) was added 4Å molecular sieves (600 mg) and NMO (149 mg, 1.27 mmol), followed by TPAP (15 mg., cat). The mixture was stirred at ambient temperature for 1 h then an additional aliquot of NMO (149 mg, 1.27 mmol), 4Å molecular sieves (600 mg), and TPAP (15 mg) was added. After an additional 2 h the reaction mixture was filtered through celite and carried forward without further purification. MS(EI) for $C_{18}H_{17}ClN_2O_2S_2$, found 393 $[M+H]^+$.

[00151] To the aldehyde (92 mg, 0.234 mmol) in THF (2 mL) at 5 °C was added a freshly prepared solution of Wittig reagent (2.0 mL of a 0.5 M solution; Wittig reagent was prepared by mixing methyltriphenylphospohnium iodide (2 g, 4.92 mmol), potassium *tert*-butoxide (0.441 g, 3.93 mmol), and THF (7.9 mL) at 5 °C). The reaction mixture was stirred at 0-5 °C for 15 min then quenched with citric acid (aq, sat.), extracted with DCM (2X), dried with sodium sulfate, filtered, and concentrated. FCC (0-40% hexanes/ethyl acetate) provided 2-(5-chloro-1-benzothiophen-3-yl)-*N*-[4-(2-methylpent-4-en-2-yl)-1,3-thiazol-2-yl]acetamide (A70) as a colorless solid. MS(EI) for $C_{19}H_{19}ClN_2OS_2$, found 391 $[M+H]^+$.

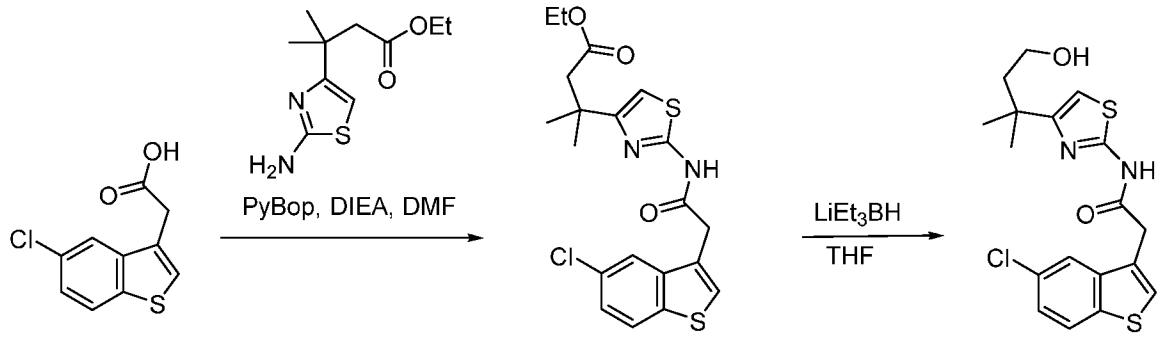
Route 12: Synthesis of Carboxamide Compounds with Alkyl Substitution at the Thiazole Group



[00152] To 2-(5-chloro-1-benzothiophen-3-yl)-*N*-[4-(2-methylpent-4-en-2-yl)-1,3-thiazol-2-yl]acetamide (A69) (12.0 mg, 30.7 mmol) in ethanol (3 mL) was added Pd/C (10%, 10 mg) and a hydrogen atmosphere was established (balloon). The reaction mixture was stirred for 30 min then diluted with DCM (3 mL), filtered, and concentrated to provide 2-(5-chloro-1-benzothiophen-3-yl)-*N*-[4-(2-methylpentan-2-yl)-1,3-thiazol-2-yl]acetamide (11 mg, quant.) as a

colorless solid. MS(EI) for $C_{19}H_{21}ClN_2OS_2$, found 393 $[M+H]^+$.

Route 13: Synthesis of Carboxamide Compounds with Hydroxyalkyl-Substitution at the Thiazole Group



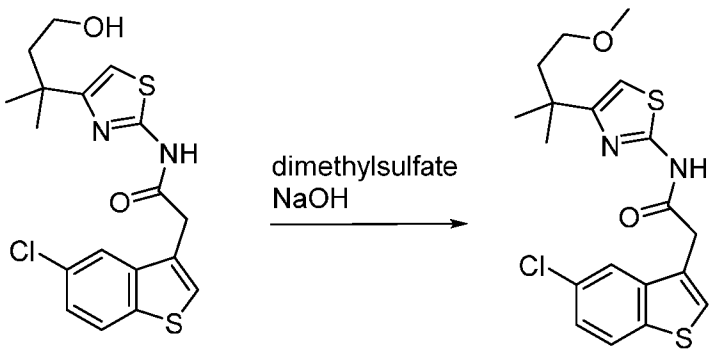
[00153] To the amine (1.07 g, 4.69 mmol) and acid (4.69 mmol, 1.065 g) in DMF (10 mL) was added PyBOP (5.16 mmol, 2.68 g) followed by DIEA (11.73 mmol, 2.00 mL). After stirring at ambient temperature for 16 h the mixture was quenched with sodium bicarbonate (sat., 20 mL), extracted with ethyl acetate (3X20 mL), washed with brine (10 mL), dried with sodium sulfate, filtered, and concentrated. The product was purified by FCC (0-40% hexanes/ethyl acetate) to provide ethyl 3-(2-(2-(5-chlorobenzo[b]thiophen-3-yl)acetamido)thiazol-4-yl)-3-methylbutanoate as an off-white amorphous solid (0.78 g, 1.79 mmol, 38%). MS(EI) for $C_{20}H_{21}ClN_2O_3S_2$, found 437 $[M+H]^+$.

[00154] To the ester (0.76 g, 1.74 mmol) in THF (0.4 mL) at -78 °C was added Superhydride (1 M solution in THF, 15.0 mL, 15 mmol) was added. After warming to ambient temp and stirring for 4 h the reaction was complete.The mixture was cooled to 5 °C, quenched with brine, extracted with ethyl acetate (3X), dried with sodium sulfate, filtered, and concentrated. FCC (0-60% hexanes/ethyl acetate) provided 2-(5-chlorobenzo[*b*]thiophen-3-yl)-*N*-(4-(4-hydroxy-2-methylbutan-2-yl)thiazol-2-yl)acetamide (A73) (0.68 g, 99%) as a colorless amorphous solid. MS(EI) for $C_{18}H_{19}ClN_2O_2S_2$, found 395 $[M+H]^+$.

[00155] The following compound was synthesized in a similar manner:

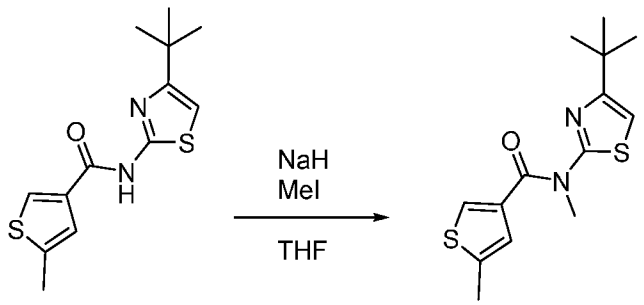
No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A96	2-(3,5-dichlorophenyl)-*N*-[4-(4-hydroxy-2-methylbutan-2-yl)-1,3-thiazol-2-yl]acetamide	373	

Route 14: Synthesis of Carboxamide Compounds with Ether Substituted at the Thiazole Group



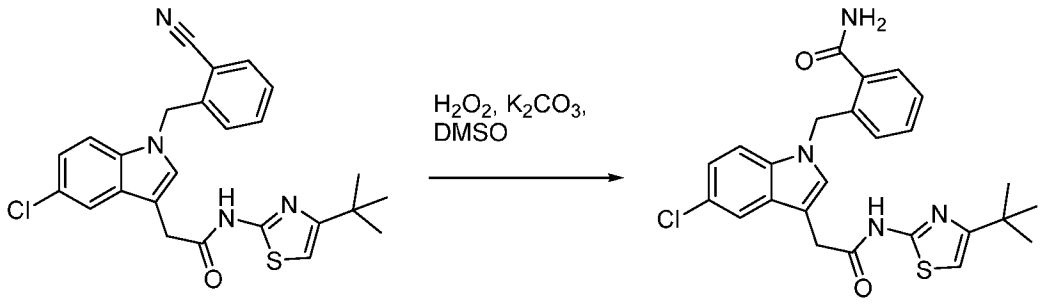
[00156] To 2-(5-chlorobenzo[b]thiophen-3-yl)-*N*-(4-(4-hydroxy-2-methylbutan-2-yl)thiazol-2-yl)acetamide (50 mg, 0.127 mmol) in 0.5 mL acetone was cooled to 5 °C and dimethylsulfate (88 uL, 0.929 mmol) was added followed by sodium hydroxide (32 mg, 0.8 mmol) and water (79 µL, 4.4 mmol). After 10 min the mixture was diluted with sat. sodium bicarbonate, extracted with DCM (3X), dried with sodium sulfate, filtered, and concentrated. FCC (0-60% hexanes/ethyl acetate) provided 2-(5-chlorobenzo[b]thiophen-3-yl)-*N*-(4-(4-methoxy-2-methylbutan-2-yl)thiazol-2-yl)acetamide (A72) (11 mg, 21%) as a colorless solid. MS(EI) for $C_{19}H_{21}ClN_2O_2S_2$, found 409 $[M+H]^+$.

Route 15: Synthesis of Methyl-Substituted Carboxamide Compounds



[00157] To *N*-(4-(*tert*-butyl)thiazol-2-yl)-5-methylthiophene-3-carboxamide (60 mg, 0.214 mmol) in THF (1 mL) at ambient temperature was added NaH (16.4 mg of a 60% dispersion in mineral oil, 0.428 mmol). After stirring for 10 min, MeI (0.428 mmol, 27 uL) was added. After stirring overnight the reaction was heated to 40 °C for 4 h then quenched with citric acid (sat., 5 mL), extracted with DCM (2X5 mL), dried with sodium sulfate, filtered, and concentrated. FCC (0-30% hexanes/ethyl acetate) provided the crude product. Further purification by washing with sodium bicarbonate (sat., 2X10 mL) provided *N*-(4-(*tert*-butyl)thiazol-2-yl)-N,5-dimethylthiophene-3-carboxamide (11.0 mg, 17%) (A154) as a colorless solid. LCMS for $C_{14}H_{14}N_2OS_2$, found 295 $[M+H]^+$.

Route 16: Synthesis of Benzamide-Substituted Carboxamide Compounds

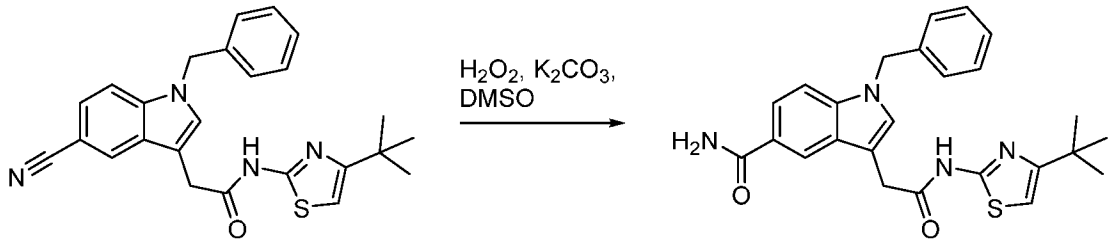


[00158] To the nitrile (200 mg, 0.432 mmol) in 2 mL of DMSO was added potassium carbonate (298 mg, 2.16 mmol) followed by H_2O_2 (0.2 mL, 30%) and the reaction mixture was stirred at ambient temperature overnight. Water (10 mL) was added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and 2-((3-(2-((4-(*tert*-butyl)thiazol-2-yl)amino)-2-oxoethyl)-5-chloro-1H-indol-1-yl)methyl)benzamide (143mg, 68.8% yield) (A32) was purified by flash chromatography. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.47 - 12.09 (s, 1H), 7.99 (s, 1H), 7.69 (d, *J*=1.9 Hz, 1H), 7.55 (s, 1H), 7.53 - 7.50 (m, 1H), 7.48 (s, 1H), 7.39 (d, *J*=8.8 Hz, 1H), 7.34 - 7.26 (m, 2H), 7.08 (dd, *J*=1.9, 8.6 Hz, 1H), 6.77 - 6.72 (m, 1H), 6.69 (s, 1H), 5.59 (s, 2H), 3.81 (s, 2H), 1.25 (s, 9H). LCMS: calc. $[M+H]^+$=481.1; Found 481.4.

[00159] The following compound was synthesized in a similar manner:

No.	IUPAC	[M+H]+	^{1}H NMR (DMSO-d_6)
A6	4-[(3-{[(4-*tert*-butyl-1,3-thiazol-2-yl)carbamoyl]methyl}-5-chloro-1*H*-indol-1-yl)methyl]benzamide	481	

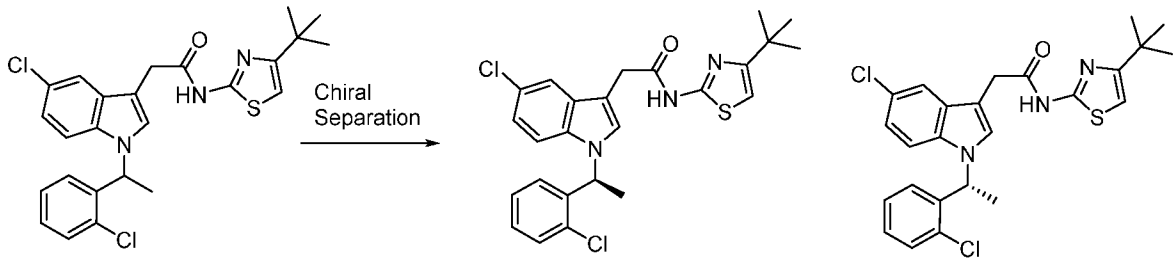
Route 17: Synthesis of Amido-Substituted Carboxamide Compounds



[00160] To a solution of starting material (100 mg, 0.233 mmol) in 1 mL of DMSO was added potassium carbonate (161 mg, 1.17 mmol) followed by adding 0.1 mL of H_2O_2 (30%) and the reaction mixture was stirred at ambient temperature overnight. 10 mL of water was added to the reaction mixture and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography and prep-HPLC to provide 1-benzyl-3-(2-((4-(*tert*-butyl)thiazol-2-yl)amino)-2-oxoethyl)-1*H*-indole-5-carboxamide (64mg, 61.4% yield) (A29) as an off-white solid. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.33 (s, 1H), 8.24 (s, 1H), 7.80 (br s, 1H), 7.66 (dd, *J*=1.3, 8.6 Hz, 1H), 7.52 - 7.42 (m, 2H), 7.36 - 7.17 (m, 5H), 7.12 (br s, 1H), 6.71 (s,

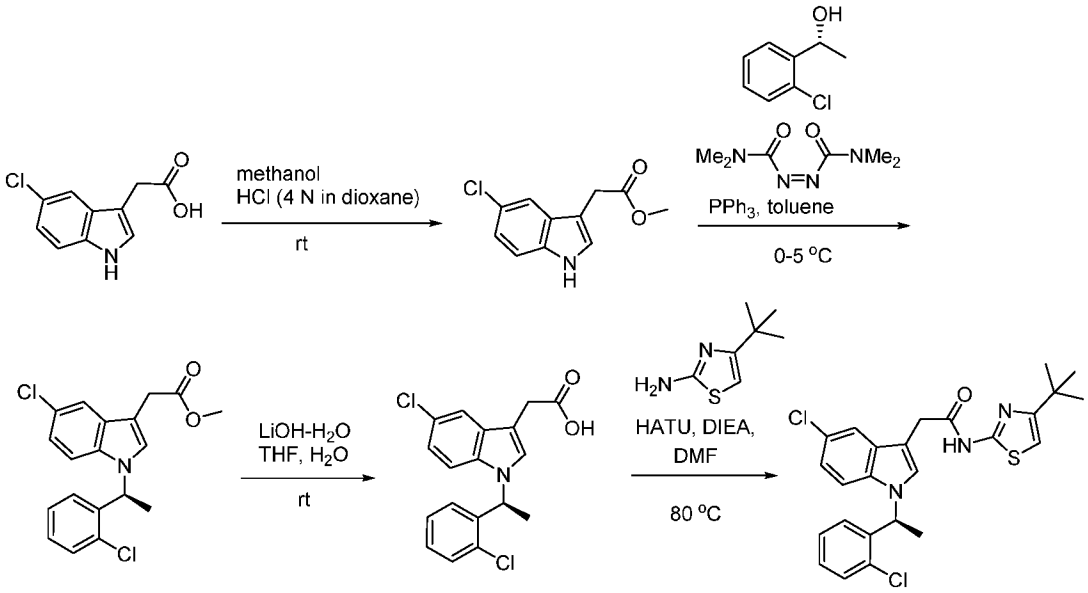
1H), 5.43 (s, 2H), 3.88 (s, 2H), 1.26 (s, 9H). LCMS: calc. $[M+H]^+$=447.2; found 447.3.

Route 18: Separation of Enantiomeric Compounds



[00161] Chiral separation of A33 was carried using chiral HPLC. Column: Chiralcel OJ SFC 250X20 mm, 10 micron. Mobile Phase: 70% CO_2/30% methanol containing 20 mM ammonia. Flow Rate: 70 mL/min. Sample concentration: 11 mg/mL. Injection Volume: 0.25 mL. A total of 100 mg of A33 was processed to provided 41.4 mg of A33a and 41.8 mg of A33b. Absolute configuration was assigned by de novo synthesis of A33.

Route 19: De Novo Synthesis of A33



[00162] To 2-(5-chloro-1*H*-indol-3-yl)acetic acid (5.00 g, 23.9 mmol) in methanol (12.8 mL) was added HCl (4 N in dioxane, 47.7 mmol, 11.9 mL). The mixture was heated to 40 °C for 48 h then concentrated to a solid, washed with saturated sodium bicarbonate (50 mL), water (50 mL), and filtered to provide methyl 2-(5-chloro-1*H*-indol-3-yl)acetate (4.61 g, 86%) as a pale red oil. LRMS (ESI): calcd. for $C_{11}H_{10}ClNO_2$: 223 $[M+H]^+$; found 224.

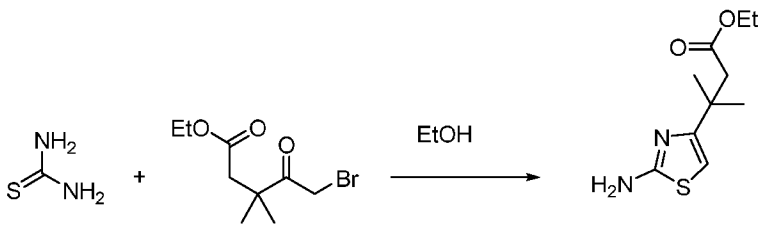
[00163] To methyl 2-(5-chloro-1*H*-indol-3-yl)acetate (0.713 g, 3.19 mmol) in toluene (15.0 mL) was added triphenylphosphine (1.26 g, 4.79 mmol) and (*R*)-1-(2-chlorophenyl)ethan-1-ol (0.500 g, 3.19 mmol). The mixture was cooled to 0-5 °C and 1,1'-azobis(*N*,*N*-dimethylformamide) was added. The reaction was sealed under argon, stirred at 0-5 °C for 30

min, then allowed to warm to ambient temperature. After stirring for an additional 48 h, the mixture was concentrated and purified by FCC (0-30% hexanes/ethyl acetate) to provide methyl (*S*)-2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetate (0.370 g, 32%) as a colorless solid. LRMS (ESI): calcd. for $C_{19}H_{17}Cl_2NO_2$: 361 $[M+H]^+$; found 362.

[00164] To (*S*)-2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetate (0.350 g, 0.966 mmol) in THF (3.7 mL) was added a solution of LiOH-H_2O (0.122 g, 2.90 mmol) pre-dissolved in H_2O (3.7 mL). The mixture was stirred for 3 h at ambient temperature before it was quenched with aqueous 1 N HCl (5 mL) and extracted with DCM (2X5 mL). The combined organics were washed with brine (5 mL), dried with sodium sulfate, filtered, and concentrated to provide (*S*)-2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetic acid (0.304 g, 90%) as an off-white solid. LRMS (ESI): calcd. for $C_{18}H_{15}Cl_2NO_2$: 347 $[M+H]^+$; found 348.

[00165] To a solution of (*S*)-2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetic acid (150 mg, 0.431 mmol) and 4-(*tert*-butyl)thiazol-2-amine (67 mg, 0.431 mmol) in DMF (1.0 mL) was added HATU (0.180 g, 0.474 mmol) followed by DIEA (150 uL, 0.862 mmol). The mixture was heated to 80 °C for 3 h then cooled to ambient temperature, diluted with ethyl acetate (5 mL) and brine (5 mL), and the aqueous phase was extracted with ethyl acetate (1X5 mL). The combined organics were washed with brine (2X5 mL), dried with sodium sulfate, filtered, and concentrated. Flash chromatography (0-40% hexanes/ethyl acetate) provided (*S*)-*N*-(4-(tert-butyl)thiazol-2-yl)-2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetamide (85 mg, 41% yield) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.32 (s, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.62, (s, 1H), 7.49 (dd, J = 7.6, 2.2 Hz, 1H), 7.33-7.25 (m, 2H), 7.21 (d, J = 8.8 Hz, 1H), 7.11 (d, J = 2.0 Hz, 1H), 7.09-7.05 (m, 1H), 6.73 (s, 1H), 6.02 (q, J = 7.2 Hz, 1H), 3.85 (s, 2H), 1.84 (d, J = 7.2 Hz, 3H), 1.26 (s, 9H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 169.7, 160.7, 157.8, 140.0, 134.7, 132.1, 130.2, 130.0, 129.5, 128.4, 127.5, 128.4, 127.5, 126.9, 124.5, 122.0, 119.1, 112.0, 108.3, 105.2, 52.1, 34.7, 32.4, 30.3, 20.7. LRMS (ESI): calcd. for $C_{25}H_{25}Cl_2N_3OS$: 485 $[M+H]^+$; found 485. HPLC purity: 98.7% (210 nM).

Synthesis of ethyl 3-(2-aminothiazol-4-yl)-3-methylbutanoate (Intermediate for A97)

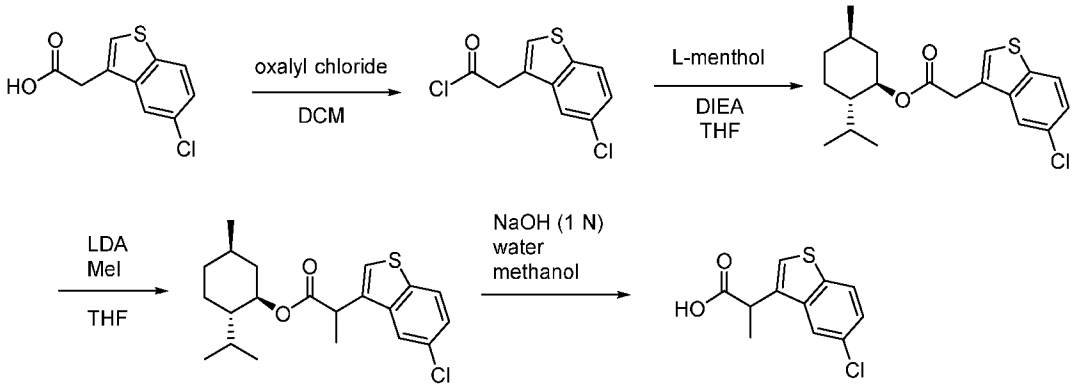


[00166] A mixture of ethyl δ-bromo-β,β-dimethyl levulinate (1.0 g, 4.0 mmol), thiourea (4.20 mmol, 319 mg), and ethanol (6.0 mL) was heated to reflux. After 10 minutes the reaction was diluted with brine (5 mL) and DCM (10 mL), extracted with DCM (2X10 mL), dried with sodium sulfate, filtered, and concentrated. Ethyl 3-(2-aminothiazol-4-yl)-3-methylbutanoate was provided as a colorless oil (910 mg, quant.) which was carried forward without further

purification. LCMS for $C_{10}H_{16}N_2O_2S$, found 229 $[M+H]^+$.

[00167] The following compounds were synthesized in a similar manner: 4-benzylthiazol-2-amine (Intermediate for C6); 4-(1-methylcyclopropyl)thiazol-2-amine (Intermediate for A57); and 4-(*tert*-pentyl)thiazol-2-amine (Intermediate for A76 and A56).

Synthesis of 2-(5-chlorobenzo[b]thiophen-3-yl)propanoic acid (Intermediate for A71)



[00168] To 2-(5-chloro-1-benzothiophene-3-yl)acetic acid (2.00 g, 8.82 mmol) in DCM (10 mL) at 0 °C was added oxalyl chloride (17.6 mmol, 1.51 mL) followed by DMF (50 uL, cat.). The mixture was stirred overnight at ambient temperature and concentrated to provide 2-(5-chlorobenzo[b]thiophen-3-yl)acetyl chloride as a brown solid (2.16 g, quant.) that was carried forward without further purification.

[00169] To the acid chloride (200 mg, 0.816 mmol) was added THF (2 mL) followed by *L*-menthol (0.979 mmol, 153 mg) and DIEA (2.45 mmol, 420 uL). The mixture was stirred overnight then quenched with sodium bicarbonate, extracted with ethyl acetate (2X), washed with brine, dried with sodium sulfate, filtered, and concentrated to provide (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(5-chlorobenzo[b]thiophen-3-yl)acetate (296 mg, quant.) that was carried forward without further purification.

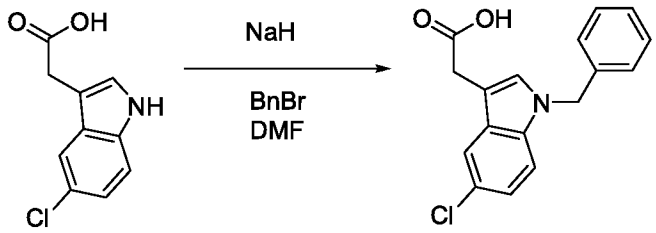
[00170] To the ester (44 mg, 0.121 mmol) was added THF (1 mL) and MeI (0.362 mmol, 23 uL). The mixture was cooled to -78 °C and LDA (2M in n-heptane/ethyl benzene/THF, 0.182 mmol, 91 uL) was added. The reaction was complete in 10 min at which time it was quenched with citric acid (sat., aq.), extracted with ethyl acetate (2X), washed with brine, dried with sodium sulfate, filtered, and concentrated. Reverse phase FCC (Redisep C18 30g column, ACN to elute) was used to provide (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 2-(5-chlorobenzo[b]thiophen-3-yl)propanoate (25 mg, 55% yield).

[00171] To the acid (25 mg, 0.066 mmol) was added 1N NaOH (5 mL), THF (5 mL), and methanol (5 mL). The mixture was heated to 60 °C for 3 h then cooled to ambient temp, concentrated to ~1/2 the volume, diluted with water and diethyl ether, washed with ether (3X), the aqueous phase was acidified with 1N HCl, extracted with DCM, dried with sodium sulfate, filtered, and concentrated to provide 2-(5-chlorobenzo[b]thiophen-3-yl)propanoic acid (14 mg,

89% yield) as a colorless solid. LCMS for $C_{11}H_9ClO_2S$, found 241 $[M+H]^+$. Reverse phase HPLC (Chiralcel AD-RH 70% acetonitrile/water +0.1% formic acid) indicated the mixture was racemic.

[00172] The following compounds were synthesized in a similar manner: 2-(5-chlorobenzo[b]thiophen-3-yl)-4-methylpentanoic acid (Intermediate for A65) and 2-(5-chlorobenzo[b]thiophen-3-yl)-3-phenylpropanoic acid (Intermediate for A66).

Synthesis of 2-(1-benzyl-5-chloro-1H-indol-3-yl)acetic acid (Intermediate for A61)



[00173] To 5-chloroindole-3-acetic acid (0.50 g, 2.39 mmol) in DMF (5 mL) at 0-5 °C was added NaH (9.56 mmol, 60% dispersion in mineral oil, 382 mg) and the mixture was stirred for 30 min. Benzyl bromide (2.39 mmol, 409 mg, 284 uL) was then added. After 1 h the reaction was quenched with 1 N HCl to acidify, extracted with ethyl acetate (2X), washed with brine, dried with sodium sulfate, filtered, and concentrated to provide 2-(1-benzyl-5-chloro-1*H*-indol-3-yl)acetic acid (7.12 mg, 100% yield) as an orange oil which was carried forward without further purification. MS(EI) for $C_{17}H_{14}ClNO_2$, found 300 $[M+H]^+$.

