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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 September 2017 (14.09.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/156181 A1

(51) International Patent Classification:
A61K 31/395 (2006.01) *C07D 237/20* (2006.01)
A61K 31/397 (2006.01) *C07D 403/02* (2006.01)
A61K 31/497 (2006.01) *C07D 403/12* (2006.01)

(21) International Application Number:
PCT/US2017/021438

(22) International Filing Date:
8 March 2017 (08.03.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/305,914 9 March 2016 (09.03.2016) US

(71) Applicant: **RAZE THERAPEUTICS, INC.** [US/US]; 400 Technology Square, 10th Floor, Cambridge, Massachusetts 02139 (US).

(72) Inventors: **MAINOLFI, Nello**; c/o Raze Therapeutics, Inc., 400 Technology Square, 10th Floor, Cambridge, Massachusetts 02139 (US). **MOYER, Mikel P.**; c/o Raze Therapeutics, Inc., 400 Technology Square, 10th Floor, Cambridge, Massachusetts 02139 (US). **SAIAH, Eddine**; c/o Raze Therapeutics, Inc., 400 Technology Square, 10th Floor, Cambridge, Massachusetts 02139 (US).

(74) Agents: **REID, Andrea L.C.** et al.; One International Place, 40th Floor, 100 Oliver Street, Boston, Massachusetts 02110-2605 (US).

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

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

Published:

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

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

WO 2017/156181 A1

(54) Title: 3-PHOSPHOGLYCERATE DEHYDROGENASE INHIBITORS AND USES THEREOF

(57) Abstract: The present invention provides compounds, compositions thereof, and methods of using the same.

3-PHOSPHOGLYCERATE DEHYDROGENASE INHIBITORS AND USES THEREOF

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds and methods useful for inhibiting 3-phosphoglycerate dehydrogenase. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

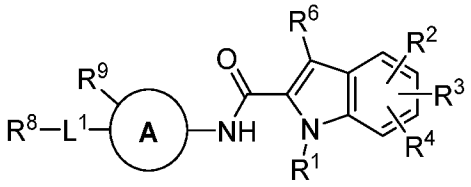
BACKGROUND OF THE INVENTION

[0002] Phosphoglycerate dehydrogenase (PHGDH) catalyzes the first step in the biosynthesis of L-serine, which is the conversion of 3-phosphoglycerate into 3-phosphohydroxypyruvate with a reduction of nicotinamide adenine dinucleotide (NAD^+) to NADH.

[0003] Certain cancers, including human melanomas and breast cancers, can have high levels of PHGDH. These cancer cells are dependent on PHGDH for their growth and survival as PHGDH catalyzes serine production and may also be a significant source of NADPH in cancer cells. Targeting PHGDH by small molecule inhibitors could be a therapeutic strategy to reduce cancer cell growth and survival. Accordingly, there remains a need to find PHGDH inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0004] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as PHGDH inhibitors. Such compounds have the general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

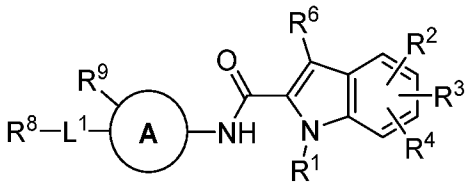
[0005] Compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with PHGDH. Such diseases, disorders, or conditions include cellular proliferative disorders (e.g., cancer) such as those described herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0006] Compounds of the present invention, and compositions thereof, are useful as inhibitors of PHGDH. Without wishing to be bound by any particular theory, it is believed that compounds of the present invention, and compositions thereof, may inhibit the activity of PHGDH and/or inhibit the production of NADPH, and thus reduce the growth of cells in proliferative disorders such as cancer.

[0007] In some embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} alkyl;

each of R^2 and R^3 is independently halogen, -OR, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'; or R^2 and R^3 are optionally taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected

from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each L is independently a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1-4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or $-SO_2-$;

each R' is independently hydrogen, C_{1-6} aliphatic, or an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen, halogen, $-OR^5$, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R';

R^5 is hydrogen, $-(CH_2)_n$-phenyl, or C_{1-6} alkyl optionally substituted with 1, 2, or 3 halogens;

n is 0, 1, 2, 3, or 4;

R^6 is hydrogen or C_{1-4} alkyl;

Ring A is phenyl or pyridyl;

L^1 is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1-5 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; or L^1 and R^8 are optionally taken together with any intervening atoms to form a 5-6 membered optionally substituted partially unsaturated heterocyclic ring that is fused with Ring A having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each -Cy- is independently a bivalent 6-membered arylene ring containing 0-2 nitrogen atoms , or a bivalent 5-membered heteroarylene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a bivalent partially unsaturated 8-10 membered bicyclic heterocyclene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR;

R^8 is hydrogen, $-CO_2R$, or a C_{1-6} optionally substituted aliphatic group; and

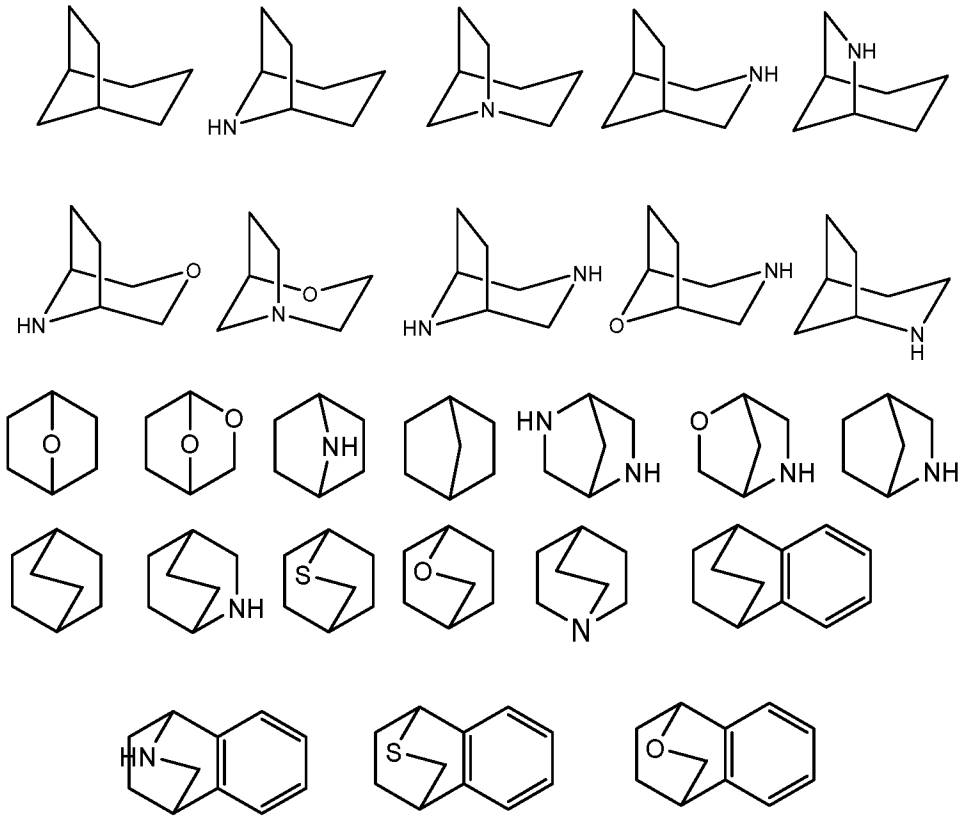
R^9 is hydrogen, halogen, C_{1-4} alkyl, optionally substituted phenyl, or C_{1-4} alkyl substituted with an optionally substituted phenyl.

2. Compounds and Definitions:

[0008] Compounds of the present invention include those described generally herein, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0009] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle," "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0010] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:



[0011] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0012] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

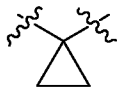
[0013] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0014] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0015] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0016] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $–(CH_2)_n–$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0017] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0018] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0019] The term "halogen" means F, Cl, Br, or I.

[0020] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl," as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings,

such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0021] The terms "heteroaryl" and "heteroar–," used alone or as part of a larger moiety, e.g., "heteroaralkyl," or "heteroaralkoxy," refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring," "heteroaryl group," or "heteroaromatic," any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0022] As used herein, the terms "heterocycle," "heterocyclyl," "heterocyclic radical," and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen" includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0023] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl, pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle," "heterocyclyl," "heterocyclyl ring," "heterocyclic group," "heterocyclic moiety," and "heterocyclic radical," are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0024] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0025] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted," whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable," as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0026] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $–(CH_2)_{0–4}R°$; $–(CH_2)_{0–4}OR°$; $-O(CH_2)_{0-4}R^o$, $–O–(CH_2)_{0–}$

$_4$C(O)OR°; –$(CH_2)_{0-4}$CH(OR°)$_2$; –$(CH_2)_{0-4}$SR°; –$(CH_2)_{0-4}$Ph, which may be substituted with R°; –$(CH_2)_{0-4}$O$(CH_2)_{0-1}$Ph which may be substituted with R°; –CH=CHPh, which may be substituted with R°; –$(CH_2)_{0-4}$O$(CH_2)_{0-1}$-pyridyl which may be substituted with R°; –NO_2; –CN; –N_3; -$(CH_2)_{0-4}$N(R°)$_2$; –$(CH_2)_{0-4}$N(R°)C(O)R°; –N(R°)C(S)R°; –$(CH_2)_{0-4}$N(R°)C(O)NR°$_2$; -N(R°)C(S)NR°$_2$; –$(CH_2)_{0-4}$N(R°)C(O)OR°; –N(R°)N(R°)C(O)R°; -N(R°)N(R°)C(O)NR°$_2$; -N(R°)N(R°)C(O)OR°; –$(CH_2)_{0-4}$C(O)R°; –C(S)R°; –$(CH_2)_{0-4}$C(O)OR°; –$(CH_2)_{0-4}$C(O)SR°; -$(CH_2)_{0-4}$C(O)OSiR°$_3$; –$(CH_2)_{0-4}$OC(O)R°; –OC(O)$(CH_2)_{0-4}$SR–, SC(S)SR°; –$(CH_2)_{0-4}$SC(O)R°; –$(CH_2)_{0-4}$C(O)NR°$_2$; –C(S)NR°$_2$; –C(S)SR°; –SC(S)SR°, -$(CH_2)_{0-4}$OC(O)NR°$_2$; -C(O)N(OR°)R°; –C(O)C(O)R°; –C(O)CH_2C(O)R°; –C(NOR°)R°; -$(CH_2)_{0-4}$SSR°; –$(CH_2)_{0-4}$S(O)$_2$R°; –$(CH_2)_{0-4}$S(O)$_2$OR°; –$(CH_2)_{0-4}$OS(O)$_2$R°; –S(O)$_2$NR°$_2$; -$(CH_2)_{0-4}$S(O)R°; -N(R°)S(O)$_2$NR°$_2$; –N(R°)S(O)$_2$R°; –N(OR°)R°; –C(NH)NR°$_2$; –P(O)$_2$R°; -P(O)R°$_2$; -OP(O)R°$_2$; –OP(O)(OR°)$_2$; –SiR°$_3$; –(C_{1-4} straight or branched alkylene)O–N(R°)$_2$; or –(C_{1-4} straight or branched alkylene)C(O)O–N(R°)$_2$.

[0027] Each R° is independently hydrogen, C_{1-6} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, -CH_2-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted by a divalent substituent on a saturated carbon atom of R° selected from =O and =S; or each R° is optionally substituted with a monovalent substituent independently selected from halogen, –$(CH_2)_{0-2}$R•, –(haloR•), –$(CH_2)_{0-2}$OH, –$(CH_2)_{0-2}$OR•, –$(CH_2)_{0-2}$CH(OR•)$_2$; -O(haloR•), –CN, –N_3, –$(CH_2)_{0-2}$C(O)R•, –$(CH_2)_{0-2}$C(O)OH, –$(CH_2)_{0-2}$C(O)OR•, –$(CH_2)_{0-2}$SR•, –$(CH_2)_{0-2}$SH, –$(CH_2)_{0-2}$$NH_2$, –$(CH_2)_{0-2}$NHR•, –$(CH_2)_{0-2}$NR•$_2$, –$NO_2$, –SiR•$_3$, –OSiR•$_3$, -C(O)SR•, –($C_{1-4}$ straight or branched alkylene)C(O)OR•, or –SSR•.

[0028] Each R• is independently selected from C_{1-4} aliphatic, –CH_2Ph, –O$(CH_2)_{0-1}$Ph, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each R• is unsubstituted or where preceded by halo is substituted only with one or more halogens; or wherein an optional substituent on a saturated carbon is a divalent substituent independently selected from =O, =S,

$=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, or a divalent substituent bound to vicinal substitutable carbons of an "optionally substituted" group is $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0029] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0030] An optional substituent on a substitutable nitrogen is independently $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; wherein when $R^\dagger$ is C_{1-6} aliphatic, $R^\dagger$ is optionally substituted with halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein each $R^\bullet$ is unsubstituted or where preceded by halo is substituted only with one or more halogens.

[0031] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by

reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0032] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0033] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the

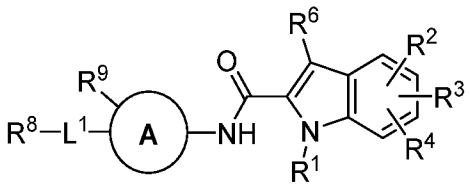
replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, a warhead moiety, R^1, of a provided compound comprises one or more deuterium atoms.

[0034] As used herein, the term "inhibitor" is defined as a compound that binds to and /or inhibits PHGDH with measurable affinity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less than about 100 μM, less than about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, less than about 10 nM, or less than about 1 nM.

[0035] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in PHGDH activity between a sample comprising a compound of the present invention, or composition thereof, and PHGDH, and an equivalent sample comprising PHGDH, in the absence of said compound, or composition thereof.

3. Description of Exemplary Embodiments:

[0036] In some embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} alkyl;

each of R^2 and R^3 is independently halogen, -OR, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'; or R^2 and R^3 are optionally taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected

from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each L is independently a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1-4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or $-SO_2-$;

each R' is independently hydrogen, C_{1-6} aliphatic, or an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen, halogen, $-OR^5$, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R';

R^5 is hydrogen, $-(CH_2)_n$-phenyl, or C_{1-6} alkyl optionally substituted with 1, 2, or 3 halogens;

n is 0, 1, 2, 3, or 4;

R^6 is hydrogen or C_{1-4} alkyl;

Ring A is phenyl or pyridyl;

L^1 is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1-5 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; or L^1 and R^8 are optionally taken together with any intervening atoms to form a 5-6 membered optionally substituted partially unsaturated heterocyclic ring that is fused with Ring A having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each -Cy- is independently a bivalent 6-membered arylene ring containing 0-2 nitrogen atoms , or a bivalent 5-membered heteroarylene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a bivalent partially unsaturated 8-10 membered bicyclic heterocyclene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR;

R^8 is hydrogen, $-CO_2R$, or a C_{1-6} optionally substituted aliphatic group; and

R^9 is hydrogen, halogen, C_{1-4} alkyl, optionally substituted phenyl, or C_{1-4} alkyl substituted with an optionally substituted phenyl.

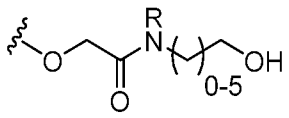
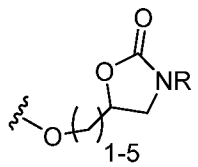
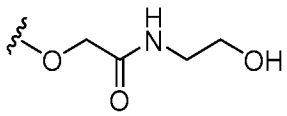
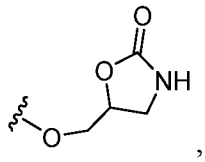
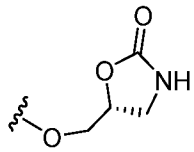
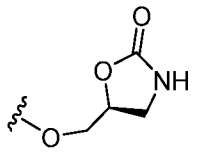
[0037] As defined generally above, R^1 is hydrogen or C_{1-4} alkyl. In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is C_{1-4} alkyl.

[0038] In some embodiments, R^1 is methyl. In some embodiments, R^1 is ethyl.

[0039] In some embodiments, R^1 is selected from those depicted in Table 1, below.

[0040] As defined generally above, R^2 is independently halogen, -OR, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'; or R^2 and R^3 are optionally taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

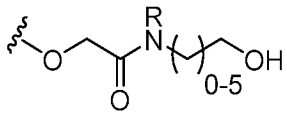
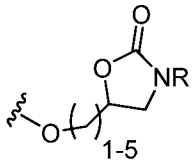
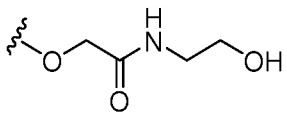
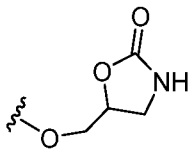
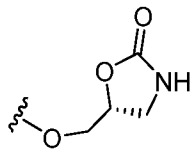
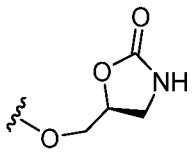
[0041] In some embodiments, R^2 is halogen. In some embodiments, R^2 is -OR. In some embodiments, R^2 is -CN. In some embodiments, R^2 is C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens. In some embodiments, R^2 is -L-R'. In some embodiments, R^2 and R^3 are taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] In some embodiments, R^2 is F, Cl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2Ph$, -OMe, -CN, $-CH_3$,  , or  . In some embodiments, R^2 is  ,  ,  , or  . In some embodiments, R^2 is F or Cl. In some embodiments, R^2 is -OMe. In some embodiments, R^2 is $-CF_3$.

[0043] In some embodiments, R^2 is selected from those depicted in Table 1, below.

[0044] As defined generally above, R^3 is independently halogen, -OR, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'; or R^2 and R^3 are optionally taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0045] In some embodiments, R^3 is halogen. In some embodiments, R^3 is -OR. In some embodiments, R^3 is -CN. In some embodiments, R^3 is C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens. In some embodiments, R^3 is -L-R'. In some embodiments, R^2 and R^3 are taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0046] In some embodiments, R^3 is F, Cl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2Ph$, -OMe, -CN, $-CH_3$,  , or  . In some embodiments, R^3 is  ,  ,  , or  . In some embodiments, R^3 is F or Cl. In some embodiments, R^3 is -OMe. In some embodiments, R^3 is $-CF_3$.

[0047] In some embodiments, R^2 and R^3 taken together with the carbon atoms to which they are attached and any intervening atoms form a cyclopentenyl or cyclohexenyl ring.

[0048] In some embodiments, R^2 and R^3 are both Cl. In some embodiments, one of R^2 and R^3 is Cl and one is $-CH_3$, F, or -OMe.

[0049] In some embodiments, R^3 is selected from those depicted in Table 1, below.

[0050] As defined generally above, each L is independently a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1-4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or $-SO_2-$.

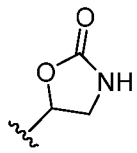
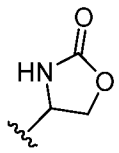
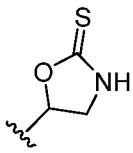
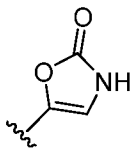
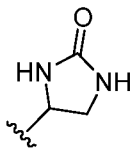
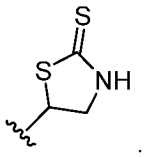
[0051] In some embodiments, L is a C_{1-6} bivalent straight or branched hydrocarbon chain. In some embodiments, L is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1-4 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or -SO_2-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -O-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -C(O)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -C(O)O-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -OC(O)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -OC(O)N(R)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -(R)NC(O)O-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -C(O)N(R)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -(R)NC(O)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -N(R)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -N(R)C(O)N(R)-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -S-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -SO-. In some embodiments, 1 or 2 methylene units of the chain are replaced with -SO_2-. In some embodiments, 1 or 2 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or -SO_2-, wherein each R is independently hydrogen or methyl.

[0052] In some embodiments, L is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, or -N(R)C(O)N(R)-, wherein each R is independently hydrogen or methyl. In some embodiments, L is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1 or 2 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)N(R)-, -(R)NC(O)-, or -N(R)-, wherein each R is independently hydrogen or methyl.

[0053] In some embodiments, L is selected from those depicted in Table 1, below.

[0054] As defined generally above, each R' is independently hydrogen, C_{1-6} aliphatic, or an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

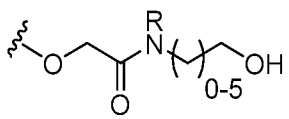
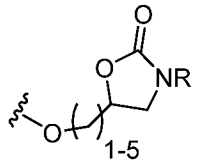
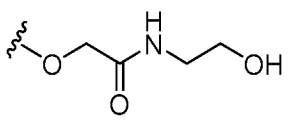
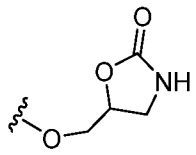
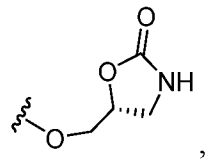
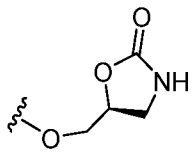
[0055] In some embodiments, R' is hydrogen. In some embodiments, R' is C_{1-6} aliphatic. In some embodiments, R' is an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0056] In some embodiments, R' is  ,  ,  ,  ,  ,  or .

[0057] In some embodiments, R' is selected from those depicted in Table 1, below.

As defined generally above, R^4 is hydrogen, halogen, $-OR^5$, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'.

[0058] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is halogen. In some embodiments, R^4 is $-OR^5$. In some embodiments, R^4 is -CN. In some embodiments, R^4 is C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens. In some embodiments, R^4 is -L-R'.

[0059] In some embodiments, R^4 is hydrogen, F, Cl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2Ph$, -OMe, -CN, $-CH_3$,  , or  . In some embodiments, R^4 is  ,  ,  , or  . In some embodiments, R^4 is F or Cl. In some embodiments, R^4 is -OMe. In some embodiments, R^4 is $-CF_3$.

[0060] In some embodiments, R^4 is selected from those depicted in Table 1, below.

[0061] As defined generally above, R^5 is hydrogen, -$(CH_2)_n$-phenyl, or C_{1-6} alkyl optionally substituted with 1, 2, or 3 halogens.

[0062] In some embodiments, R^5 is hydrogen. In some embodiments, R^5 is -$(CH_2)_n$-phenyl. In some embodiments, R^5 is C_{1-6} alkyl optionally substituted with 1, 2, or 3 halogens.

[0063] In some embodiments, R^5 is hydrogen, -CH_2-phenyl, phenyl, -CH_3, -CH_2CH_3, -CH_2F, -CHF_2, -CF_3, -CH_2CHF_2, or -CH_2CF_3.

[0064] In some embodiments, R^5 is selected from those depicted in Table 1, below.

[0065] As defined generally above, n is 0, 1, 2, 3, or 4. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3. In some embodiments, n is 4.

[0066] As defined generally above, R^6 is hydrogen or C_{1-4} alkyl. In some embodiments, R^6 is hydrogen. In some embodiments, R^6 is C_{1-4} alkyl.

[0067] In some embodiments, R^6 is methyl.

[0068] In some embodiments, R^6 is selected from those depicted in Table 1, below.

[0069] As defined generally above, Ring A is phenyl or pyridyl. In some embodiments, Ring A is phenyl. In some embodiments, Ring A is pyridyl.

[0070] In some embodiments, Ring A is selected from those depicted in Table 1, below.

[0071] As defined generally above, L^1 is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1-5 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, -SO_2-, -SO_2N(R)-, -(R)NSO_2-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; or L^1 and R^8 are optionally taken together with any intervening atoms to form a 5-6 membered optionally substituted partially unsaturated heterocyclic ring that is fused with Ring A having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0072] In some embodiments, L^1 is a covalent bond. In some embodiments, L^1 is a C_{1-10} bivalent straight or branched hydrocarbon chain. In some embodiments, L^1 is a C_{1-10} bivalent

straight or branched hydrocarbon chain wherein 1-5 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2$-, $-SO_2N(R)$-, $-(R)NSO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -O-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(O)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(O)O- or -OC(O)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -N(R)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(O)N(R)- or -(R)NC(O)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -OC(O)N(R)- or -(R)NC(O)O-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -N(R)C(O)N(R)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -S-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -SO-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with $-SO_2$-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with $-SO_2N(R)$- or $-(R)NSO_2$-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(S)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(S)O- or -OC(S)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -C(S)N(R)- or -(R)NC(S)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -(R)NC(S)N(R)-. In some embodiments, 1, 2, or 3 methylene units of the chain are replaced with -Cy-. In some embodiments, L^1 is a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, or 4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2$-, $-SO_2N(R)$-, $-(R)NSO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; wherein each R is independently hydrogen, $-CH_2$-phenyl, phenyl, $-CH_3$, $-CH_2CH_3$, cyclopentyl, cyclohexyl, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CF_3$; or each R is independently hydrogen or methyl; or R is hydrogen. In some embodiments, L^1 and R^8 are taken together with any intervening atoms to form a 5-6 membered optionally substituted partially unsaturated heterocyclic ring that is fused with Ring A having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

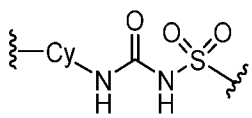
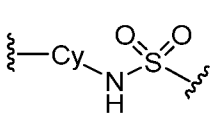
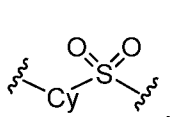
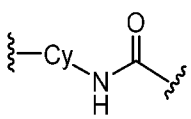
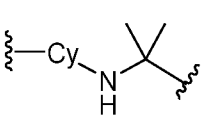
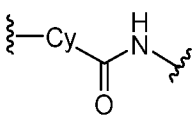
[0073] In some embodiments, L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, or 4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -NH-, -C(O)NH-, -NHC(O), -NHC(O)NH-, -SO_2-, or -Cy-.