[00174] The following compounds were synthesized in a similar manner:

- 2-(5-chloro-1-(2-chlorobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A55)
- 2-(5-chloro-1-(3-chlorobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A54)
- 2-(5-chloro-1-(4-chlorobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A53)
- 2-(5-chloro-1-(cyclohexylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A52)
- 2-(5-chloro-1-isopropyl-1*H*-indol-3-yl)acetic acid (Intermediate for A51)
- 2-(5-chloro-1-(pyridin-2-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A50)
- 2-(5-chloro-1-(pyridin-3-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A49)
- 2-(5-chloro-1-(pyridin-4-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A48)
- 2-(5-chloro-1-(1-phenylethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A47)
- 2-(1-benzoyl-5-chloro-1*H*-indol-3-yl)acetic acid (Intermediate for A46)
- 2-(5-chloro-1-(2,3-dihydro-1*H*-inden-1-yl)-1*H*-indol-3-yl)acetic acid (Intermediate for A20)
- 2-(1-(2-chlorobenzyl)-2-methyl-1*H*-indol-3-yl)acetic acid (Intermediate for A15)

- 2-(1-benzyl-5-methoxy-1*H*-indol-3-yl)acetic acid (Intermediate for A38)
- 2-(1-benzyl-5-bromo-1*H*-indol-3-yl)acetic acid (Intermediate for A37)
- 2-(5-chloro-1-(2-cyanobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A31)
- 2-(5-chloro-1-phenethyl-1*H*-indol-3-yl)acetic acid (Intermediate for A26)
- 2-(5-chloro-1-(2-chloro-6-fluorobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A9)
- 2-(5-chloro-1-(2-chloro-4-fluorobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A8)
- 1-benzyl-5-methyl-1*H*-pyrrole-3-carboxylic acid (Intermediate for A189)
- 2-(5-chloro-1-(4-cyanobenzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A7)

[00175] The following compound was synthesized in a similar manner from the heteroaryl fluoride: 2-(5-chloro-1-(pyridin-2-yl)-1*H*-indol-3-yl)acetic acid (Intermediate for A40)

[00176] The following compounds were synthesized in a similar manner from the alkyl or aryl iodide:

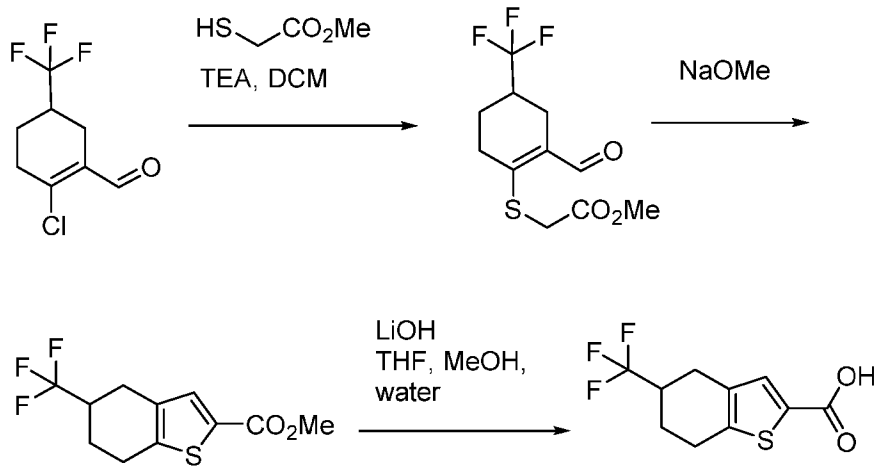
- 2-(5-chloro-1-cyclopentyl-1*H*-indol-3-yl)acetic acid (Intermediate for A39)
- 2-(5-chloro-1-isobutyl-1*H*-indol-3-yl)acetic acid (Intermediate for A36)
- 2-(5-chloro-1-(2-chlorobenzyl)-1*H*-indazol-3-yl)acetic acid (Intermediate for A34)
- 2-(5-chloro-1-(1-(2-chlorophenyl)ethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A33)
- 2-(1-(*sec*-butyl)-5-chloro-1*H*-indol-3-yl)acetic acid (Intermediate for A27)

[00177] The following compounds were synthesized in a similar manner from the heteroaryl chloride:

- 2-(5-chloro-1-((3-fluoropyridin-4-yl)methyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A30)
- 2-(5-chloro-1-(oxazol-2-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A22)
- 2-(5-chloro-1-(pyrimidin-2-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A21)
- 2-(1-(benzo[d]oxazol-2-ylmethyl)-5-chloro-1*H*-indol-3-yl)acetic acid (Intermediate for A18)
- 2-(5-chloro-1-(oxazol-4-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A17)
- 2-(5-chloro-1-(isoxazol-3-ylmethyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A16)
- 2-(5-chloro-1-((2-methylpyridin-4-yl)methyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A11)

[00178] The following compound was synthesized in a similar manner from the p-toluenesulfonate: 2-(5-chloro-1-cyclohexyl-1*H*-indol-3-yl)acetic acid (Intermediate for A12)

Synthesis of 5-(trifluoromethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylic acid (Intermediate forA191)



[00179] To a solution of DMF (302 µl, 3.91 mmol) in 1,2-dichloroethane (5 ml) maintained at 5 °C under the blanket of nitrogen, phosphoryl oxychloride (258 µl, 2.77 mmol) was added dropwise maintaining the temperature below 10 °C. The mixture was then allowed to warm to ambient temperature. To this mixture, 4-(trifluoromethyl)cyclohexan-1-one (500 mg, 3.01 mmol) 1,2-dichloroethane (5 ml) was added dropwise to maintain the temperature below 60 °C. The mixture was heated at 60 °C for 3 hours. After the completion of the reaction as observed by the TLC, the reaction mixture was cooled to 10 °C and sodium acetate solution (30 ml) was added. The reaction mixture was partitioned between ice water and 1,2-dichloroethane. The organic phase was collected, dried over sodium sulfate, and filtered. The dried organic layer containing 2-chloro-5-(trifluoromethyl)cyclohex-1-ene-1-carbaldehyde was taken to the next step directly.

[00180] A mixture of 2-chloro-5-(trifluoromethyl)cyclohex-1-ene-1-carbaldehyde (500 mg, 2.35 mmol) and methyl 2-mercaptoacetate (250 mg, 2.35 mmol) and triethylamine (262 mg, 2.59 mmol) in dichlomethane was stirred overnight. Completion of the reaction was observed by TLC. The reaction mixture was washed with a mixture of 0.1 N hydrochloric acid solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Methyl 2-((2-formyl-4-(trifluoromethyl)cyclohex-1-en-1-yl)thio)acetate was taken to the next step without further purification.

[00181] A mixture of methyl 2-((2-formyl-4-(trifluoromethyl)cyclohex-1-en-1-yl)thio)acetate (350 mg, 1.24 mmol) and sodium methoxide (67.0 mg, 1.24 mmol) was heated under reflux for 2 hours. The reaction mixture was poured into water, and acidified with 5 N aq HCl. The product was extracted into ethyl acetate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give a red oil. The product was purified by flash chromatography over silica with 0-40% ethyl acetate in hexane to obtain methyl 5-(trifluoromethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylate (220 mg, 67%). ^{1}H NMR (400MHz, DMSO-d_6) δ

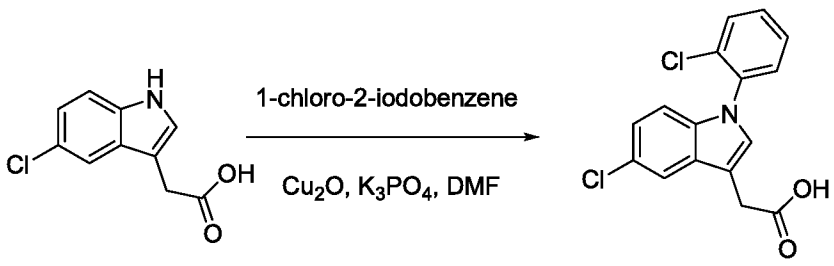
7.59 (s, 1H), 3.79 (s, 3H), 3.02 - 2.70 (m, 4H), 2.62 - 2.53 (m, 1H), 2.15 (br d, *J* = 10.1 Hz, 1H), 1.68 (dq, *J* = 5.6, 12.1 Hz, 1H).

[00182] Methyl 5-(trifluoromethyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-2-carboxylate (215 mg, 814µmol) was dissolved in 8:2:2 THF: Methanol:water. Lithium hydroxide (102 mg, 2.44 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 hours. After completion of the reaction, pH of the reaction mixture was adjusted to pH=3 by adding 1N HCl dropwise. The reaction mixture was concentrated to remove the organic solvent. The aqueous layer was extracted with ethyl acetate, the organic layer was washed with brine, filtered and dried over sodium sulfate to provide 5-(trifluoromethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-carboxylic acid (170 mg, 83%). ^{1}H NMR (400MHz, DMSO-d_6) δ 12.89 (br s, 1H), 7.49 (s, 1H), 2.99 - 2.65 (m, 5H), 2.62 - 2.53 (m, 1H), 2.19 - 2.10 (m, 1H), 1.68 (dq, *J* = 5.9, 12.1 Hz, 1H).

Synthesis of 4-(*tert*-butyl)-5-chlorothiazol-2-amine (Intermediate for A184)

[00183] A solution of 4-(*tert*-butyl)thiazol-2-amine (500 mg, 3.20 mmol) and *N*-chlorosuccinimide (513 mg, 3.84 mmol) in acetonitrile (15 ml) was stirred at ambient temperature for one hour. After the completion of the reaction, acetonitrile was evaporated under reduced pressure and the residue was partitioned between water (25 ml) and ethyl acetate (25 ml). The layers were separated and the aqueous layer was extracted with ethyl acetate (2×25 ml). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated. The residue was purified over silica gel (0-30% ethyl acetate in hexane) to obtain 400 mg (66%) of product. ^{1}H NMR (400MHz, DMSO-d_6) δ 6.98 (br s, 2H), 1.29 (s, 9H). LCMS for $C_7H_{11}ClN_2S$ calculated 191.03 [M+H$^+$]; found 191.00.

Synthesis of 2-(5-chloro-1-(2-chlorophenyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A43)

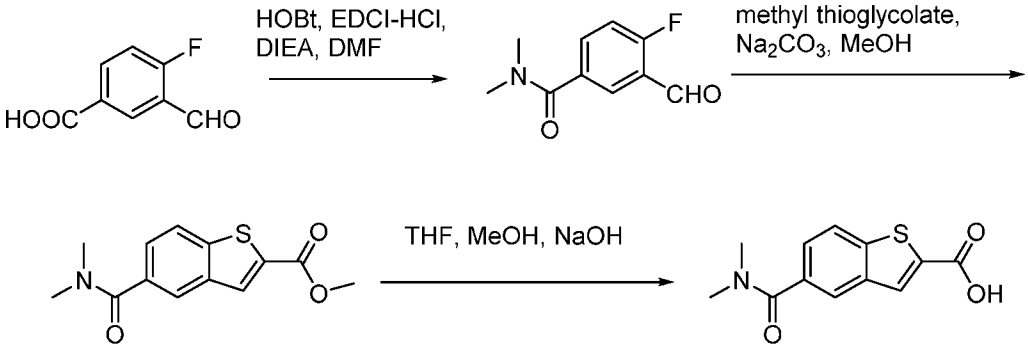


[00184] To 5-chloroindole-3-acetic acid (0.1 g, 0.478 mmol) in DMF (0.5 mL) was added Cu_2O (0.478 mmol, 6.8 mg), 17.6 mg), K_3PO_4 (0.956 mmol, 101 mg) and 1-chloro-2-iodobenzene (0.718 mmol, 170.6 mg). The mixture was sealed and heated to 130 °C. After

stirring for 16 h the reaction was complete. The mixture was filtered and carried forward without further purification. LCMS for $C_{16}H_{11}ClNO_2$ calculated 320 [M+H$^+$]; found 320.

[00185] The following compounds were synthesized in a similar manner: 2-(5-chloro-1-(3-chlorophenyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A42) and 2-(5-chloro-1-(4-chlorophenyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A41).

Synthesis of 5-(dimethylcarbamoyl)benzo[*b*]thiophene-2-carboxylic acid (Intermediate for A192):



[00186] 4-Fluoro-3-formylbenzoic acid (500 mg, 2.97 mmol) was dissolved in DMF (6.7 ml). HOBT monohydrate (683 mg, 4.46 mmol) and DIPEA (769 mg, 5.95 mmol) were added. The reaction mixture was cooled to 0 °C. Dimethylamine (2.0 M in THF, 2.97 mmol) was added, followed by EDCI*HCl (693 mg, 4.46 mmol). The reaction mixture was stirred overnight at ambient temperature and then diluted with DCM, washed with dilute aq HCl, aq $NaHCO_3$, water, and brine. The organic layer was dried with sodium sulfate, filtered, and concentrated. The crude product was purified by flash chromatography with silica gel using a gradient of 0-90% hexanes/ethyl acetate. The desired fractions were combined and concentrated to yield the title compound (420 mg, 72%). LCMS: calc. M+H+=196.2; Found 196.1.

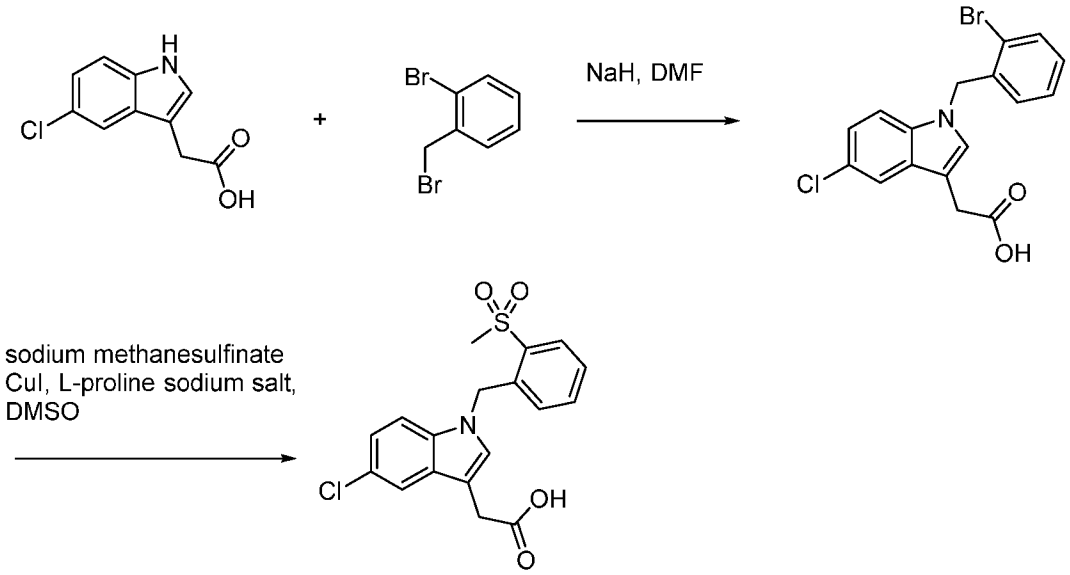
[00187] 4-Fluoro-3-formyl-*N,N*-dimethylbenzamide (400 mg, 2.05 mmol), methyl thioglycolate (218 mg, 2.05 mmol) and sodium carbonate (217 mg, 2.05 mmol) were mixed in MeOH (4.0 ml) and refluxed for 1 h. The reaction mixture was cooled to ambient temperature, diluted with brine and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude product was purified by flash chromatography with silica gel using a gradient of EtOAc in hexanes. The desired fractions were combined and concentrated to yield the title compound (330 mg, 61%). LCMS: calc. [M+H]$^+$=264.3; Found 264.2.

[00188] Methyl 5-(dimethylcarbamoyl)benzo[b]thiophene-2-carboxylate (320 mg, 1.22 mmol) was dissolved in THF (3.52 ml) and MeOH (0.96 ml) and treated with aq NaOH (1.0 M, 3.16 ml). The mixture was stirred for 1 hr at ambient temperature. Aq HCl (1.0 M) was added dropwise to adjust the acidity to pH=3. The aq phase was extracted with EtOAc (2X). The organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated

to obtain the desired product (260 mg, 86%). LCMS (+esi): calc. $[M+H]^+$=250.1; Found 250.1.

[00189] The following compound was synthesized in a similar manner: 5-(methylcarbamoyl)benzo[*b*]thiophene-2-carboxylic acid (Intermediate for A186).

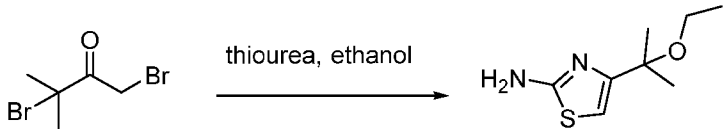
Synthesis of 2-(5-chloro-1-(2-(methylsulfonyl)benzyl)-1*H*-indol-3-yl)acetic acid (Intermediate for A25)



[00190] 2-(5-Chloro-1*H*-indol-3-yl)acetic acid (1.5 g, 7.16 mmol) was dissolved in DMF (15.0 ml) and the solution was cooled in an ice bath. NaH (1.14 g, 28.6 mmol, 60% in mineral oil) was added and the mixture was stirred for 30 minutes. 2-Bromobenzyl bromide (1.79 g, 7.16 mmol) was added and the mixture was stirred for 1 h and then quenched with 1 N HCl. The mixture was extracted with EtOAc (2X) and the organic extracts were washed with brine, dried with sodium sulfate, filtered, and concentrated to obtain the crude compound which was used without further purification (2.4 g, 89%). LCMS: calc. $[M+H]^+$=378.0; Found 378.1.

[00191] 2-(1-(2-Bromobenzyl)-5-chloro-1*H*-indol-3-yl)acetic acid (350 mg, 0.924 mmol), sodium methanesulfinate (131 mg, 1.11 mmol), copper iodide (17.6 mg, 92.4 µmol), *L*-proline sodium salt (25.3 mg, 185 µmol) and DMSO (2.0 ml) were mixed in a sealed tube and heated between 80-95 °C for 24 h under Argon. The cooled reaction mixture was partitioned with water and EtOAc and the aqueous phase was extracted twice more with EtOAc. The organic phases were combined, washed with brine, dried with sodium sulfate, filtered and concentrated to yield crude compound which was carried forward without additional purification (65 mg, 18%). LCMS: calc. $[M+H]^+$=378.0; Found 378.3.

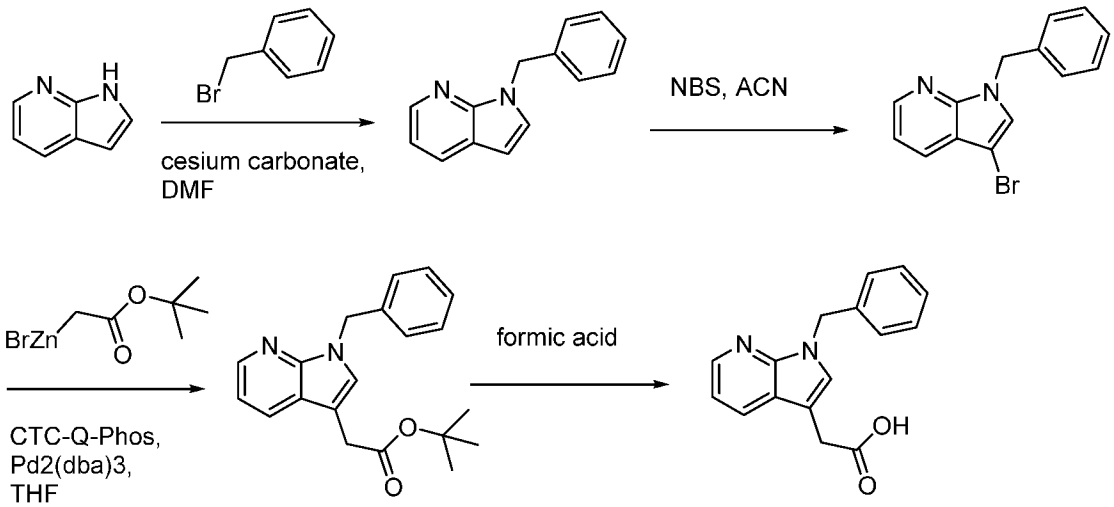
Synthesis of 4-(2-ethoxypropan-2-yl)thiazol-2-amine (Intermediate for A2)



[00192] 1,3-Dibromo-3-methylbutan-2-one (500 mg, 2.05 mmol, SM-00299), thiourea (156 mg, 2.05 mmol) and ethanol (10 mL) was stirred at ambient temperature for 2 h. The reaction mixture was quenched with NaHCO3 and extracted with ethyl acetate (3X). The organic layer was washed with water, brine, dried over Na2SO4 and concentrated to provide yellow solid (280 mg, 73%). ^{1}H NMR (400MHz, DMSO-d_6) δ = 6.87 (br s, 2H), 6.30 (s, 1H), 3.20 (q, *J*=6.9 Hz, 2H), 1.37 (s, 6H), 1.02 (t, *J*=7.0 Hz, 3H).

[00193] The following compounds were synthesized in a similar manner: 4-(2-isopropoxypropan-2-yl)thiazol-2-amine (Intermediate for A24) and 4-(2-methoxypropan-2-yl)thiazol-2-amine (Intermediate for A23).

Synthesis of 2-(1-benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetic acid (Intermediate for A19)



[00194] 1*H*-Pyrrolo[2,3-*b*]pyridine (8.00 g, 67.7 mmol) and benzyl bromide (17.4 g, 102 mmol) was dissolved in DMF (80 ml). Cesium carbonate (44.1 g, 135 mmol) was added. The reaction mixture was stirred at 60 °C overnight and then partitioned with EtOAc and water. The organic layer was washed with brined, dried with sodium sulfate, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel using a gradient of EtOAc in hexanes. The desired fractions were pooled and concentrated to yield the title compound (7.9 g, 56%). LCMS: calc. $[M+H]^+$=209.1; Found 209.1.

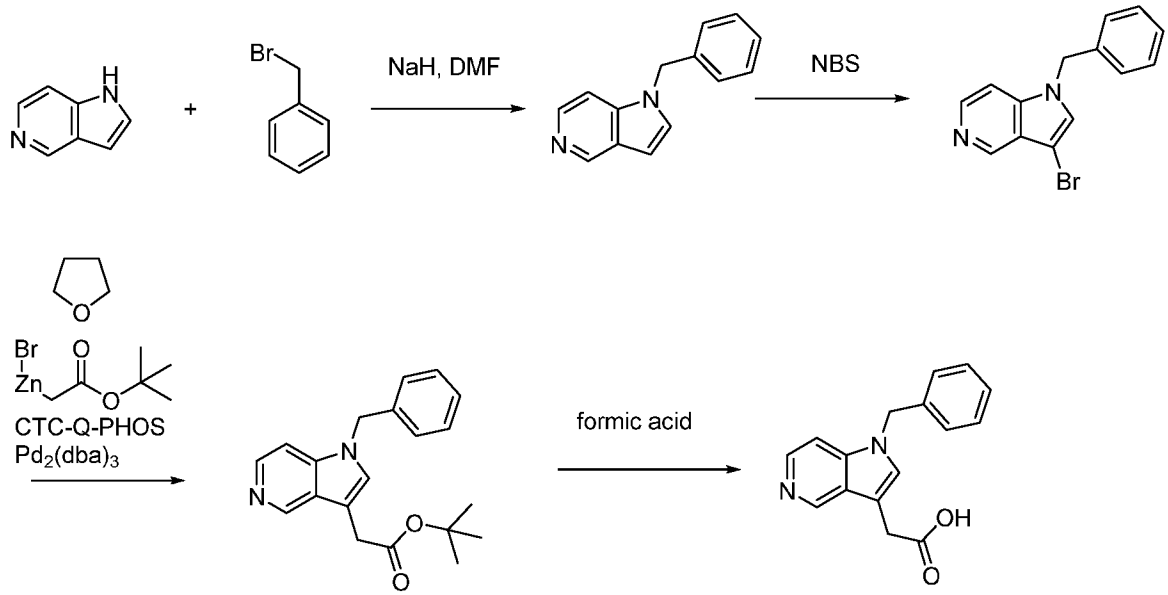
[00195] 1-Benzyl-1*H*-pyrrolo[2,3-b]pyridine (3.75 g, 18.0 mmol) was dissolved in acetonitrile (113 ml). The solution was cooled in an ice-water bath, NBS (3.04 g, 17.1 mmol) was added and the mixture was allowed to stir for one hour. The mixture was partitioned with EtOAc and water. The organic layer was dried with sodium sulfate, filtered and concentrated. The crude compound was purified by flash chromatography on silica gel using a gradient of 0-30% EtOAc in hexanes. The desired fractions were pooled and concentrated to yield the title compound (3.7 g, 72%). LCMS: calc. $[M+H]^+$=287.0; Found 287.0.

[00196] 1-Benzyl-3-bromo-1*H*-pyrrolo[2,3-*b*]pyridine (5.00 g, 17.4 mmol) was dissolved in

THF (50 ml). Argon was bubbled through the mixture. (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (38.3 mmol) was added, followed by CTC-Q-PHOS (247 mg, 0.34 mmol) and $Pd_2(dba)_3$ (319 mg, 0.34 mmol). The reaction mixture was stirred overnight at ambient temperature and partitioned between EtOAc and water. The organic phase was rinsed with brine, dried over sodium sulfate, filtered, and concentrated to yield the crude product which was further purified by flash chromatography using silica gel with a gradient of 0-25% EtOAc in hexanes. The desired fractions were pooled and concentrated to yield the title compound (2.55 g, 45.4%). LCMS: calc. $[M+H]^+$=323.2; found 323.3.

[00197] *tert*-Butyl 2-(1-benzyl-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetate (350 mg, 1.09 mmol) was dissolved in formic acid (3.5 ml) and stirred at 50 °C for 1 h. The reaction mixture was partitioned with EtOAc and water. The organic layer was washed with brine, dried with sodium sulfate, filtered, and concentrated to obtain the title compound (280 mg, 97%). LCMS: calc. $[M+H]^+$=267.1; found 267.1.

Synthesis of 2-(1-benzyl-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl)acetic acid (Intermediate for A13)



[00198] In a dry round bottom flask, the starting material (5 g, 41.1 mmol) was dissolved in 50 mL of dry DMF and cooled to 0 °C, followed by NaH (60%, 6.57g, 164 mmol) was added to the reaction mixture and stirred for 30 min. 2-(bromomethyl)benzonitrile (7.02 g, 41.1 mmol) was added to the reaction mixture at 0 °C and it was stirred at ambient temperature until the starting material was consumed. The reaction mixture was quenched with 1N HCl under ice cooled water bath and the pH of the aqueous layer was adjusted to 7 and extracted with ethyl acetate (3 times). The combined organics were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography. (2.5g, 29.2% yield) LCMS: calc. $[M+H]^+$=209.1; found 209.1.

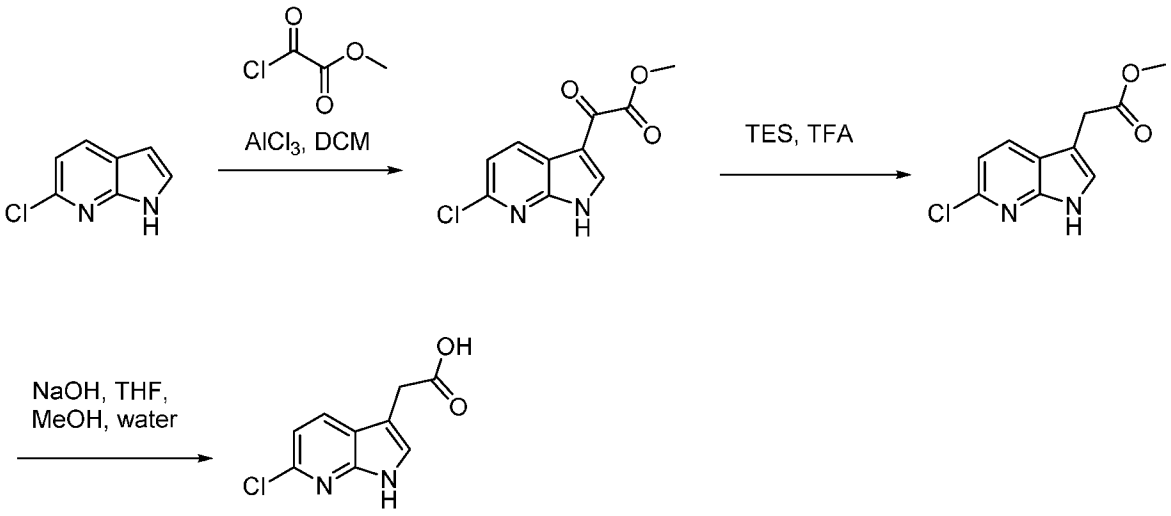
[00199] To a solution of the azaindole starting material (1g, 4.80 mmol) in 30 mL of DCM at 0

°C was added n-bromosuccinimide 812mg (4.56 mmol) and the mixture was stirred for 1 hour. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography. (0.55g, 39.9% yield) LCMS: calc. $[M+H]^+$=287.0; found 287.1.

[00200] To a solution of bromide starting material (500mg, 1.74 mmol) in 50 mL of dry THF was added (2-(*tert*-butoxy)-2-oxoethyl)zinc(II) bromide (1.27 g, 3.83 mmol) under argon followed by adding 1,2,3,4,5-pentaphenyl-1'-(di-*tert*-butylphosphino)ferrocene (CTC-Q-PHOS) (24.7 mg, 0.035 mmol) and $Pd_2(dba)_3$ (31.9mg, 0.035 mmol). The reaction mixture was stirred at RT overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography. (480mg, 85.8% yield) LCMS: calc. $[M+H]^+$=323.2; found 323.4.

[00201] The ester starting material (100 mg, 0.310 mmol) was dissolved in 1 mL of formic acid and stirred at 50 °C for 1 h. The reaction mixture was diluted with water, cooled to 0 °C, and acidified with 1 N HCl. The pH of aqueous layer was adjusted to 5~6 and extracted with ethyl acetate (3 times). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was taken forward for the next step reaction without any further purification. (80 mg, 96.9% yield) LCMS: calc. $[M+H]^+$=267.1; found 267.3.

Synthesis of 2-(1-benzyl-6-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetic acid (Intermediate for A5)



[00202] In a dry RBF, $AlCl_3$ (2.18 g, 16.4 mmol) and DCM (5 mL) were combined followed by 6-chloro-1*H*-pyrrolo[2,3-b]pyridine (500 mg, 3.28 mmol) which was added slowly and stirred at ambient temperature for 1 h. Methyloxalyl chloride (2.01 g, 16.4 mmol) was added to the

reaction mixture and it was stirred vigorously for 12 h. The reaction mixture was cooled to 0 °C and quenched with methanol (20 mL). The off white precipitate (600 mg, 77%) was filtered and taken forward without any further purification.

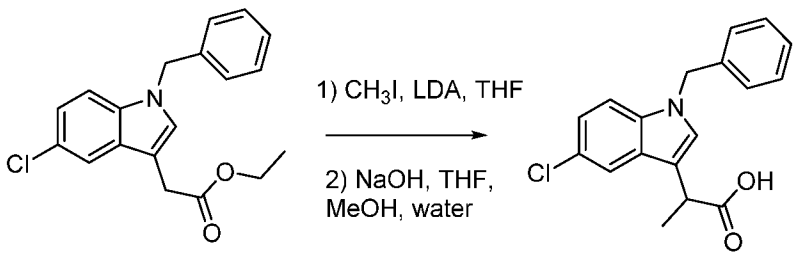
[00203] Triethylsilane (171 mg, 1.47 mmol) and TFA (1 mL) was cooled to -10 °C and methyl 2-(6-chloro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)-2-oxoacetate (100 mg, 0.419 mmol) was added to the reaction mixture portion-wise. The reaction mixture was stirred at -10 °C for 1 h and then at RT for 12 h. The reaction mixture was evaporated to get oil and the traces of TFA was removed by azeotropically using DCM. The crude oil (94 mg, 99%) was taken forward without any further purification.

[00204] Methyl 2-(6-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetate (94 mg, 0.418 mmol) was dissolved in mixture of THF : MeOH : H_2O (1:1:0.5). To the reaction mixture granulated NaOH (20.1 mg, 0.502 mmol), was added and stirred at 50 °C for 1 h. The reaction mixture was diluted with water, cooled to 0 °C and acidified with 1 N HCl. The aqueous layer was extracted with ethyl acetate (3 times). The combined organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude product was taken forward without any further purification (85 mg, 96% yield). (Note: During acidification pH was maintained between 5-6).

[00205] In a dry round bottom flask, the starting material (85 mg, 0.40 mmol) was dissolved in dry DMF (0.8 mL) and cooled to 0 °C, followed by NaH (60%, 64.6 mg, 1.61 mmol) was added to the reaction mixture and stirred at RT for 30 min. Benzyl bromide (69 mg, 0.404 mmol) was dissolved in dry DMF (0.8 mL) and added to the reaction mixture at 0 °C and the reaction mixture was stirred at RT until completion of starting material. The reaction mixture was quenched in ice cooled water and the aqueous layer was extracted with ethyl acetate (3X). The combined organic layers were washed with water (2 times), brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography (181 mg, 149% crude yield). LCMS: calc. $[M+H]^+$=301.07; Found 301.1.

[00206] The following compound was synthesized in a similar manner: 2-(1-benzyl-6-chloro-1*H*-pyrrolo[3,2-*c*]pyridin-3-yl)acetic acid (Intermediate for A1).

Synthesis of 2-(1-benzyl-5-chloro-1*H*-indol-3-yl)propanoic acid (Intermediate for A4)



[00207] To a solution of starting material (220 mg, 0.671 mmol) in THF (2.2 mL) at -78 °C was added 0.403 mL of 2M lithium diisopropylamide and the mixture was stirred for 30 minutes. Iodomethane (105 mg, 0.212 mmol) in THF (2.2 mL) was added and the resulting reaction mixture was stirred at -78 °C for 1 hour. The reaction mixture was quenched with saturated NH_4Cl solution and partitioned between ethyl acetate and water. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was purified using flash chromatography. (190mg, 82.8% yield) LCMS: calc. $[M+H]^+$=342.1; found 342.2.

[00208] Ethyl 2-(1-benzyl-5-chloro-1*H*-indol-3-yl)propanoate (160mg (0.468 mmol) was dissolved in 2 mL of mixture of THF: MeOH: H_2O (1:1:0.5). To the reaction mixture granulated NaOH (22.5 mg, 0.562 mmol) was added and the mixture was stirred at 50 °C for 1 h. The reaction mixture was diluted with water, cooled to 0 °C and acidified with 1 N HCl. The aqueous layer was extracted with ethyl acetate (3 times). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the residue was taken forward to the next step reaction without further purification. (140mg, 95.3% yield) LCMS: calc. $[M+H]^+$=314.1; Found 314.1.

[00209] The following compound was synthesized in a similar manner: 2-(1-benzyl-5-chloro-1*H*-indol-3-yl)-3-phenylpropanoic acid (Intermediate for A3).

Assays

Constitutively Active VCAM-ss-Gluc Assay

[00210] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding VCAM signal sequence plus 10 amino acids (N-MPGKMVVILGASNILWIMFAASQAFKIETTPESR-C). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that constitutively expressed the VCAMss+10aa/Gaussia Luciferase fusion protein. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, culture media was removed from the wells and replaced with fresh media. Compound dilutions in DMSO/media were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00211] Results for select compounds provided herein are shown in Tables A, B, C, and D. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox Induced VCAM-ss-Gluc Assay

[00212] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding VCAM signal

sequence plus 10 amino acids (N-MPGKMVVILGASNILWIMFAASQAFKIETTPESR-C). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the VCAMss+10aa/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00213] Results for select compounds provided herein are shown in Tables A, B, C, and D. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox Induced TNFα-FL-Gluc Assay

[00214] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding full length TNFα (amino acids 1-233). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the TNFα-FL/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00215] Results for select compounds provided herein are shown in Tables A, B, C, and D. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Dox Induced PD1-ss-Gluc Assay

[00216] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding PD1 signal sequence plus 10 amino acids (N-MQIPQAPWPVVWAVLQLGWRPGWFLDSPDR-C). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the PD1-ss+10aa/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00217] Results for select compounds provided herein are shown in Tables A, B, C, and D.

For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

Constitutively Active Pr1-ss-Gluc Assay

[00218] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding Prl signal sequence plus 10 amino acids (MNIKGSPWKGSLLLLLVSNLLLCQSVAPLPICPGGAAR; (SEQ ID NO: 1)). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that constitutively expressed the Prlss+10aa/Gaussia Luciferase fusion protein. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, culture media was removed from the wells and replaced with fresh media. Compound dilutions in DMSO/media were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00219] Results for select compounds provided herein are shown in Tables A, B, C, and D. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

24hr Dox Inducible Pr1-ss-Gluc Assay

[00220] Flp-In 293 T-REx™ cells were transfected with pcDNA™5/FRT/TO plasmid inserted with cDNA encoding Gaussia Luciferase fused to the 3' end of cDNA encoding Prl signal sequence plus 10 amino acids (SEQ ID NO: 1). Transfected cells were selected for resistance to the selectable markers Hygromycin and Blasticidin to create a stable cell line that contained the Prl-ss+10aa/Gaussia Luciferase cDNA insert whose expression was regulated under the T-REx™ system. The day before assay, cells were trypsinized and plated in 384-well tissue culture plates. The next day, compound dilutions in DMSO/media containing doxycycline were added to the wells and incubated at 37°C, 5% CO_2. 24 hours later, coelenterazine substrate was added to each well and luciferase signal was quantified using Tecan Infinite M1000 Pro for potency determination.

[00221] Results for select compounds provided herein are shown in Tables A, B, C, and D. For chemical structures that include one or more stereoisomers, but are illustrated without indicating stereochemistry, the assay data refers to a mixture of stereoisomers.

High-Throughput Screen to Identify Substrate-Selective Inhibitors of Protein Secretion

[00222] CT8, a macrocyclic Sec61 modulator, blocks protein secretion in a signal sequence-dependent manner (FIG. 1A). A cellular high-throughput screening assay based on a secreted luciferase reporter was performed (see the schematic in FIG. B). The N-terminal signal sequence from human VCAM (+4 amino acids of the mature domain) was fused to the mature domain Gaussia luciferase (VCAMss-GLuc). CT8 blocks Sec61-mediated translocation of

VCAMss-GLuc into the ER, resulting in a loss of luciferase activity. A HEK293 cell line stably expressing doxycycline-inducible VCAMss-GLuc was used to screen ~30,000-compounds (FIG. 1C). After adding test compounds (10 μM) and doxycycline (1 μg/ml), cells were incubated for 24 hours in humidified chambers. Gaussia luciferase substrate was added to each well and the plates were shaken for 10 sec. Luminescence was quantified with an Envision plate reader. A total of 232 compounds were found to significantly inhibit VCAMss-GLuc expression at 10 μM (>3 standard deviations from the mean). These compounds were next tested for dose-dependent inhibition of VCAMss-GLuc secretion. In addition, to assess signal sequence selectivity, the 232 primary hits were tested for effects on a second luciferase reporter, PRLss-GLuc, which contains the prolactin signal sequence in place of VCAMss. Only two compounds, 1a and 1b (FIG. 1D) , were found to selectively inhibit VCAMss-GLuc secretion. Both compounds show dose-dependent inhibition of VCAMss-GLuc, with little to no effect on PRLss-GLuc. IC_{50} values were determined by fitting luminescence data to a three-parameter non-linear fit in GraphPad Prism.

Structure-activity relationships and inhibition of full-length VCAM expression

[00223] To determine preliminary structure-activity relationships (SAR) (FIG. 2A), analogs of **1a** were purchased and tested in cellular VCAMss-GLuc and PRLss-GLuc assays (FIG. 2B). IC_{50} values of 8 analogs of **1a** demonstrate essential roles for both A- and B-rings (FIG. 2B). For example, changing either the A-ring thiazole or the B-ring thiophene to an isosteric isoxazole eliminated activity (see compounds **3** and **9**). By contrast, changing the substitution pattern of the B-ring thiophene to give the 2-halo 5-carboxamido thiophenes **2** and **4** led to increased potency (FIG. 2B). Dose-response curves were generated for active compound **2** and inactive analog **3** in cellular VCAMss-GLuc and PRLss-GLuc assays (FIG. 2C). Inhibition of full-length VCAM expression was exhibited by compound **2** (IC_{50} ~1 μM), but not **3** (IC_{50} >25 μM) (FIG. 2D). COS7 cells were transiently transfected with a VCAM expression construct. Cells were treated with the indicated concentrations of compounds **2** and **3** for 24 hours. Cell lysates were prepared analyzed by western blotting.

Compound 2 is a substrate-selective inhibitor of protein secretion.

[00224] Expression constructs for doxycycline-inducible Gaussia luciferase, fused to the indicated N-terminal signal sequence (+4 amino acids of the mature domain), were transfected into HEK293 Trex cells and treated with increasing concentrations of compound 2 (+1 μg/ml of doxycycline). Of the 14 signal sequence-GLuc reporters tested, five were inhibited by compound 2 with IC_{50} < 5 μM (top graph of FIG. 3A, VCAM, HER3, TLR9, ROS1 and PD1). By contrast, the other 9 signal sequences were unaffected (bottom graph of FIG. 3A, IC_{50} > 20 μM). Compound 2 inhibits full-length HER3 expression (IC_{50} ~5 μM), with partial inhibition of HER2 at 25 μM (FIG. 3B). HEK293 cells were transiently transfected with HER2 and HER3 expression constructs containing a C-terminal V5 tag. Cells were treated with compounds for 24 hours and analyzed by western blotting.

Compound 2 inhibits secretory and membrane protein expression by targeting Sec61α.

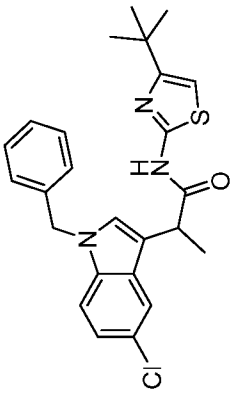
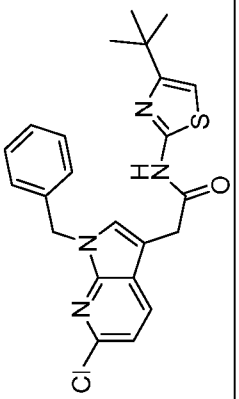
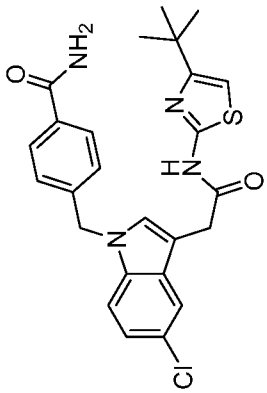
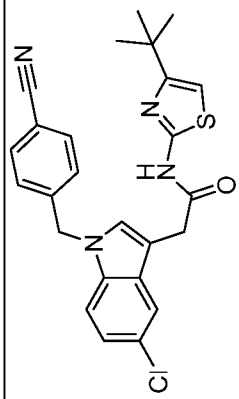
[00225] HEK293 TRex cells stably expressing either mutant (R66I) or wild-type Sec61α (WT) were transfected with the VCAMss-GLuc reporter and treated with increasing concentrations of compound **2** (+1 μg/ml of doxycycline). GLuc activity was measured as described in Fig. 1. The data indicate that R66I Sec61α confers substantial resistance to compound **2** (FIG. 4A). Compound **2** competes with photo-affinity probe CT7 (FIG. 4B) for binding to Sec61α. Rough ER microsomes were treated with probe CT7 (0.1 μM) along with the indicated concentrations of **2** and **3**. After photolysis for 1 min at 350 nm, samples were subjected to copper-catalyzed click conjugation with rhodamine-azide (TAMRA), resolved by SDS-PAGE, and analyzed by fluorescence gel scanning (Typhoon) and western blotting with Sec61α antibodies. Normalized TAMRA fluorescence (% DMSO control), corresponding to CT7-modified Sec61α, is indicated. (FIG. 4B).

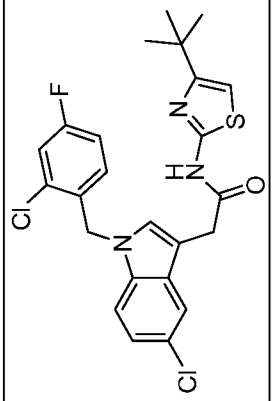
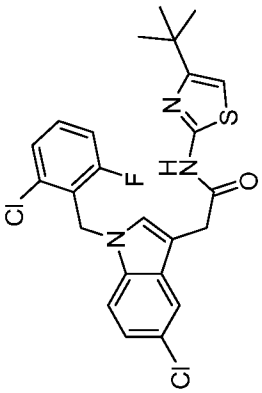
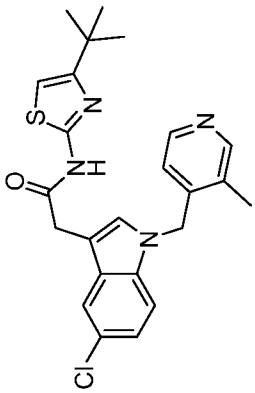
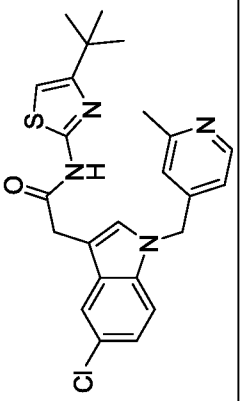
Compound 10-(*S*) potently blocks expression of a subset of secreted and membrane proteins.

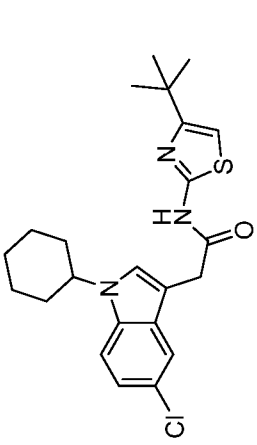
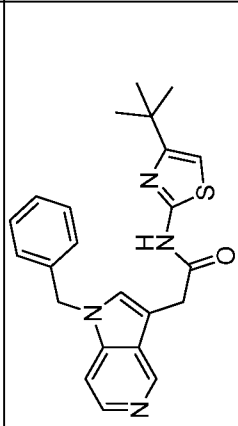
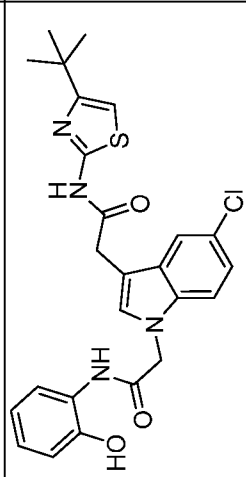
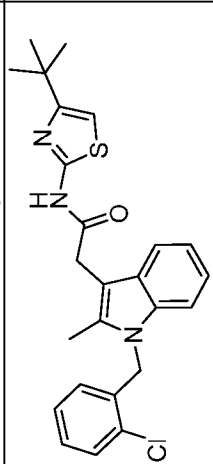
[00226] Compounds **10-(*R*)** and **10-(*S*)** (FIG. 5A) were tested for their ability to inhibit the expression of Gaussia luciferase C-terminally fused to the indicated signal sequence (+4 amino acids of the mature domain) (FIG. 5B) or full-length secretory protein (FIG. 5C). Depending on the signal sequence or full-length protein fused to GLuc, compound **10-(*S*)** blocks expression with varying degrees of potency; yet, **10-(*S*)** is consistently more potent than **10-(*R*)** in all assays. The effect of **10-(*R*)** and **10-(*S*)** on the expression of full-length VCAM was determined (FIG. 5D). HEK293 Trex cells stably expressing doxycycline-inducible VCAM were treated with the indicated concentrations of **10-(*R*)** and **10-(*S*)** (+1 μg/ml doxycycline). After 24 hours, cellular VCAM levels were quantified by flow cytometry using a PE-conjugated VCAM antibody. The effect of **10-(*R*)** and **10-(*S*)** on endogenous HGF secretion was determined (FIG. 5E). JJN3 cells were treated with the indicated concentrations of **10-(*R*)** and **10-(*S*)** for 24 hours. Supernatants were analyzed for HGF using an ELISA kit. The effects of **10-(*S*)** in primary human cell-based assays (DiscoverX BioMap Diversity Plus panel) was determined (FIG. 5F). BT System (T cell-dependent B cell differentiation): B cells were added to peripheral blood mononuclear cells (PBMCs) and treated with anti-IgM, superantigen cocktail, and the indicated concentrations of **10-(*S*)**. After 3 days (for all markers except secreted IgG) or 4 days (for secreted IgG), supernatants were analyzed using quantitative immunoassays. PBMC cytotoxicity and B cell proliferation were assessed by AlamarBlue reduction after 42 and 72 hours, respectively. LPS system: peripheral blood mononuclear cells and endothelial cells were treated with lipopolysaccharide and the indicated concentrations of **10-(*S*)**. After 24 hours, cells and supernatants were analyzed for the indicated markers by quantitative immunoassays. Cytotoxicity was assessed by staining with sulforhodamine B (SRB).

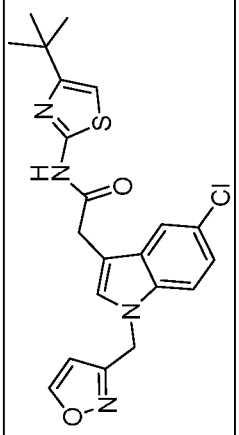
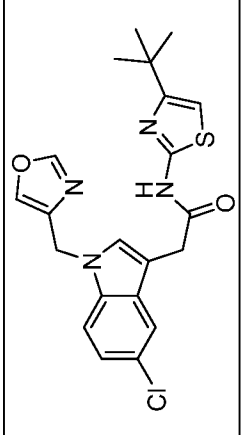
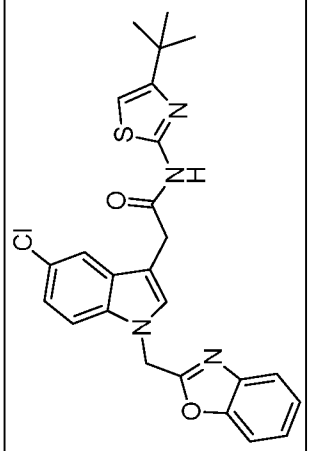
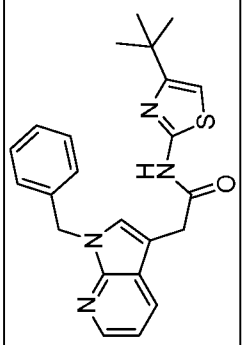
Table A. Examples of Compounds of Formula (I) and Their Activities

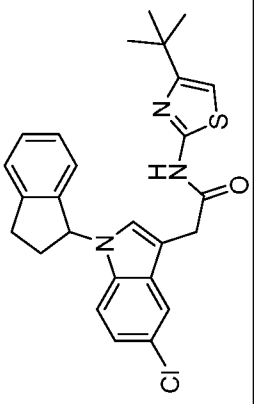
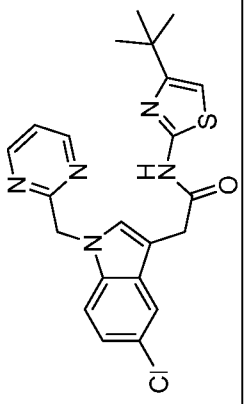
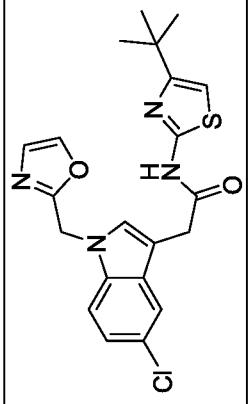
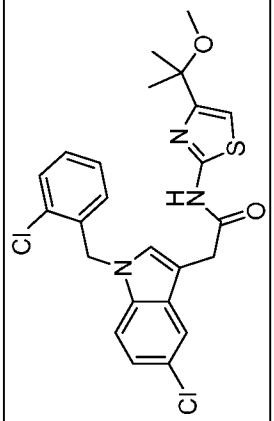
No.	Structure	Constitutively Active VCAMss-Gluc Mean IC_{50} (nM)	Dox Induced VCAM-ssGluc Mean IC_{50} (nM)	Dox Induced TNFa-FLGluc Mean IC_{50} (nM)	Dox Induced PD1-ssGluc Mean IC_{50} (nM)	Constitutively Active Prl-ssGluc Mean IC_{50} (nM)	24hr Dox Inducible Prl-ssGluc Mean IC_{50} (nM)
1				23671.61	8335.38		20695.83
2				24352.78	968.03		> 25000.00
3				> 25000.00	> 25000.00		> 25000.00

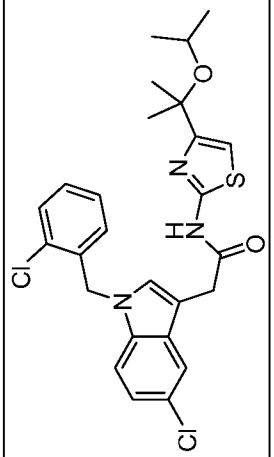
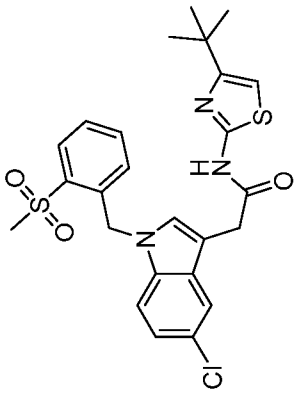
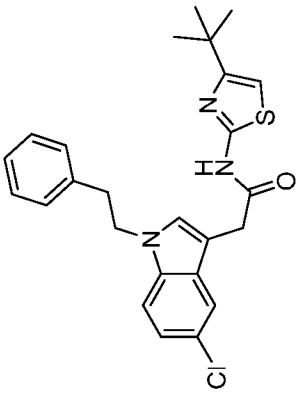
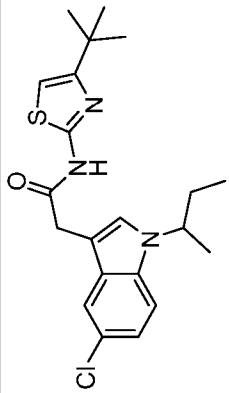
4				> 25000.00	6060.84	> 25000.00
5				> 25000.00	10042.2	> 25000.00
6				> 25000.00	8836.48	> 25000.00
7				23751.6	4141.74	> 25000.00

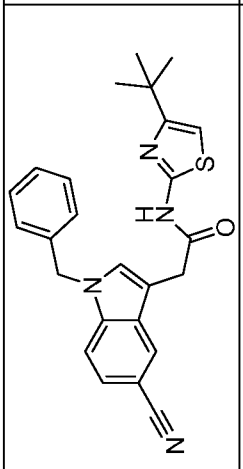
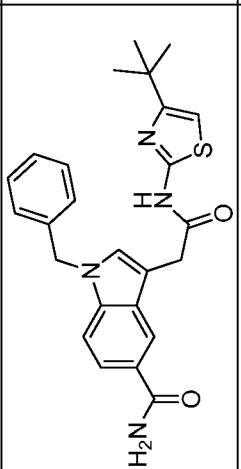
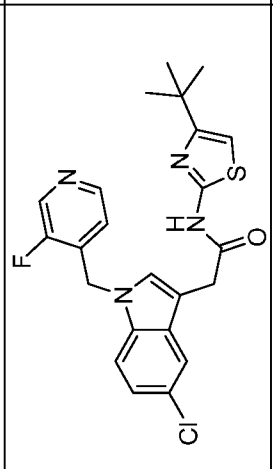
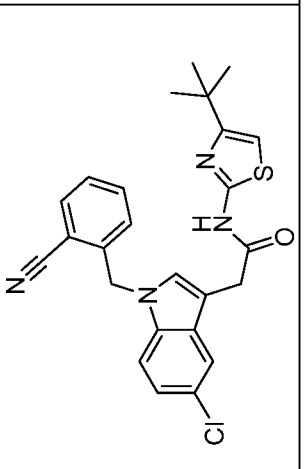
8				> 25000.00	1146.18	> 25000.00
9				> 25000.00	6329.27	> 25000.00
10				19129.99	2683.56	> 25000.00
11				> 25000.00	6099.6	24026.49