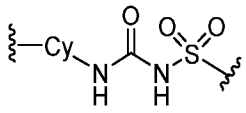
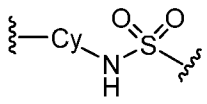
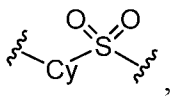
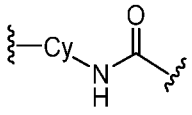
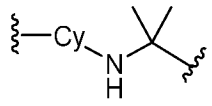
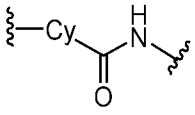
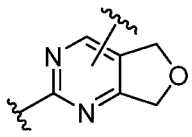
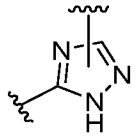
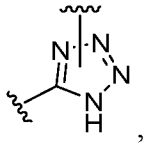
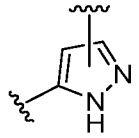
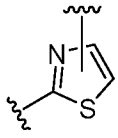
[0074] In some embodiments, L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -NH-, -C(O)NH-, -NHC(O), -NHC(O)NH-, -SO_2-, or -Cy-.

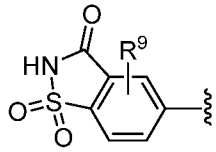
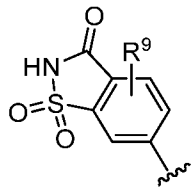
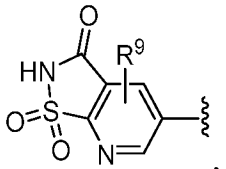
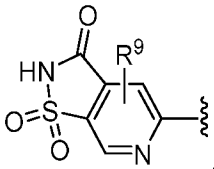
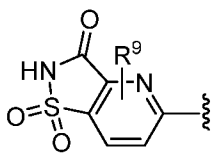
[0075] In some embodiments, L^1 is a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently replaced with -C(O)-, -NH-, -C(O)NH-, -NHC(O), -NHC(O)NH-, -SO_2-, or -Cy-.

[0076] In some embodiments, L^1 is a C_{3-6} bivalent straight or branched hydrocarbon chain wherein 2 or 3 methylene units of the chain are independently replaced with -SO_2-, -SO_2NH-, -C(O)O-, -C(O)NH-, or -NHC(O)NH-. In some embodiments, L^1 is a C_{3-6} bivalent branched hydrocarbon chain wherein 2 or 3 methylene units of the chain are independently replaced with -SO_2-, -SO_2NH-, -C(O)O-, -C(O)NH-, or -NHC(O)NH-.

[0077] In some embodiments, the methylene unit of L^1 attached to Ring A is replaced with -SO_2-. In some embodiments, the methylene unit of L^1 attached to Ring A is replaced with -SO_2NH-. In some embodiments, the methylene unit of L^1 attached to Ring A is substituted with two methyl groups. In some embodiments, the methylene unit of L^1 attached to Ring A is replaced with -C(O)NH-. In some embodiments, the methylene unit of L^1 attached to Ring A is replaced with -SO_2- and the adjacent methylene unit is replaced with -NHC(O)NH-. In some embodiments, the methylene unit of L^1 attached to Ring A is substituted with two methyl groups and the adjacent methylene unit is replaced with -NHC(O)NH-.

[0078] In some embodiments, L^1 is  ,  ,  ,  ,  , or  .

[0079] In some embodiments, L^1 is  ,  ,  ,  ,  , or  , wherein each -Cy- is independently phenylene, pyridinylene, pyrimidinylene, pyrazinylene,  ,  ,  ,  , or  .

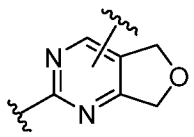
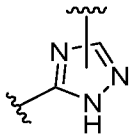
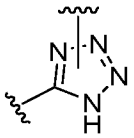
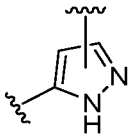
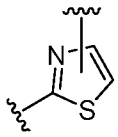
[0080] In some embodiments, L^1 and R^8 are taken together with Ring A to form  ,  ,  ,  , or  .

[0081] In some embodiments, L^1 is selected from those depicted in Table 1, below.

As defined generally above, each -Cy- is independently a bivalent 6-membered arylene ring containing 0-2 nitrogen atoms, a bivalent 5-membered heteroarylene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a bivalent partially unsaturated 8-10 membered bicyclic heterocyclene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR.

[0082] In some embodiments, each -Cy- is independently a bivalent 6-membered arylene ring containing 0-2 nitrogen atoms, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR, wherein each R is independently hydrogen or methyl. In some embodiments, each -Cy- is independently a bivalent 5-membered heteroarylene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR, wherein each R is independently hydrogen or methyl. In some embodiments, each

-Cy- is independently a bivalent partially unsaturated 8-10 membered bicyclic heterocyclene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR, wherein each R is independently hydrogen or methyl.

[0083] In some embodiments, -Cy- is phenylene, pyridinylene, pyrimidinylene, pyrazinylene,  ,  ,  ,  , or  .

[0084] In some embodiments, -Cy- is selected from those depicted in Table 1, below.

[0085] As defined generally above, R^8 is hydrogen, $-CO_2R$, or a C_{1-6} optionally substituted aliphatic group. In some embodiments, R^8 is hydrogen. In some embodiments, R^8 is $-CO_2R$, wherein R is hydrogen, C_{1-6} alkyl, or phenyl. In some embodiments, R^8 is a C_{1-6} optionally substituted aliphatic group.

[0086] In some embodiments, R^8 is hydrogen, methyl, ethyl, cyclobutyl, or $-CO_2H$. In some embodiments, R^8 is hydrogen or $-CO_2H$.

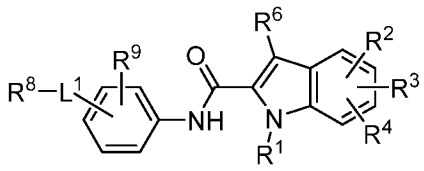
[0087] In some embodiments, R^8 is selected from those depicted in Table 1, below.

[0088] As defined generally above, R^9 is hydrogen, halogen, C_{1-4} alkyl, optionally substituted phenyl, or C_{1-4} alkyl substituted with an optionally substituted phenyl. In some embodiments, R^9 is hydrogen. In some embodiments, R^9 is halogen. In some embodiments, R^9 is C_{1-4} alkyl. In some embodiments, R^9 is optionally substituted phenyl. In some embodiments, R^9 is C_{1-4} alkyl substituted with an optionally substituted phenyl.

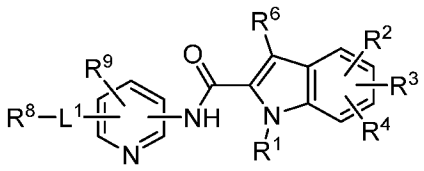
[0089] In some embodiments, R^9 is hydrogen, F, Cl, methyl, or $-CH_2$-phenyl. In some embodiments, R^9 is hydrogen, F, or $-CH_2$-phenyl.

[0090] In some embodiments, R^9 is selected from those depicted in Table 1, below.

[0091] In some embodiments, the present invention provides a compound of formulae **II-a** or **II-b**:



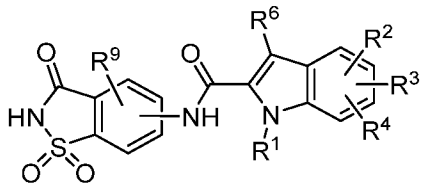
II-a



II-b

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

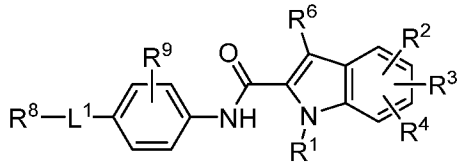
[0092] In some embodiments, the present invention provides a compound of formula **II-c**:



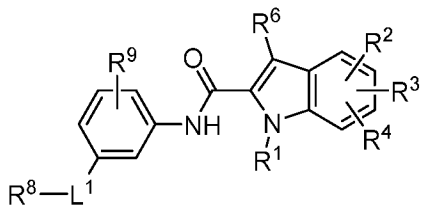
II-c

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^9, R, R', L, and n is as defined above and described in embodiments herein, both singly and in combination.

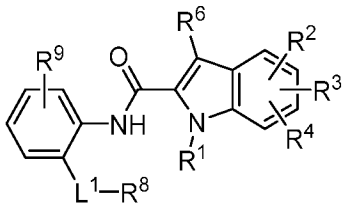
[0093] In some embodiments, the present invention provides a compound of formulae **III-a**, **III-b**, **III-c**, or **III-d**:



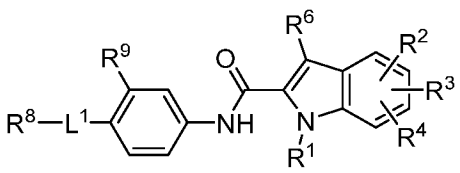
III-a



III-b



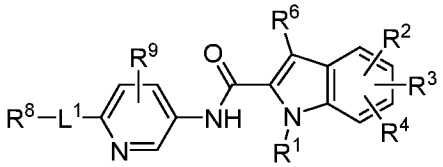
III-c



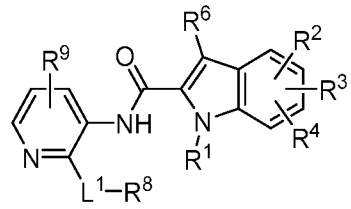
III-d

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

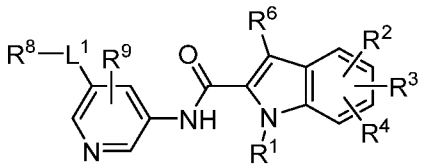
[0094] In some embodiments, the present invention provides a compound of formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



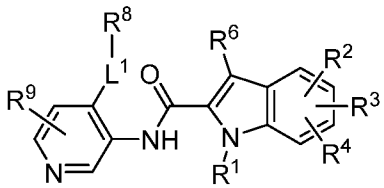
IV-a



IV-b



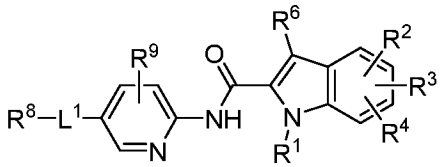
IV-c



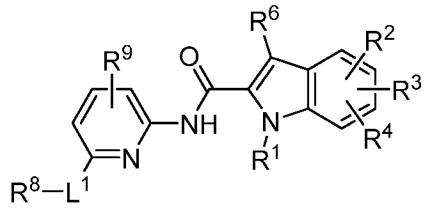
IV-d

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

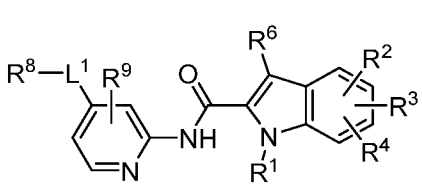
[0095] In some embodiments, the present invention provides a compound of formulae **V-a**, **V-b**, **V-c**, or **V-d**:



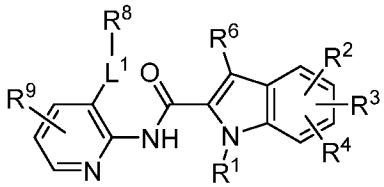
V-a



V-b



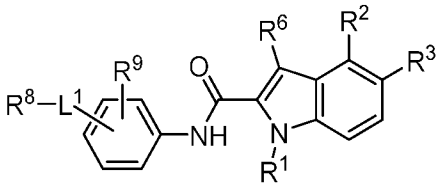
V-c



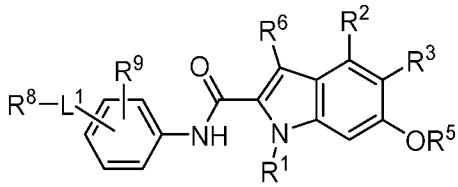
V-d

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

[0096] In some embodiments, the present invention provides a compound of formulae **VI-a** or **VI-b**:



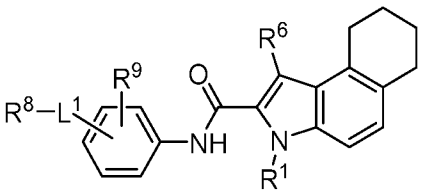
VI-a



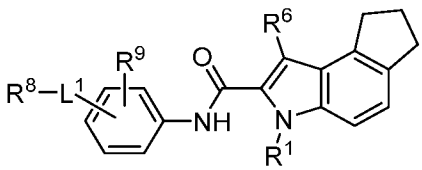
VI-b

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^5, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

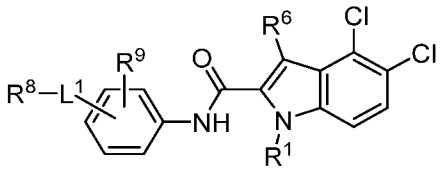
[0097] In some embodiments, the present invention provides a compound of formulae **VI-c**, **VI-d**, or **VI-e**:



VI-c



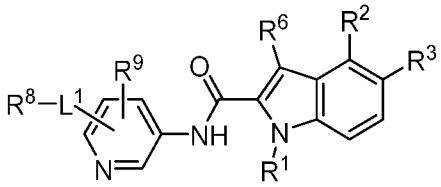
VI-d



VI-e

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^6, R^8, R^9, R, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

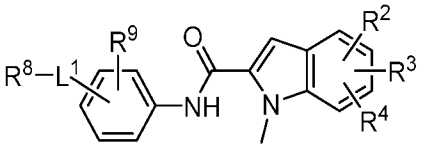
[0098] In some embodiments, the present invention provides a compound of formula **VII**:



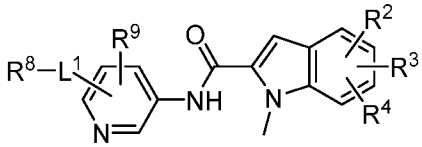
VII

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^6, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

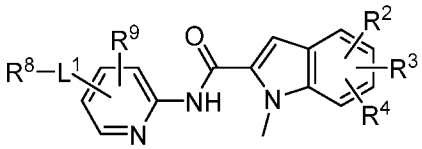
[0099] In some embodiments, the present invention provides a compound of formulae **VIII-a**, **VIII-b**, or **VIII-c**:



VIII-a



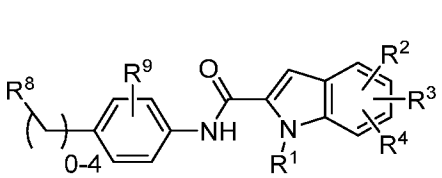
VIII-b



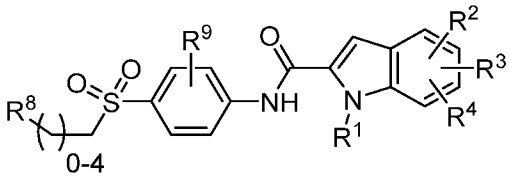
VIII-c

or a pharmaceutically acceptable salt thereof, wherein each of R^2, R^3, R^4, R^5, R^8, R^9, R, R', L, L^1, -Cy-, and n is as defined above and described in embodiments herein, both singly and in combination.

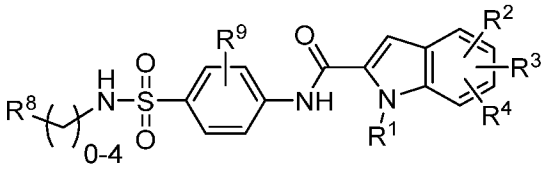
[00100] In some embodiments, the present invention provides a compound of formulae **IX-a**, **IX-b**, **IX-c**, **IX-d**, **IX-e**, **IX-f**, **IX-g**, **IX-h**, **IX-i**, **IX-j**, **IX-k**, **IX-l**, **IX-m**, **IX-n**, **IX-o**, **IX-p**, or **IX-q**:



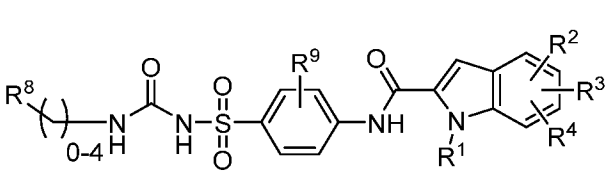
IX-a



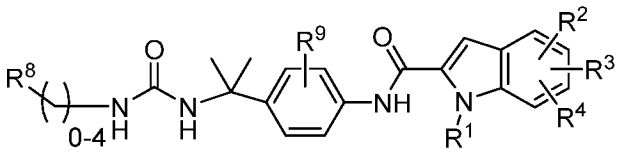
IX-b



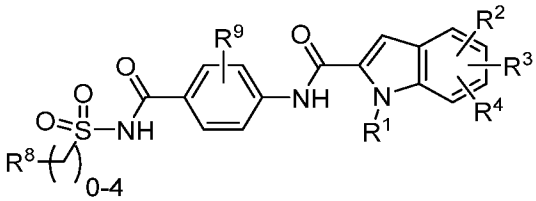
IX-c



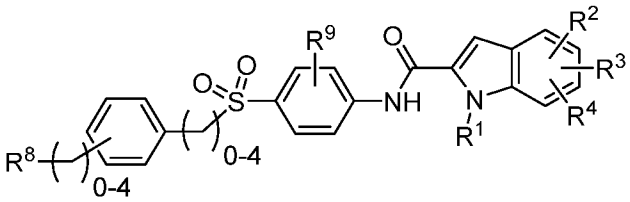
IX-d



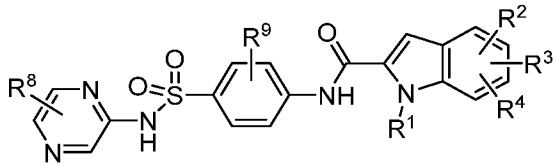
IX-e



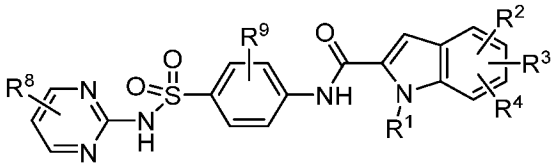
IX-f



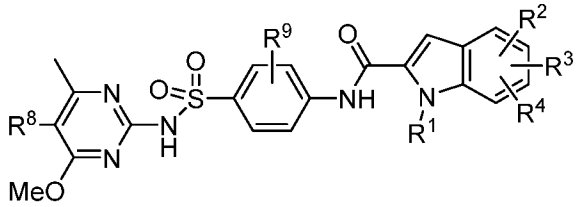
IX-g



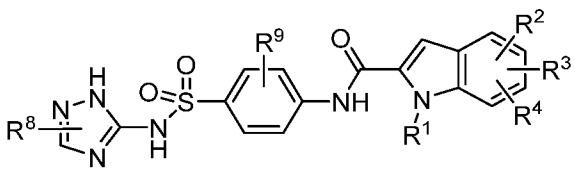
IX-h



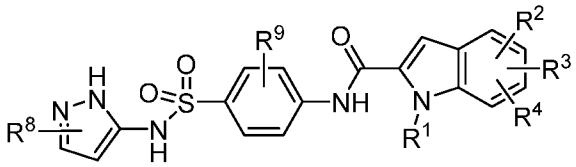
IX-i



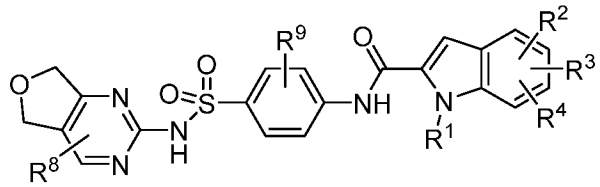
IX-j



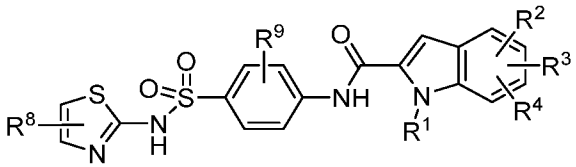
IX-k



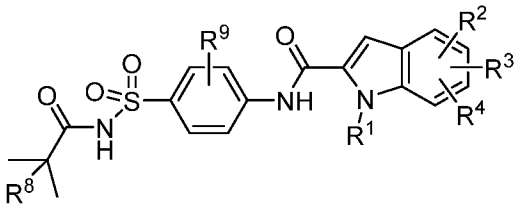
IX-l



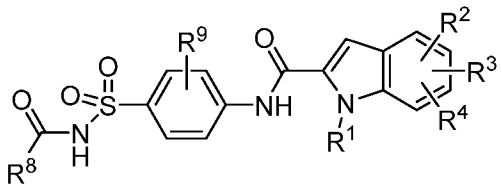
IX-m



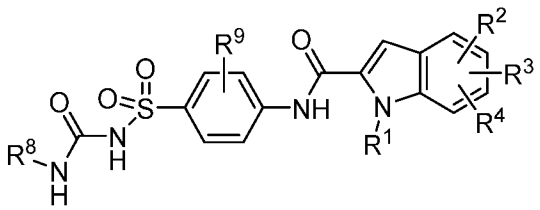
IX-n



IX-o



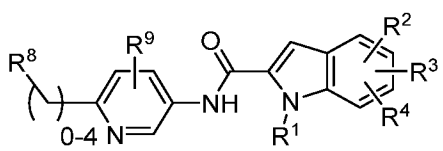
IX-p



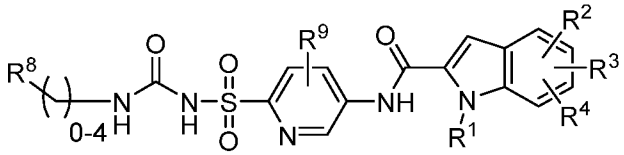
IX-q

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R, R', L, and n is as defined above and described in embodiments herein, both singly and in combination.

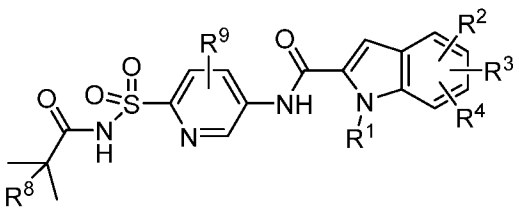
[00101] In some embodiments, the present invention provides a compound of formulae **X-a**, **X-b**, **X-c**, **X-d**, **X-e**, **X-f**, or **X-g**:



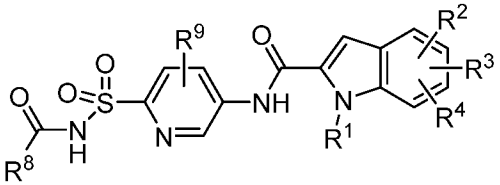
X-a



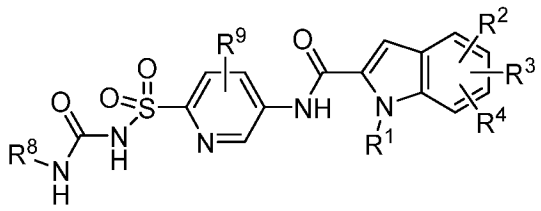
X-b



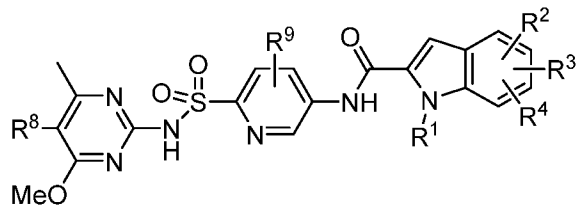
X-c



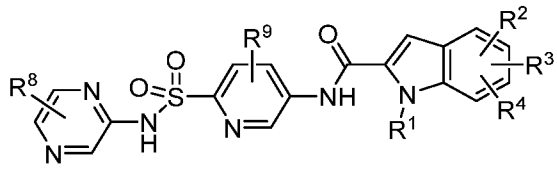
X-d



X-e



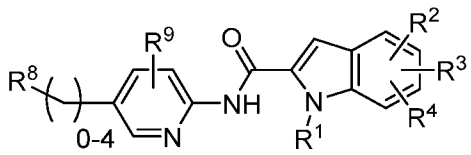
X-f



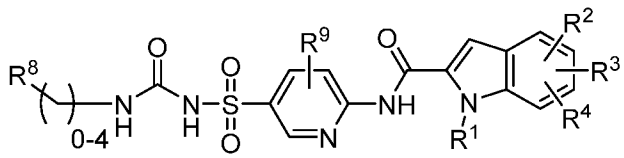
X-g

or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R, R', L, and n is as defined above and described in embodiments herein, both singly and in combination.