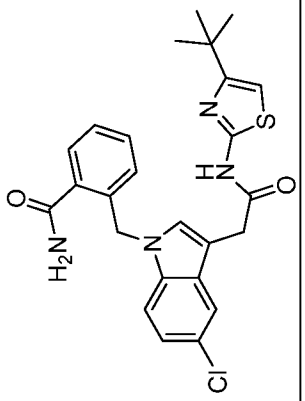
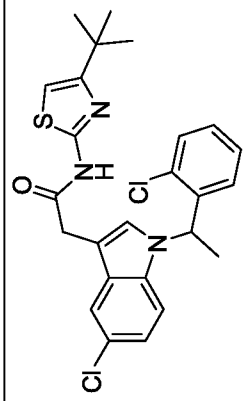
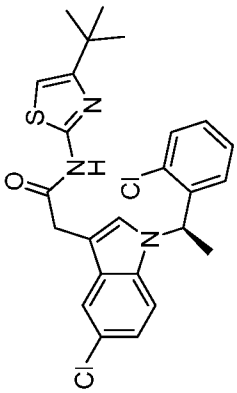
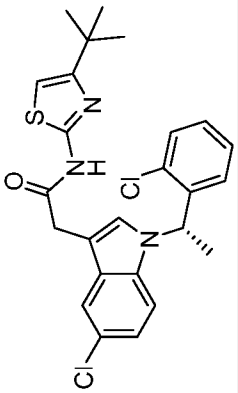
12				> 25000.00	3364.44	> 25000.00
13				> 25000.00	8602.44	> 25000.00
14				17691.61	10384.3	19111.14
15				> 21277.90	1884.99	> 25000.00

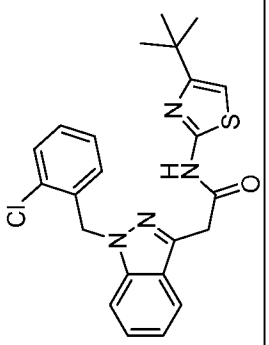
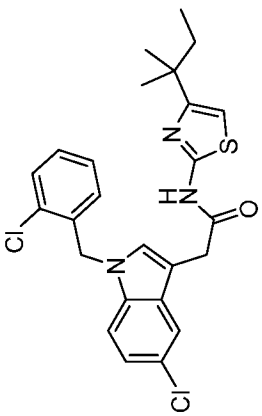
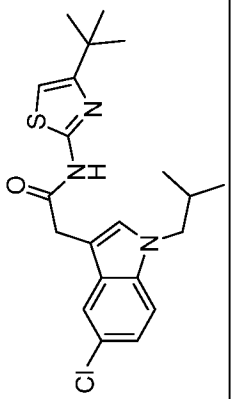
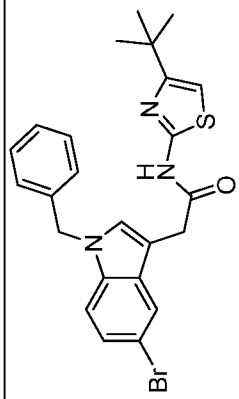
16			> 25000.00	10340.57		
17			> 25000.00	22007.86		
18			> 25000.00	9707.11	> 25000.00	
19			> 25000.00	12220.45	> 25000.00	

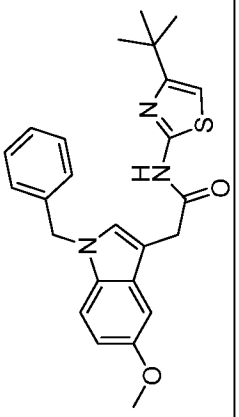
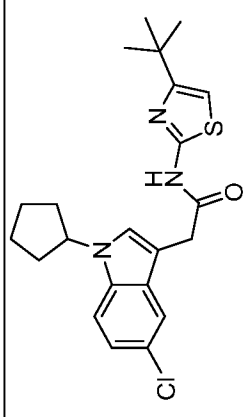
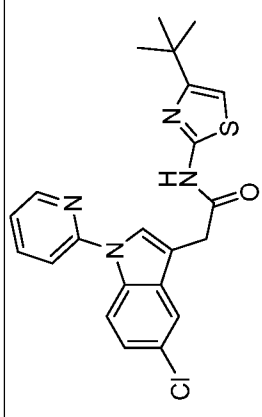
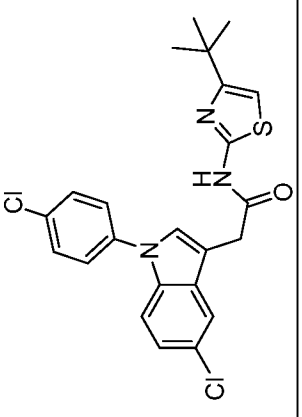
20				> 25000.00	6619.36	> 25000.00
21				> 25000.00	23304.36	> 25000.00
22				> 25000.00	23457.97	> 25000.00
23				13596.34	1043.34	> 25000.00

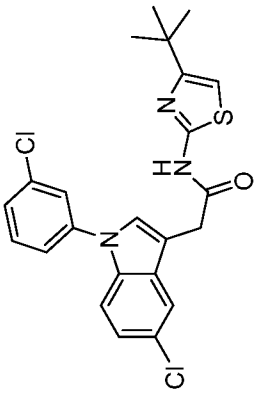
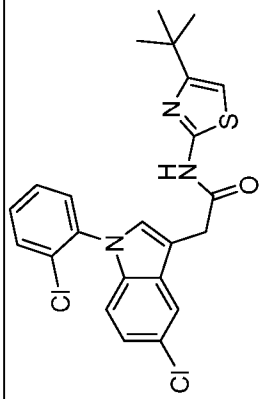
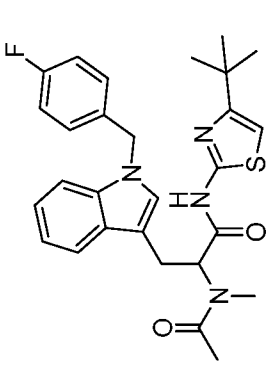
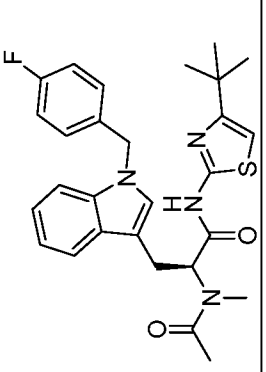
24			14766.28	715.4	> 25000.00
25				13217.16	> 25000.00
26				4147.85	> 25000.00
27				4376.8	> 25000.00

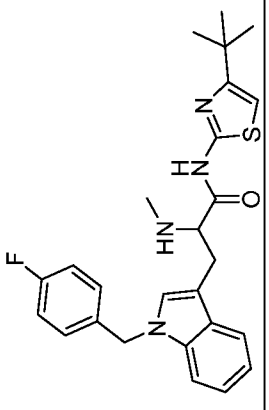
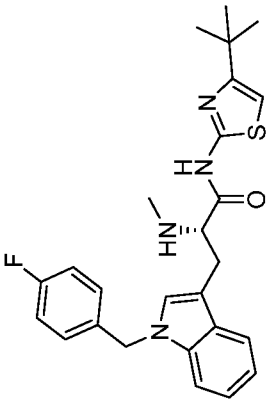
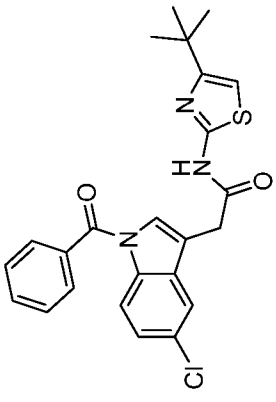
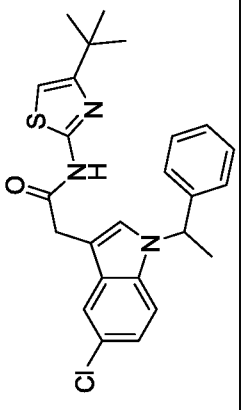
28				6055.21	> 25000.00
29				> 25000.00	> 25000.00
30				2417.15	> 25000.00
31				3654.17	> 25000.00

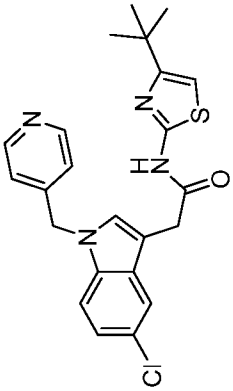
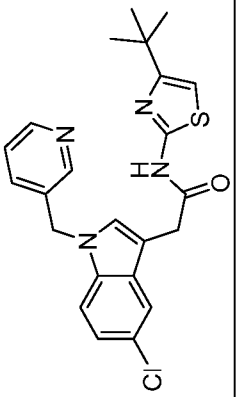
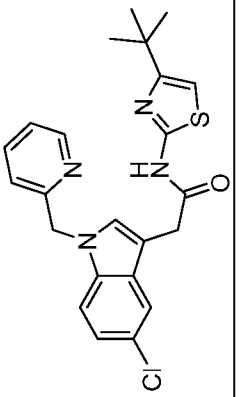
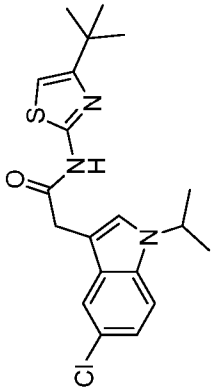
32				> 25000.00	> 25000.00	> 25000.00
33			> 25000.00	1549.37		> 25000.00
33a			> 25000.00	4158.7		> 25000.00
33b			> 25000.00	874.5		> 25000.00

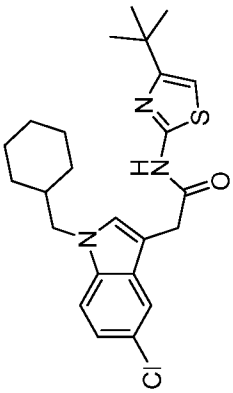
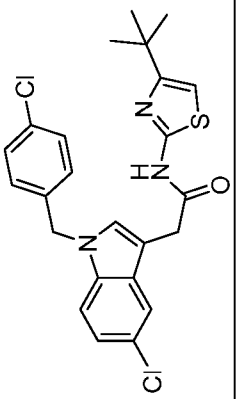
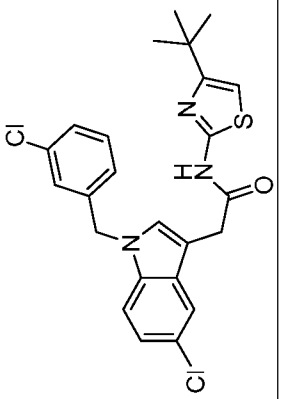
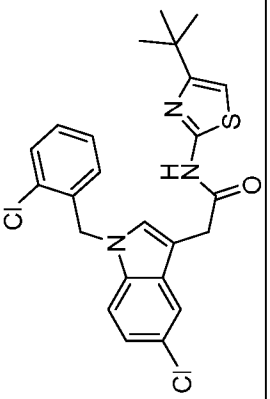
34				23441.39		> 25000.00
35			> 24200.99	726.7		> 25000.00
36				5375.5		> 25000.00
37				6129.41		> 25000.00

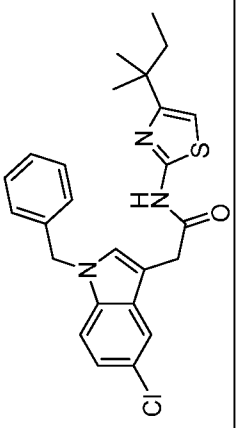
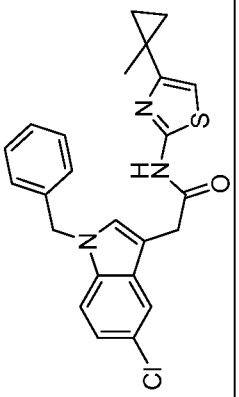
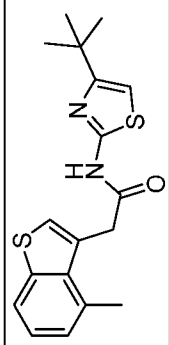
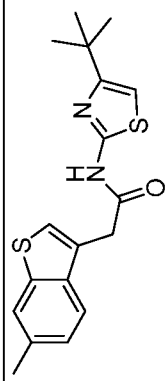
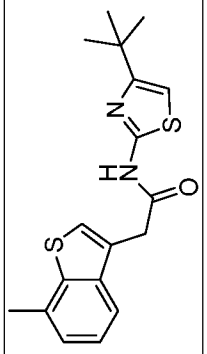
38				3409.01	> 25000.00
39				6515.27	> 25000.00
40				8715.15	> 25000.00
41				2690.87	> 25000.00

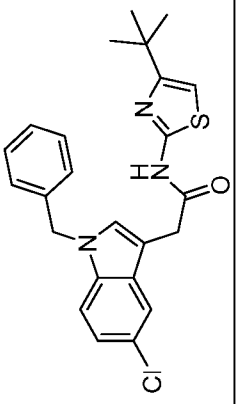
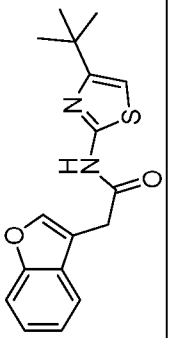
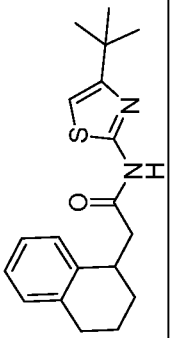
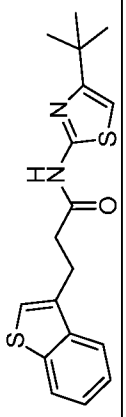
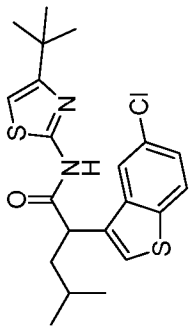
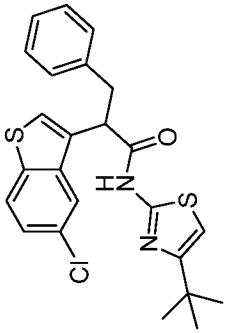
42				4135.92		> 25000.00
43				4399.71		> 25000.00
44						
44a				> 25000.00		> 25000.00

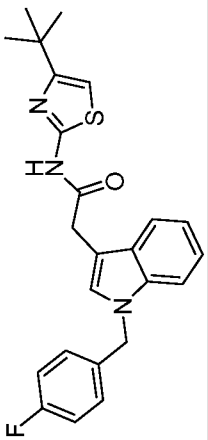
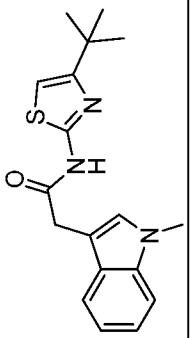
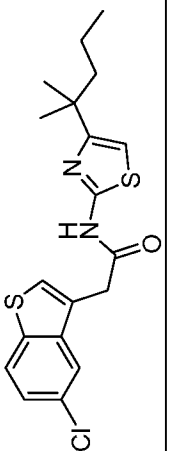
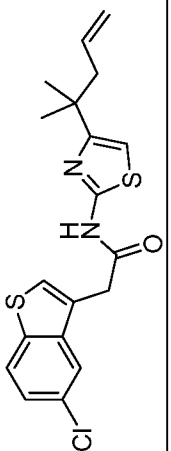
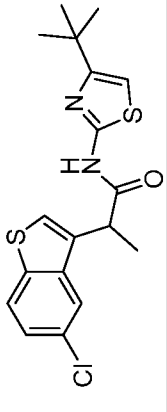
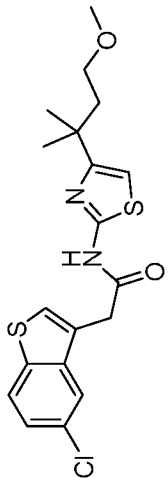
45						
45a			> 25000.00	> 25000.00		
46		2054.82		> 25000.00		
47		217.41		> 25000.00	2660.13	> 25000.00

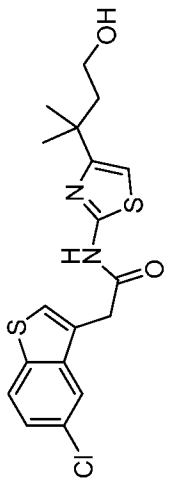
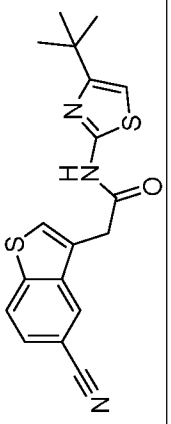
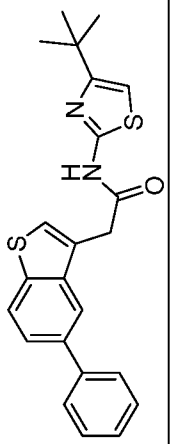
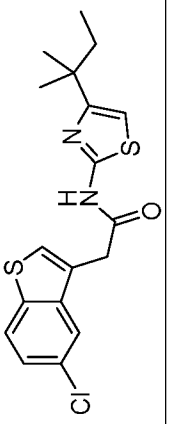
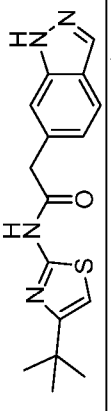
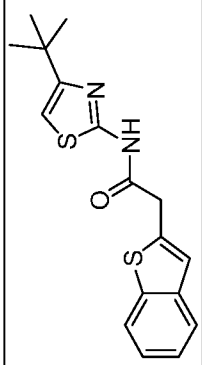
48		1411.96		10972.99	2755.78	> 25000.00 > 25000.00
49		3673.41				> 25000.00
50		2080.13				> 25000.00
51		587.48			4404.3	> 25000.00 > 25000.00

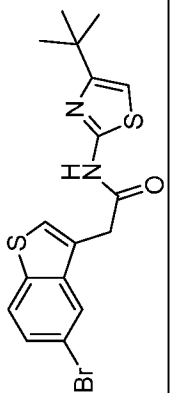
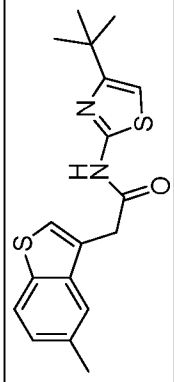
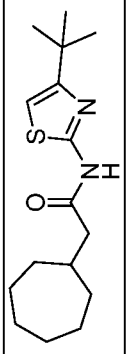
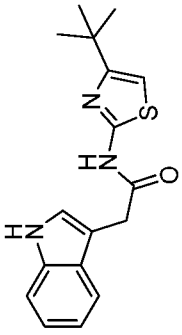
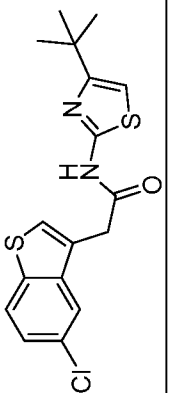
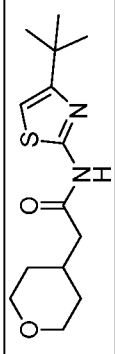
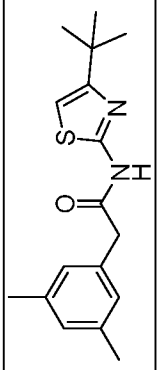
52		714.21			> 25000.00	
53		324.86			> 25000.00	
54		464.16		> 25000.00	> 25000.00	
55		147.46		> 25000.00	1150.88	> 25000.00

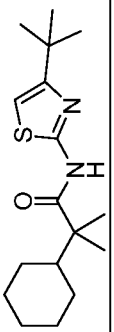
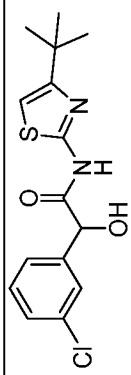
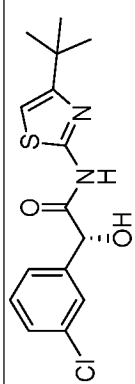
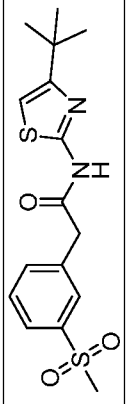
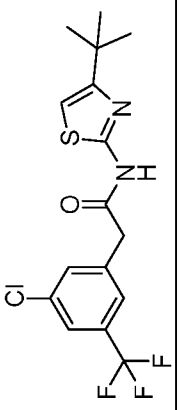
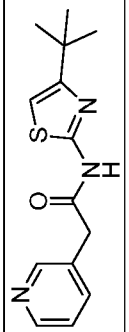
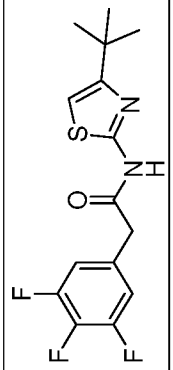
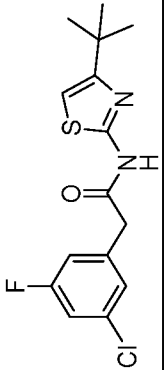
56		108.86		9795.96	2198.88	> 25000.00 > 25000.00
57		907.69			> 25000.00	
58		3195.85			> 25000.00	
59		6822.87	5904.02		22225.77	> 25000.00 > 25000.00
60		2419.16	3558.98		20373.84	> 25000.00 > 25000.00

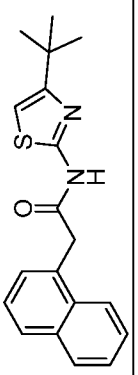
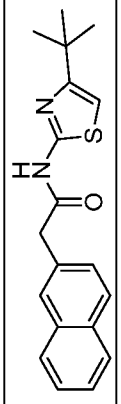
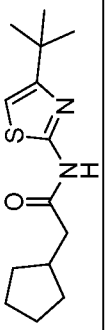
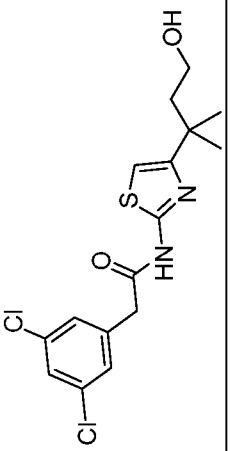
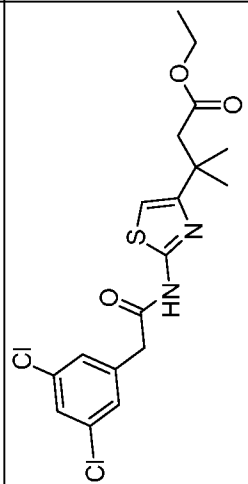
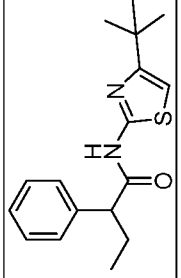
61		505.69	587.35	13108.26	4248.17	> 25000.00	> 25000.00
62		5300.16				> 25000.00	
63		9010.49				> 25000.00	
64		23100.25				> 25000.00	
65		6531.97				> 25000.00	
66		3919.97				> 25000.00	

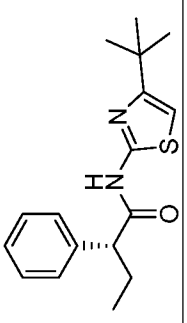
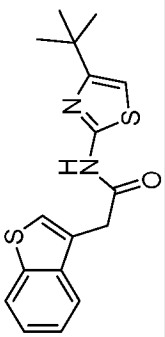
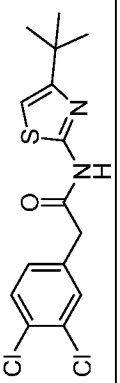
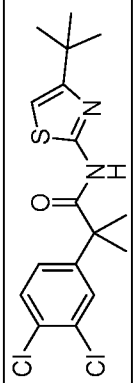
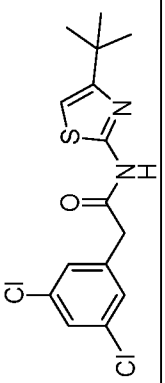
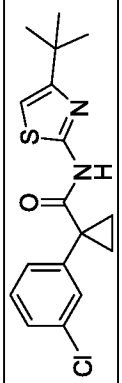
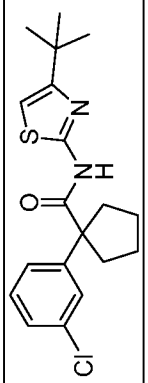
67		2106.47	1138.58		12877.02	> 25000.00	> 25000.00
68		4507.61				> 25000.00	
69		1001.85	744.47		1745.88	> 25000.00	> 25000.00
70		774.51				> 25000.00	
71		3208.05				> 25000.00	
72		> 25000.00				> 25000.00	

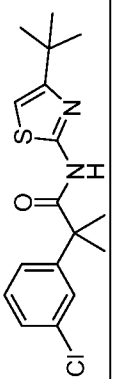
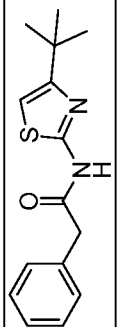
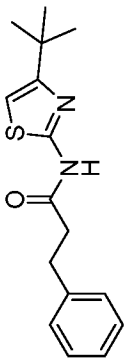
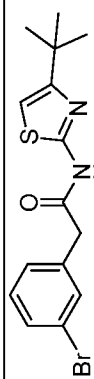
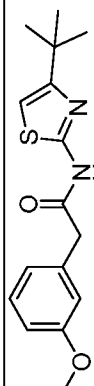
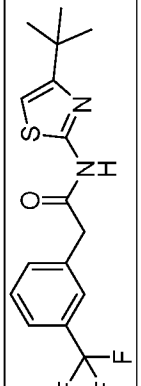
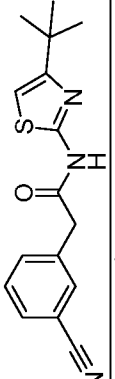
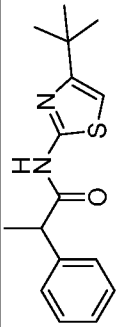
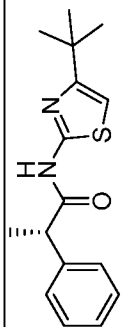
73		> 25000.00				> 25000.00
74		1249.21	1564.05		7821.76	> 25000.00 > 25000.00
75		4565.98				> 25000.00
76		1231.98	825.94		2752.63	> 25000.00 > 25000.00
77		> 25000.00				> 25000.00
78		> 25000.00				> 25000.00

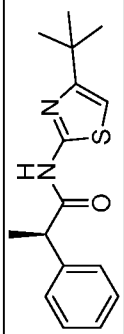
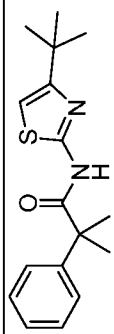
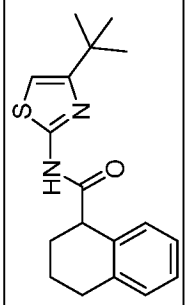
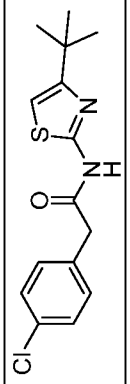
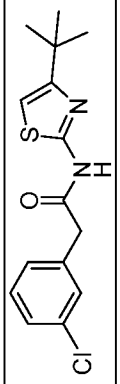
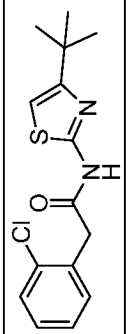
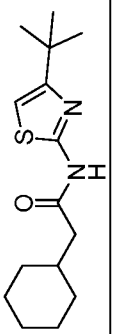
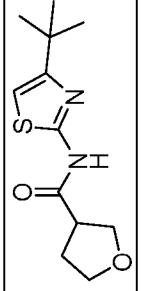
79		1400.14			> 25000.00	> 25000.00	
80		1630.12	2240.27		> 25000.00	8265.2	> 25000.00
81		5069.72			> 25000.00		
82		> 25000.00			> 25000.00		
83		915.28	1110.46	> 25000.00	> 25000.00	5367.03	> 25000.00
84		> 25000.00			> 25000.00		
85		7453.48			> 25000.00		

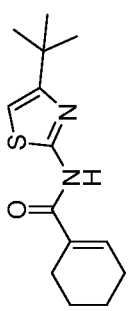
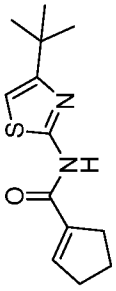
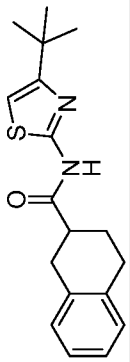
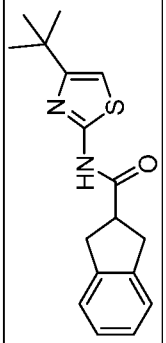
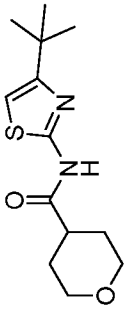
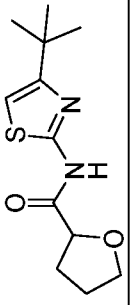
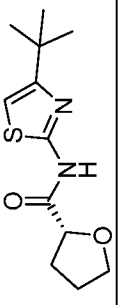
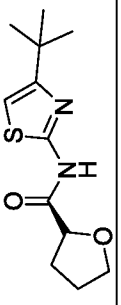
86		9013.38					> 25000.00
87							
87a		> 25000.00					> 25000.00
88		> 25000.00					> 25000.00
89		1540.05					> 25000.00
90		> 25000.00					> 25000.00
91		8175.8					> 25000.00
92		1914.16					> 25000.00