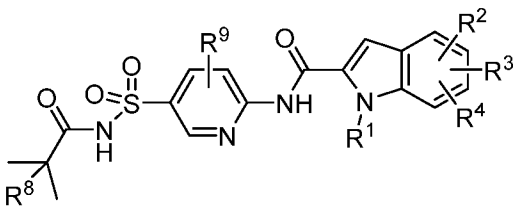
[00102] In some embodiments, the present invention provides a compound of formulae **XI-a**, **XI-b**, **XI-c**, **XI-d**, **XI-e**, **XI-f**, or **XI-g**:



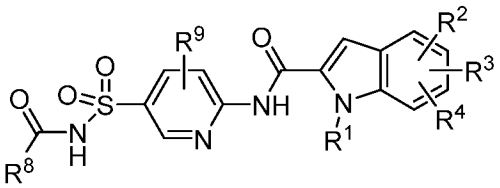
XI-a



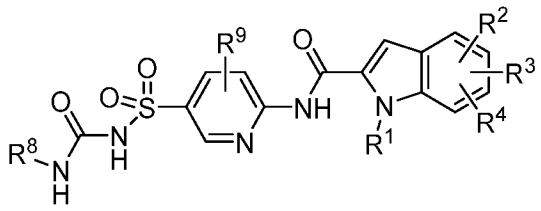
XI-b



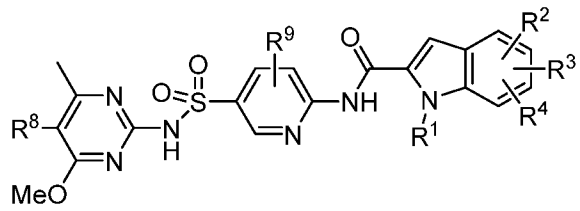
XI-c



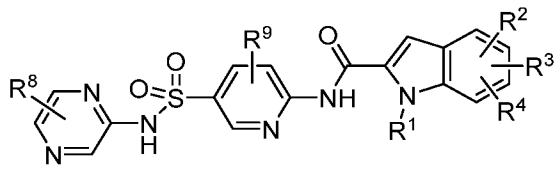
XI-d



XI-e



XI-f

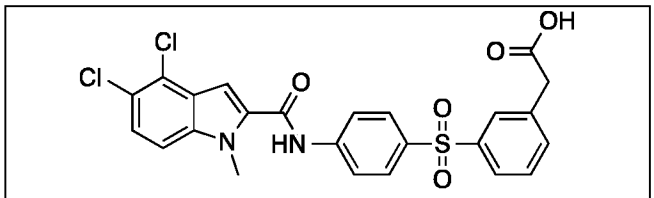


XI-g

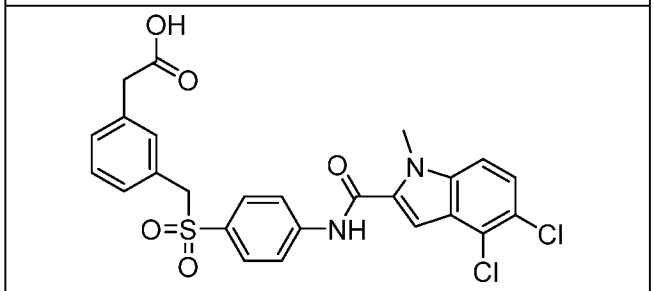
[00103] or a pharmaceutically acceptable salt thereof, wherein each of R^1, R^2, R^3, R^4, R^5, R^8, R^9, R, R', L, and n is as defined above and described in embodiments herein, both singly and in combination.

[00104] Exemplary compounds of the invention are set forth in **Table 1**, below.

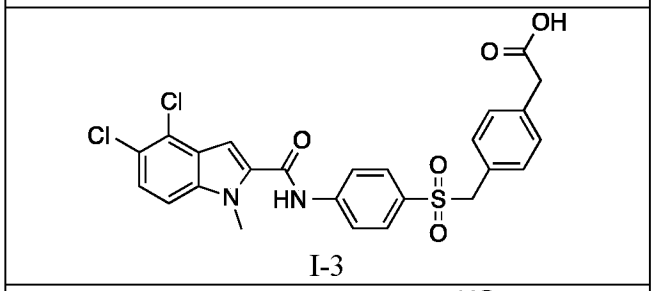
Table 1. Exemplary Compounds



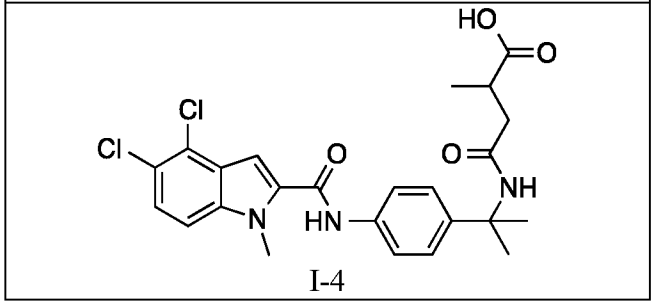
I-1



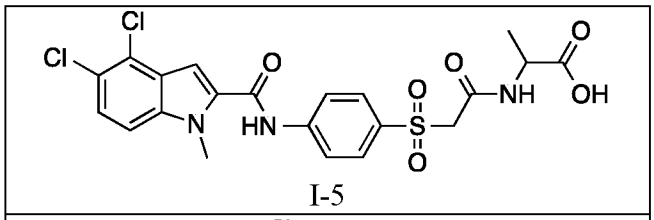
I-2



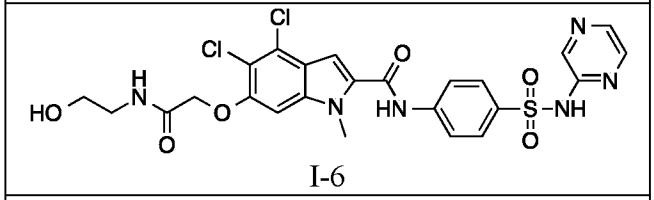
I-3



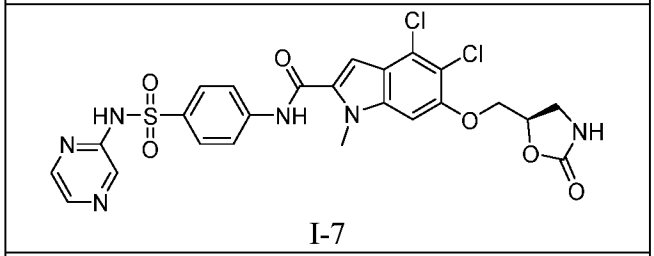
I-4



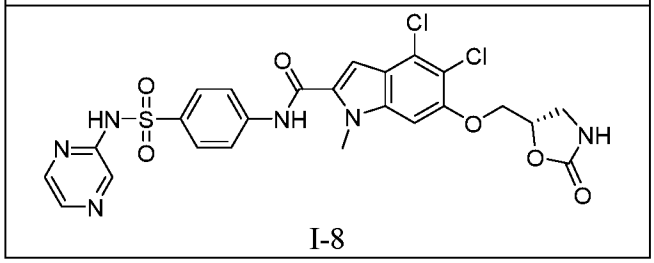
I-5



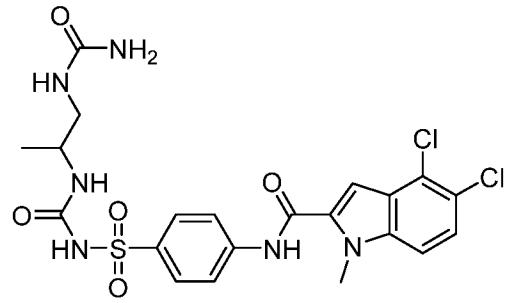
I-6



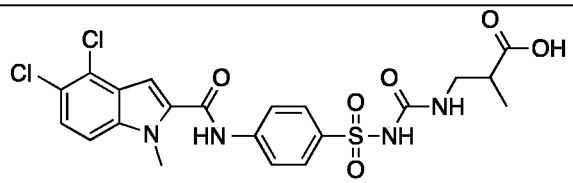
I-7



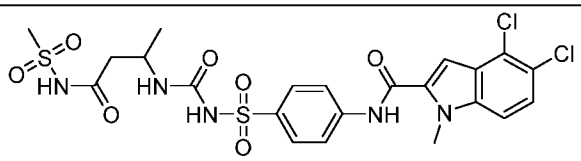
I-8



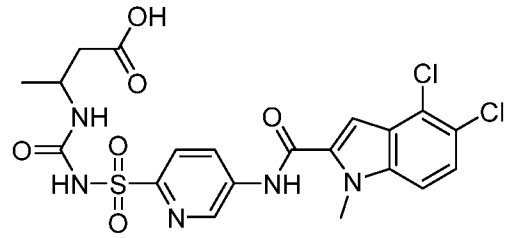
I-9



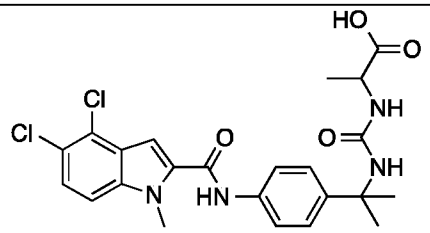
I-10



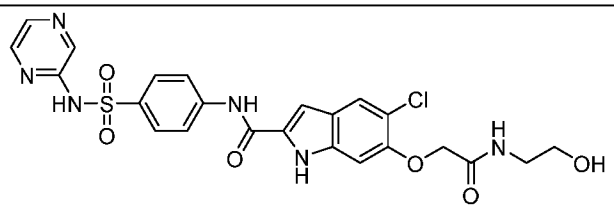
I-11



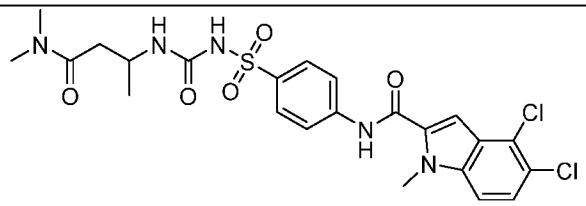
I-12



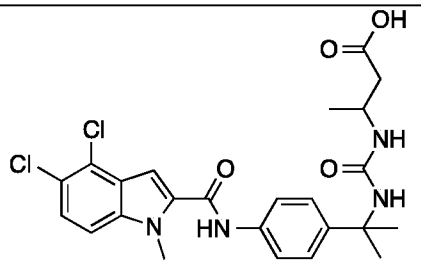
I-13



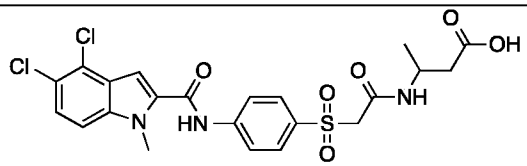
I-14



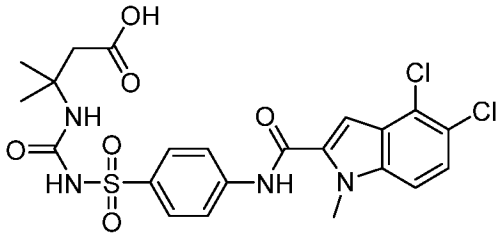
I-15



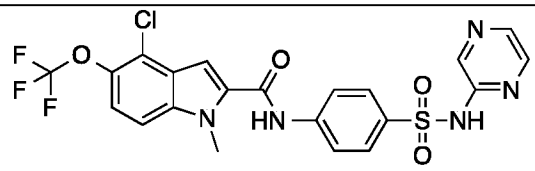
I-16



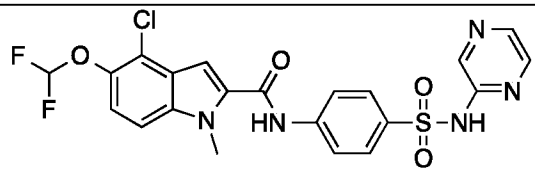
I-17



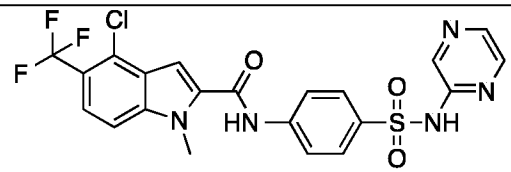
I-18



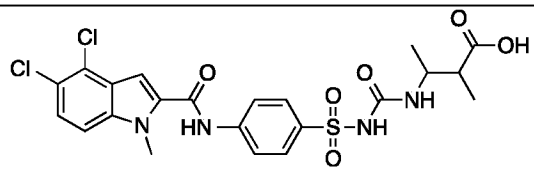
I-19



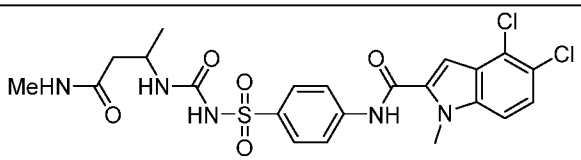
I-20



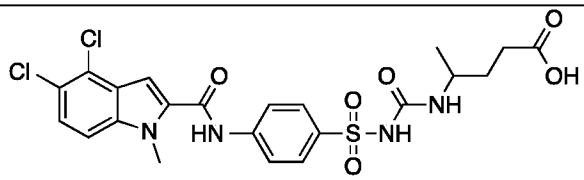
I-21



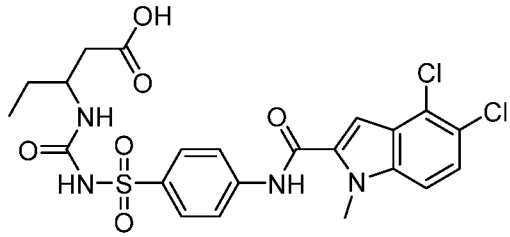
I-22



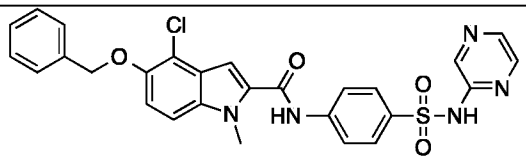
I-23



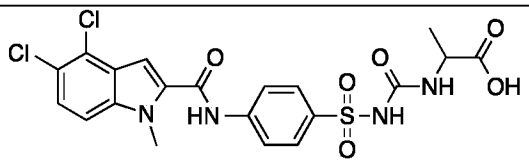
I-24



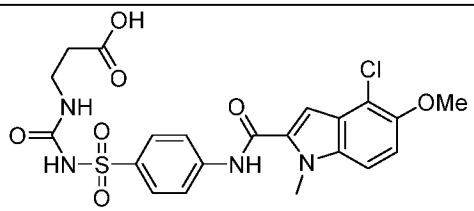
I-25



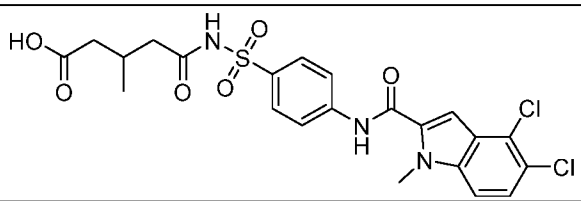
I-26



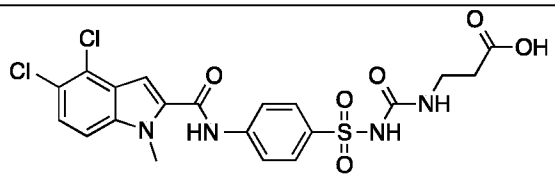
I-27



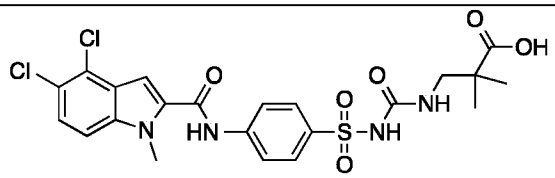
I-28



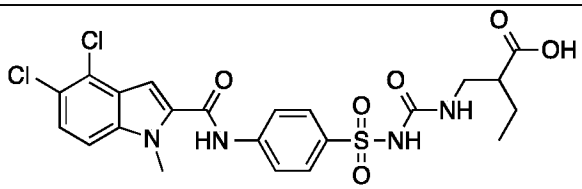
I-29



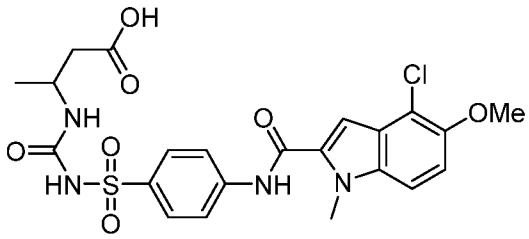
I-30



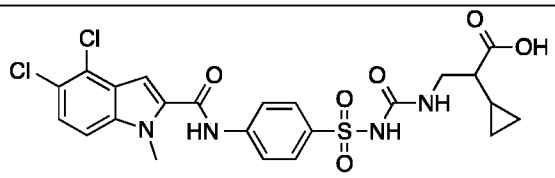
I-31



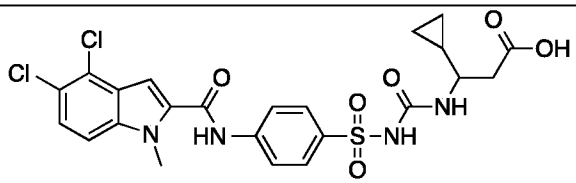
I-32



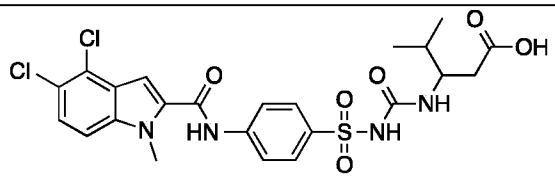
I-33



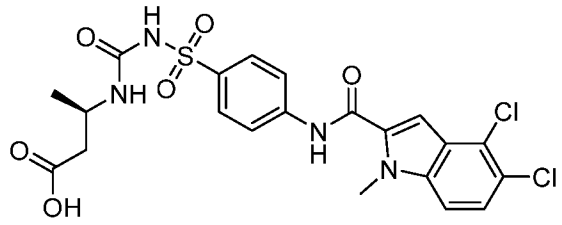
I-34



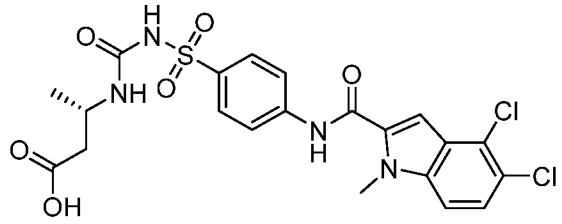
I-35



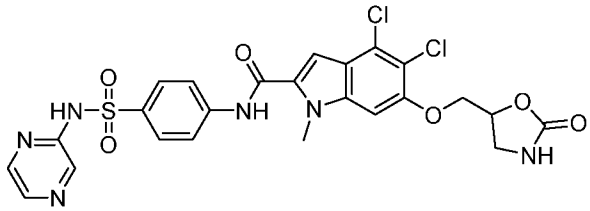
I-36



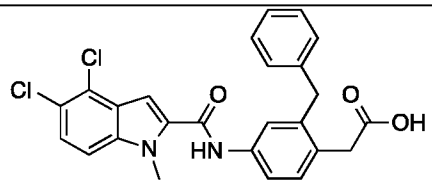
I-37



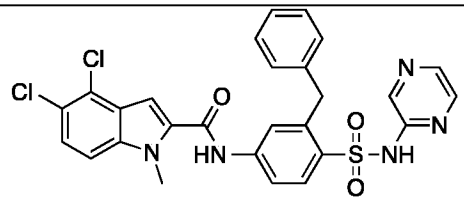
I-38



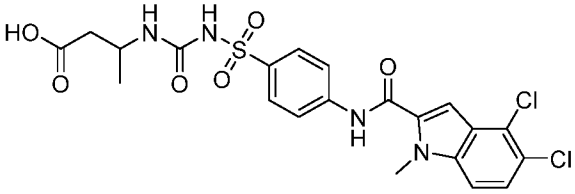
I-39



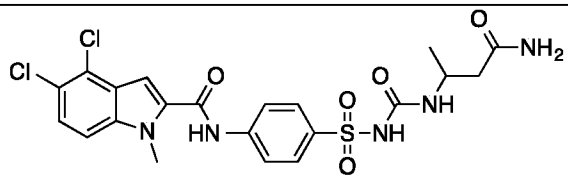
I-40



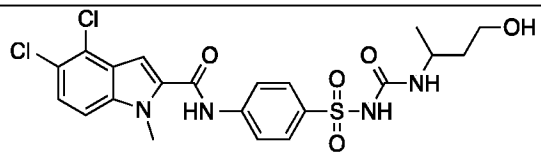
I-41



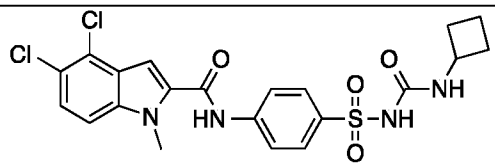
I-42



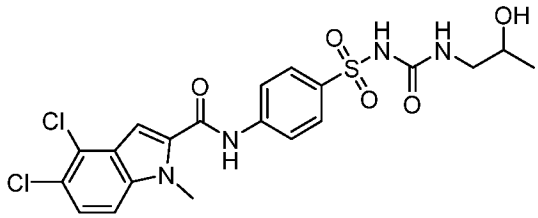
I-43



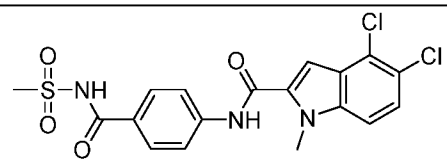
I-44



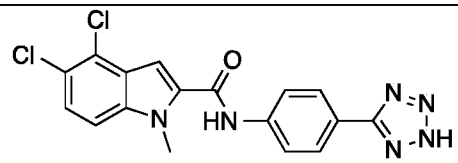
I-45



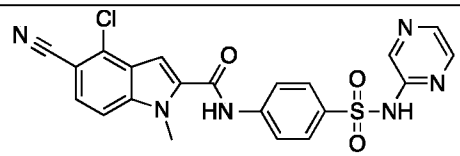
I-46



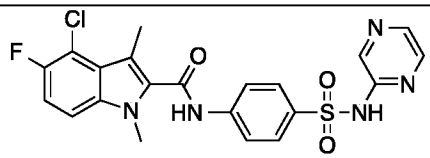
I-47



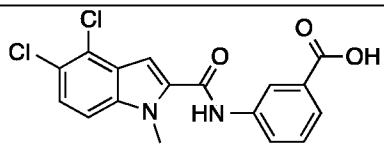
I-48



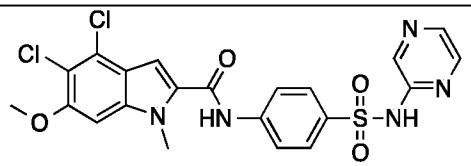
I-49



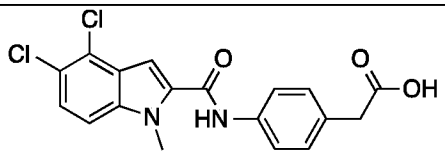
I-50



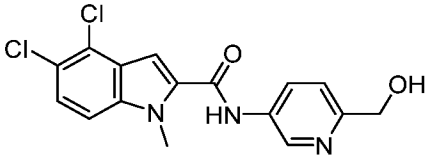
I-51



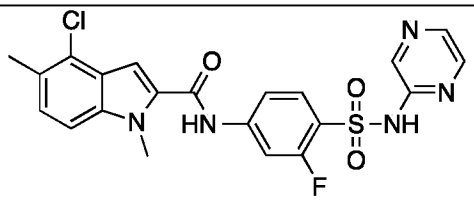
I-52



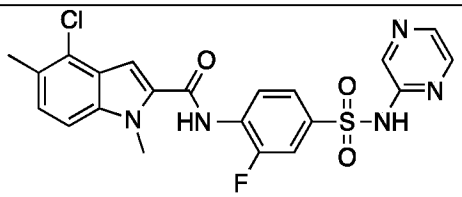
I-53



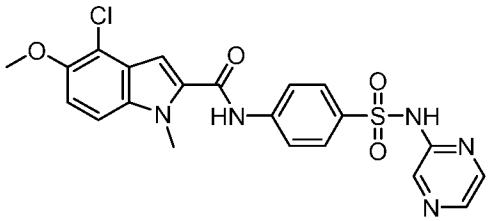
I-54



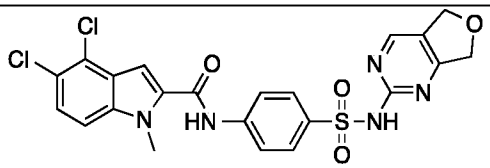
I-55



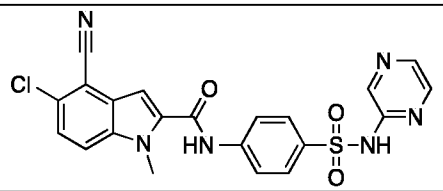
I-56



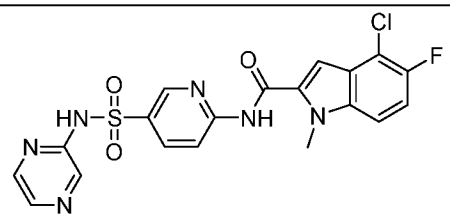
I-57



I-58

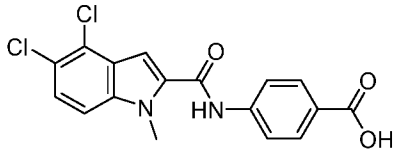


I-59

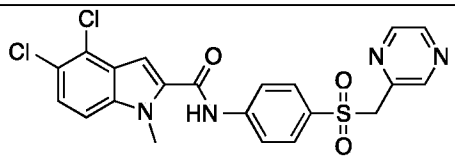


Free base or HCl salt

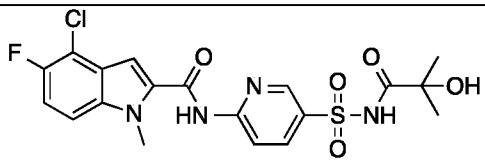
I-60



I-61

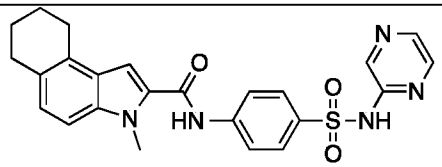


I-62

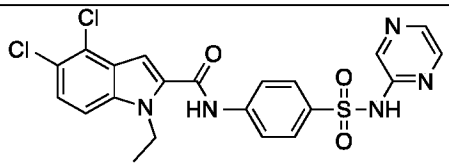


Free base or TFA salt

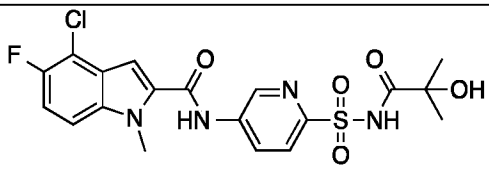
I-63



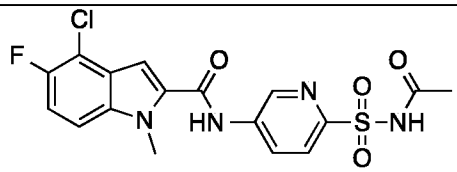
I-64



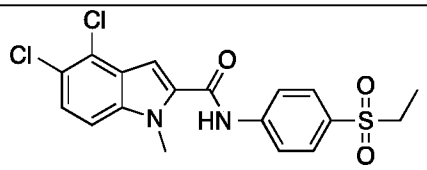
I-65



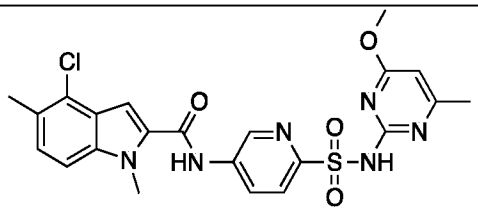
I-66



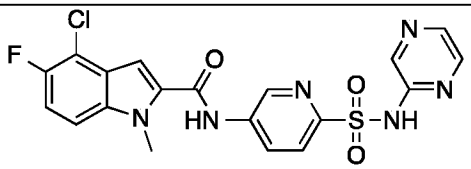
I-67



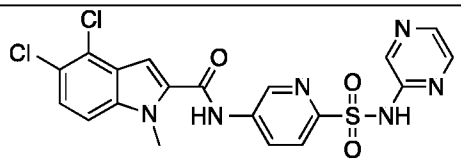
I-68



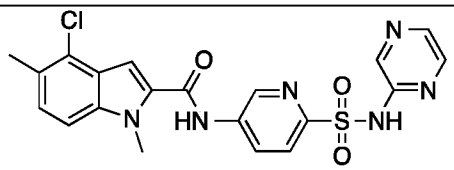
I-69



I-70

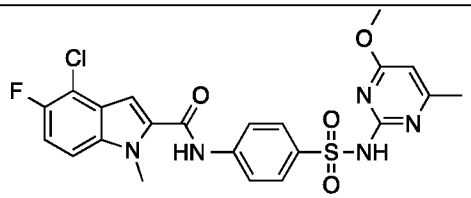


I-71

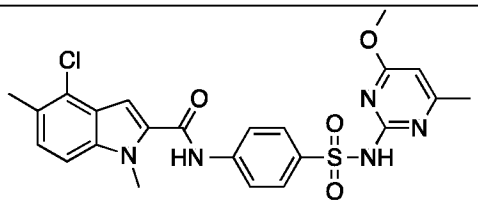


I-72

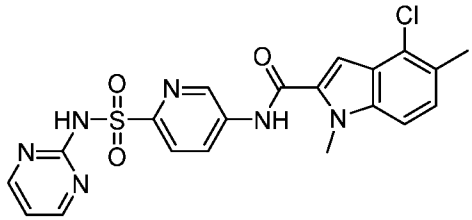
I-73



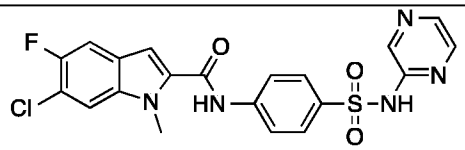
I-74



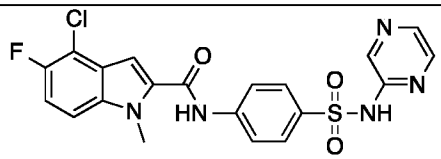
I-75



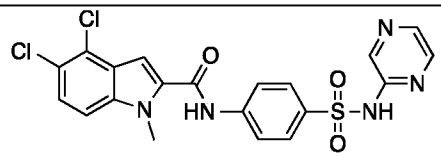
I-76



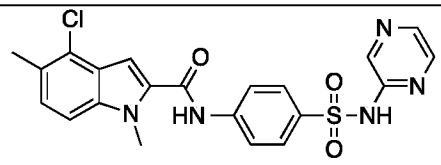
I-77



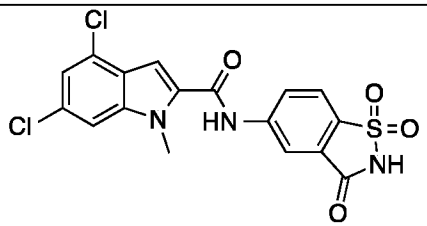
I-78



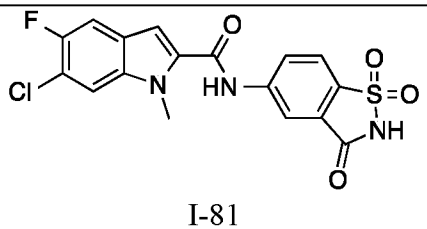
I-79



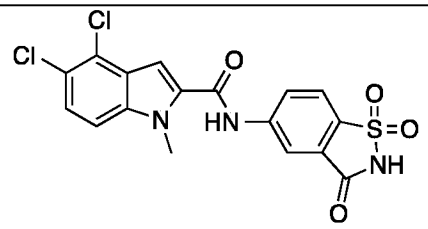
I-80



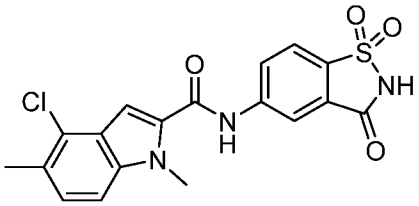
I-81



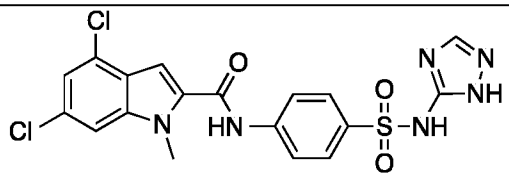
I-82



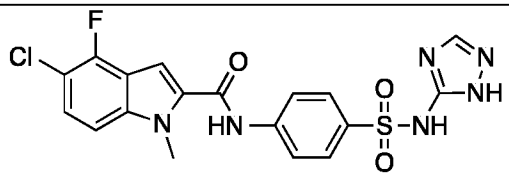
I-83



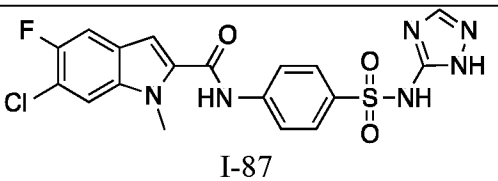
I-84



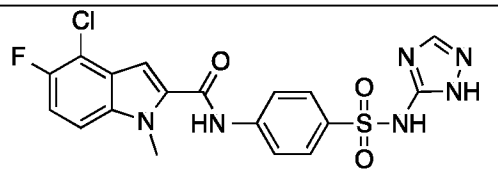
I-85



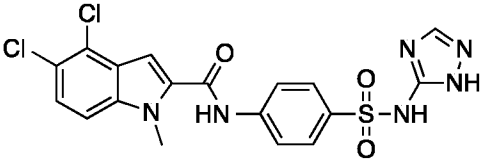
I-86



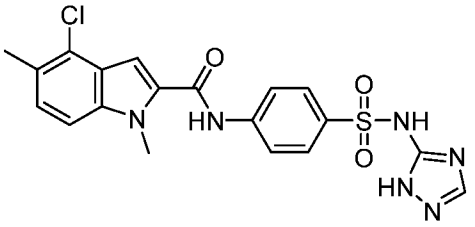
I-87



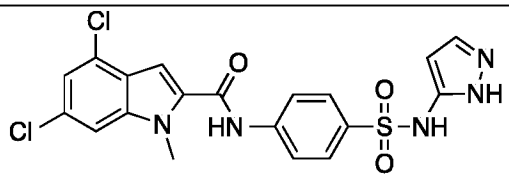
I-88



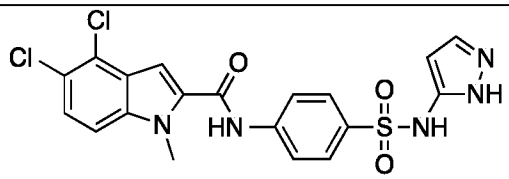
I-89



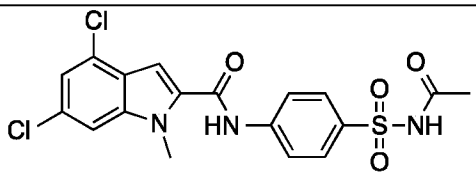
I-90



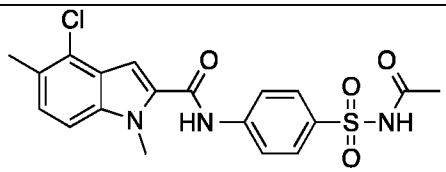
I-91



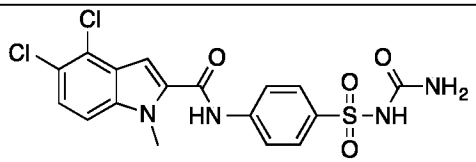
I-92



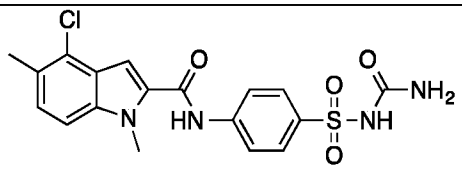
I-93



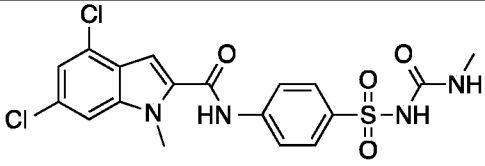
I-94



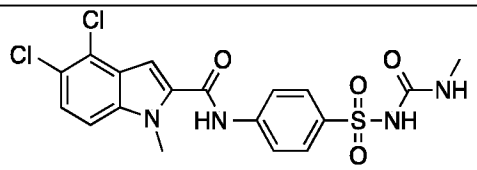
I-95

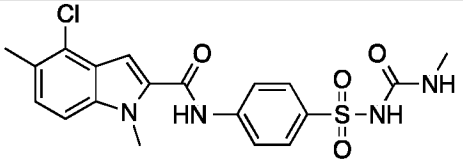


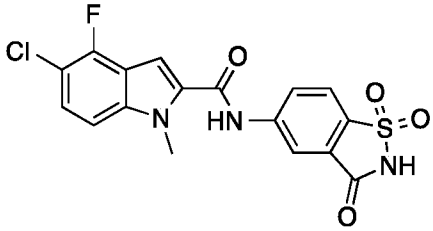
I-96

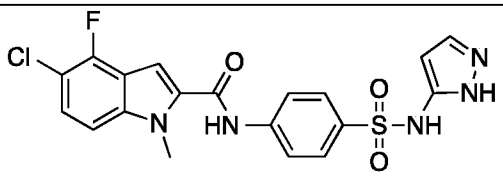


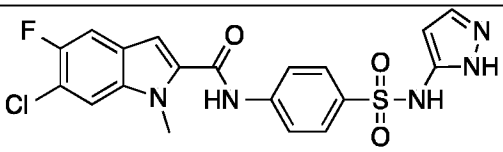
I-97

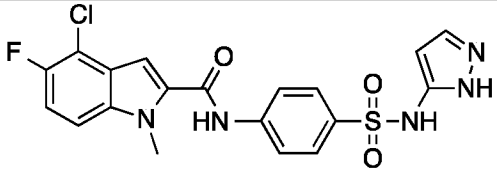

I-98

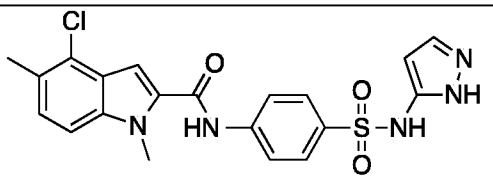

I-99

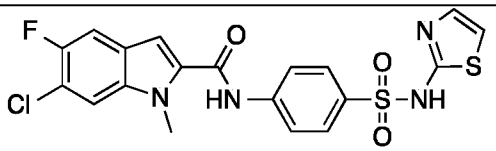

I-100

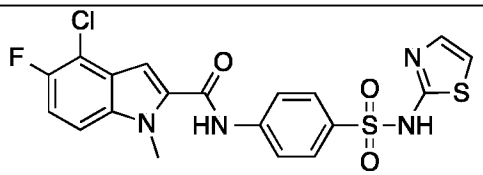

I-101

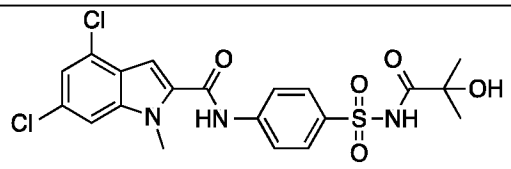

I-102

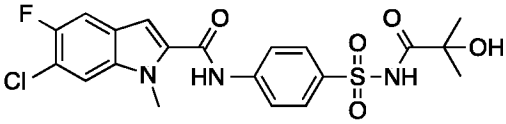

I-103

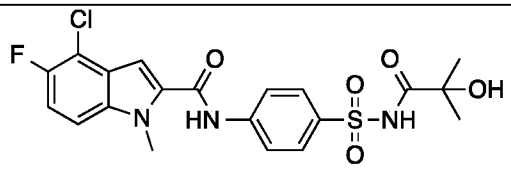

I-104

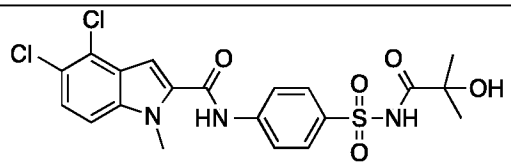

I-105

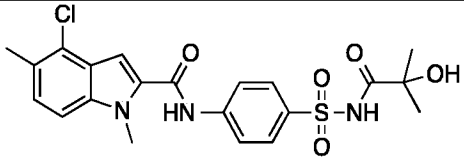

I-106

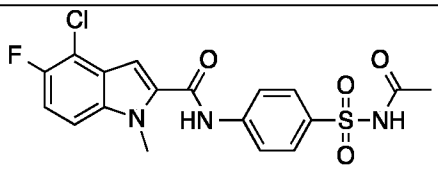

I-107

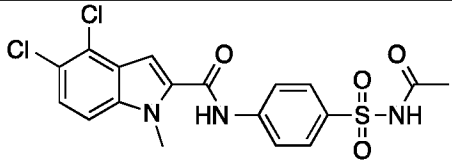

I-108

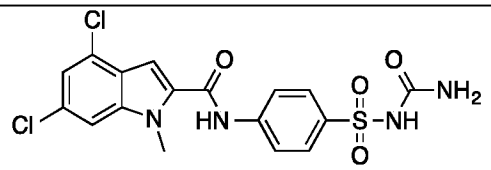

I-109

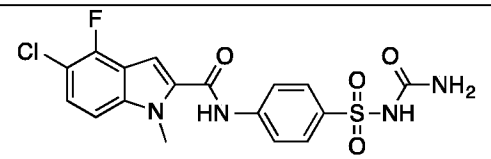

I-110

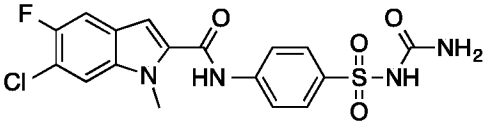

I-111

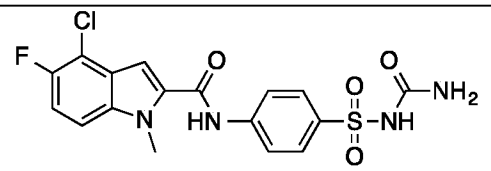

I-112

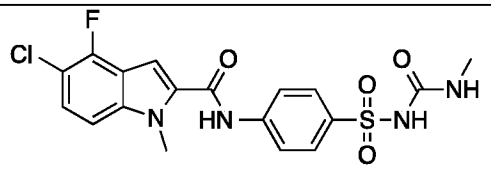

I-113

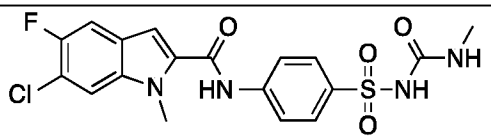

I-114

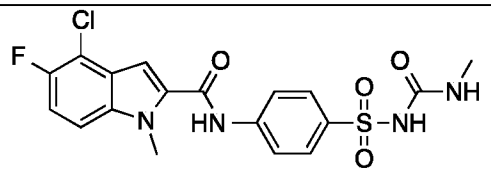

I-115

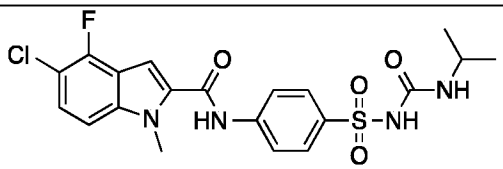

I-116

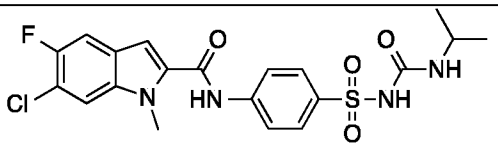

I-117

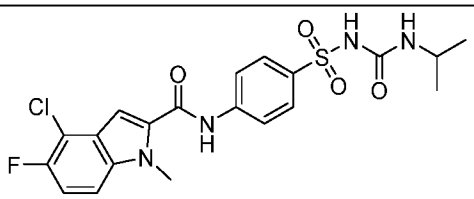

I-118

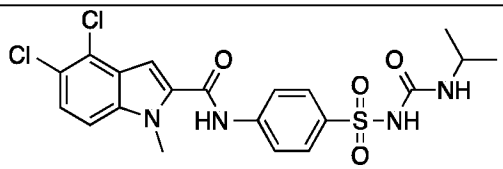

I-119

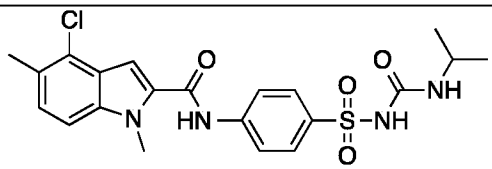

I-120

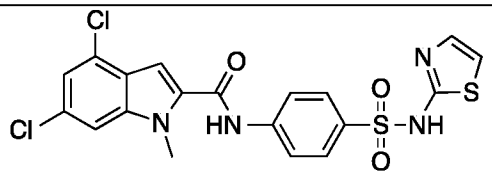

I-121

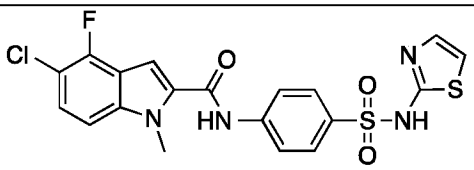

I-122

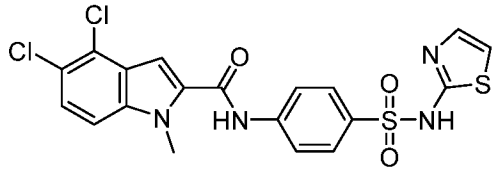

I-123

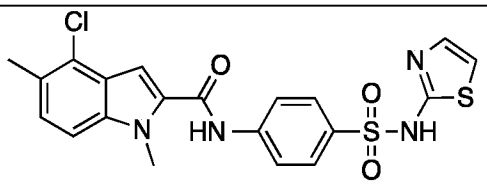

I-124

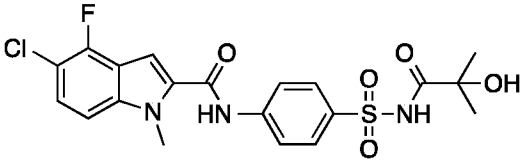

I-125

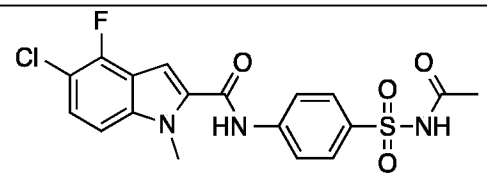

I-126

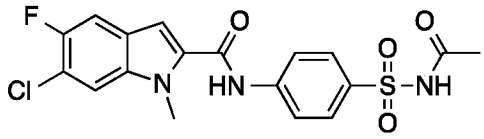

I-127

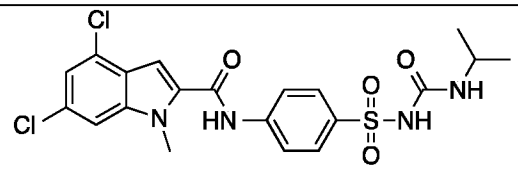

I-128

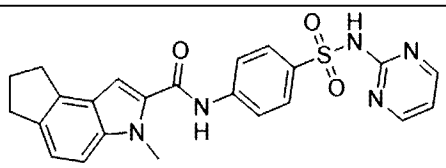

I-129

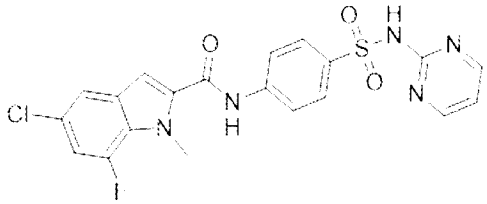

I-130

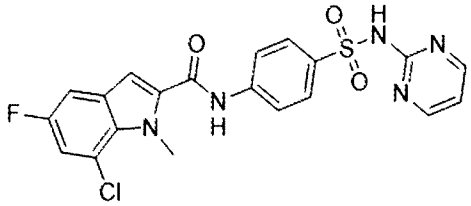

I-131

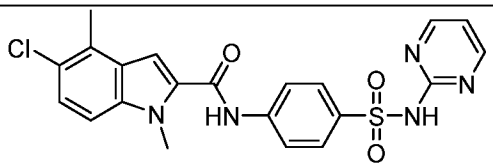

I-132

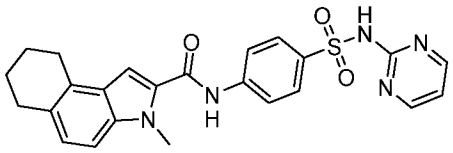

I-133

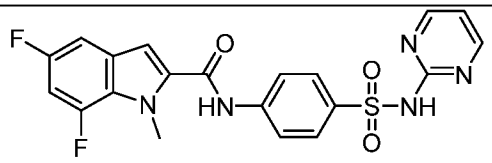

I-134

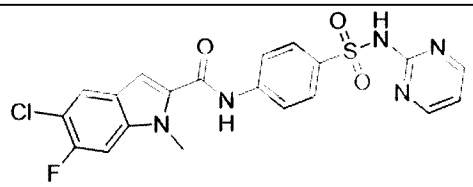

I-135

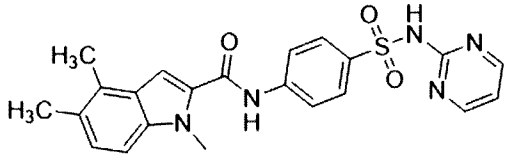

I-136

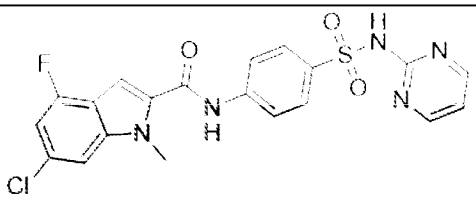

I-137

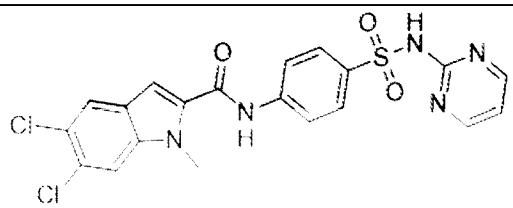

I-138

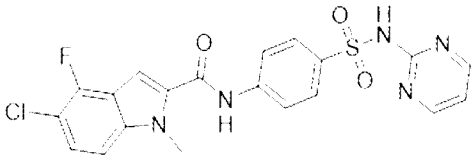

I-139

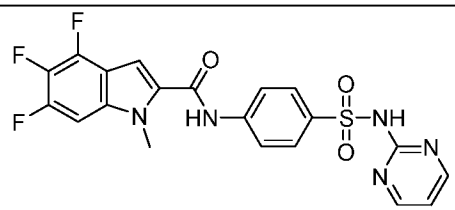

I-140

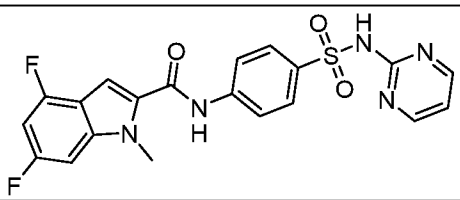

I-141


I-142

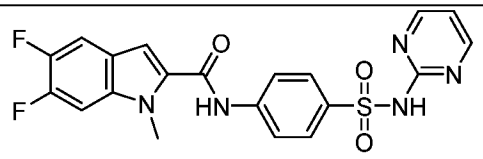

I-143


I-144

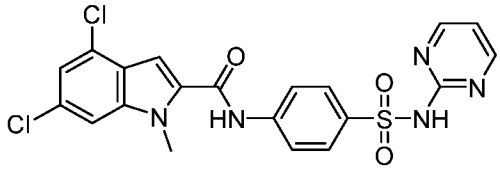

I-145



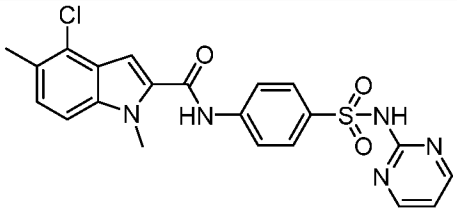
I-146



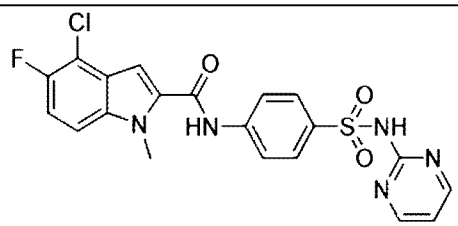
I-147



I-148

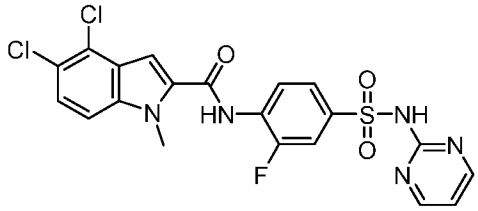


I-149

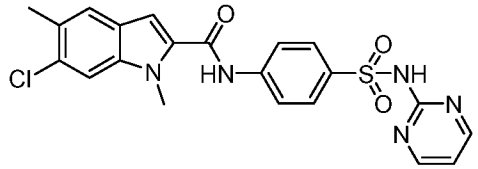


I-150

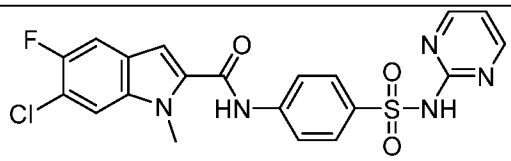
I-151



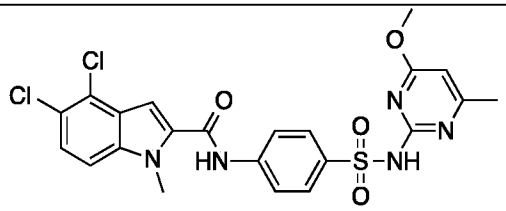
I-152



I-153



I-154



[00105] In some embodiments, the present invention provides a compound set forth in **Table 1**, above, or a pharmaceutically acceptable salt thereof.

4. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00106] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit PHGDH, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit PHGDH, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such

composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00107] The term "patient," as used herein, means an animal, which is in some embodiments a mammal, and in other embodiments a human.

[00108] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00109] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[00110] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of PHGDH, or a mutant thereof.

[00111] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol.

Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00112] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00113] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00114] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00115] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00116] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00117] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00118] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00119] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00120] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00121] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be

formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00122] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00123] Compounds and compositions described herein are generally useful for the inhibition of PHGDH or a mutant thereof.

[00124] The activity of a compound utilized in this invention as an inhibitor of PHGDH, or a mutant thereof, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of PHGDH, or a mutant thereof. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to PHGDH. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of PHGDH, or a mutant thereof, are set forth in the Examples below.

[00125] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00126] Provided compounds are inhibitors of PHGDH and are therefore useful for treating one or more disorders associated with activity of PHGDH. Thus, in certain embodiments, the present invention provides a method for treating a PHGDH-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00127] As used herein, the terms "PHGDH-mediated" disorders, diseases, and/or conditions as used herein means any disease or other deleterious condition in which PHGDH, or a mutant thereof, is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which PHGDH, or a mutant thereof, are known to play a role.

[00128] In some embodiments, the present invention provides a method for treating one or more disorders, diseases, and/or conditions wherein the disorder, disease, or condition includes, but is not limited to, a cellular proliferative disorder.

Cellular Proliferative Disorders

[00129] The present invention features methods and compositions for the diagnosis and prognosis of cellular proliferative disorders (e.g., cancer) and the treatment of these disorders by targeting PHGDH of the serine biosynthetic pathway. Cellular proliferative disorders described herein include, e.g., cancer, obesity, and proliferation-dependent diseases. Such disorders may be diagnosed using methods known in the art.

Cancer

[00130] Cancer includes, in one embodiment, without limitation, leukemias (e.g., acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute monocytic leukemia, acute erythroleukemia, chronic leukemia, chronic myelocytic leukemia, chronic lymphocytic leukemia), polycythemia vera, lymphoma (e.g., Hodgkin's disease or non-Hodgkin's disease), Waldenstrom's macroglobulinemia, multiple myeloma, heavy chain disease, and solid tumors such as sarcomas and carcinomas (e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, uterine cancer, testicular cancer, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma,

craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, meningioma, melanoma, neuroblastoma, and retinoblastoma). In some embodiments, the cancer is melanoma or breast cancer.

[00131] Cancers includes, in another embodiment, without limitation, mesothelioma, hepatobilliary (hepatic and billiary duct), bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular melanoma, ovarian cancer, colon cancer, rectal cancer, cancer of the anal region, stomach cancer, gastrointestinal (gastric, colorectal, and duodenal), uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, prostate cancer, testicular cancer, chronic or acute leukemia, chronic myeloid leukemia, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter, renal cell carcinoma, carcinoma of the renal pelvis, non-Hodgkin's lymphoma, spinal axis tumors, brain stem glioma, pituitary adenoma, adrenocortical cancer, gall bladder cancer, multiple myeloma, cholangiocarcinoma, fibrosarcoma, neuroblastoma, retinoblastoma, or a combination of one or more of the foregoing cancers.

[00132] In some embodiments, the present invention provides a method for treating a tumor in a patient in need thereof, comprising administering to the patient any of the compounds, salts or pharmaceutical compositions described herein. In some embodiments, the tumor comprises any of the cancers described herein. In some embodiments, the tumor comprises melanoma cancer. In some embodiments, the tumor comprises breast cancer. In some embodiments, the tumor comprises lung cancer. In some embodiments the tumor comprises small cell lung cancer (SCLC). In some embodiments the tumor comprises non-small cell lung cancer (NSCLC).

[00133] In some embodiments, the tumor is treated by arresting further growth of the tumor. In some embodiments, the tumor is treated by reducing the size (e.g., volume or mass) of the tumor by at least 5%, 10%, 25%, 50 %, 75%, 90% or 99% relative to the size of the tumor prior to treatment. In some embodiments, tumors are treated by reducing the quantity of the tumors in the patient by at least 5%, 10%, 25%, 50 %, 75%, 90% or 99% relative to the quantity of tumors prior to treatment.

Other Proliferative Diseases

[00134] Other proliferative diseases include, e.g., obesity, benign prostatic hyperplasia, psoriasis, abnormal keratinization, lymphoproliferative disorders (e.g., a disorder in which there is abnormal proliferation of cells of the lymphatic system), chronic rheumatoid arthritis, arteriosclerosis, restenosis, and diabetic retinopathy. Proliferative diseases that are hereby incorporated by reference include those described in U.S. Pat. Nos. 5,639,600 and 7,087,648.

Inflammatory Disorders and Diseases

[00135] It has recently been reported that PHGDH gene expression, dictated by IL-2R signaling, is a crucial event for DNA synthesis during S phase of activated T cells. Jun do Y *et al.*, *Cell Immunol.* 2014 Feb;287(2):78-85. Compounds according to the invention are useful in the treatment of inflammatory or obstructive airways diseases, resulting, for example, in reduction of tissue damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics.

[00136] Compounds according to the invention are useful in the treatment of heteroimmune diseases. Examples of such heteroimmune diseases include, but are not limited to, graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander, dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[00137] Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, such as therapy for or intended to restrict or abort symptomatic attack when it occurs, for example antiinflammatory or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a

substantial percentage of asthmatics and characterized by asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

[00138] Compounds of the current invention can be used for other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable and include acute lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis or dyspnea associated therewith, emphysema, as well as exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. The invention is also applicable to the treatment of bronchitis of whatever type or genesis including, but not limited to, acute, arachidic, catarrhal, croupus, chronic or phthinoid bronchitis. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis.

[00139] With regard to their anti-inflammatory activity, in particular in relation to inhibition of eosinophil activation, compounds of the invention are also useful in the treatment of eosinophil related disorders, e.g. eosinophilia, in particular eosinophil related disorders of the airways (e.g. involving morbid eosinophilic infiltration of pulmonary tissues) including hypereosinophilia as it effects the airways and/or lungs as well as, for example, eosinophil-related disorders of the airways consequential or concomitant to Loffler's syndrome, eosinophilic pneumonia, parasitic (in particular metazoan) infestation (including tropical eosinophilia), bronchopulmonary aspergillosis, polyarteritis nodosa (including Churg-Strauss syndrome), eosinophilic granuloma and eosinophil-related disorders affecting the airways occasioned by drug-reaction.

[00140] Compounds of the invention are also useful in the treatment of inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, lupus erythematosus, systemic lupus erythematosus, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus,

epidermolysis bullosa acquisita, acne vulgaris, and other inflammatory or allergic conditions of the skin.