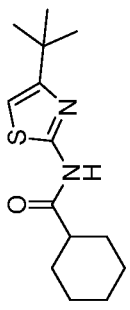
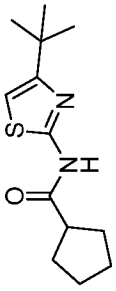
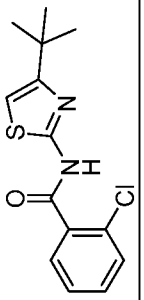
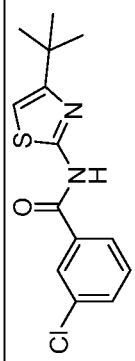
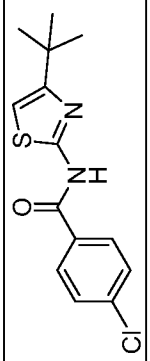
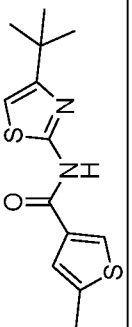
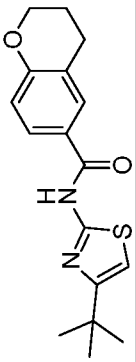
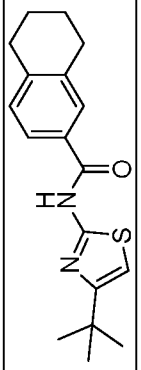
93		3450				> 25000.00
94		14987.77				> 25000.00
95		9823.77				> 25000.00
96		> 25000.00				> 25000.00
97		8929.8				> 25000.00
98						

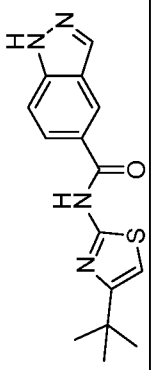
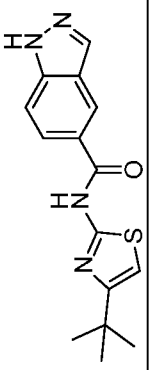
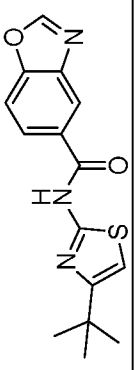
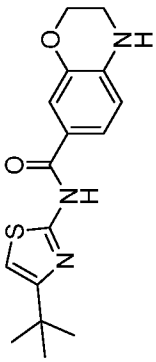
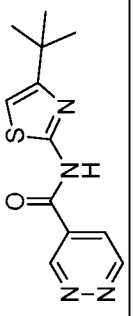
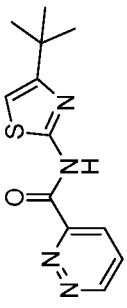
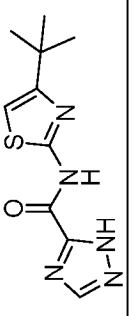
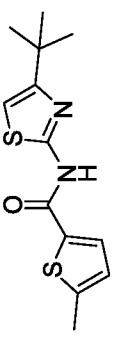
98a		9544.47					> 25000.00
99		1757.18					> 25000.00
100		2638.82					> 25000.00
101		6488.42					> 25000.00
102		1686.05					> 25000.00
103		19614.48					> 25000.00
104		8154.13					> 25000.00

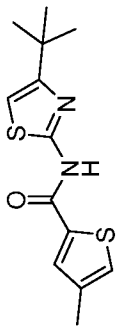
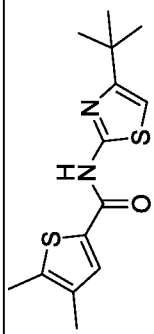
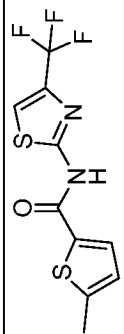
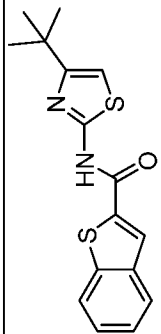
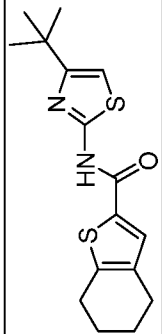
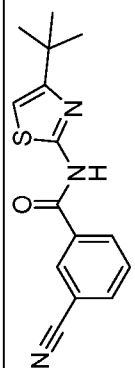
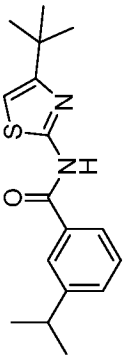
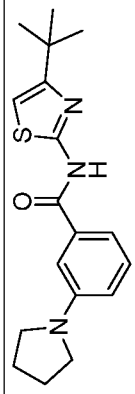
105		8603.6					> 25000.00	
106		24111.17					> 25000.00	
107		17351.28					> 25000.00	
108		5713.4					> 25000.00	
109		10337.69					> 25000.00	
110		6809.38					> 25000.00	
111		15363.13					> 25000.00	
112								
112a		> 25000.00					> 25000.00	

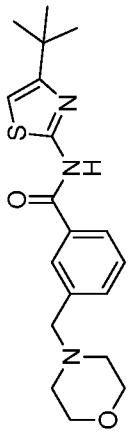
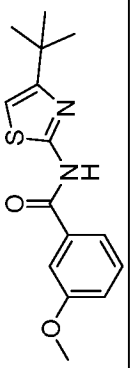
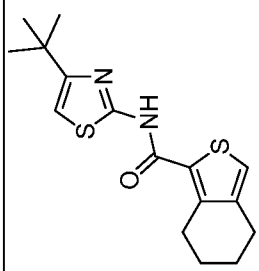
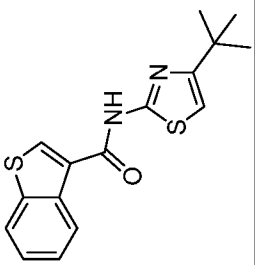
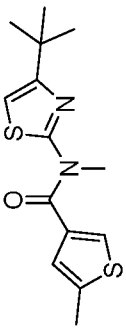
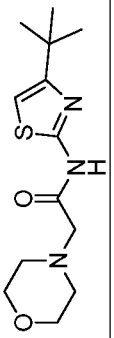
112b		11124.64						> 25000.00
113		14716.92						> 25000.00
114		> 25000.00						> 25000.00
115		4880.65						> 25000.00
116		7848.99						> 25000.00
117		18380.41						> 25000.00
118		6086.36						> 25000.00
119		> 25000.00						> 25000.00

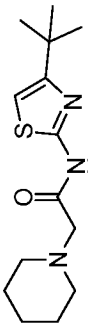
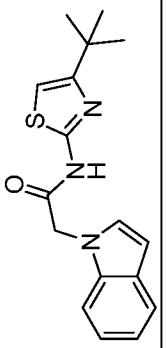
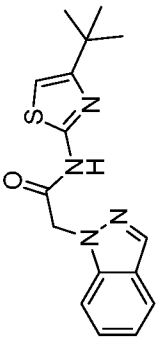
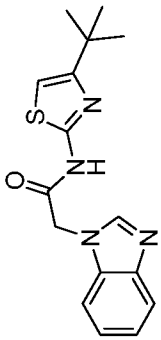
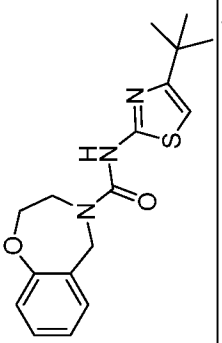
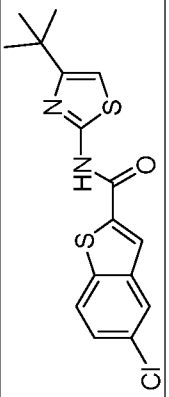
120		23697.85			> 25000.00			
121		> 25000.00			> 25000.00			
122		11846.81			> 25000.00			
123		11169.65			> 25000.00			
124		> 25000.00			> 25000.00			
125								
125a								
125b		> 25000.00			> 25000.00			

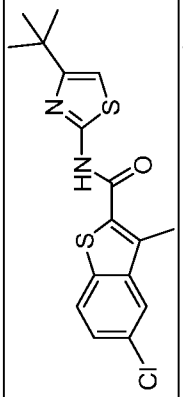
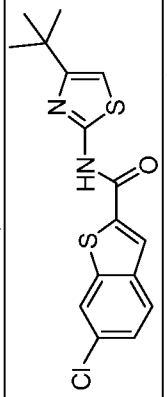
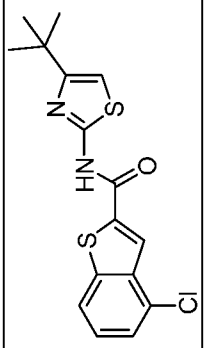
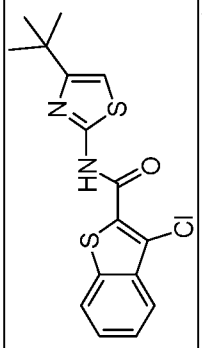
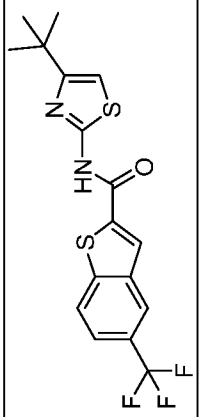
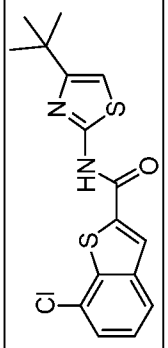
126		9798.71				> 25000.00		
127		16991.25				> 25000.00		
128		> 25000.00				> 25000.00		
129		8403.1				> 25000.00		
130						> 25000.00		
131		12500	19063	> 25000.00	9837.4	> 25000.00	> 25000.00	
132		6094.2				> 25000.00		
133		10901				> 25000.00		

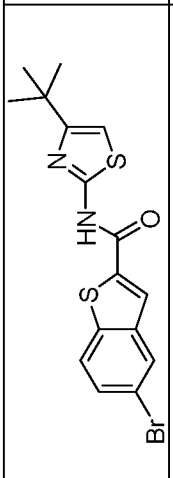
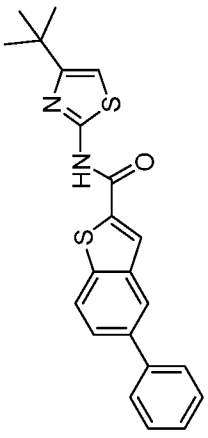
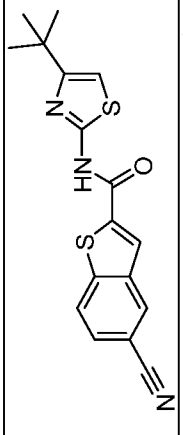
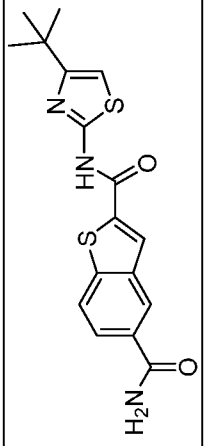
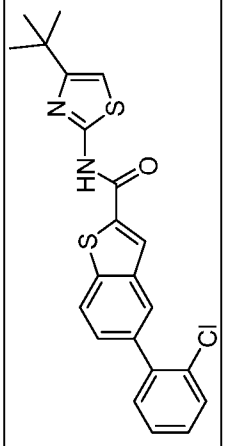
134		20680					> 25000.00
135		> 25000.00					> 25000.00
136		> 25000.00					> 25000.00
137		> 25000.00					> 25000.00
138		> 25000.00					> 25000.00
139		> 25000.00					> 25000.00
140		> 25000.00					> 25000.00
141		7651.3					> 25000.00

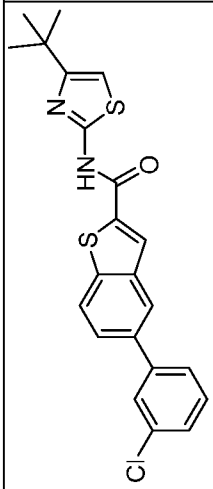
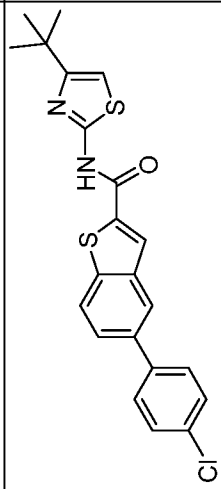
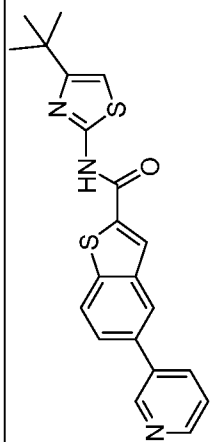
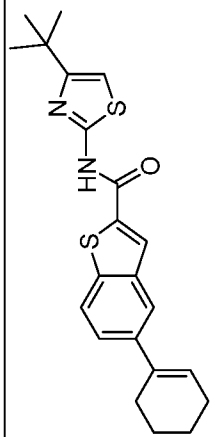
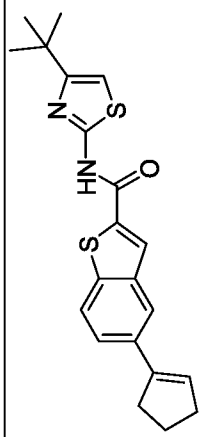
142		17081				> 25000.00		
143		9076				> 25000.00		
144		> 25000.00				> 25000.00		
145		4932.1				> 25000.00		
146		5349.6		22683	4442	> 25000.00	> 25000.00	
147		> 25000.00				> 25000.00		
148		> 25000.00				> 25000.00		
149		> 25000.00				> 25000.00		

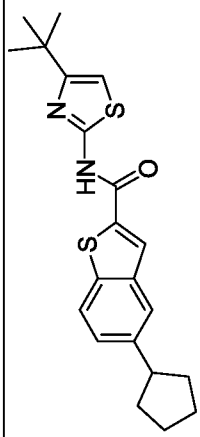
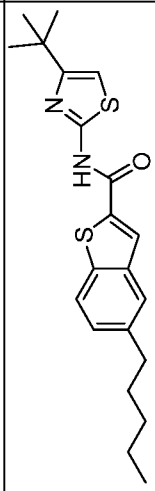
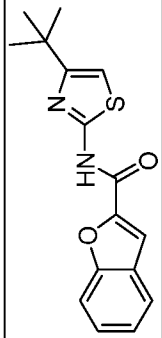
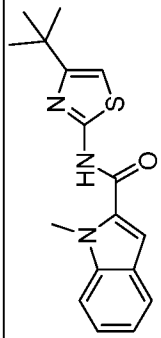
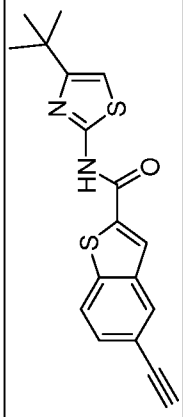
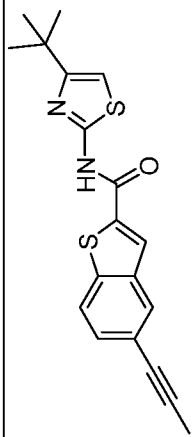
150		> 25000.00				
151		> 25000.00				
152		> 25000.00				
153		22550				
154		> 25000.00				
155		> 25000.00				

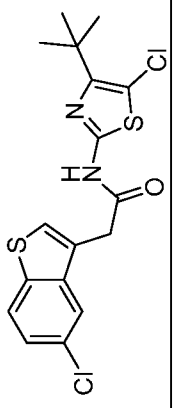
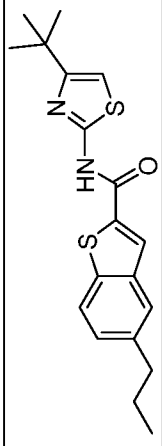
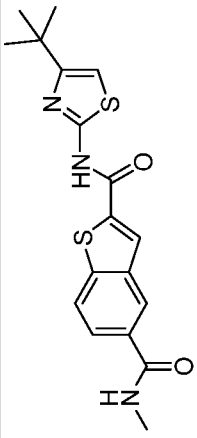
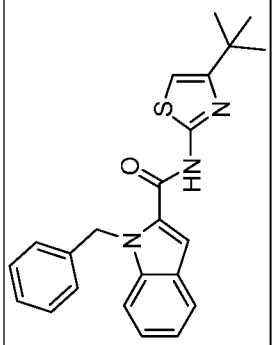
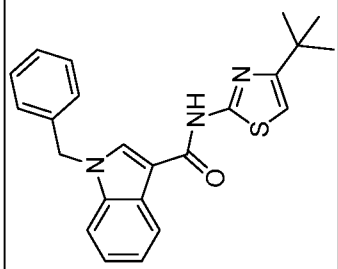
156		> 25000.00				> 25000.00
157		8746.3				> 25000.00
158		> 25000.00				> 25000.00
159		> 25000.00				> 25000.00
160		10091				> 25000.00
161		9270.1				> 25000.00

162		> 25000.00			> 25000.00	
163		> 25000.00			> 25000.00	
164		5702.2			> 25000.00	
165		> 25000.00			> 25000.00	
166		16493			> 25000.00	
167		3221.4			> 25000.00	

168		> 25000.00			> 25000.00	
169		10959			> 25000.00	
170		> 25000.00	> 25000.00	> 25000.00	> 25000.00	> 25000.00
171		> 25000.00			> 25000.00	
172		4112.7	9531.1	3870.5	> 25000.00	> 25000.00

173		5022.8			> 25000.00
174		13962			> 25000.00
175		> 25000.00			> 25000.00
176		16224			> 25000.00
177		> 25000.00			> 25000.00

178		> 25000.00				> 25000.00
179		8135.2				> 25000.00
180		23777				> 25000.00
181		2212.1				> 25000.00
182		> 25000.00				> 25000.00
183		4971.4				> 25000.00

184		11823			> 25000.00
185		14059			> 25000.00
186				8804.5	7444.1
187				8292.2	> 25000.00
188				7054.1	> 25000.00

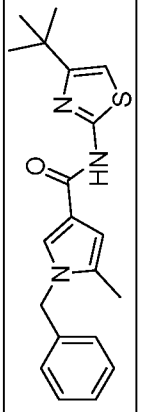
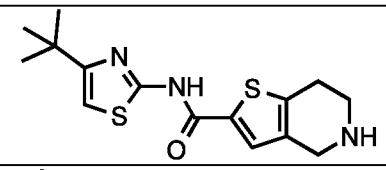
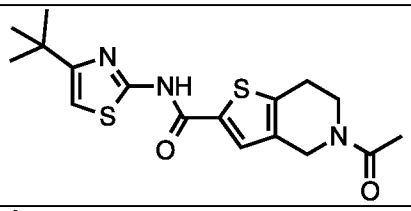
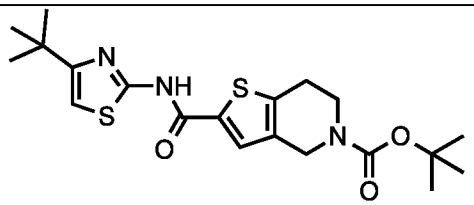
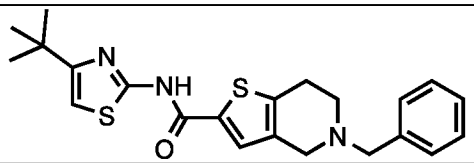
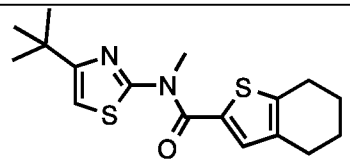
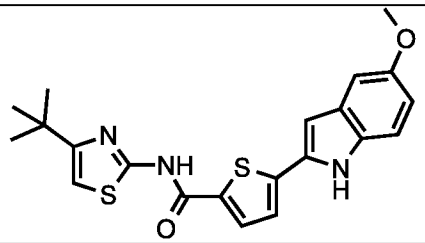
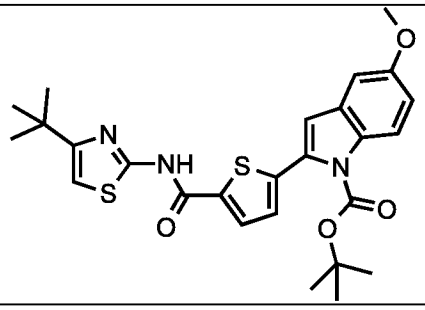
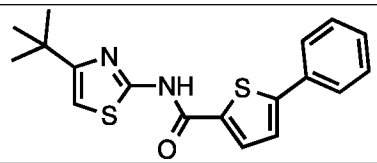
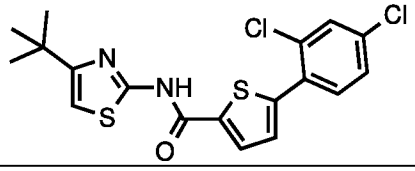
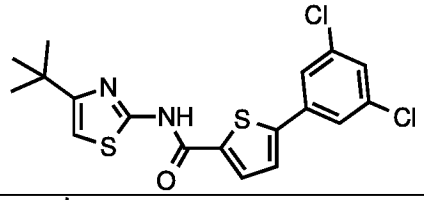
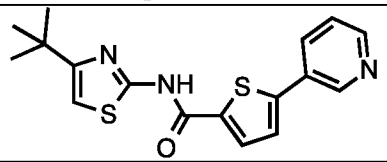
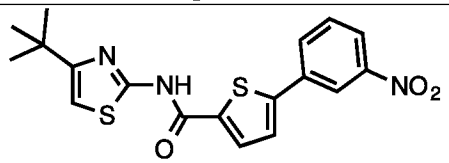
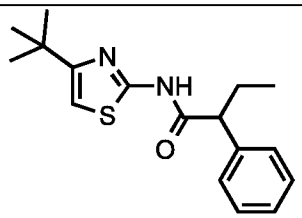
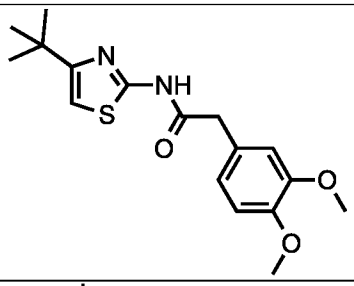
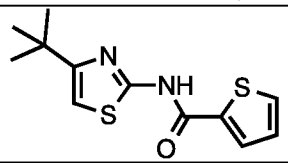
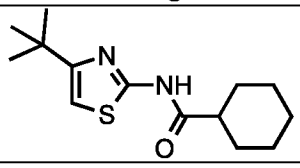
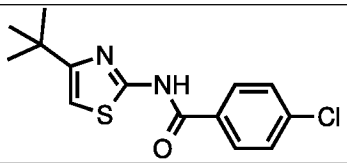
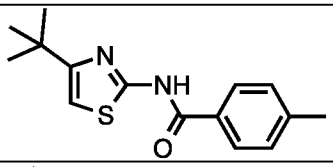
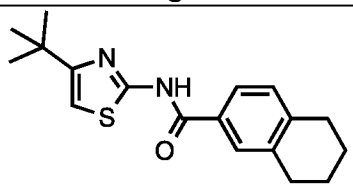
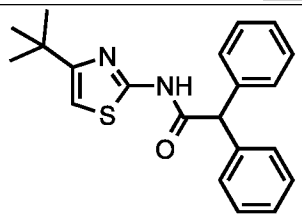
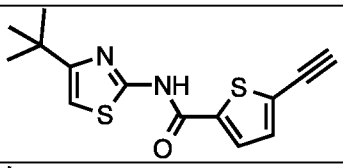
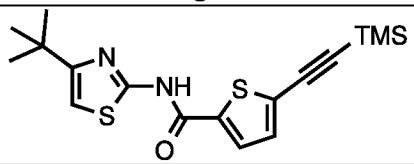
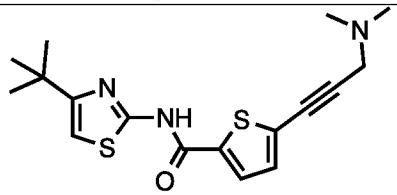
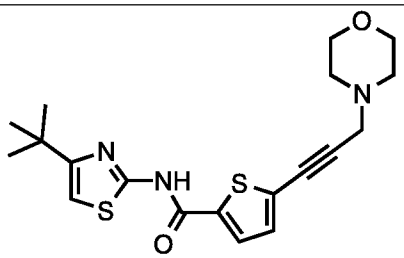
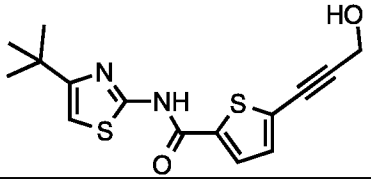
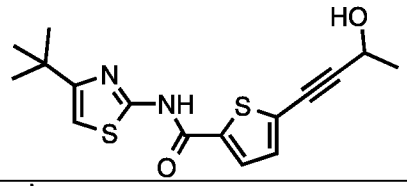
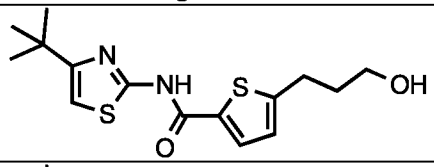
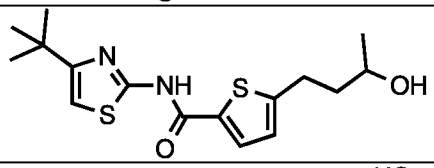
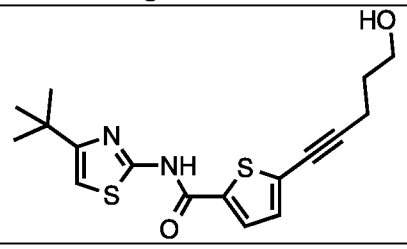
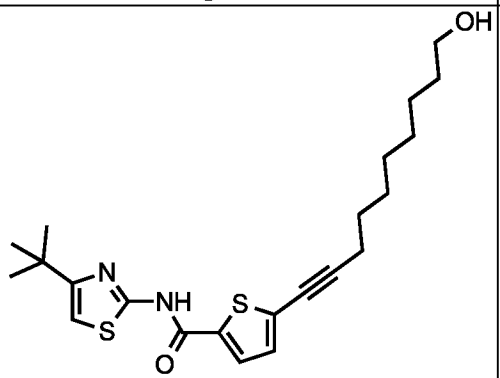
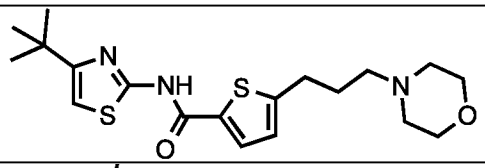
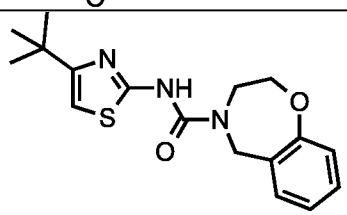
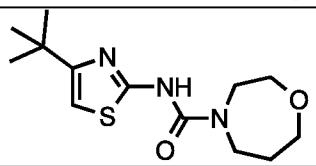
189				> 25000.00	4744.3	> 25000.00

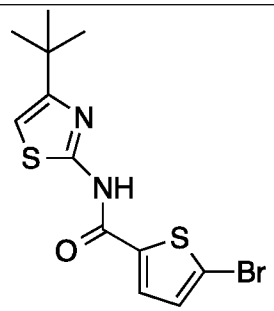
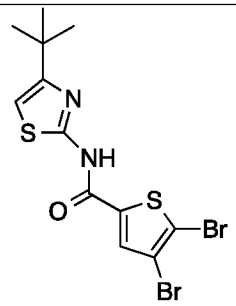
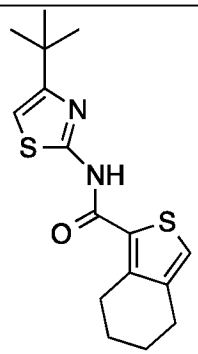
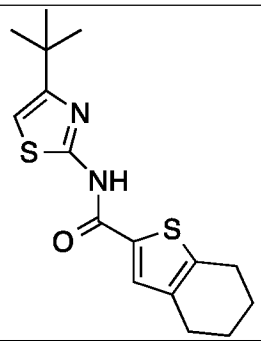
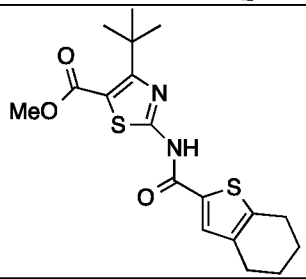
Table B. Additional Examples of Compounds of Formula (I)