[00141] Compounds of the invention may also be used for the treatment of other diseases or conditions, such as diseases or conditions having an inflammatory component, for example, treatment of diseases and conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca, and vernal conjunctivitis, diseases affecting the nose including allergic rhinitis, and inflammatory disease in which autoimmune reactions are implicated or having an autoimmune component or etiology, including autoimmune hematological disorders (e.g. hemolytic anemia, aplastic anemia, pure red cell anemia and idiopathic thrombocytopenia), systemic lupus erythematosus, rheumatoid arthritis, polychondritis, scleroderma, Wegener granulamatosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis and Crohn's disease), irritable bowel syndrome, celiac disease, periodontitis, hyaline membrane disease, kidney disease, glomerular disease, alcoholic liver disease, multiple sclerosis, endocrine opthalmopathy, Grave's disease, sarcoidosis, alveolitis, chronic hypersensitivity pneumonitis, multiple sclerosis, primary biliary cirrhosis, uveitis (anterior and posterior), Sjogren's syndrome, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, systemic juvenile idiopathic arthritis, cryopyrin-associated periodic syndrome, nephritis, vasculitis, diverticulitis, interstitial cystitis, glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minal change nephropathy), chronic granulomatous disease, endometriosis, leptospiriosis renal disease, glaucoma, retinal disease, ageing, headache, pain, complex regional pain syndrome, cardiac hypertrophy, musclewasting, catabolic disorders, obesity, fetal growth retardation, hyperchlolesterolemia, heart disease, chronic heart failure, mesothelioma, anhidrotic ecodermal dysplasia, Behcet's disease, incontinentia pigmenti, Paget's disease, pancreatitis, hereditary periodic fever syndrome, asthma (allergic and non-allergic, mild, moderate, severe, bronchitic, and exercise-induced), acute lung injury, acute respiratory distress syndrome, eosinophilia, hypersensitivities, anaphylaxis, nasal sinusitis, ocular allergy, silica induced diseases, COPD (reduction of damage, airways inflammation, bronchial hyperreactivity, remodeling or disease progression), pulmonary disease, cystic fibrosis, acid-induced lung injury, pulmonary hypertension, polyneuropathy, cataracts, muscle inflammation in conjunction with systemic sclerosis, inclusion body myositis,

myasthenia gravis, thyroiditis, Addison's disease, lichen planus, Type 1 diabetes, or Type 2 diabetes, appendicitis, atopic dermatitis, asthma, allergy, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, chronic graft rejection, colitis, conjunctivitis, Crohn's disease, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, Henoch-Schonlein purpura, hepatitis, hidradenitis suppurativa, immunoglobulin A nephropathy, interstitial lung disease, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, polymyositis, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, ulcerative colitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00142] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is an disease of the skin. In some embodiments, the inflammatory disease of the skin is selected from contact dermatitits, atompic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, epidermolysis bullosa acquisita, and other inflammatory or allergic conditions of the skin.

[00143] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from acute and chronic gout, chronic gouty arthritis, psoriasis, psoriatic arthritis, rheumatoid arthritis, Juvenile rheumatoid arthritis, Systemic juvenile idiopathic arthritis (SJIA), Cryopyrin Associated Periodic Syndrome (CAPS), and osteoarthritis.

[00144] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is a TH17 mediated disease. In some embodiments the TH17 mediated disease is selected from Systemic lupus erythematosus, Multiple sclerosis, and inflammatory bowel disease (including Crohn's disease or ulcerative colitis).

[00145] In some embodiments the inflammatory disease which can be treated according to the methods of this invention is selected from Sjogren's syndrome, allergic disorders, osteoarthritis, conditions of the eye such as ocular allergy, conjunctivitis, keratoconjunctivitis sicca and vernal conjunctivitis, and diseases affecting the nose such as allergic rhinitis.

Metabolic Disease

[00146] In some embodiments the invention provides a method of treating a metabolic disease. In some embodiments the metabolic disease is selected from Type 1 diabetes, Type 2 diabetes, metabolic syndrome or obesity.

[00147] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer, an autoimmune disorder, a proliferative disorder, an inflammatory disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term “patient”, as used herein, means an animal, preferably a mammal, and most preferably a human.

[00148] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), buccally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00149] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, 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, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00150] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00151] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00152] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsulated matrices of the compound in biodegradable polymers such as polylactide-

polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00153] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00154] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00155] 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 sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

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 sugar as well as high molecular weight polethylene glycols and the like.

[00156] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00157] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00158] According to one embodiment, the invention relates to a method of inhibiting PHGDH activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00159] According to another embodiment, the invention relates to a method of inhibiting PHGDH, or a mutant thereof, activity in a biological sample comprising the step of contacting

said biological sample with a compound of this invention, or a composition comprising said compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting PHGDH, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00160] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00161] Another embodiment of the present invention relates to a method of inhibiting PHGDH in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00162] According to another embodiment, the invention relates to a method of inhibiting PHGDH, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of irreversibly inhibiting PHGDH, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by PHGDH, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00163] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00164] A compound of the current invention may also be used to advantage in combination with other antiproliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP

inhibitors; mTOR inhibitors; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; matrix metalloproteinase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies; compounds which target, decrease or inhibit the activity of Flt-3; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics; temozolomide (Temodal®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; MEK inhibitors such as ARRY142886 from Array BioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer and leucovorin. The term "aromatase inhibitor" as used herein relates to a compound which inhibits estrogen production, for instance, the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane is marketed under the trade name Aromasin™. Formestane is marketed under the trade name Lentaron™. Fadrozole is marketed under the trade name Afema™. Anastrozole is marketed under the trade name Arimidex™. Letrozole is marketed under the trade names Femara™ or Femar™. Aminoglutethimide is marketed under the trade name Orimeten™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, such as breast tumors.

[00165] The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen is marketed under the trade name Nolvadex™. Raloxifene hydrochloride is marketed under the trade name Evista™. Fulvestrant can be administered under the trade name Faslodex™. A combination of

the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, such as breast tumors.

[00166] The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (Casodex™). The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin can be administered under the trade name Zoladex™.

[00167] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecin and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148. Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark Camptosar™. Topotecan is marketed under the trade name Hycamptin™.

[00168] The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, such as Caelyx™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide is marketed under the trade name Etopophos™. Teniposide is marketed under the trade name VM 26-Bristol Doxorubicin is marketed under the trade name Acriblastin ™ or Adriamycin™. Epirubicin is marketed under the trade name Farmorubicin™. Idarubicin is marketed. under the trade name Zavedos™. Mitoxantrone is marketed under the trade name Novantron.

[00169] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtubulin polymerization inhibitors including, but not limited to taxanes, such as paclitaxel and docetaxel; vinca alkaloids, such as vinblastine or vinblastine sulfate, vincristine or vincristine sulfate, and vinorelbine; discodermolides; colchicine and epothilones and derivatives thereof. Paclitaxel is marketed under the trade name Taxol™. Docetaxel is marketed under the trade name Taxotere™. Vinblastine sulfate is marketed under the trade name Vinblastin R.P™. Vincristine sulfate is marketed under the trade name Farmistin™.

[00170] The term "alkylating agent" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide

is marketed under the trade name Cyclostin™. Ifosfamide is marketed under the trade name Holoxan™.

[00171] The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes, but is not limited to, suberoylanilide hydroxamic acid (SAHA).

[00172] The term "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine is marketed under the trade name Xeloda™. Gemcitabine is marketed under the trade name Gemzar™.

[00173] The term "platin compound" as used herein includes, but is not limited to, carboplatin, cis-platin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Carboplat™. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark Eloxatin™.

[00174] The term "compounds targeting/decreasing a protein or lipid kinase activity; or a protein or lipid phosphatase activity; or further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, such as a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib, SU101, SU6668 and GFB-111; b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR); c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors; d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors; e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family; f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase; g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, such as imatinib; h) compounds targeting,

decreasing or inhibiting the activity of the C-kit receptor tyrosine kinases, which are part of the PDGFR family, such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, such as imatinib; i) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, such as an N-phenyl-2-pyrimidine-amine derivative, such as imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825); j) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK/pan-JAK, FAK, PDK1, PKB/Akt, Ras/MAPK, PI3K, SYK, TYK2, BTK and TEC family, and/or members of the cyclin-dependent kinase family (CDK) including staurosporine derivatives, such as midostaurin; examples of further compounds include UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds; FTIs; PD184352 or QAN697 (a P13K inhibitor) or AT7519 (CDK inhibitor); k) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (Gleevec™) or tyrphostin such as Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin); l) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases ($EGFR_1$ ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, such as EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, CP 358774, ZD 1839, ZM 105180; trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, Cl-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives; m) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor,

such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF, n) compounds targeting, decreasing or inhibiting the kinase activity of one or more JAK family members (JAK1/JAK2/JAK3/TYK2 and/or pan-JAK), including but not limited to PRT-062070, SB-1578, baricitinib, pacritinib, momelotinib, VX-509, AZD-1480, TG-101348, tofacitinib, and ruxolitinib; o) compounds targeting, decreasing or inhibiting the kinase activity of PI3 kinase (PI3K) including but not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib; and; and q) compounds targeting, decreasing or inhibiting the signaling effects of hedgehog protein (Hh) or smoothened receptor (SMO) pathways, including but not limited to cyclopamine, vismodegib, itraconazole, erismodegib, and IPI-926 (saridegib).

[00175] The term "PI3K inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against one or more enzymes in the phosphatidylinositol-3-kinase family, including, but not limited to PI3Kα, PI3Kγ, PI3Kδ, PI3Kβ, PI3K-C2α, PI3K-C2β, PI3K-C2γ, Vps34, p110-α, p110-β, p110-γ, p110-δ, p85-α, p85-β, p55-γ, p150, p101, and p87. Examples of PI3K inhibitors useful in this invention include but are not limited to ATU-027, SF-1126, DS-7423, PBI-05204, GSK-2126458, ZSTK-474, buparlisib, pictrelisib, PF-4691502, BYL-719, dactolisib, XL-147, XL-765, and idelalisib.

[00176] The term "Bcl-2 inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against B-cell lymphoma 2 protein (Bcl-2), including but not limited to ABT-199, ABT-731, ABT-737, apogossypol, Ascenta's pan-Bcl-2 inhibitors, curcumin (and analogs thereof), dual Bcl-2/Bcl-xL inhibitors (Infinity Pharmaceuticals/Novartis Pharmaceuticals), Genasense (G3139), HA14-1 (and analogs thereof; see WO2008118802), navitoclax (and analogs thereof, see US7390799), NH-1 (Shenayng Pharmaceutical University), obatoclax (and analogs thereof, see WO2004106328), S-001 (Gloria Pharmaceuticals), TW series compounds (Univ. of Michigan), and venetoclax. In some embodiments the Bcl-2 inhibitor is a small molecule therapeutic. In some embodiments the Bcl-2 inhibitor is a peptidomimetic.

[00177] The term "BTK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against Bruton's Tyrosine Kinase (BTK), including, but not limited to AVL-292 and ibrutinib.

[00178] The term "SYK inhibitor" as used herein includes, but is not limited to compounds having inhibitory activity against spleen tyrosine kinase (SYK), including but not limited to PRT-062070, R-343, R-333, Excellair, PRT-062607, and fostamatinib.

[00179] Further examples of BTK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2008039218 and WO2011090760, the entirety of which are incorporated herein by reference.

[00180] Further examples of SYK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2003063794, WO2005007623, and WO2006078846, the entirety of which are incorporated herein by reference.

[00181] Further examples of PI3K inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2004019973, WO2004089925, WO2007016176, US8138347, WO2002088112, WO2007084786, WO2007129161, WO2006122806, WO2005113554, and WO2007044729 the entirety of which are incorporated herein by reference.

[00182] Further examples of JAK inhibitory compounds, and conditions treatable by such compounds in combination with compounds of this invention can be found in WO2009114512, WO2008109943, WO2007053452, WO2000142246, and WO2007070514, the entirety of which are incorporated herein by reference.

[00183] Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (Thalomid™) and TNP-470.

[00184] Examples of proteasome inhibitors useful for use in combination with compounds of the invention include, but are not limited to bortezomib, disulfiram, epigallocatechin-3-gallate (EGCG), salinosporamide A, carfilzomib, ONX-0912, CEP-18770, and MLN9708.

[00185] Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, such as okadaic acid or a derivative thereof.

[00186] Compounds which induce cell differentiation processes include, but are not limited to, retinoic acid, α- γ- or δ- tocopherol or α- γ- or δ-tocotrienol.

[00187] The term cyclooxygenase inhibitor as used herein includes, but is not limited to, Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (Celebrex™), rofecoxib (Vioxx™), etoricoxib, valdecoxib or a 5-alkyl-2- arylaminophenylacetic acid, such as 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

[00188] The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid is marketed under the trade name Didronel™. Clodronic acid is marketed under the trade name Bonefos™. Tiludronic acid is marketed under the trade name Skelid™. Pamidronic acid is marketed under the trade name Aredia™. Alendronic acid is marketed under the trade name Fosamax™. Ibandronic acid is marketed under the trade name Bondranat™. Risedronic acid is marketed under the trade name Actonel™. Zoledronic acid is marketed under the trade name Zometa™. The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

[00189] The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88. The term "biological response modifier" as used herein refers to a lymphokine or interferons.

[00190] The term "inhibitor of Ras oncogenic isoforms", such as H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras; for example, a "farnesyl transferase inhibitor" such as L-744832, DK8G557 or R115777 (Zarnestra™). The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, such as telomestatin.

[00191] The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase include, but are not limited to, bengamide or a derivative thereof.

[00192] The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include, but are not limited to, Bortezomib (Velcade™) and MLN 341.

[00193] The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211 , MMI270B or AAJ996.

[00194] The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors, which are compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-β-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors, which are compounds which target, decrease or inhibit anaplastic lymphoma kinase.

[00195] Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, such as PKC412, midostaurin, a staurosporine derivative, SU11248 and MLN518.

[00196] The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90, such as 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors.

[00197] The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1, erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40) and 2C4 Antibody. By antibodies is meant intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

[00198] For the treatment of acute myeloid leukemia (AML), compounds of the current invention can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of the current invention can be administered in combination with, for example, farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

[00199] Other anti-leukemic compounds include, for example, Ara-C, a pyrimidine analog, which is the 2'-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065 including, but not limited to, N-hydroxy-3-[4-[[[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof and N-hydroxy-3-[4-[(2-hydroxyethyl){2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, or a pharmaceutically acceptable salt thereof, especially the lactate salt. Somatostatin receptor antagonists as used herein refer to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230. Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in Principles and Practice of Oncology, Devita et al., Eds., 4th Edition, Vol. 1 , pp. 248-275 (1993).

[00200] Also included are EDG binders and ribonucleotide reductase inhibitors. The term "EDG binders" as used herein refers to a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720. The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine

(especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1H-isoindole-1 ,3-dione derivatives.

[00201] Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF such as 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine succinate; Angiostatin™; Endostatin™; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, such as rhuMAb and RHUFab, VEGF aptamer such as Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgGI antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

[00202] Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy include treatment with compounds, such as Visudyne™ and porfimer sodium.

[00203] Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone, hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

[00204] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00205] Other chemotherapeutic compounds include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

[00206] The structure of the active compounds identified by code numbers, generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

[00207] A compound of the current invention may also be used in combination with known therapeutic processes, for example, the administration of hormones or radiation. In certain embodiments, a provided compound is used as a radiosensitizer, especially for the treatment of tumors which exhibit poor sensitivity to radiotherapy.

[00208] A compound of the current invention can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of

fixed combinations or the administration of a compound of the invention and one or more other therapeutic compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of the current invention can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

[00209] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00210] As used herein, the term “combination,” “combined,” and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a compound of the current invention, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00211] The amount of both an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive compound can be administered.

[00212] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a

monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00213] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00214] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

EXEMPLIFICATION

[00215] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

General Methods of Providing the Present Compounds

[00216] The compounds of this invention may be prepared or isolated in general by synthetic and/or semi-synthetic methods known to those skilled in the art for analogous compounds and by methods described in detail in the Examples, herein.

[00217] In the Schemes below, where a particular protecting group ("PG"), leaving group ("LG"), or transformation condition is depicted, one of ordinary skill in the art will appreciate that other protecting groups, leaving groups, and transformation conditions are also suitable and

are contemplated. Such groups and transformations are described in detail in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, M. B. Smith and J. March, 5th Edition, John Wiley & Sons, 2001, *Comprehensive Organic Transformations*, R. C. Larock, 2nd Edition, John Wiley & Sons, 1999, and *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of each of which is hereby incorporated herein by reference.

[00218] As used herein, the phrase "leaving group" (LG) includes, but is not limited to, halogens (e.g. fluoride, chloride, bromide, iodide), sulfonates (e.g. mesylate, tosylate, benzenesulfonate, brosylate, nosylate, triflate), diazonium, and the like.

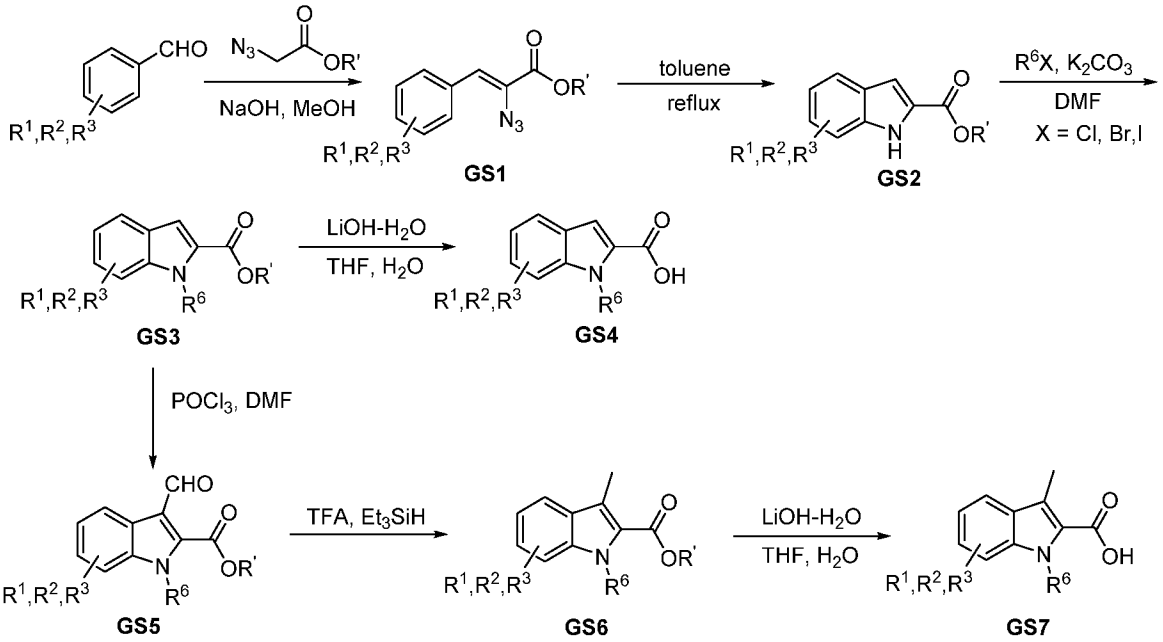
[00219] As used herein, the phrase "oxygen protecting group" includes, for example, carbonyl protecting groups, hydroxyl protecting groups, etc. Hydroxyl protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Examples of suitable hydroxyl protecting groups include, but are not limited to, esters, allyl ethers, ethers, silyl ethers, alkyl ethers, arylalkyl ethers, and alkoxyalkyl ethers. Examples of such esters include formates, acetates, carbonates, and sulfonates. Specific examples include formate, benzoyl formate, chloroacetate, trifluoroacetate, methoxyacetate, triphenylmethoxyacetate, p-chlorophenoxyacetate, 3-phenylpropionate, 4-oxopentanoate, 4,4-(ethylenedithio)pentanoate, pivaloate (trimethylacetyl), crotonate, 4-methoxy-crotonate, benzoate, p-benylbenzoate, 2,4,6-trimethylbenzoate, carbonates such as methyl, 9-fluorenylmethyl, ethyl, 2,2,2-trichloroethyl, 2-(trimethylsilyl)ethyl, 2-(phenylsulfonyl)ethyl, vinyl, allyl, and p-nitrobenzyl. Examples of such silyl ethers include trimethylsilyl, triethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl, and other trialkylsilyl ethers. Alkyl ethers include methyl, benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, trityl, t-butyl, allyl, and allyloxycarbonyl ethers or derivatives. Alkoxyalkyl ethers include acetals such as methoxymethyl, methylthiomethyl, (2-methoxyethoxy)methyl, benzyloxymethyl, beta-(trimethylsilyl)ethoxymethyl, and tetrahydropyranyl ethers. Examples of arylalkyl ethers include benzyl, p-methoxybenzyl (MPM), 3,4-dimethoxybenzyl, O-nitrobenzyl, p-nitrobenzyl, p-halobenzyl, 2,6-dichlorobenzyl, p-cyanobenzyl, and 2- and 4-picolyl.

[00220] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition,

John Wiley & Sons, 1999, the entirety of which is incorporated herein by reference. Suitable amino protecting groups include, but are not limited to, aralkylamines, carbamates, cyclic imides, allyl amines, amides, and the like. Examples of such groups include t-butyloxycarbonyl (BOC), ethyloxycarbonyl, methyloxycarbonyl, trichloroethyloxycarbonyl, allyloxycarbonyl (Alloc), benzyloxocarbonyl (CBZ), allyl, phthalimide, benzyl (Bn), fluorenylmethylcarbonyl (Fmoc), formyl, acetyl, chloroacetyl, dichloroacetyl, trichloroacetyl, phenylacetyl, trifluoroacetyl, benzoyl, and the like.

[00221] In one aspect, certain compounds of the present invention of formula **I**, or subformulae thereof, are generally prepared according to **Scheme 1** set forth below:

Scheme 1



[00222] In **Scheme 1** above, R' is a group such as C_{1-6} aliphatic, 5- to 8-membered aromatic ring, or other functionality compatible with an ester; and R^1, R^2, R^3, and R^6 are selected consistent with formula **I** above and below and in classes and subclasses as described herein.

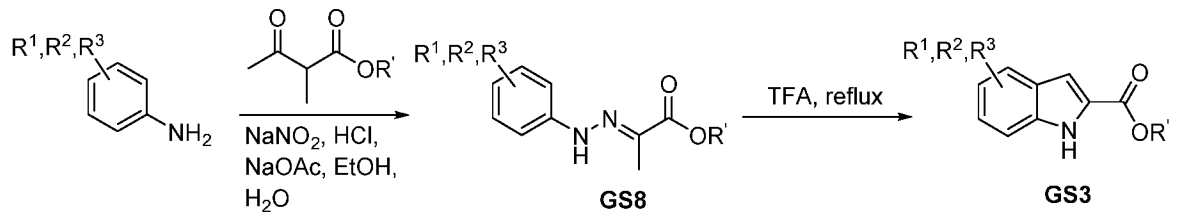
[00223] In one aspect, the present invention provides methods for preparing compounds of formula GS7 as described in **Scheme 1**. An optionally substituted benzaldehyde may be condensed with an azidoacetate in the presence of base such as sodium hydroxide or sodium methoxide to give intermediate GS1. Heating GS1 in a solvent such as toluene (e.g., at reflux) provides the indole-2-carboxylate ester. In some embodiments, the indole nitrogen is alkylated using an appropriate alkyl halide such as methyl or ethyl iodide and a suitable base such as, but

not limited, to sodium hydride, potassium *tert*-butoxide, or potassium carbonate in a suitable solvent to provide GS3. In some embodiments, the ester of GS3 is hydrolyzed using a base such as LiOH, KOH or NaOH in a solvent mixture of water and THF to provide an intermediate used in the synthesis of compounds of the invention of general structure GS4.

[00224] Alternatively, in some embodiments GS3 may be treated with appropriate reagents such as $POCl_3$ and DMF to give GS5. In some embodiments, the aldehyde in GS5 is then reduced to a methyl group with appropriate reagents such as Et_3SiH and TFA to give GS6. Finally, in some embodiments, hydrolysis of the ester in GS6 provides an intermediate used in the synthesis of compounds of the invention of general structure GS7.

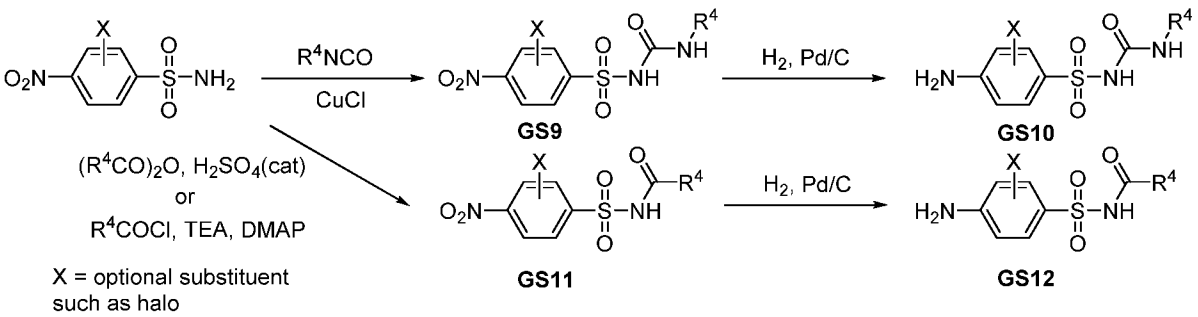
[00225] In another aspect, compounds of the present invention of formula **I**, or subformulae thereof, are generally prepared according to **Scheme 2** set forth below:

Scheme 2



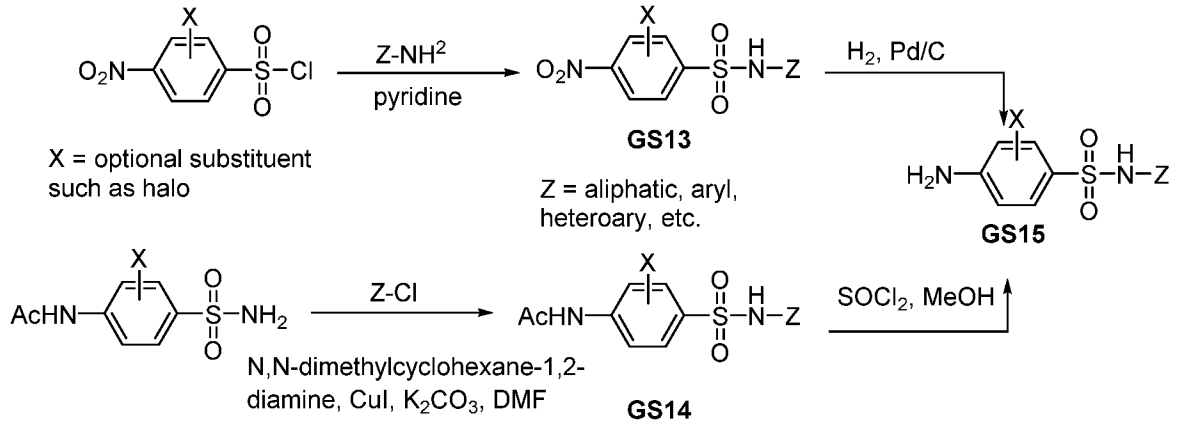
[00226] **Scheme 2** describes an alternate route to prepare compounds of formula GS3. In some embodiments, treatment of an aniline with a nitrite compound and a ketoacetate of choice in a suitable solvent (for example, a mixture of ethanol/water) produces an aryl hydrazine intermediate that reacts with the ketoacetate (such as ethyl 2-methyl-3-oxo-butanoate) to provide GS8. Treatment of GS8 with TFA with heat, e.g., reflux, provides general intermediate GS3 that can be elaborated to GS4 and GS7 as described above.

Scheme 3



[00227] In another aspect, additional exemplary compounds of the invention can be synthesized using compounds with general structures GS10 and GS12 as described in **Scheme 3**. In **Scheme 3**, R^4 is selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, treatment of a nitroarylsulfonamide such as the commercially available 4-nitrobenzenesulfonamide with an isocyanate, optionally in the presence of an appropriate reagent or catalyst such as CuCl, produces GS9. In some embodiments, hydrogenation of GS9 using a catalyst such as palladium on carbon in an appropriate solvent such as methanol, ethanol, or ethyl acetate or a combination thereof provides a key intermediate of general structure GS10. Alternatively, the nitroarylsulfonamide such as 4-nitrobenzenesulfonamide can be treated with an acid anhydride or acid chloride or other acylating agent to give GS11. Hydrogenation of GS11 as described above provides key intermediates with the general structure GS12.

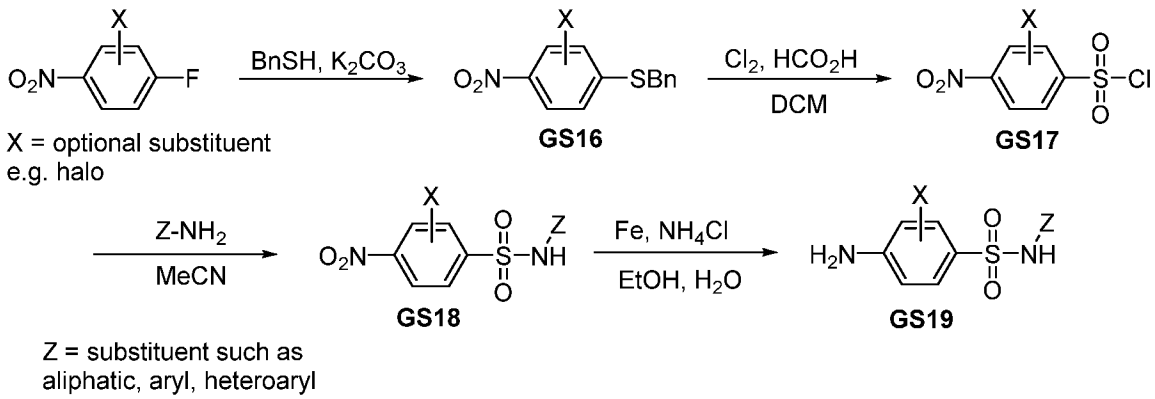
Scheme 4



[00228] In a further aspect, additional exemplary compounds of the invention can be synthesized using key intermediates with the general structures GS15 as described in **Scheme 4**. In **Scheme 4**, X and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, treatment of a nitroarylsulfonyl halide such as the commercially available 4-nitrophenylsulfonyl chloride with an amine such as an aliphatic, aryl, or heteroaryl amine affords GS13. In some embodiments, hydrogenation of the nitro group, for example as described in **Scheme 3**, then provides key intermediates with the general structures GS15. Alternatively, in some embodiments, a sulfamoyl compound (such as the commercially available *N*-[(4-sulfamoyl)phenyl]acetamide) is treated with an aliphatic, aryl, or heteroaryl halide (such as the chloride) using appropriate coupling conditions such as a copper

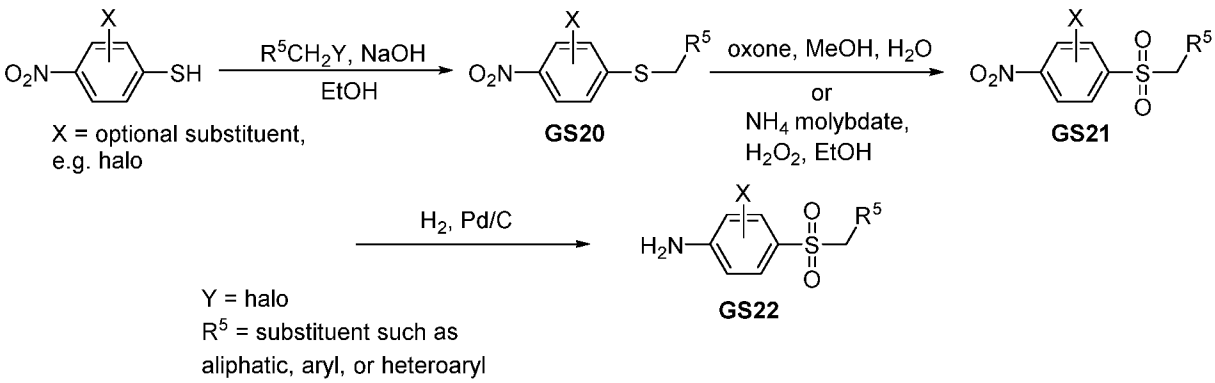
catalyst system shown in **Scheme 4** to afford GS14. In some embodiments, removal of the acetamide group with methanolic HCl (generated using $SOCl_2$ in methanol) provides the requisite key intermediates with general structure GS15.

Scheme 5



[00229] In another aspect, a compound of general structure GS19 can be obtained from an optionally substituted 4-fluoronitrobenzene as shown in **Scheme 5**. In **Scheme 5**, X and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. Displacement of the 4-fluoro with a thiol such as benzenethiol affords GS16. In some embodiments, treatment of GS16 with chlorine gas as described provides the sulfonyl chloride GS17. Subsequently, in some embodiments, by using the procedures described above GS17 can be converted to GS18 and then to the requisite structure GS19 by reduction of the nitro group using iron/NH_4Cl or another reducing agent.

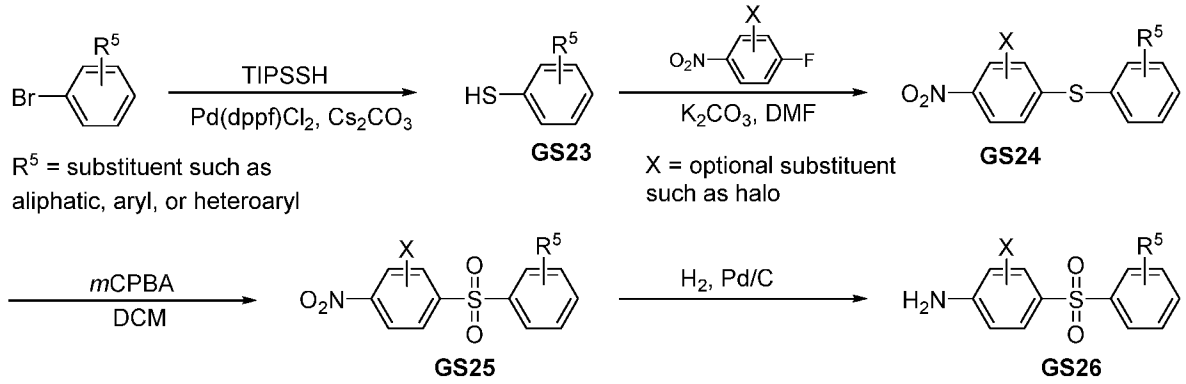
Scheme 6



[00230] In another aspect, a disclosed compound may be prepared as shown in **Scheme 6**. In **Scheme 6**, X, R^5, and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, 4-nitrobenzenethiol is alkylated using

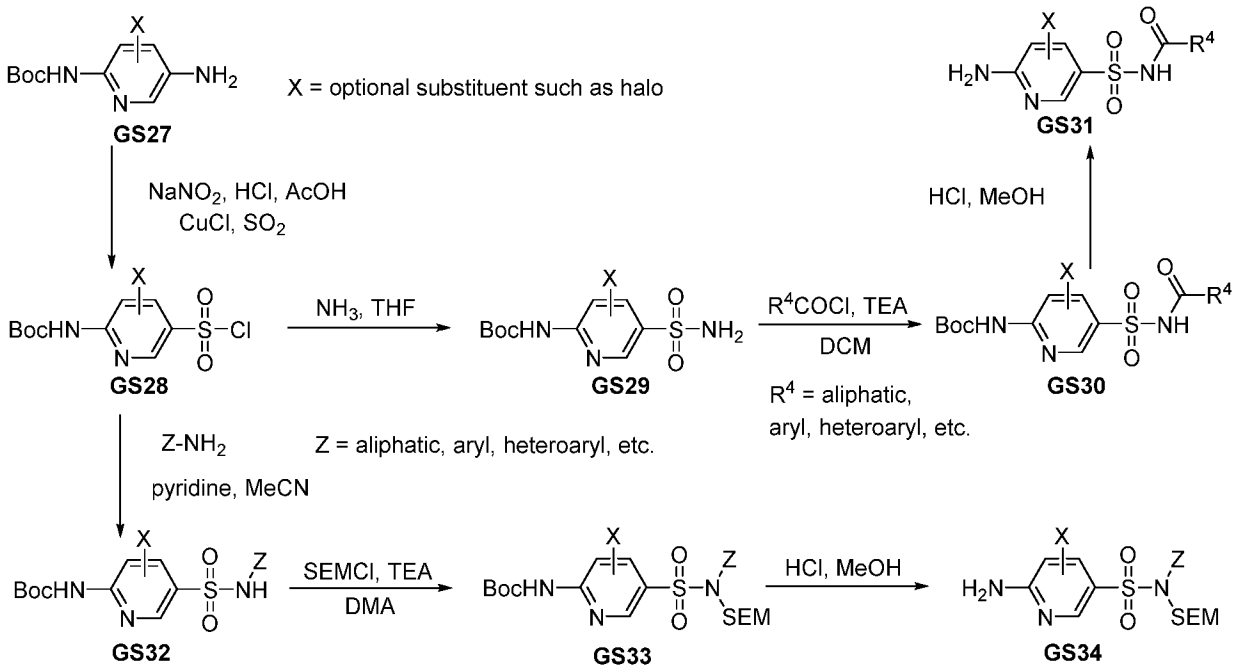
an aliphatic, e.g. alkyl halide, in the presence of a base to give GS20. In some embodiments, the sulfur is oxidized using an appropriate oxidizing agent, for example Oxone or ammonium molybdate/hydrogen peroxide. Finally, the nitro group can be reduced as described above or below.