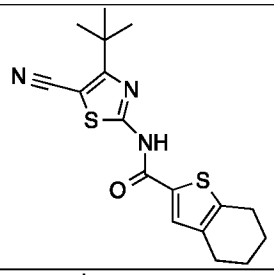
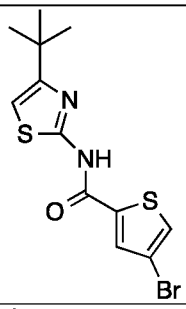
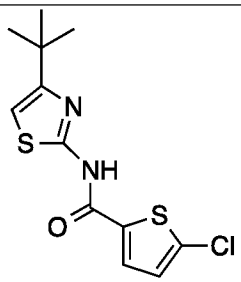
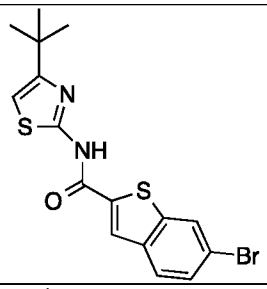
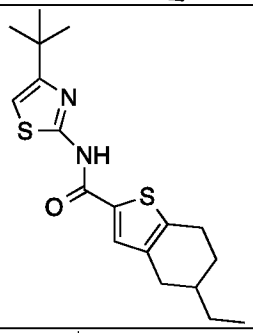
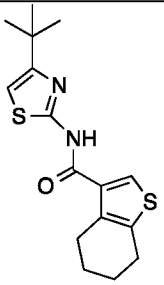
No.	Structure	VCAMss (μM)	TNF (μM)
1		0% @ 2.5 uM	0% @ 2.5 uM
2		> 50 uM	> 50 uM
3		~20 uM	>50 uM
4		33% @ 2.5 uM	22% @ 2.5 uM
5		19% @ 2 uM	
6		42% @ 2.5 uM	27% @ 2.5 uM
7		56% @ 2.5 uM	0% @ 2.5 uM

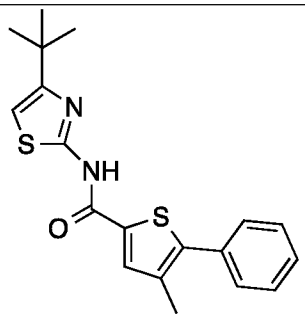
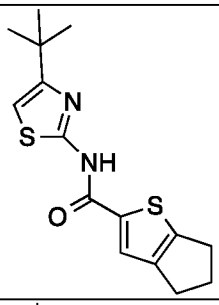
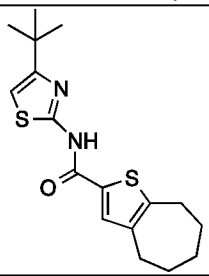
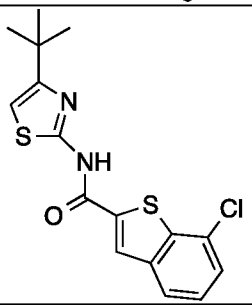
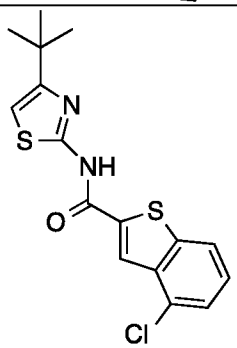
8		1.30 uM	4.50 uM
9		2.27 uM	4.31 uM
10		35% @ 2 uM	
11		19% @ 2 uM	
12		59% @ 2 uM	
13		ND	
14		ND	
15		23% @ 2.5 uM	24% @ 2.5 uM
16		30% @ 2 uM	

17		66% @ 2.5 uM	0% @ 2.5 uM
18		9% @ 2 uM	
19		20% @ 2 uM	
20		ND	
21		66% @ 2.5 uM	
22		54% @ 2 uM	
23		76% @ 2 uM	
24		38% @ 2 uM	
25		80% @ 2 uM	

26		24% @ 2 uM	
27		31% @ 2 uM	
28		30% @ 2 uM	
29		53% @ 2 uM	
30		52% @ 2 uM	
31		45% @ 2 uM	
32		24% @ 2 uM	
33		0% @ 2 uM	

34		23 uM	>80 uM
35		3.8 uM	26 uM
36		5.7 uM	>80 uM
37		0.13 uM	6.4 uM
38		3.9 uM	>80 uM

39		>80 uM	>80 uM
40		14 uM	72 uM
41		2.0 uM	8.0 uM
42		3.3 uM	>80 uM
43		7.9 uM	>80 uM
44		14 uM	73 uM

45		4.5 uM	31 uM
46		1.0 uM	18 uM
47		0.58 uM	4.3 uM
48		2.5 uM	>80 uM
49		6.4 uM	46 uM

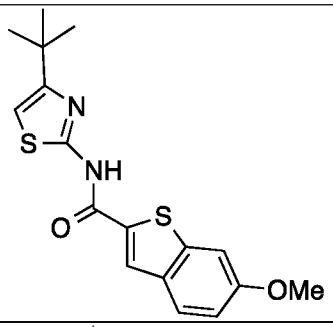
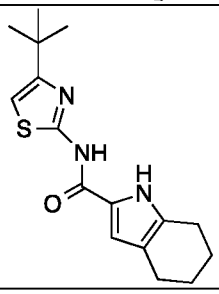
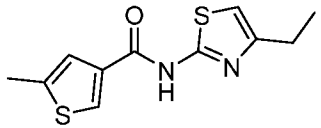
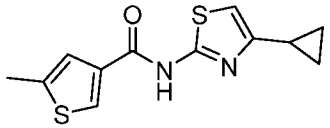
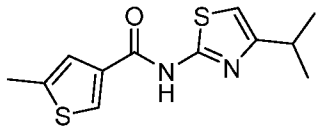
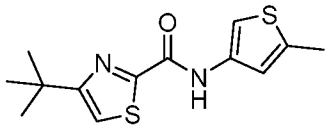
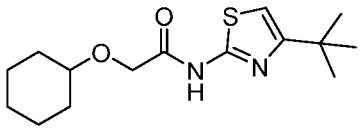
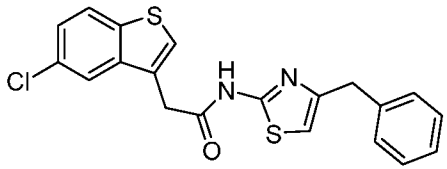
50		1.8 uM	>80 uM
51		2.5 uM	>80 uM

Table C. Additional Examples of Sec61 Inhibitors of the Disclosure

No.	Structure	Constitutively Active VCAMss-Gluc Mean IC50 (nM)	Dox Induced VCAM-ssGluc Mean IC50 (nM)	Dox Induced TNFa-FLGluc Mean IC50 (nM)	Dox Induced PD1-ssGluc Mean IC50 (nM)	Constitutively Active Prl-ssGluc Mean IC50 (nM)	24hr Dox Inducible Prl-ssGluc Mean IC50 (nM)
1		> 25000.00				> 25000.00	
2		> 25000.00				> 25000.00	
3		22767				> 25000.00	
4		> 25000.00				> 25000.00	
5		> 25000.00				> 25000.00	
6		19870				> 25000.00	

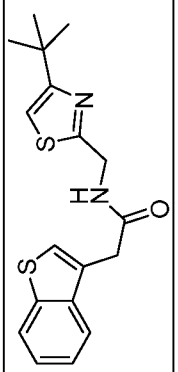
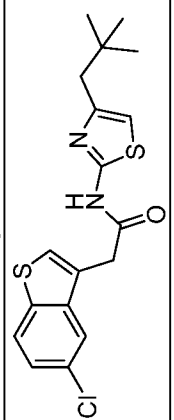
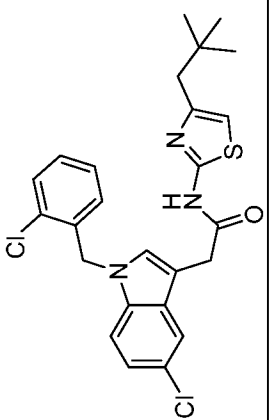
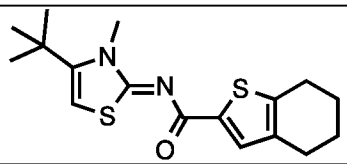
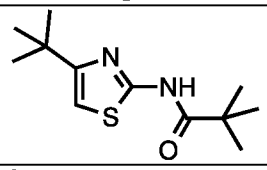
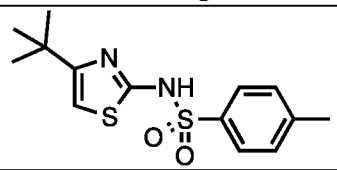
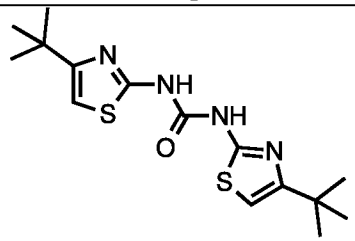
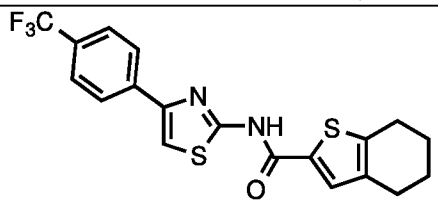
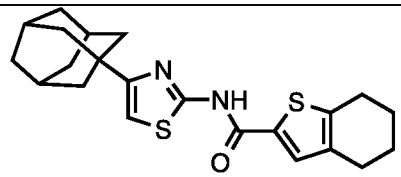
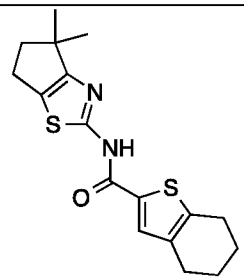
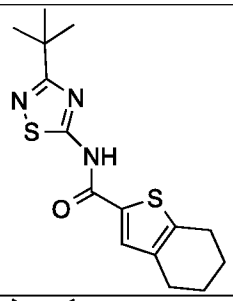
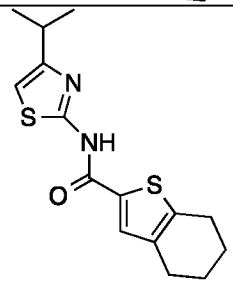
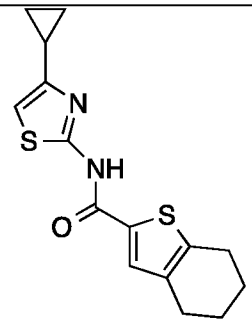
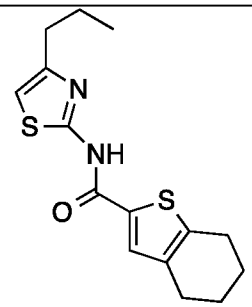
7		> 25000.00			> 25000.00	
8		2475.2		6986	> 25000.00	
9			> 25000.00	6179		> 25000.00

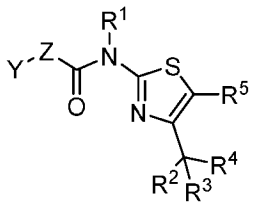
Table D. Additional Examples of Sec61 Inhibitors of the Disclosure

No.	Structure	VCAMss (μM)	TNF (μM)
1		63% @ 2 uM	
2		0% @ 2 uM	
3		0% @ 2 uM	
4		19% @ 2 uM	
5		3% @ 2 uM	
6		55% @ 2 uM	
7		0.40 uM	> 80 uM

8		0.43 uM	4.7 uM
9		1.2 uM	>80 uM
10		11 uM	>80 uM
11		2.6 uM	>80 uM

We Claim:

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein:

Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzoimidazolyl, pyrrolopyridinyl, benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, tetrahydrobenzooxazepinyl, phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, dihydroindenyl, thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiopheneyl, dihydrothienopyridinyl, tetrahydrocycloheptathiopheneyl, triazolyl, thiadiazolyl, pyridinyl, pyridazinyl, C_{5-7}cycloalkyl, C_{3-7}heterocycloalkyl, or C_{5-7}cycloalkenyl;

Z is C_{0-2}alkylene and

when Z is C_{1-2}alkylene, then (a) one carbon can be substituted with one or two substituents selected from C_{1-6}alkyl, unsubstituted C_{0-3}alkylene-aryl, $NR^1C(O)C_{1-3}$alkyl, NR^1C_{1-3}alkyl, and OH, with the proviso that the carbon is not substituted with two OH, or (b) one carbon and its two substituents form a 3- to 6-membered ring;

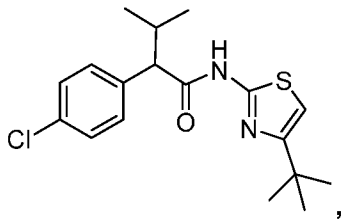
R^1 is H or C_{1-3}alkyl;

R^2 and R^3 are each independently unsubstituted C_{1-3}alkyl or halo, or R^2 and R^3, together with the carbon to which they are attached, form a 3- to 6-membered ring;

R^4 is C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-3}alkylene-OH, C_{0-3}alkylene-C_{1-6}alkoxyl, C_{1-3}alkylene-$C(O)OC_{1-4}$alkyl, or halo; and

R^5 is H, halo, CN, or $C(=O)OC_{1-3}$alkyl;

with the proviso that the compound of Formula (I) is not: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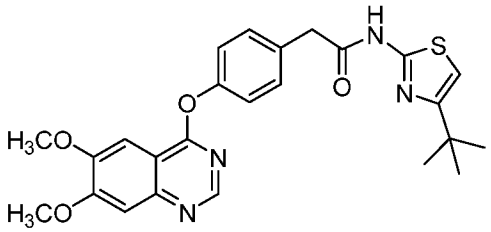
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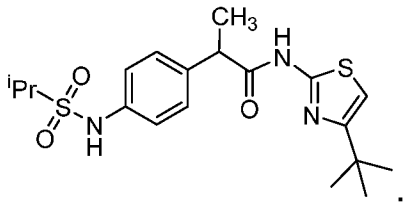
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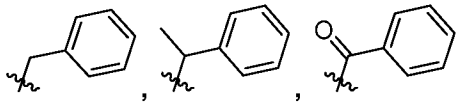
2. The compound of claim 1, wherein Y comprises pyrrolyl, indolyl, tetrahydroindolyl, indazolyl, benzodimidzolyl, or pyrrolopyridinyl.

3. The compound of claim 2, wherein the ring nitrogen of Y is unsubstituted.

4. The compound of claim 2, wherein the ring nitrogen of Y is substituted with $C_{1\text{-}6}$alkyl, $C(O)OC_{1\text{-}6}$alkyl, $C_{0\text{-}3}$alkylene-aryl, $C_{1\text{-}3}$alkylene-heteroaryl, $C_{3\text{-}6}$cycloalkyl, or $C_{1\text{-}3}$alkylene-amide.

5. The compound of claim 4, wherein the nitrogen ring atom of Y is substituted with methyl, isopropyl, isobutyl, sec-butyl, phenyl, indene, pyridinyl, pyrmidinyl, isooxazolyl, oxazolyl, benzooxazolyl, cyclohexyl, or cyclopentyl.

6. The compound of claim 4 or 5, wherein is the ring nitrogen is substituted with a moiety selected from the group consisting of:

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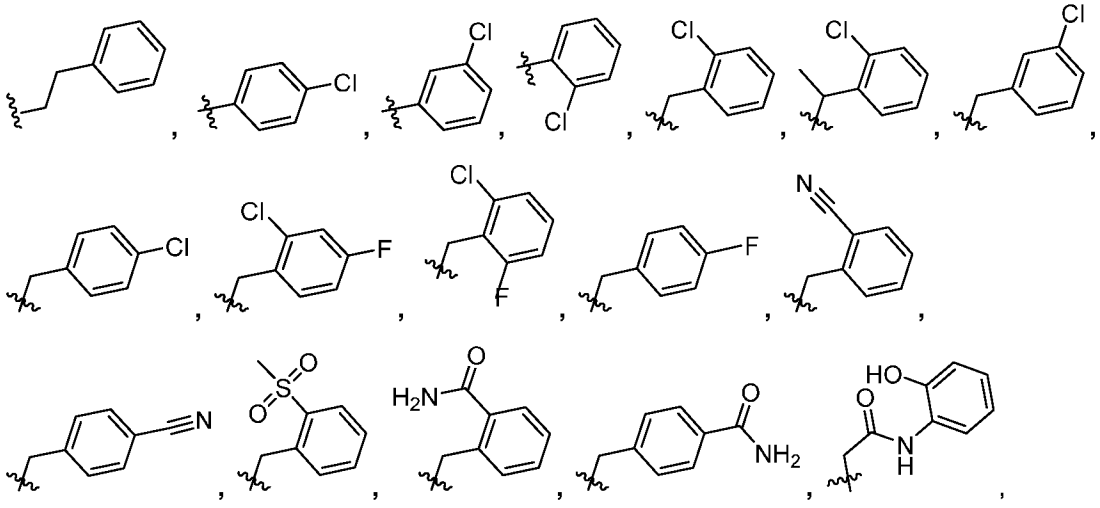
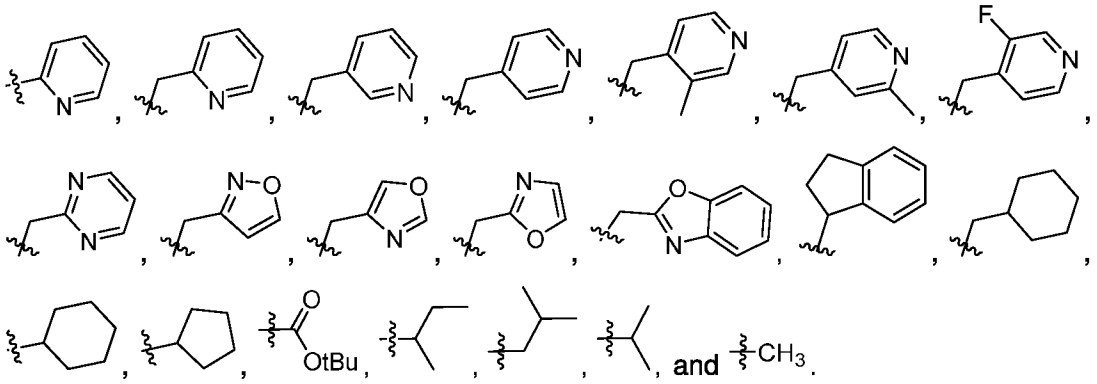
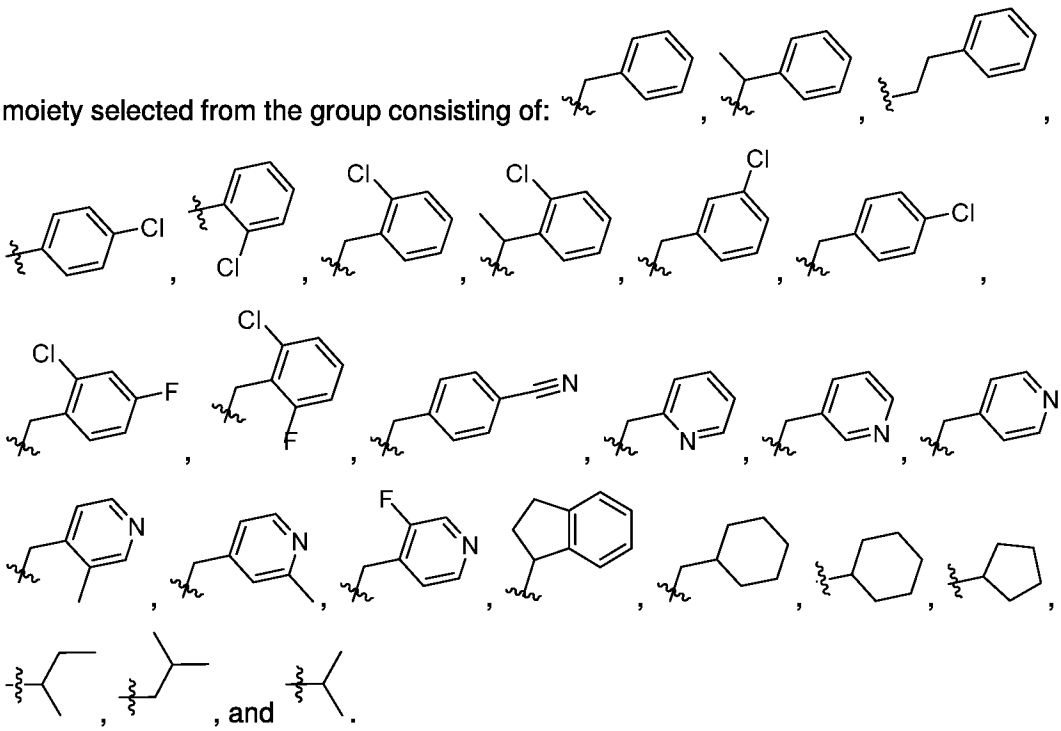




7. The compound of claim 6, wherein the ring nitrogen is substituted with a moiety selected from the group consisting of:



8. The compound of claim 1, wherein Y comprises benzofuranyl, benzooxazolyl, chromanyl, dihydrobenzooxazinyl, dihydrobenzooxazepinyl, or tetrahydrobenzooxazepinyl.

9. The compound of claim 1, wherein Y comprises phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, or dihydroindenyl.

10. The compound of claim 1, wherein Y comprises thiophenyl, benzothiophenyl, cyclopentathiophenyl, tetrahydrobenzothiophenyl, dihydrothienopyridinyl, or tetrahydrocycloheptathiopheneyl.

11. The compound of claim 10, wherein Y comprises dihydrothienopyridinyl and the ring nitrogen atom is unsubstituted or substituted with acetyl, $C(O)OC_{1-6}$alkyl, or C_{0-3}alkylene-aryl.

12. The compound of claim 1, wherein Y comprises triazolyl, thiadiazolyl, pyridinyl or pyridazinyl.

13. The compound of claim 1, wherein Y comprises C_{5-7}cycloalkyl, C_{3-7}heterocycloalkyl, or C_{5-7}cycloalkenyl.

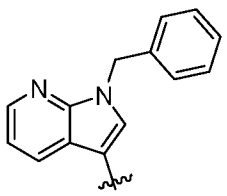
14. The compound of claim 13, wherein Y comprises cyclopentyl, cyclohexyl, cycloheptyl, tetrahydrofuranyl, tetrahydropyranyl, morpholine, piperidine, oxazepaneyl, cyclopentenyl or cyclohexenyl.

15. The compound of any one of claims 2-14, wherein Y is unsubstituted at all ring carbon atoms.

16. The compound of any one of claims 2-14, wherein Y is substituted at one or more ring carbon atom with a substituent selected from halo, CN, C_{1-6}alkyl, C_{2-12}alkynyl, C_{1-3}alkoxyl, amido, sulfonyl, C_{3-8}cycloalkyl, C_{5-7}cycloalkenyl, C_{0-3}alkylene-heterocycloalkyl, C_{0-3}alkylene-aryl, and C_{0-3}alkylene-heteroaryl.

17. The compound of claim 16, wherein the ring carbon substituent is chloro.

18. The compound of claim 1, wherein Y is selected from the group consisting of: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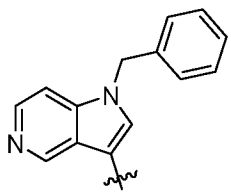
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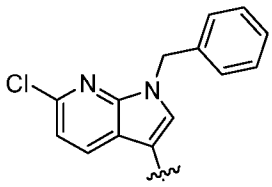
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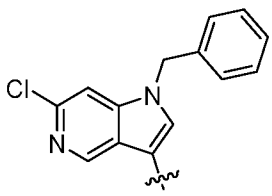
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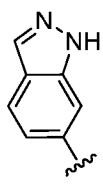
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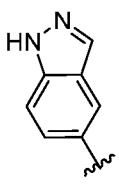
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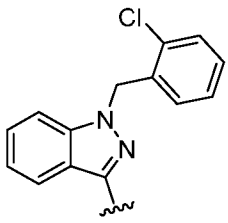
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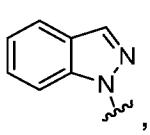
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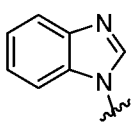
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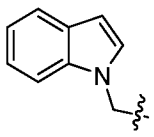
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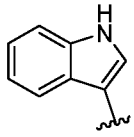
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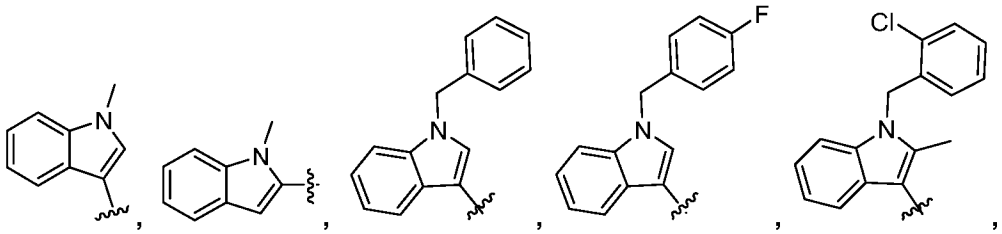
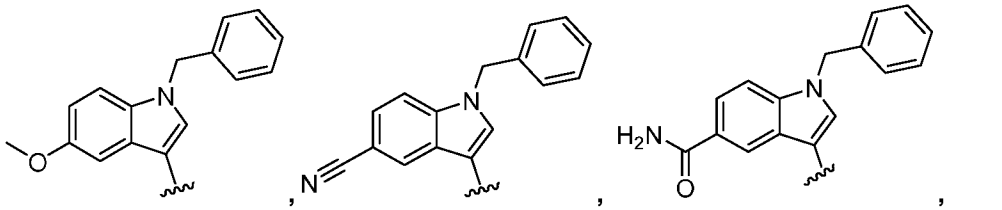
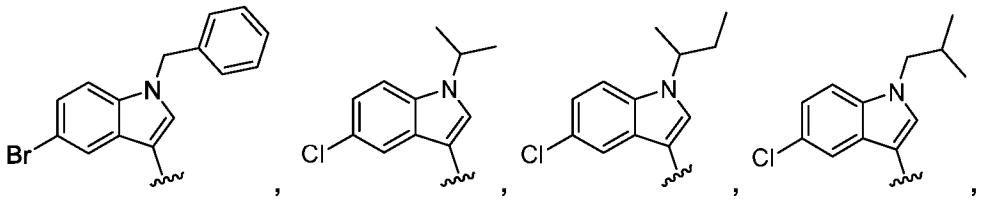
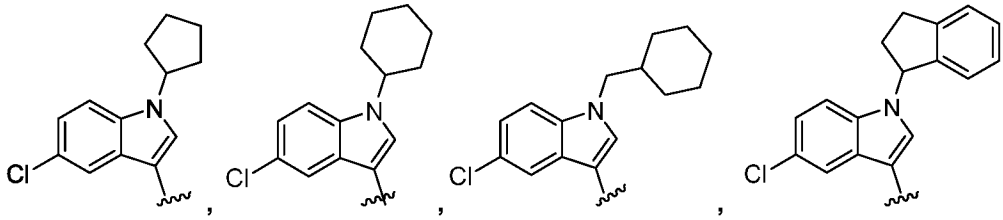
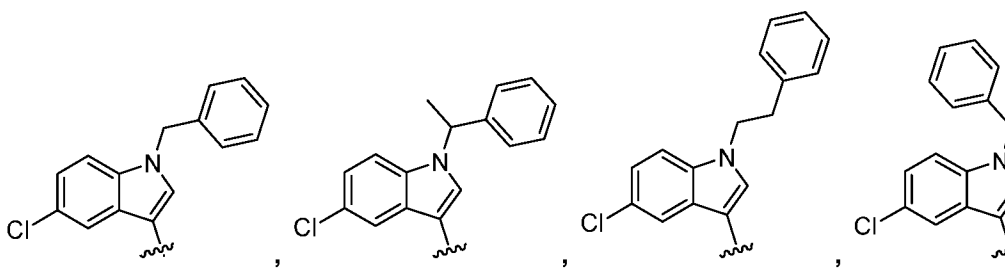
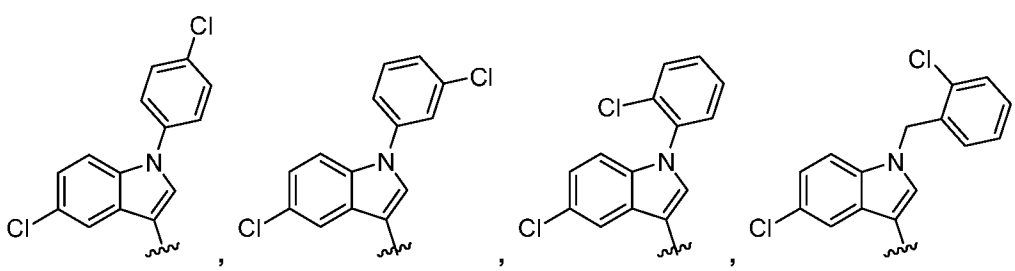
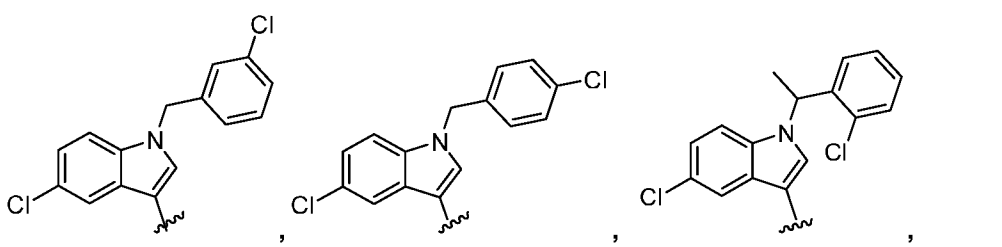
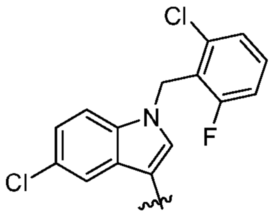
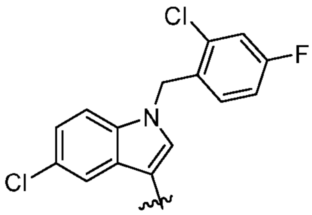
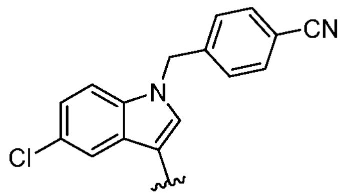
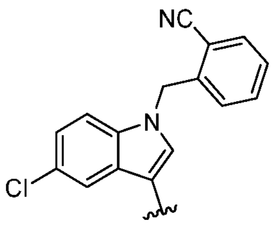
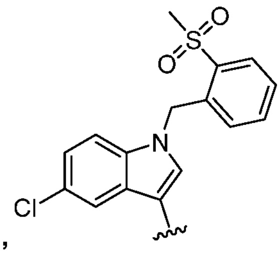
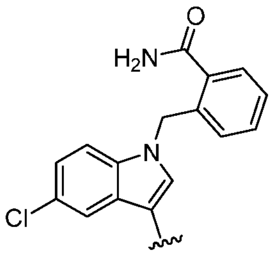
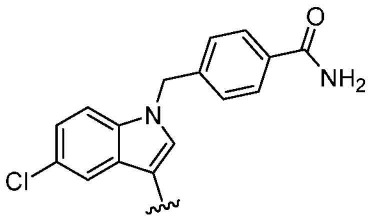
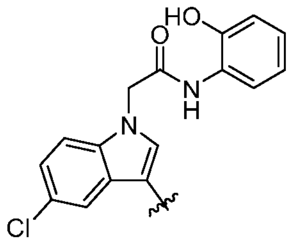
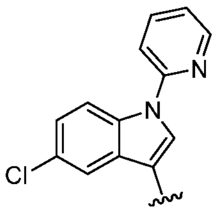
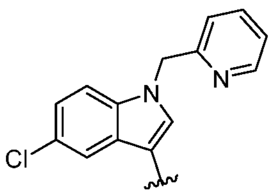
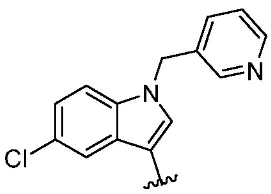
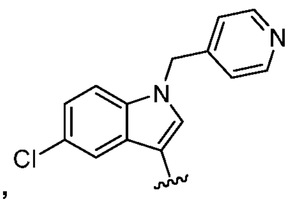
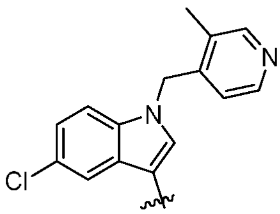
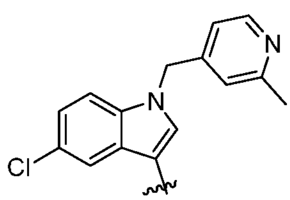
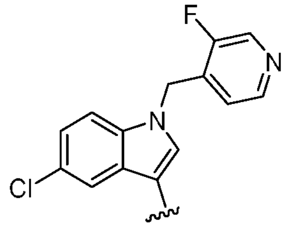