Scheme 7



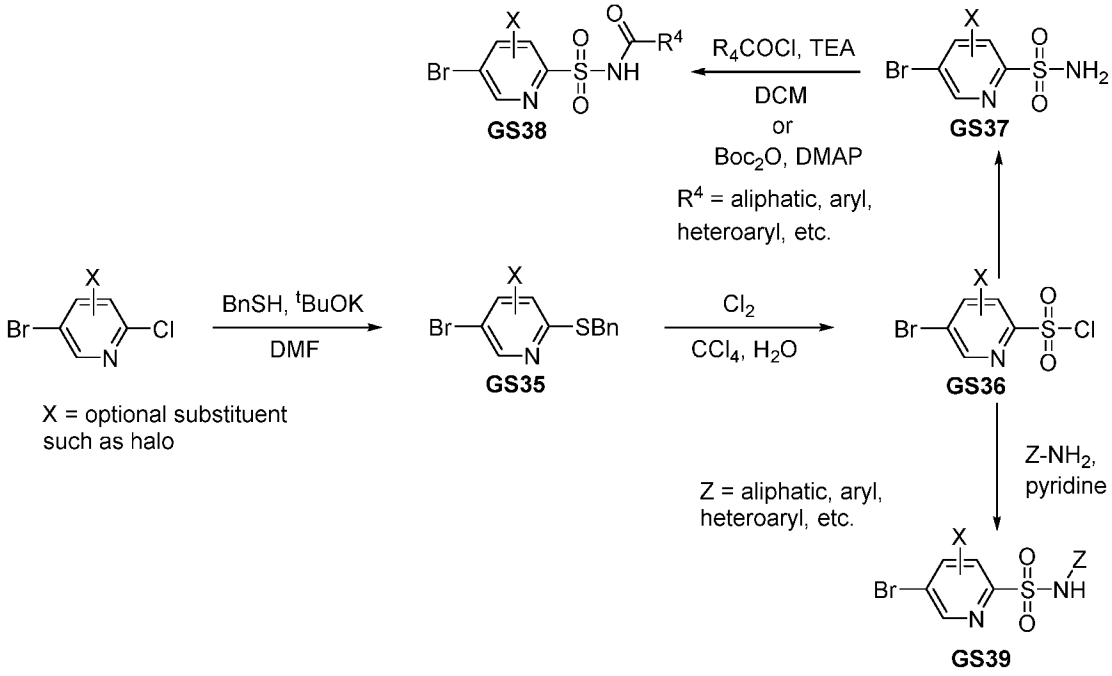
[00231] In another aspect, a disclosed compound may be prepared as described in **Scheme 7**. In **Scheme 7**, X and R^5 are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, an optionally substituted aryl halide, such as a phenyl bromide, can be converted to the benzene thiol using an appropriate reagent such as TIPSSH and a palladium catalyst such as $Pd(dppf)Cl_2$ and a base, for example Cs_2CO_3, to afford GS23. In some embodiments, reaction of GS23 and a 4-fluoronitrobenzene in the presence of a base such as potassium carbonate in a solvent such as DMF affords GS24. In some embodiments, oxidation of the sulfur with an appropriate oxidant such as m-CPBA followed by reduction of the nitro group as described previously affords compounds with the general structure GS26.

Scheme 8



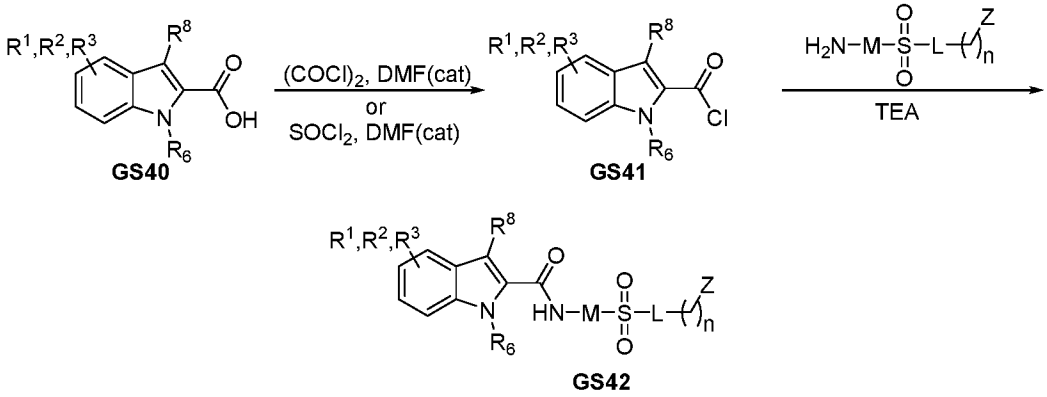
[00232] In another aspect, a disclosed compound may be prepared as described in **Scheme 8**. In **Scheme 8**, X, R^4, and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. Compounds such as those represented by general formulas GS31 or GS34 may be prepared from optionally substituted 2-aminopyridine derivatives of formula GS27 (for example, *tert*-butyl (5-aminopyridin-2-yl)carbamate). In some embodiments, GS27 can be converted to the sulfonyl chloride GS28 by diazotization with an appropriate reagent and conditions such as sodium nitrite in aqueous acid followed by treatment with a sulfur source such as sulfur dioxide and a catalyst such as CuCl. In some embodiments, GS28 may be converted to the sulfonamide, GS29, with ammonia and then to the acylsulfonamide as described previously in **Scheme 3**. In some embodiments, removal of the Boc protecting group with acidic conditions such as HCl in methanol affords compounds with the general structure GS31. In some embodiments, GS28 can also be converted into structures like GS32 using an amine such as an aliphatic, aryl, or heteroaryl amine. In some embodiments, protection of the sulfonamide nitrogen with an appropriate protecting group, such as a SEM group, using standard conditions followed by removal of the Boc protecting group provides compounds of the general structure GS34.

Scheme 9



[00233] In another aspect, a disclosed compound may be prepared as described in **Scheme 9**. In **Scheme 9**, X, R^4, and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In another embodiment of the invention the required intermediate is a 5-bromopyridine-2-sulfonamide derivative such as GS38 or GS39. These can be prepared as described in **Scheme 9** in an analogous fashion as described in **Schemes 4** and **5**.

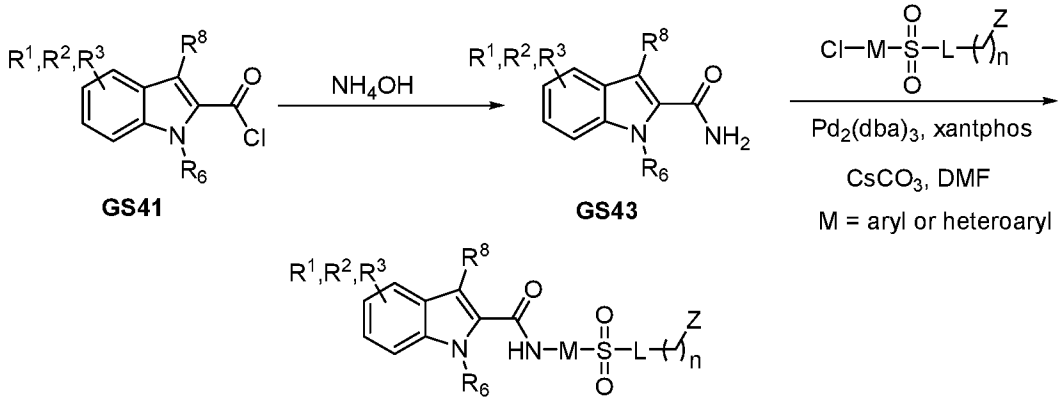
Scheme 10



[00234] In another aspect, a disclosed compound may be prepared as described in **Scheme 10**. In **Scheme 10**, R^1, R^2, R^3, R^6, R^8, n, M, and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, an optionally substituted indole-2 carboxylic acid GS40 is reacted with a suitable reagent such as oxalyl

chloride or sulfonyl chloride with a catalytic amount of DMF in an appropriate solvent such as methylene chloride, toluene, or 1,2-dichloroethane to provide the acid chloride GS41. In some embodiments, the acid chloride is reacted with an aliphatic, aryl, or other amine-containing intermediate in the presence of a base such as triethylamine or diisopropylethylamine in an appropriate solvent such as methylene chloride or 1,2-dichloroethane or toluene to provide example compounds of the invention of general structure GS42.

Scheme 11



[00235] In another aspect, a disclosed compound may be prepared as described in **Scheme 11**. In **Scheme 11**, R^1, R^2, R^3, R^6, R^8, n, M, and Z are selected consistent with formula **I** above and below and in classes and subclasses as described herein. In some embodiments, the acid chloride GS41 described above in **Scheme 10** can be converted to the carboxamide GS43 using ammonium hydroxide in an appropriate co-solvent such as THF, methanol, or ethanol. The carboxamide can be reacted with an appropriately substituted aryl or heteroaryl chloride to afford exemplary compounds of the invention.

[00236] According to a further general process compounds of General Formula GS42 can be converted to alternative compounds of General Formula GS42, employing suitable interconversion techniques well known by a person skilled in the art. For generally discussion of protection and deprotection methods see Philip Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994 and Theodora W. Greene and Peter G.M. Wuts in "Protecting Groups in Organic Synthesis" Wiley Interscience 3rd Edition 1999.

One of skill in the art will appreciate that various functional groups present in compounds of the invention such as aliphatic groups, alcohols, carboxylic acids, esters, amides, aldehydes,

halogens and nitriles can be interconverted by techniques well known in the art including, but not limited to reduction, oxidation, esterification, hydrolysis, partial oxidation, partial reduction, halogenation, dehydration, partial hydration, and hydration. See, for example, "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entirety of which is incorporated herein by reference. Such interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described below.

Abbreviations Table

Abbreviation	Chemical Name
Ac	acetyl
MeCN	acetonitrile
DME	1,2-dimethoxyethane
DIPEA	diisopropylethylamine
DMAP	*N*,*N*-4-dimethylaminopyridine
FA	formic acid
SFC	supercritical fluid chromatography
cSFC	chiral supercritical fluid chromatography
Na_2SO_4	sodium sulfate
$Pd(OAc)_2$	palladium acetate
BH_3	borane
Me_2S	dimethyl sulfide
MeONa	sodium methoxide
DMF	*N*,*N*-dimethylformamide
K_2CO_3	potassium carbonate
MeI	iodomethane
$NaNO_2$	sodium nitrite
Pd/C	palladium on carbon
AcCl	acetyl chloride
Py	pyridine
DCM	methylene chloride

TEA	triethylamine
LDA	lithium diisopropylamide
m-CPBA	meta-chloroperbenzoic acid
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
NCS	*N*-chlorosuccinimide
NaOH	sodium hydroxide
HCl	hydrochloric acid
THF	tetrahydrofuran
DMA	*N*,*N*-dimethylacetamide
TFA	trifluoroacetic acid
$POCl_3$	phosphorus oxychloride
NMP	*N*-methyl-2-pyrrolidinone
TBAB	tetrabutylammonium bromide
LAH	lithium aluminum hydride
MsCl	methanesulfonyl chloride
Boc_2O	di-*tert*-butyl dicarbonate
ACN or MeCN	acetonitrile
NBS	*N*-bromosuccinimide
dppf	1,1'-bis(diphenylphosphino)ferrocene
HOAc	acetic acid
dba	dibenzylideneacetone
$SOCl_2$	thionyl chloride
SEMCl	2-(chloromethoxy)ethyl-trimethyl-silane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
EtOAc	ethyl acetate
AIBN	2,2'-azo bisisobutyronitrile
MTBE	*tert*-butylmethylether
DCE	1,2-dichloroethane

General Synthetic Methods

[00237] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Unless otherwise stated, one or more tautomeric forms of compounds of the examples described hereinafter may be prepared in situ and/or isolated. All tautomeric forms of compounds of the examples described hereafter should be considered to be disclosed. Temperatures are given in degrees centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical methods, e.g., microanalysis and spectroscopic characteristics, e.g., MS, IR, NMR. Abbreviations used are those conventional in the art.

[00238] All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

[00239] All reactions are carried out under nitrogen or argon unless otherwise stated. Optical rotations were measured in MeOH.

[00240] Proton NMR (^{1}H NMR) is conducted in deuterated solvent. In certain compounds disclosed herein, one or more ^{1}H shifts overlap with residual protio solvent signals; these signals have not been reported in the experimental provided hereinafter.

Analytical instruments Table

LCMS	Shimadzu UFLC MS: LCMS-2020 Agilent Technologies 1200 series MS: Agilent Technologies 6110 Agilent Technologies 1200 series MS: LC/MSD VL
NMR	BRUKER AVANCE III/400; Frequency (MHz) 400.13; Nucleus: ^{1}H; Number of Transients: 8
Prep-HPLC	Gilson GX-281 systems: instruments GX-A, GX-B, GX-C, GX-D, GX-E, GX-F, GX-G and GX-H
GCMS	SHIMADZU GCMS-QP2010 Ultra

Analytical cSFC	Agilent Technologies 1290 Infinity
Prep-cSFC	Waters SFC Prep 80

For acidic LCMS data:

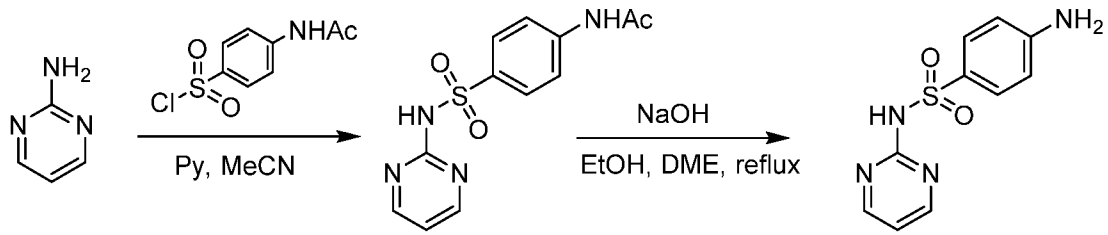
[00241] LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^+] and equipped with Chromolith Flash RP-18e 25*2.0 mm, eluting with 0.0375 vol% TFA in water (solvent A) and 0.01875 vol% TFA in acetonitrile (solvent B).

For basic LCMS data:

[00242] LCMS was recorded on an Agilent 1200 Series LC/MSD or Shimadzu LCMS 2020 equipped with electro-spray ionization and quadruple MS detector [ES+ve to give MH^+] and equipped with Xbridge C18, 2.1X50 mm columns packed with 5 µm C18-coated silica or Kinetex EVO C18 2.1X30mm columns packed with 5 µm C18-coated silica, eluting with 0.05 vol% $NH_3 \cdot H_2O$ in water (solvent A) and acetonitrile (solvent B).

Synthesis of Intermediates

4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A)



A

Step 1 – *N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]acetamide

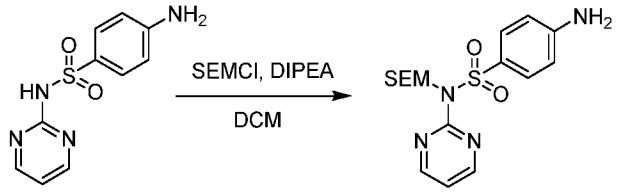
[00243] To a suspension of pyrimidine-2-amine (9.70 g, 102 mmol) and 4-acetamidobenzenesulfonyl chloride (23.8 g, 102 mmol) in acetonitrile (150 mL) was added pyridine (8.88 g, 112 mmol) dropwise over 5 minutes. The temperature of the resulting mixture was raised to 60 °C, and the reaction was allowed to continue at 60 °C for 3 hours. On completion, the reaction mixture was concentrated and the residue was diluted with water, the

solid was filtered, washed with dichloromethane (30 mL), and dried under vacuum to give the titled compound. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.45 (d, *J* = 4.8 Hz, 2H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 6.99 (t, *J* = 4.8 Hz, 1H).

Step 2 – 4-amino-*N*-phenyl-benzenesulfonamide

[00244] To a solution of *N*-[4-(phenylsulfamoyl)phenyl]acetamide (15 g, 51.7 mmol) in methanol (125 mL) and DME (125 mL) was added NaOH (2.07 g, 51.7 mmol). The reaction mixture was stirred at 120 °C for 16 hrs. On completion, the reaction mixture was concentrated and the residue was dissolved in 300 mL of water, and adjusted pH to 1 by addition of concentrated hydrochloric acid. The resulting solution was cooled to 0 °C. The insoluble material was removed by filtration, and the filtrate was extracted with methylene chloride (450 mL). The water phase was adjusted to pH 7 by using 2 M NaOH solution and a yellow solid was formed. The resulting precipitates were filtered and dried under vacuum to give 4-amino-*N*-phenyl-benzenesulfonamide. ^{1}H NMR (400 MHz, CD_3OD) δ = 11.25 (brs, 1 H), 8.47 (d, *J* = 4.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.01 (t, *J* = 4.8 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.03 (brs, 2H).

4-amino-*N*-pyrimidin-2-yl-*N*-(2-trimethylsilylethoxymethyl) benzenesulfonamide (Intermediate B)

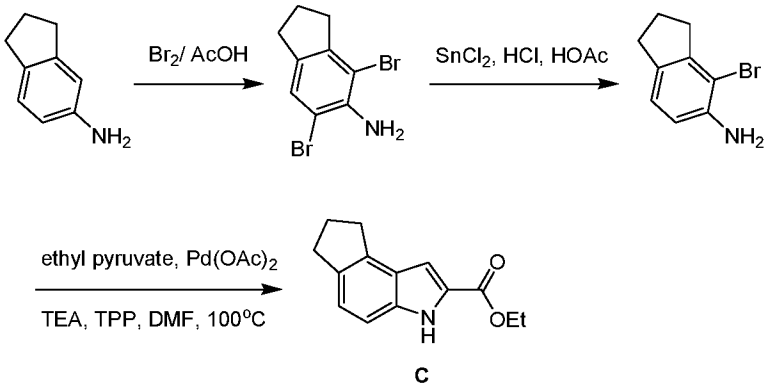


A B

[00245] To a solution of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (2.00 g, 7.99 mmol), DIPEA (1.55 g, 11.9 mmol) and DMAP (97.6 mg, 799 µmol) in dichloromethane (50 mL) was added 2-(chloromethoxy)ethyl-trimethyl-silane (1.33 g, 7.99 mmol) at 20 °C. The reaction mixture was stirred at 20 °C for 20 hrs. On completion, water (50 mL) was added and the mixture extracted with dichloromethane, dried over anhydrous Na_2SO_4, and concentrated, and the residue was purified by silica gel column chromatography [petroleum ether: ethyl acetate = 5:1] to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.48 (d, J = 4.8 Hz, 2H), 7.94

(d, J = 8.8 Hz, 2H), 6.89 (t, J = 4.8 Hz, 1H), 6.64 (d, J = 8.8 Hz, 2H), 5.77 (s, 2H), 4.13 (s, 2H), 3.75 - 3.60 (m, 2H), 1.04 - 0.91 (m, 2H), -0.02 (s, 9H).

Ethyl 3,6,7,8-tetrahydrocyclopenta[e]indole-2-carboxylate (Intermediate C)



C

Step 1 - 4,6-Dibromoindan-5-amine

[00246] To a solution of indan-5-amine (9.00 g, 67.5 mmol) in acetic acid (360 mL) was added bromine (83.8 g, 524 mmol) and the mixture reaction was stirred at 20 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* and 200 mL chloroform was added. The resulting mixture was filtered and the filter cake was washed with chloroform, dried *in vacuo* to give the title compound (crude). ^{1}H NMR (400MHz, DMSO-d_6) δ= 7.27 (s, 1H), 4.62 (br. s., 2H), 2.87 (t, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.99 (m, *J* = 7.5 Hz, 2H).

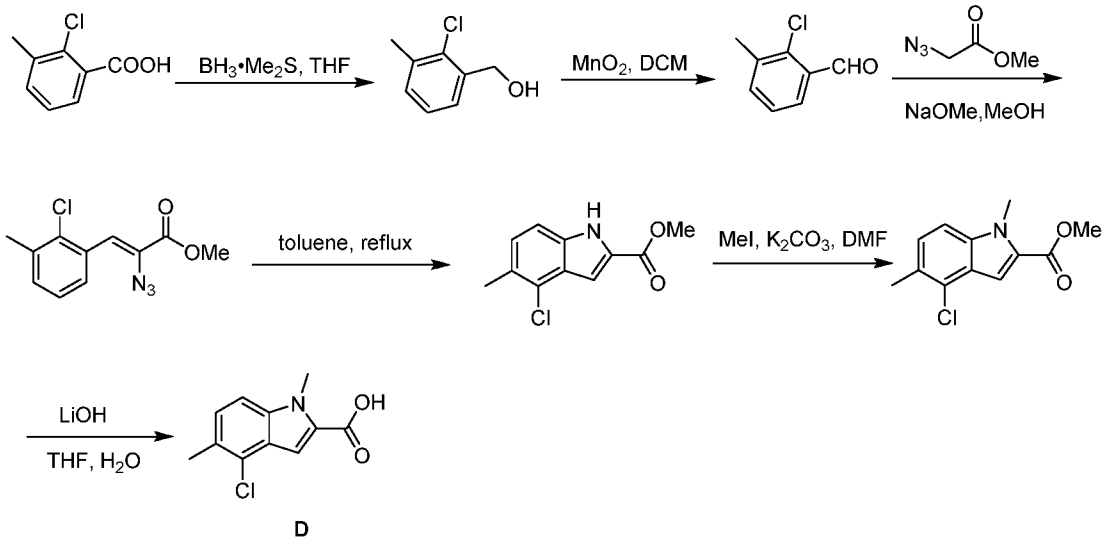
Step 2 - 4-Bromoindan-5-amine

[00247] To a solution of 4,6-dibromoindan-5-amine (10.0 g, 26.8 mmol) in a mixture of concentrated hydrochloric acid (50.0 mL) and acetic acid (50.0 mL) was added stannous chloride (13.0 g, 57.6 mmol) and the reaction mixture was stirred at 100 °C for 4 hrs. Then the reaction mixture was cooled to 20 °C and stirred at 20 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* and the resulting mixture was basified with aqueous sodium hydroxide until pH = 11. The aqueous layer was extracted with dichloromethane (3 x 150 mL). The combined layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give a crude product, which was purified by silica gel chromatography (petroleum ether : ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ= 6.97 (d, *J* = 7.8 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 3.99 (br. s., 2H), 2.94 (m, *J* = 7.8 Hz, 4H), 2.17 - 2.01 (m, 2H)

Step 3 - Ethyl 3,6,7,8-tetrahydrocyclopenta[e]indole-2-carboxylate

[00248] To a mixture of 4-bromoindan-5-amine (2.00 g, 9.43 mmol), triphenylphosphine (2.23 g, 8.49 mmol) and $Pd(OAc)_2$ (1.06 g, 4.72 mmol) in *N,N*-dimethylformamide (100 mL) was added triethylamine (4.20 g, 41.4 mmol) and ethyl pyruvate (6.30 g, 54.2 mmol) in turn and the reaction mixture was stirred at 100 °C under nitrogen for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*, the residue was diluted with water (50 mL) and dichloromethane (50 mL) and further extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give a black oil, which was purified by silica gel chromatography (petroleum ether : ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.87 (br. s., 1H), 7.25 (s, 2H), 7.17 (d, *J* = 2.0 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 3.14 (t, *J* = 7.4 Hz, 2H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.23 (m, *J* = 7.4 Hz, 2H), 1.49 - 1.40 (m, 3H).

4-Chloro-1,5-dimethyl-1*H*-indole-2-carboxylic acid (Intermediate D)



D

Step 1 - (2-Chloro-3-methylphenyl)methanol

[00249] To a solution of 2-chloro-3-methyl-benzoic acid (30 g, 175 mmol) in anhydrous tetrahydrofuran (240 mL) was added dropwise BH_3•Me_2S (10 M, 21 mL) under nitrogen. The reaction mixture was stirred at reflux at 70 °C for 12 hrs. On completion, the reaction mixture was quenched with methanol (50 mL), diluted with water (230 mL) and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title

product. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.42 - 7.34 (m, 1H), 7.24 (d, J=4.8 Hz, 2H), 5.36 (t, J=5.6 Hz, 1H), 4.55 (d, J=5.5 Hz, 2H), 2.32 (s, 3H).

Step 2 - 2-Chloro-3-methylbenzaldehyde

[00250] To a solution of (2-chloro-3-methyl-phenyl)methanol (26.2 g, 167 mmol) in dichloromethane (350 mL) was added manganese dioxide (116 g, 1.34 mol) under nitrogen. After the addition, the reaction mixture was stirred at 25 °C for 12 hrs. The solid was filtered, and the filtrate was concentrated under vacuum. The residue was purified by column chromatography (eluted with petroleum ether:ethyl acetate = 20:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.42 - 10.34 (m, 1H), 7.68 (t, J=8.2 Hz, 2H), 7.42 (t, J=7.5 Hz, 1H), 2.39 (s, 3H).

Step 3 - (Z)-Methyl 2-azido-3-(2-chloro-3-methylphenyl)acrylate

[00251] To a solution of MeONa (17.2 g, 319 mmol) in methanol (150 mL) was added a solution of methyl 2-azidoacetate (41.2 g, 319 mmol) and 2-chloro-3-methyl-benzaldehyde (16.4 g, 106 mmol) in methanol (150 mL) dropwise at -20 °C. After the mixture was stirred at -20 °C for 2 hrs, it was warmed up to 25 °C for 12 hrs. During this time a fine precipitate was formed. The suspension was poured onto ice water and the azido derivative was collected by filtration and washed with cold water. The solid was dissolved in dichloromethane (200 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.04 - 7.95 (m, 1H), 7.37 (s, 1H), 7.26 - 7.20 (m, 2H), 3.96 (s, 3H), 2.48 - 2.37 (m, 3H).