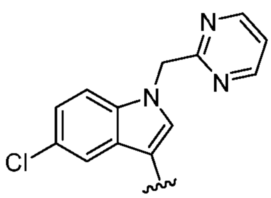
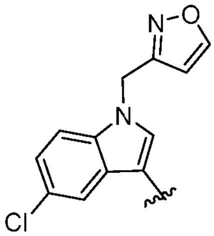
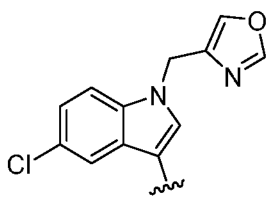
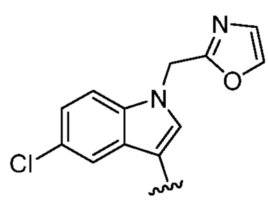
 ,  ,  ,

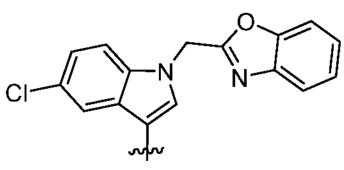
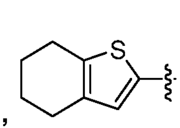
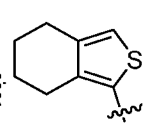
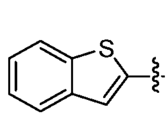
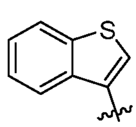
 ,  ,  ,

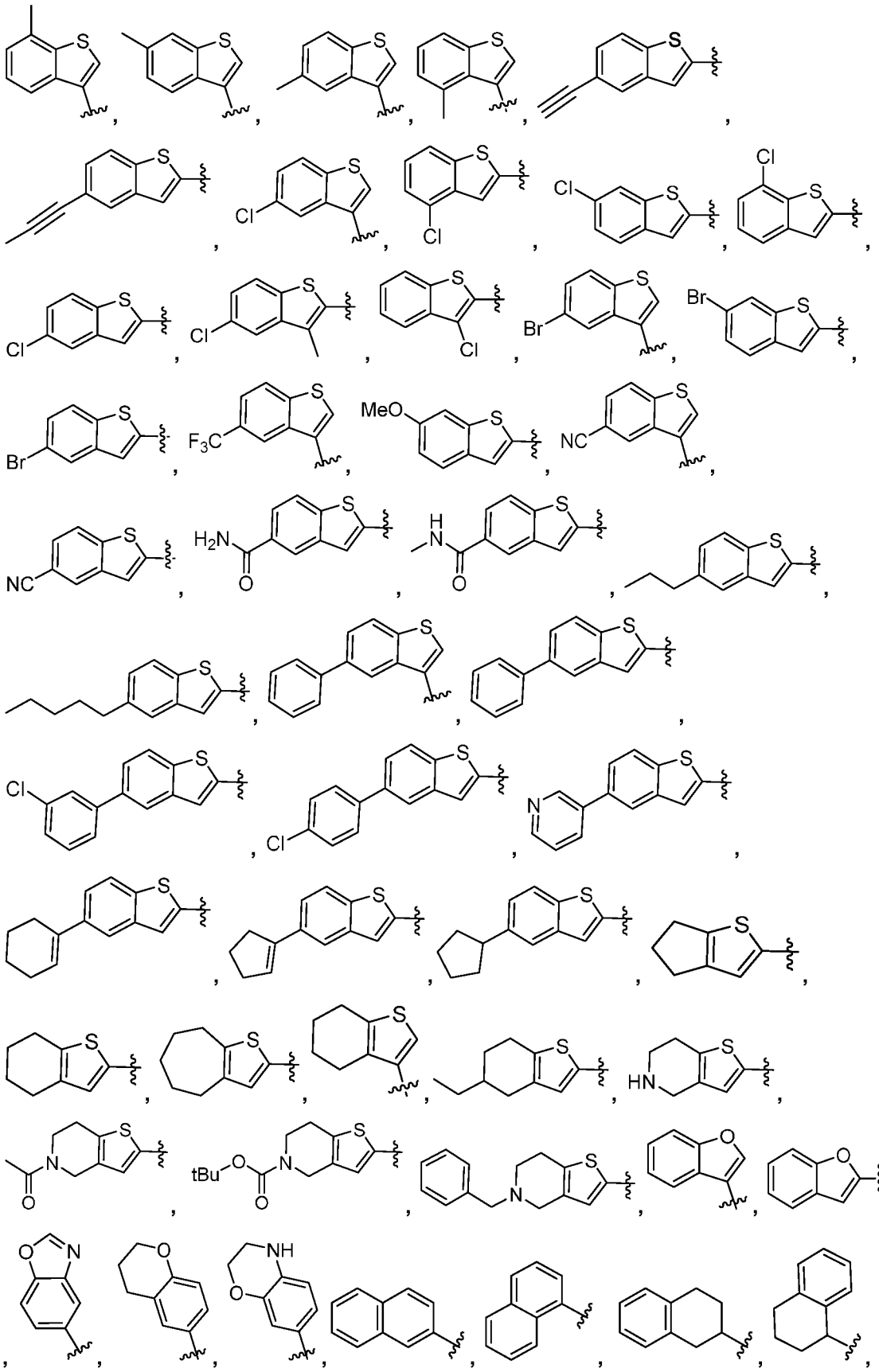
 ,  ,  ,

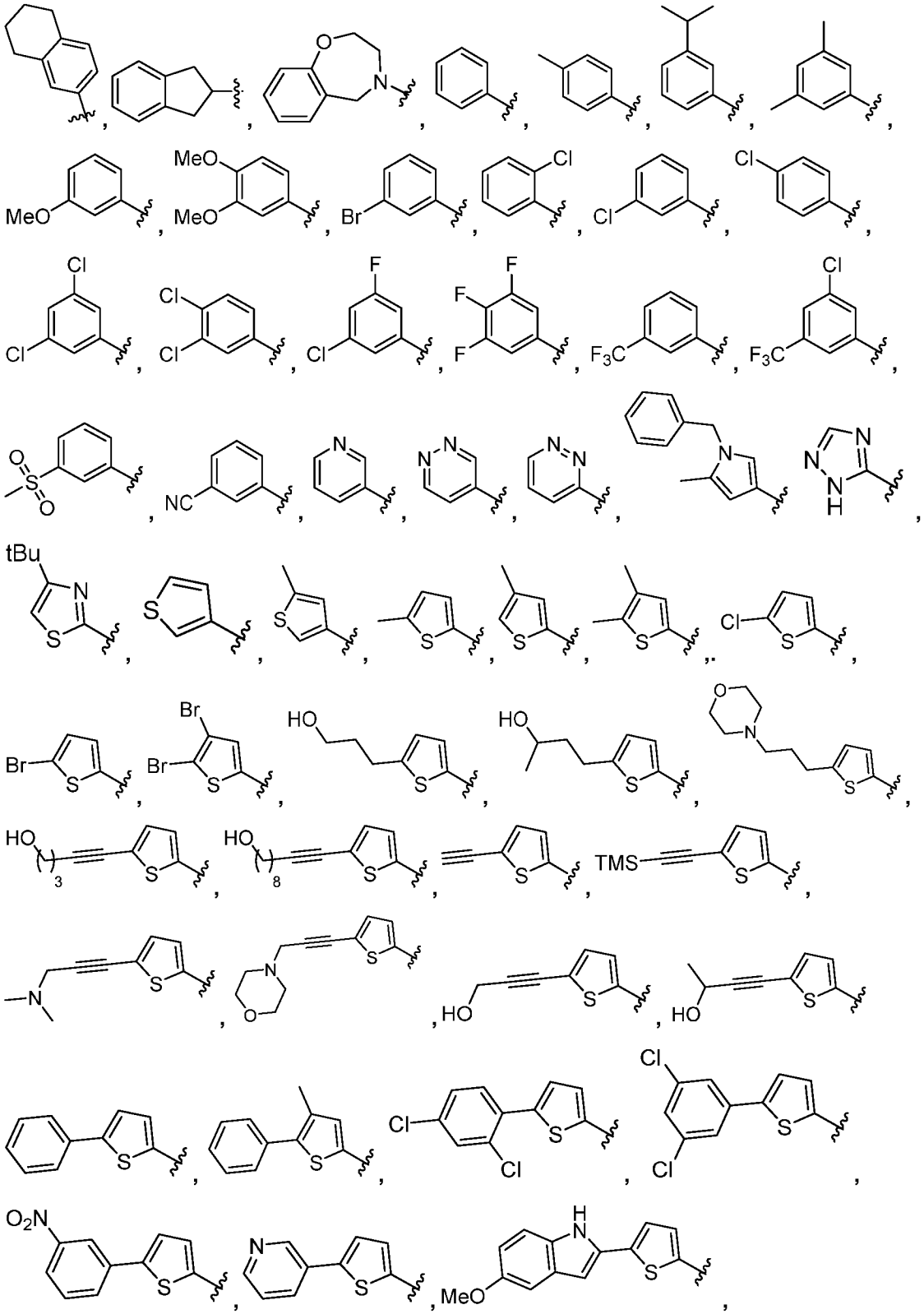
 ,  ,  ,

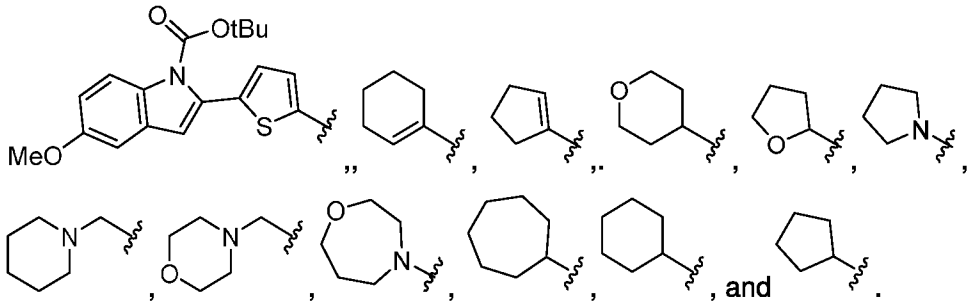
 ,  ,  ,

 ,  ,  ,  ,

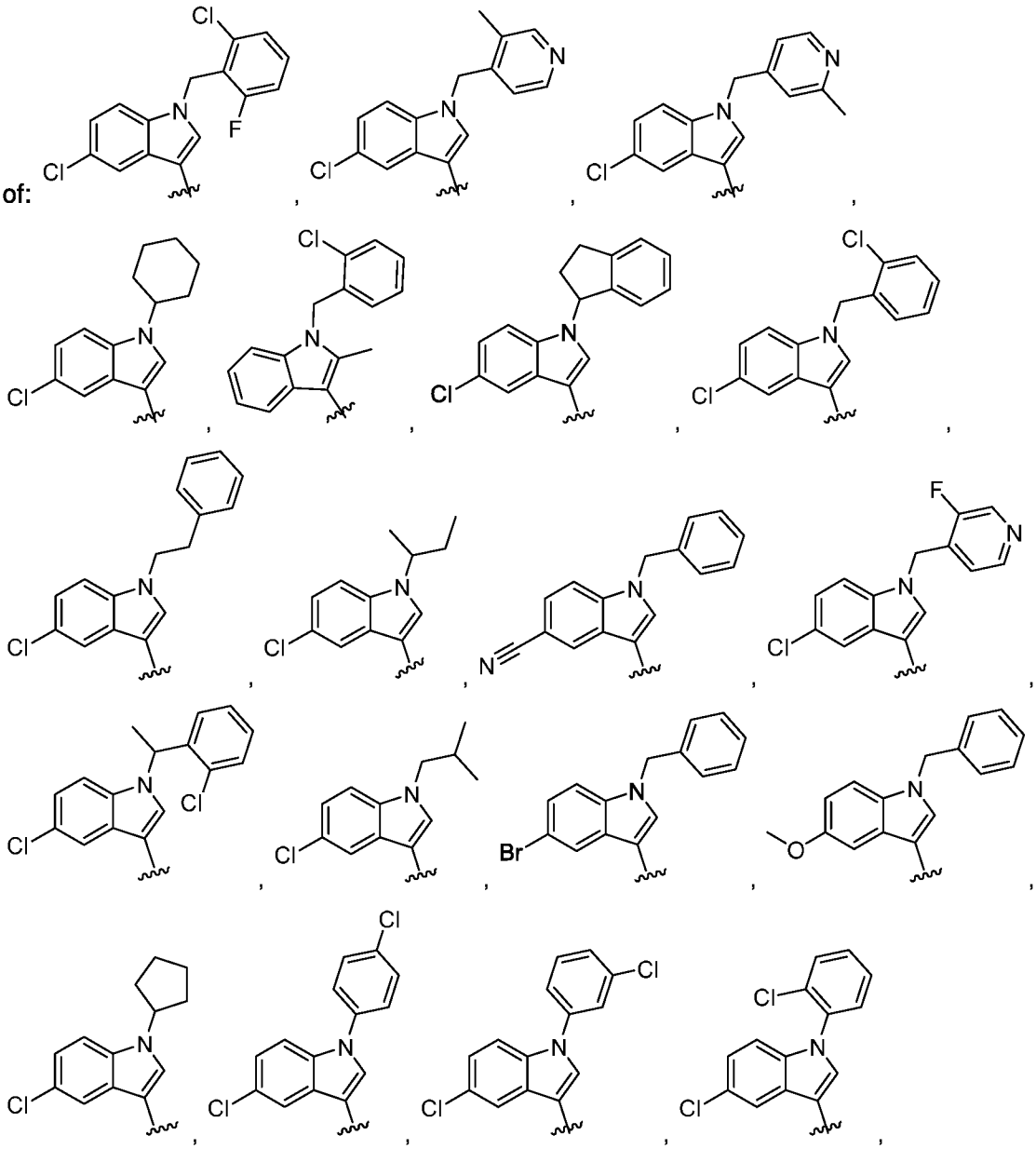
 ,  ,  ,  ,  ,

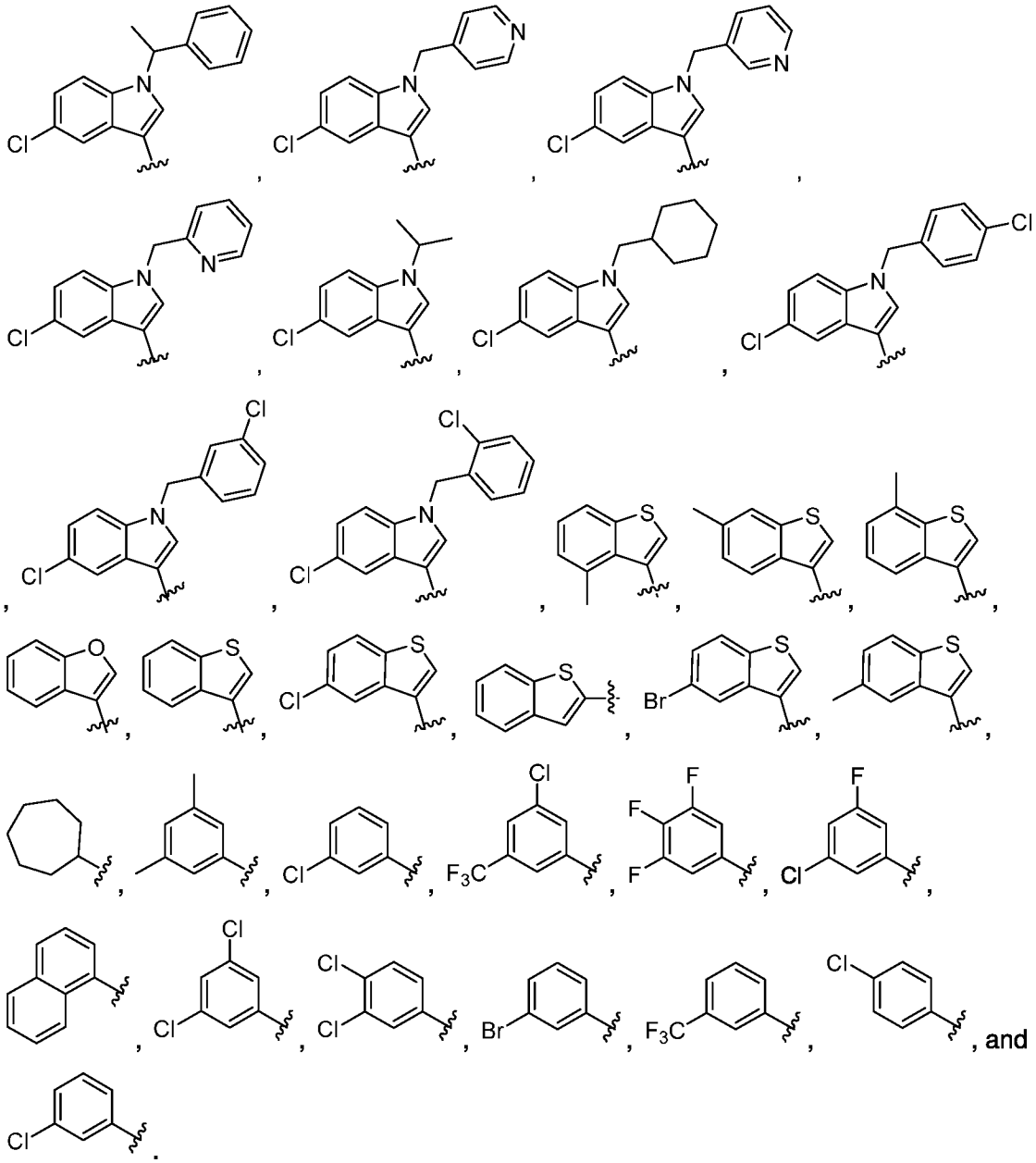






19. The compound of claim 13, wherein Y is selected from the group consisting of:





20. The compound of any one of claims 1-19, wherein Z is C_0alkylene.

21. The compound of any one of claims 1-19, wherein Z is C_{1-2}alkylene.

22. The compound of claim 21, wherein Z is CH_2.

23. The compound of claims 21, wherein Z is CH_2CH_2.

24. The compound of claim 21, wherein Z is substituted with one substituent.

25. The compound of claim 21, wherein Z is substituted with two substituents.

26. The compound of claim 25, wherein at least one of the one or two substituents is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, isobutyl, phenyl, benzyl, hydroxyl, methylamido, and methylamino.

27. The compound of claim 26, wherein the two substituents together with the carbon atom to which they are attached form a cyclopropyl or cyclopentyl group.

28. The compound of any one of claims 1-27, wherein R^1 is H.

29. The compound of any one of claims 1-28, wherein R^2 and R^3 are each CH_3.

30. The compound of any one of claims 1-28, wherein R^2 and R^3, together with the carbon to which they are attached from a cyclopropyl group.

31. The compound of any one of claims 1-30, wherein R^4 is methyl, ethyl, or propyl.

32. The compound of claim 29 or 31, wherein R^4 is methyl.

33. The compound of any one of claims 1-30, wherein R^4 is methoxy, ethoxy, isopropoxy, methoxyethyl, ethanolyl, $CH_2C(O)OEt$, or 2-propenyl.

34. The compound of any one of claims 1-30, wherein R^2, R^3, and R^4 are each fluoro.

35. The compound of any one of claims 1-34, wherein R^5 is H.

36. The compound of any one of claims 1-34, wherein R^5 is halo, CN, or $C(=O)OC_{1\text{-}3}$alkyl.

37. The compound of claim 1, wherein Z is CH_2 or C_0alkylene, R^1 is H, and each of R^2, R^3, and R^4 is CH_3.

38. A compound as recited in Table A or Table B, or a pharmaceutically acceptable salt thereof.

39. A compound as recited in Table C or D, or a pharmaceutically acceptable salt thereof.

40. A pharmaceutical composition comprising the compound of any one of claims 1 to 39 and a pharmaceutically acceptable excipient.

41. A method of inhibiting protein secretion in a cell comprising contacting the cell with the compound of any one of claims 1-39 or the composition of claim 40 in an amount effective to inhibit secretion.

42. The method of claim 41, wherein the contacting is *in vivo*.

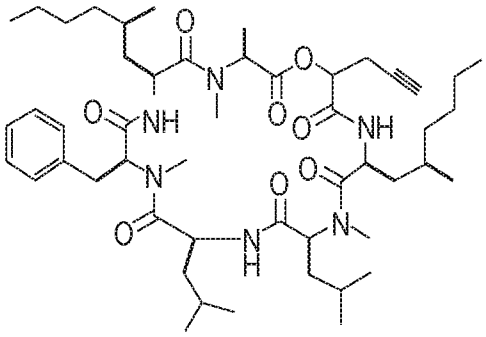
43. The method of claim 41 or 42, wherein the contacting comprises administering the compound or the composition to a subject.

44. A method for treating inflammation in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-39 or the composition of claim 40.

45. A method for treating cancer in a subject comprising administering to the subject a therapeutically effective amount of the compound of any one of claims 1-39 or the composition of claim 40.

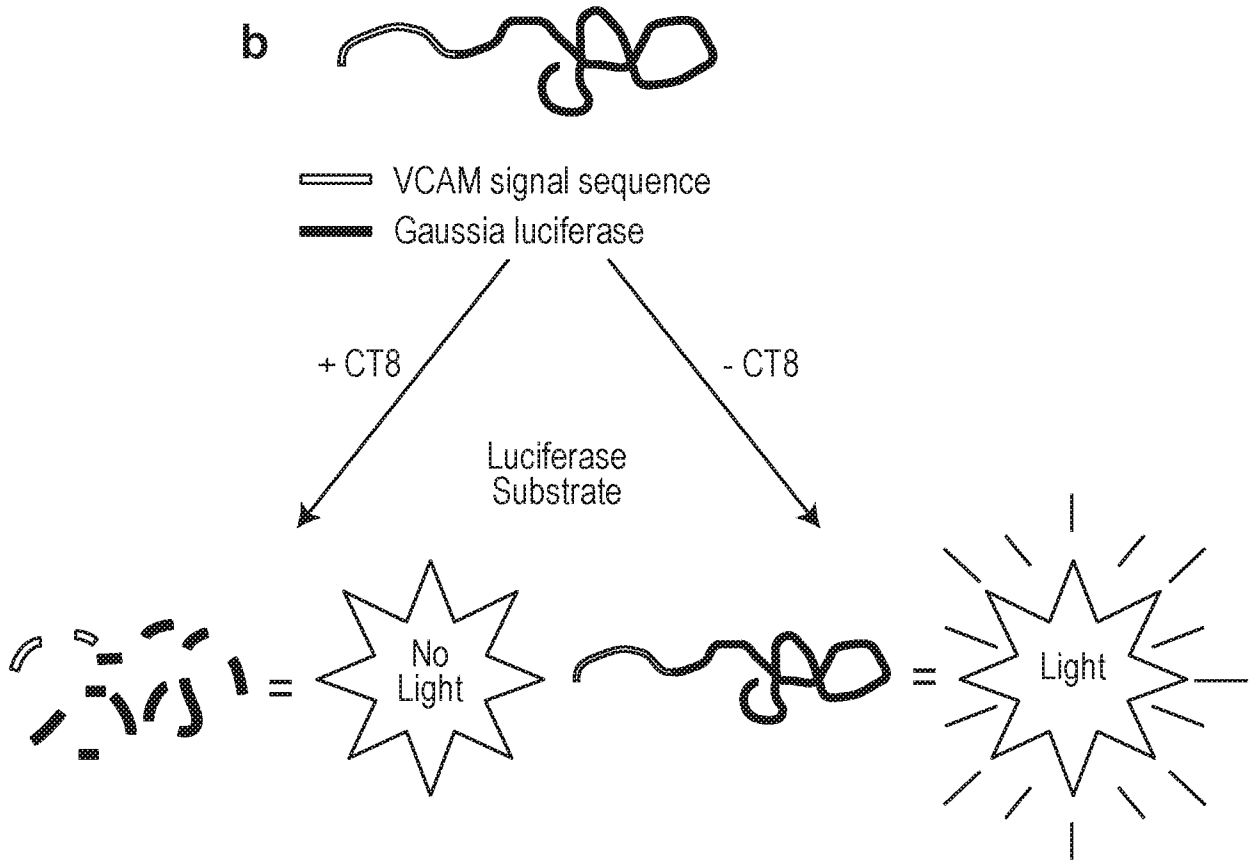
Figure 1

a



CT8
MW: 893.22

b



c

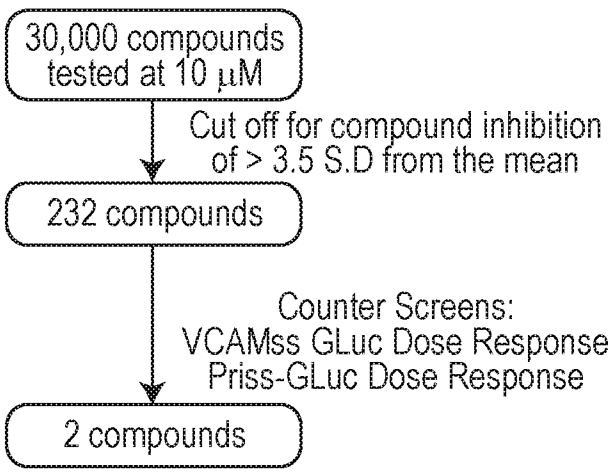
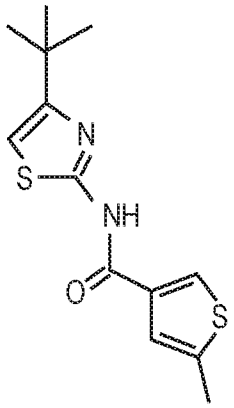
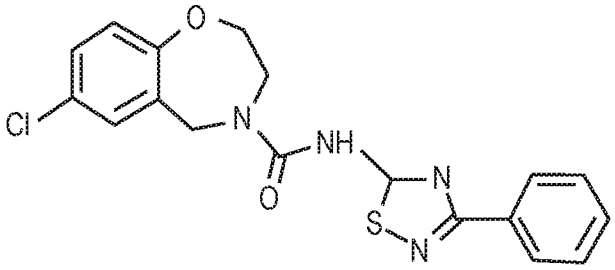


Figure 1 (cont'd)

d

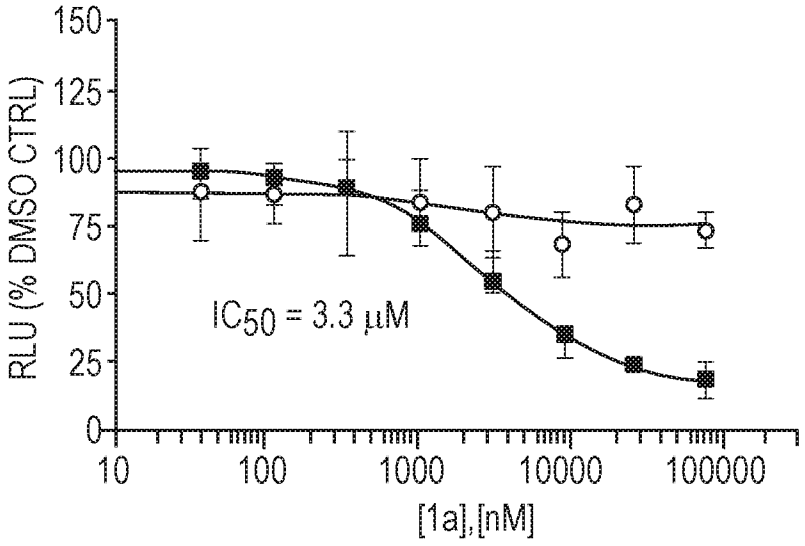


1a
MW:280.40



1b
MW:386.85

Expression of Signal Sequences Fused to Gaussia Luciferase



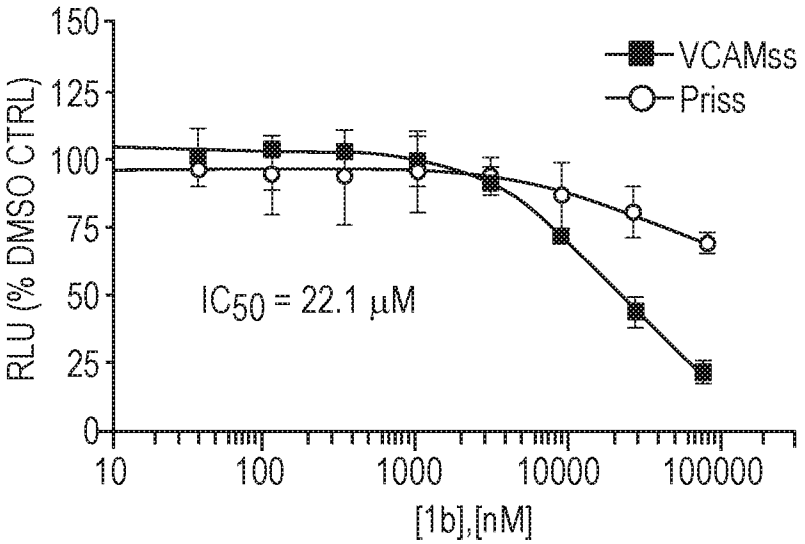
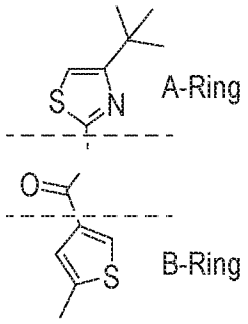


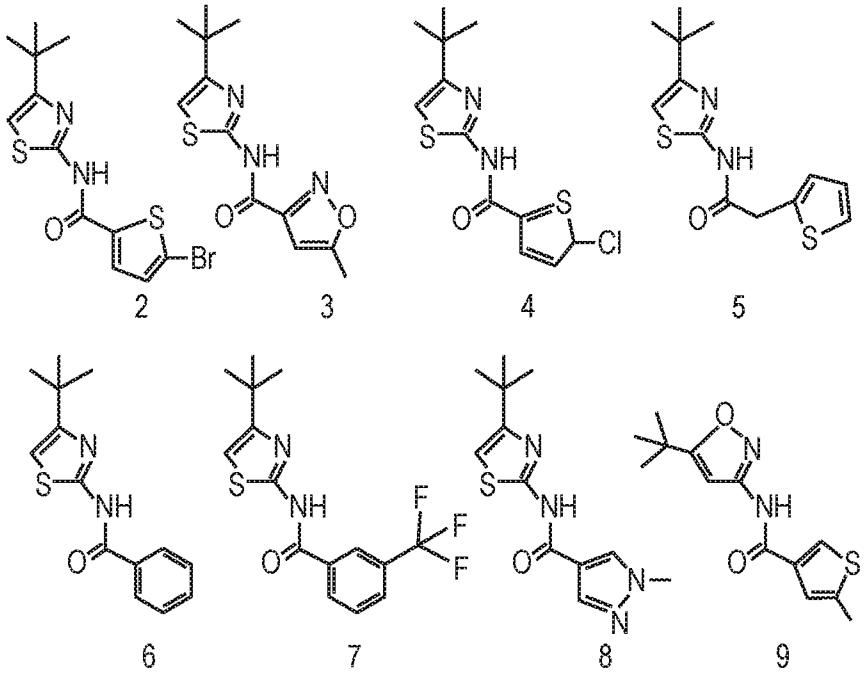
Figure 2

a



1a

b



Inhibition (IC_{50}, μM) of VCAMss and Priss fused to gaussia expression

Compound	VCAMss	Priss
1a	3.3	>80
2	1.1	>80
3	>80	>80
4	1.6	>80
5	5.7	>80
6	10.4	>80
7	7.6	>80
8	22.2	-
9	>80	>80

Figure 2 (cont'd)

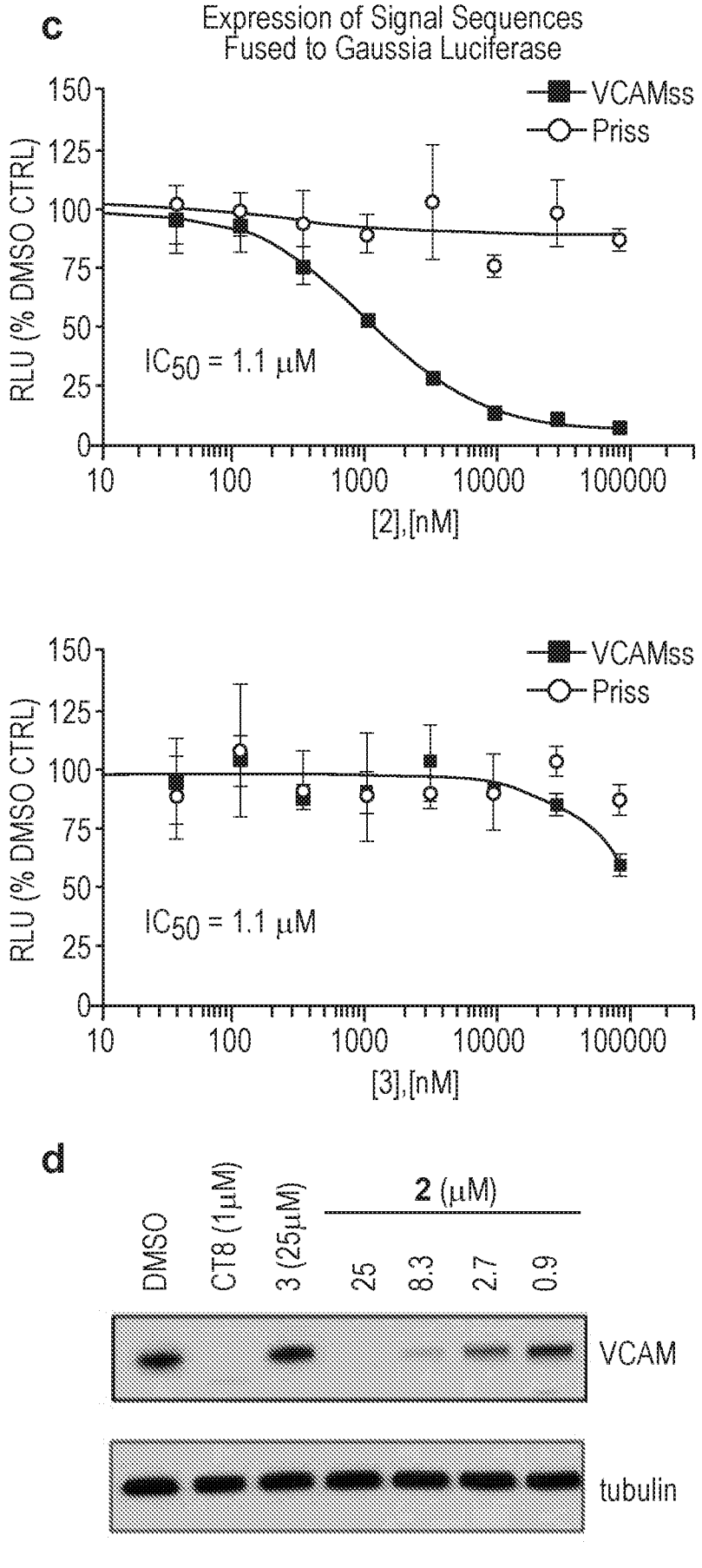


Figure 3

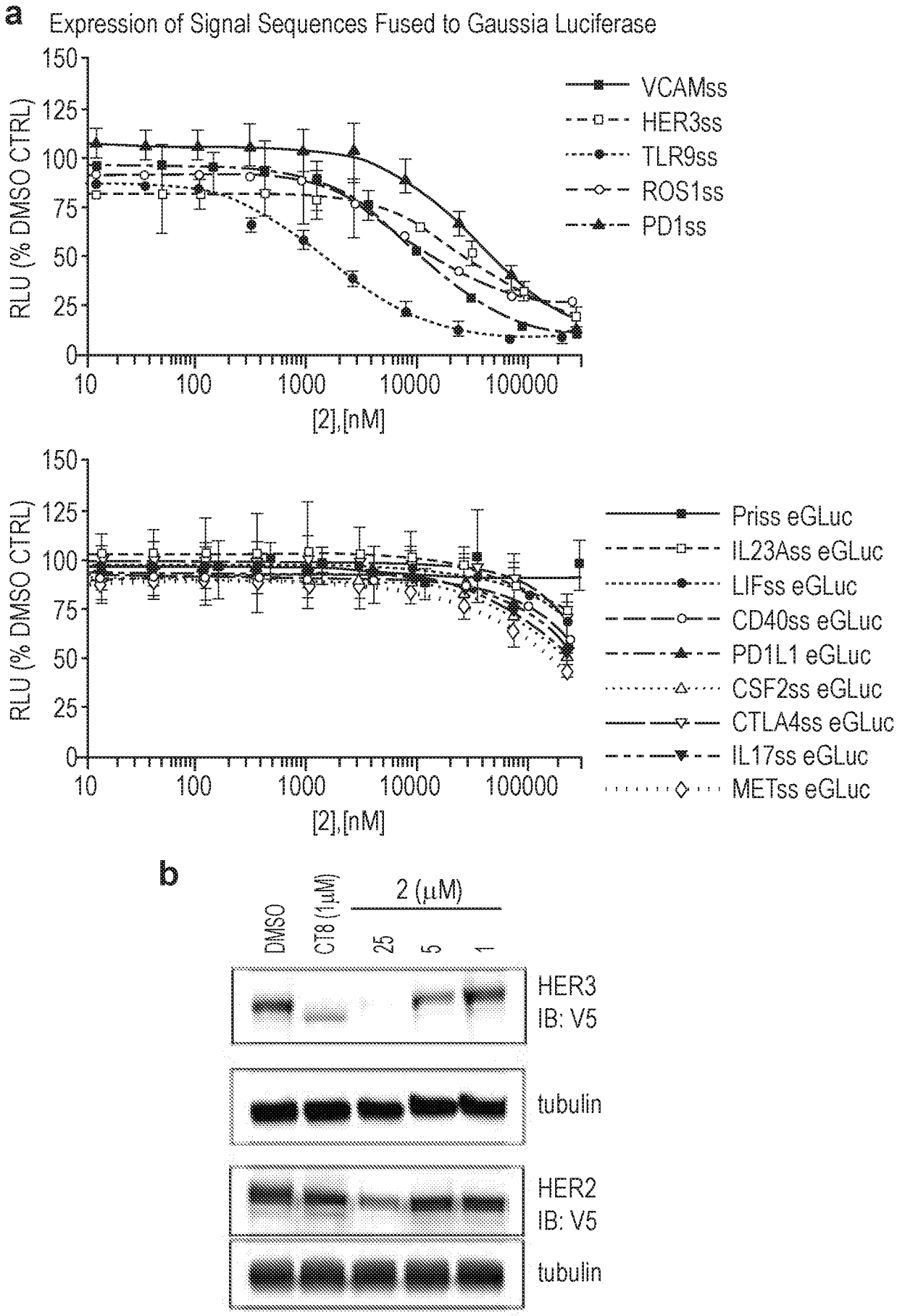

a
Expression of Signal Sequences Fused to Gaussia Luciferase
RLU (% DMSO CTRL)
150
125
100
75
50
25
0
10
100
1000
10000
100000
[2],[nM]
VCAMss
HER3ss
TLR9ss
ROS1ss
PD1ss
Priss eGLuc
IL23Ass eGLuc
LIFss eGLuc
CD40ss eGLuc
PD1L1 eGLuc
CSF2ss eGLuc
CTLA4ss eGLuc
IL17ss eGLuc
METss eGLuc
b
DMSO
CT8 (1μM)
2 (μM)
25
5
1
HER3
IB: V5
tubulin
HER2
IB: V5
tubulin

Figure 4

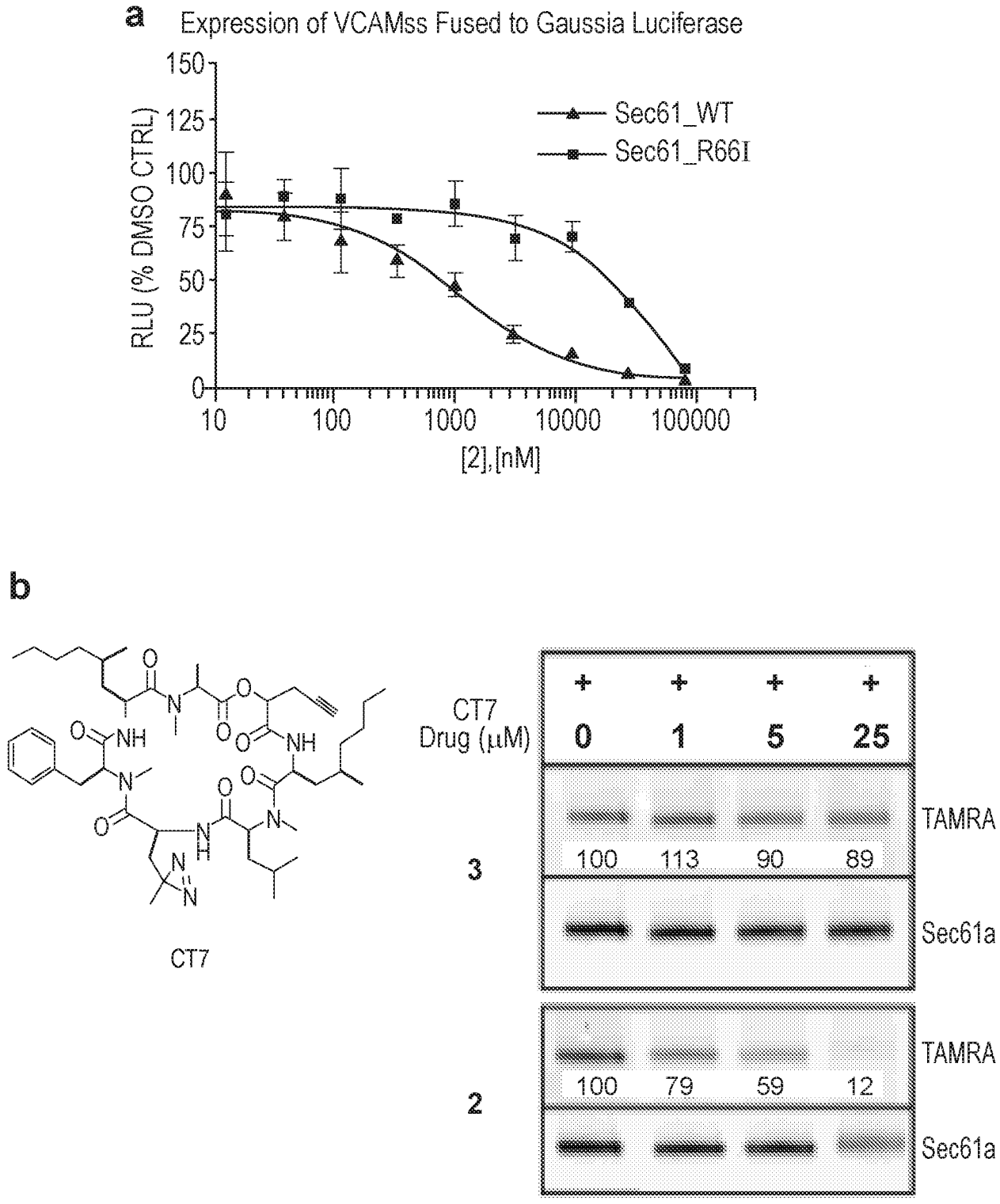

a
Expression of VCAMss Fused to Gaussia Luciferase
RLU (% DMSO CTRL)
150
125
100
75
50
25
0
10
100
1000
10000
100000
[2],[nM]
Sec61_WT
Sec61_R66I
b
CT7
CT7
Drug (μM)
+ + + +
0 1 5 25
TAMRA
100 113 90 89
3
Sec61a
TAMRA
100 79 59 12
2
Sec61a

Figure 5

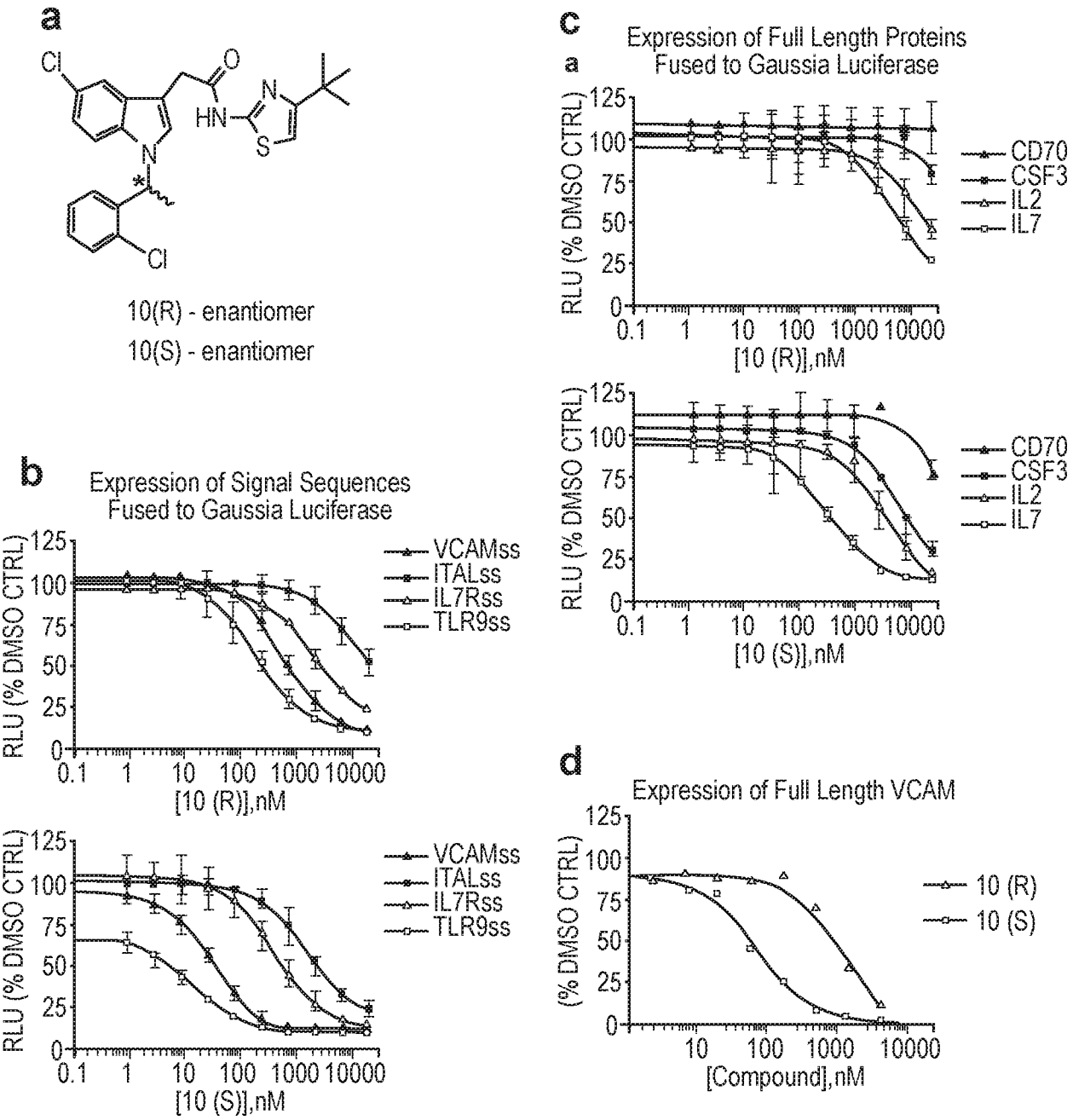
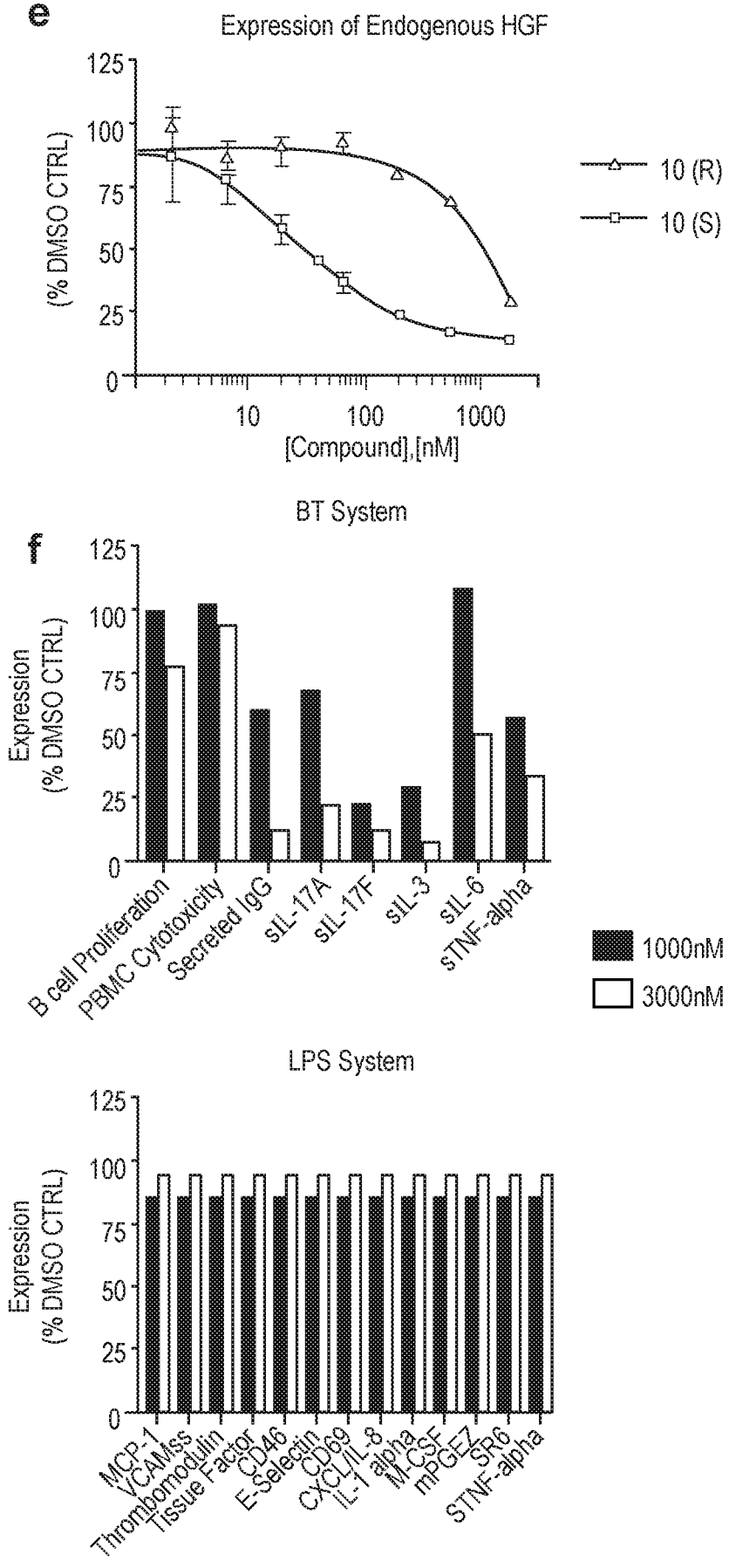

a
Cl
O
HN
N
S
N
*
Cl
10(R) - enantiomer
10(S) - enantiomer
b
Expression of Signal Sequences
Fused to Gaussia Luciferase
RLU (% DMSO CTRL)
125
100
75
50
25
0
0.1 1 10 100 1000 10000
[10 (R)],nM
VCAMss
ITALss
IL7Rss
TLR9ss
RLU (% DMSO CTRL)
[10 (S)],nM
c
Expression of Full Length Proteins
Fused to Gaussia Luciferase
a
RLU (% DMSO CTRL)
[10 (R)],nM
CD70
CSF3
IL2
IL7
[10 (S)],nM
d
Expression of Full Length VCAM
(% DMSO CTRL)
[Compound],nM
10 (R)
10 (S)

Figure 5 (cont'd)



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/048997

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12 C07D277/46 A61K31/426 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/020767 A2 (AMPHORA DISCOVERY CORP [US]; DICKSON JOHN K JR [US]; HODGE CARL NICHOL) 23 February 2006 (2006-02-23) claim 1	1-45
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X	EP 1 535 610 A1 (INST MED MOLECULAR DESIGN INC [JP]) 1 June 2005 (2005-06-01) examples 185-189,202,224	1-45

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 October 2018	26/11/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baston, Eckhard

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/048997

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 28 November 2016 (2016-11-28), XP002785957, retrieved from STN Database accession no. 2039610-14-3 5-Thiazolecarboxylic acid, 2-[[(2-amino-2-methylcyclohexyl)carbonyl]a mino]-4-(1,1-dimeth)-, methyl ester, hydrochloride (1:1); examples 2039610-14-3	1

-/--

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/048997

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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International application No
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