Step 4 - Methyl 4-chloro-5-methyl-1*H*-indole-2-carboxylate

[00252] A solution of methyl (Z)-Methyl 2-azido-3-(2-chloro-3-methylphenyl)acrylate (20.9 g, 83.2 mmol) in toluene (250 mL) was heated to 120 °C under a nitrogen for 16 hrs. On completion of the reaction, the reaction mixture was concentrated to afford the crude product as a yellow solid. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.21 (br. s., 1H), 7.34 (d, *J*=8.3 Hz, 1H), 7.23 (d, *J*=8.5 Hz, 1H), 7.07 (d, *J*=1.3 Hz, 1H), 3.89 (s, 3H), 2.40 (s, 3H).

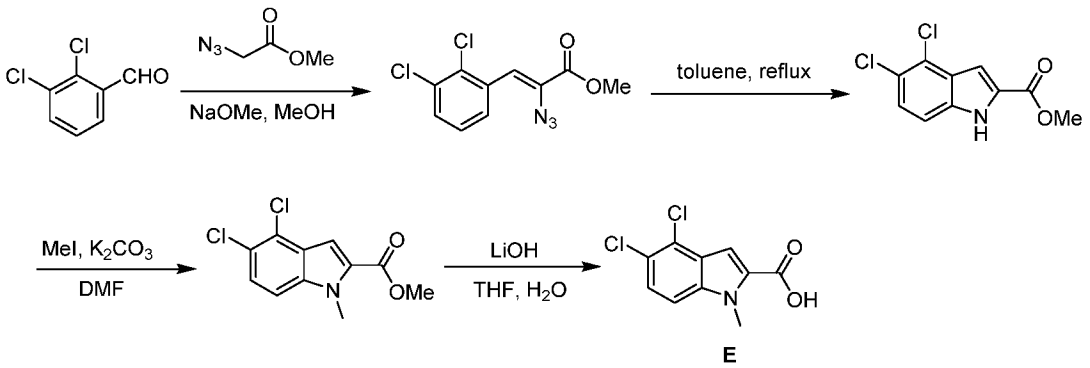
Step 5 - Methyl 4-chloro-1,5-dimethyl-1*H*-indole-2-carboxylate

[00253] To a solution of methyl 4-chloro-5-methyl-1*H*-indole-2-carboxylate (16.0 g, 71.8 mmol) in DMF (300 mL) was added K_2CO_3 (9.93 g, 71.8 mmol) and MeI (30.4 g, 215 mmol) at 20 °C. The reaction was stirred at 60 °C under nitrogen for 16 hrs. On completion, the reaction mixture was filtered and the filter cake was washed with dichloromethane (30 mL), the filtrate was concentrated to afford the crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.36 (s, 1H), 7.21 (d, *J*=1.5 Hz, 2H), 4.07 (s, 3H), 3.94 (s, 3H), 2.49 (s, 3H).

Step 6- 4-Chloro-1,5-dimethyl-1*H*-indole-2-carboxylic acid

[00254] To a solution of methyl 4-chloro-1,5-dimethyl-indole-2-carboxylate (11.0 g, 46.4 mmol) in a mixture of tetrahydrofuran (90 mL) and H_2O (30 mL) was added $LiOH•H_2O$ (7.80 g, 186 mmol) at 25 °C under nitrogen. The reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*, and the residue was acidified with 2 N HCl (20 mL) to pH = 3, and then was filtered. The filter cake was washed with water (20 mL) and dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.14 (br. s., 1H), 7.49 (d, *J*=8.5 Hz, 1H), 7.29 (d, *J*=8.5 Hz, 1H), 7.11 (s, 1H), 4.01 (s, 3H), 2.41 (s, 3H).

4,5-Dichloro-1-methyl-indole-2-carboxylic acid (Intermediate E)



E

Step 1 - Methyl (Z)-2-azido-3-(2,3-dichlorophenyl)prop-2-enoate

[00255] To a solution of sodium methoxide (11.1 g, 205 mmol) in anhydrous methanol (80 mL) was added a mixed solution of 2,3-dichlorobenzaldehyde (12.0 g, 68.5 mmol) and methyl 2-azidoacetate (26.5 g, 205 mmol) in anhydrous methanol (80 mL) at -50 °C. After stirring at -50

°C for 2 hrs, the mixture was warmed to 25 °C, and stirred for 14 hrs. On completion, the suspension was poured onto ice and the azido derivative was collected by filtration and washed with cold water. The filter cake was dried *in vacuo* and purified by column chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.06 (dd, *J*=1.3, 8.0 Hz, 1H), 7.45 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.30 - 7.24 (m, 2H), 3.97 (s, 3H).

Step 2 - Methyl 4,5-dichloro-1*H*-indole-2-carboxylate

[00256] A solution of methyl (*Z*)-2-azido-3-(2,3-dichlorophenyl)prop-2-enoate (7.80 g, 28.6) in toluene (150 mL) was stirred at 120 °C for 16 hrs. On completion, the toluene was removed *in vacuo* to give a residue. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 12:1 to 5:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.52 (br. s., 1H), 7.47 - 7.41 (m, 2H), 7.12 (d, *J* = 2.1 Hz, 1H), 3.90 (s, 3H).

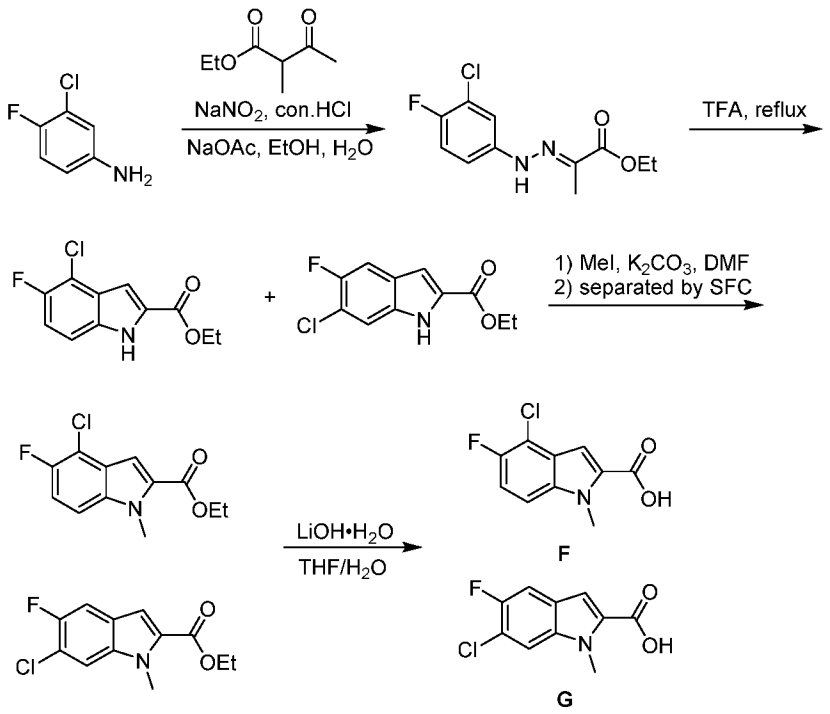
Step 3 - Methyl 4,5-dichloro-1-methyl-indole-2-carboxylate

[00257] To a solution of methyl 4,5-dichloro-1*H*-indole-2-carboxylate (4.50 g, 18.4 mmol) in *N*,*N*-dimethylformamide (40 mL) was added potassium carbonate (6.37 g, 46.1 mmol) and iodomethane (10.4 g, 73.7 mmol). The mixture was stirred at 60 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* to remove solvent. The residue was diluted with water 30 mL and extracted with dichloromethane (3 x 15 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 8:1 to 3:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.69 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.9 Hz, 1H), 7.22 (br. s., 1H), 4.05 (br. s., 3H), 3.89 (br. s., 3H).

Step 4 - 4, 5-Dichloro-1-methyl-indole-2-carboxylic acid

[00258] To a solution of methyl 4,5-dichloro-1-methyl-indole-2-carboxylate (4.10 g, 15.8 mmol) in a mixture of tetrahydrofuran (40 mL) and water (10 mL) was added lithium hydroxide (1.14 g, 47.6 mmol). The mixture was stirred at 18 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The residue was acidified with 1 M hydrochloric acid to pH = 3. A fine precipitate formed which was filtered and the filter cake was washed with water and dried under vacuum to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.35 (br. s., 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.14 (s, 1H), 4.03 (s, 3H).

4-Chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate F) and 6-Chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate G)



Step 1 - Ethyl (2E)-2-[(3-chloro-4-fluoro-phenyl) hydrazono] propanoate

[00259] To a solution of 3-chloro-4-fluoro-aniline (15.0 g, 103 mmol) in ethanol (15 mL) and water (15 mL) was added hydrochloric acid (37%, 30 mL). The mixture was cooled to -5 °C, and then a solution of $NaNO_2$ (8.00 g, 116 mmol) in water (40 mL) was added dropwise while the temperature was maintained below 5 °C. A cold solution of ethyl 2-methyl-3-oxo-butanoate (15.0 g, 104 mmol) and sodium acetate (30.0 g, 366 mmol) in a mixture of ethanol (75 mL) and water (30 mL) was added to the reaction mixture, and the reaction mixture was stirred at -5 °C for 4 hours. On completion, the reaction mixture was extracted with dichloromethane and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 30:1 to 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.33 - 7.25 (m, 1H), 7.10 - 7.02 (m, 1H), 6.98 - 6.90 (m, 1H), 4.41 - 4.17 (m, 2H), 2.17 (s, 3H), 1.38 (t, J = 7.2 Hz, 3H).

Step 2 - Ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate and Ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate

[00260] A solution of ethyl (2*E*)-2-[(3-chloro-4-fluoro-phenyl) hydrazono] propanoate (6.70 g, 25.9 mmol) in trifluoroacetic acid (30 mL) was refluxed at 80 °C for 12 hours. On completion, the solvent was evaporated *in vacuo*, and the residue was diluted with ethyl acetate and was washed with a saturated aqueous sodium hydrogen carbonate solution and brine, then dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 30:1 to 20:1) to give ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate, ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate and a mixture of ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate and ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate. Ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate ^{1}H NMR (300MHz, DMSO-d6) δ = 12.11 (br. s., 1H), 7.67 (d, *J* = 10.0 Hz, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.15 (d, *J* = 1.1 Hz, 1H), 4.47 - 4.19 (m, 2H), 1.46 - 1.24 (m, 3H). Mixture ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate and ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate ^{1}H NMR (300MHz, DMSO-d_6) δ = 12.38 (br. s., 0.5H), 12.11 (br. s., 0.5H), 7.66 (d, *J* = 10.0 Hz, 0.5H), 7.57 (d, *J* = 6.4 Hz, 0.5H), 7.45 (dd, *J* = 4.0, 8.9 Hz, 0.5H), 7.37 - 7.26 (m, 0.5H), 7.14 (dd, *J* = 1.5, 5.8 Hz, 0.5H), 4.56 - 4.06 (m, 2H), 1.61 - 1.04 (m, 3H).

Step 3 - Ethyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate and ethyl 6-chloro-5-fluoro-1-methyl-indole-2-carboxylate

[00261] To a solution of a mixture of ethyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate and ethyl 6-chloro-5-fluoro-1*H*-indole-2-carboxylate (5.00 g, 20.7 mmol) in *N,N*-dimethylformamide (20 mL) was added potassium carbonate (11.4 g, 82.7 mmol) and iodomethane (14.7 g, 103 mmol). Then the mixture was stirred at 60 °C for 12 hrs. On completion, the residue was diluted with water (100 mL), extracted with ethyl acetate (3 x 80 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated. The residue was purified by prep-SFC (Condition: Base-MeOH; Column: AD (250 mm*30 mm*10 μm) to give ethyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate and ethyl 6-chloro-5-fluoro-1-methyl-indole-2-carboxylate as yellow solids. Ethyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 (s, 1H), 7.31 - 7.22 (m, 1H), 7.22 - 7.15 (m, 1H), 4.42 (q, *J* = 7.3 Hz, 2H), 4.09 (s, 3H), 1.45 (t, *J* = 7.2 Hz, 3H). Ethyl 6-chloro-5-fluoro-1-methyl-indole-2-carboxylate ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.49 - 7.37 (m, 2H), 7.27 - 7.21 (m, 1H), 4.40 (q, *J* = 7.3 Hz, 2H), 4.16 - 3.96 (m, 3H), 1.48 - 1.36 (m, 3H).

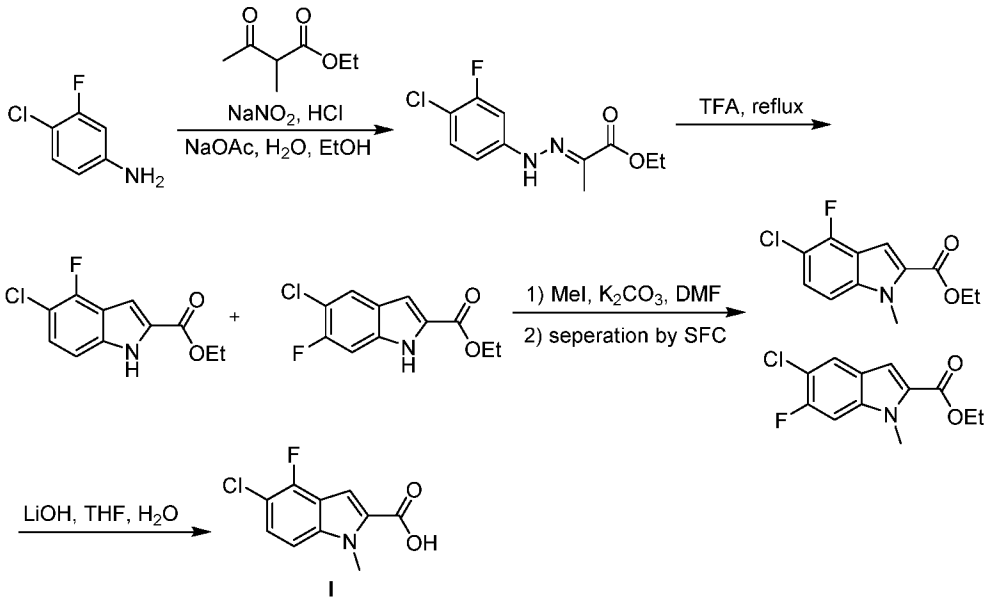
Step 4 - 4-Chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate F)

[00262] To a mixture of ethyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate (2.60 g, 10.2 mmol) in tetrahydrofuran (20 mL) and water (20 mL) was added lithium hydroxide (1.71 g, 40.7 mmol). Then the mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was concentrated *in vacuo*. The residue was diluted water (50 mL). The mixture was acidified with 2 M hydrochloric acid to pH = 3 and extracted with ethyl acetate (3 x 50 mL). The organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.75 - 7.57 (m, 1H), 7.39 (t, *J* = 9.4 Hz, 1H), 7.19 (s, 1H), 4.05 (s, 3H).

Step 5 - 6-Chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate G)

[00263] To a solution of ethyl 6-chloro-5-fluoro-1-methyl-indole-2-carboxylate (2.40 g, 9.39 mmol) in a mixture of tetrahydrofuran (20 mL) and water (20 mL) was added lithium hydroxide (1.58 g, 37.6 mmol). The mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was concentrated *in vacuo*. The residue was diluted water (50 mL), acidified with 2 M hydrochloric acid to pH = 3 and extracted with ethyl acetate (3 x 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.07 - 7.85 (m, 1H), 7.68 (d, *J* = 9.8 Hz, 1H), 7.21 (s, 1H), 4.09 - 3.90 (m, 3H).

5-Chloro-4-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate I)



I

Step 1 - Ethyl (2E)-2-[(4-chloro-3-fluoro-phenyl)hydrazono]propanoate

[00264] To a solution of 4-chloro-3-fluoro-aniline (8.20 g, 56.3 mmol) in a mixture of ethanol (50 mL) and water (50 mL) was added hydrochloric acid (16 mL) and subsequently a solution of sodium nitrite (4.28 g, 61.9 mmol) in water (50 mL) dropwise during a period of 30 min, during which the temperature of the mixture was maintained at -10 °C to -5 °C. A solution of ethyl 2-methyl-3-oxo-butanoate (8.40 g, 58.2 mmol) and sodium acetate (16.1 g, 197 mmol) in ethanol (100 mL) and water (100 mL) was added to the reaction mixture dropwise at -5 °C over 30 min. The mixture was stirred at -5 °C for 2 hours. On completion, the mixture was concentrated *in vacuo*, and the residue was washed with water (120 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 40:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.85 (t, *J*=8.2 Hz, 1H), 7.77 (dd, *J*=2.0, 9.8 Hz, 1H), 7.68 (dd, *J*=1.3, 8.5 Hz, 1H), 4.25 - 4.17 (m, 2H), 2.38 (s, 3H), 1.18 (t, *J*=7.0 Hz, 3H).

Step 2 – Ethyl 5-Chloro-4-fluoro-1*H*-indole-2-carboxylate and Ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate

[00265] A solution of ethyl (2E)-2-[(4-chloro-3-fluoro-phenyl)hydrazono]propanoate (4.60 g, 17.7 mmol) in trifluoroacetic acid (20 mL) was refluxed at 90 °C under a nitrogen atmosphere for 16 hrs. On completion, the mixture was concentrated *in vacuo* and the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 40:1) to afford a mixture of ethyl 5-Chloro-4-fluoro-1*H*-indole-2-carboxylate and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.44 (br. s., 1H), 7.90 (d, *J*=7.5 Hz, 1H), 7.33 - 7.30 (m, 1H), 7.19 (d, *J*=1.5 Hz, 1H), 4.40 - 4.36 (q, 2H), 1.37 - 1.35 (t, 3H); ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.17 (br. s., 1H), 7.90 (d, *J*=7.5 Hz, 1H), 7.37 (d, *J*=9.8 Hz, 1H), 7.15 (d, *J*=1.3 Hz, 1H), 4.36 - 4.30 (q, 2H), 1.35 - 1.31 (t, 3H).

Step 3 - Ethyl 5-chloro-4-fluoro-1-methyl-indole-2-carboxylate and ethyl 5-chloro-6-fluoro-1-methyl-indole-2-carboxylate

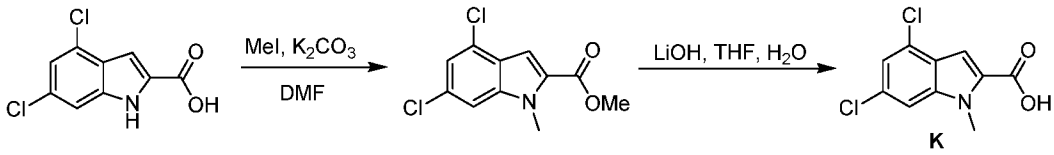
[00266] To a solution of a mixture of ethyl 5-chloro-4-fluoro-1*H*-indole-2-carboxylate and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate (1.50 g, 6.21 mmol) and potassium carbonate (3.43 g, 24.8 mmol) in *N,N*-dimethylformamide (10 mL) was added methyl iodide (2.64 g, 18.6 mmol) at 60 °C under a nitrogen atmosphere. The reaction mixture was then stirred at 60 °C for 16 hours. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with water (30 mL) and extracted with ethyl acetate (2 x 30 mL), the combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* to afford crude product (1.8 g). The crude product (1 g) was separated by SFC to afford the ethyl 5-chloro-4-fluoro-1-methyl-indole-2-carboxylate (230 mg, 14% yield) and ethyl 5-chloro-6-fluoro-1-methyl-indole-2-carboxylate (450 mg, 28% yield) as yellow solids. Ethyl 5-chloro-4-fluoro-1-methyl-indole-2-carboxylate: ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.55 - 7.50 (m, 1H), 7.47 - 7.41 (m, 1H), 7.27 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 4.04 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H). Ethyl 5-chloro-6-fluoro-1-methyl-indole-2-carboxylate: ^{1}H NMR (400MHz, DMSO-d6) δ = 7.92 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 10.5 Hz, 1H), 7.26 (s, 1H), 4.32 (q, *J* = 7.0 Hz, 2H), 3.99 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

Step 4 - 5-Chloro-4-fluoro-1-methyl-indole-2-carboxylic acid (Intermediate I)

[00267] To a solution of ethyl 5-chloro-4-fluoro-1-methyl-indole-2-carboxylate (230 mg, 0.899 mmol) in a mixture of tetrahydrofuran (4 mL) and water (2.00 mL) was added lithium hydroxide (43.0 mg, 1.80 mmol) at 25 °C. The mixture was stirred at 25 °C for 16 hours. On

completion, the mixture was concentrated *in vacuo*, the residue was diluted with water and extracted with ethyl acetate (3 x 15 mL), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound (crude). ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.32 (br. s., 1H), 7.54 - 7.48 (m, 1H), 7.46 - 7.39 (m, 1H), 7.24 (s, 1H), 4.04 (s, 3H).

4,6-Dichloro-1-methyl-indole-2-carboxylic acid (Intermediate K)



K

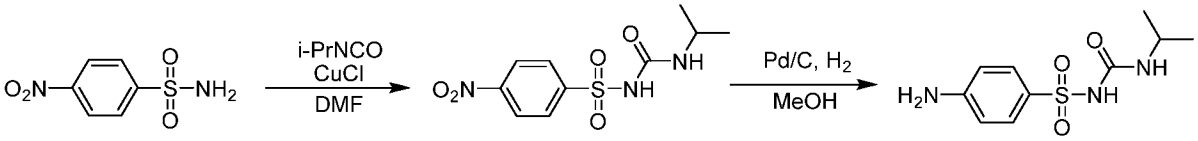
Step 1 - Methyl 4,6-dichloro-1-methyl-indole-2-carboxylate

[00268] To a mixture of 4,6-dichloro-1*H*-indole-2-carboxylic acid (950 mg, 4.13 mmol, CAS#101861-63-6) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (2.28 g, 16.5 mmol). Iodomethane (3.52 g, 24.8 mmol) was added to the mixture dropwise. Then the mixture was stirred at 60 °C for 12 hrs. On completion, the mixture was quenched with water (30 mL). The mixture was extracted with ethyl acetate (2 x 20 mL). The organic layers were dried with anhydrous sodium sulfate, filtrated, and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.34 (s, 1H), 7.30 (s, 1H), 7.17 (d, *J* = 1.3 Hz, 1H), 4.15 (s, 3H), 4.01 (s, 3H).

Step 2 - 4,6-Dichloro-1-methyl-indole-2-carboxylic acid (Intermediate K)

[00269] To a mixture of methyl 4,6-dichloro-1-methyl-indole-2-carboxylate (1.10 g, 4.26 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide (715 mg, 17.0 mmol). Then the mixture was stirred at 30 °C for 12 hours. On completion, the mixture was concentrated. To the residue was added 20 mL water and acidified with 6 M hydrochloric acid to pH = 2. The mixture was extracted with ethyl acetate (2 x 30 mL). Then the organic layers were dried with anhydrous sodium sulfate, filtrated and concentrated to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.79 (s, 1H), 7.31 (d, *J* = 1.3 Hz, 1H), 7.17 (s, 1H), 4.03 (s, 3H).

4-Amino-*N*-(isopropylcarbamoyl)benzenesulfonamide (Intermediate L)



L

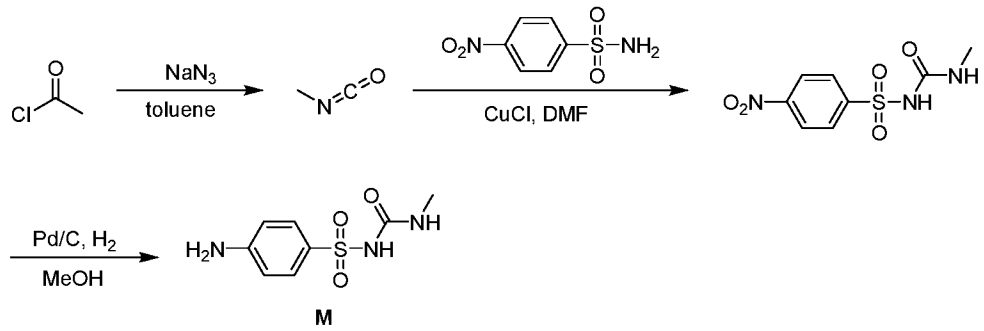
Step 1 - *N*-(Isopropylcarbamoyl)-4-nitrobenzenesulfonamide

[00270] To a mixture of 4-nitrobenzenesulfonamide (10.0 g, 49.5 mmol) and 2-isocyanatopropane (12.6 g, 148 mmol) in *N,N*-dimethylformamide (100 mL) was added copper (I) chloride (979 mg, 9.89 mmol). The mixture was stirred at 30 °C for 12 hrs. The mixture was poured into ice water (500 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (dichloromethane:methanol = 100:1 to 5:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.41 (d, 2 H), 7.94 (d, 2H), 3.60 (m, 1H), 1.00 (d, 6H).

Step 2 - 4-Amino-*N*-(isopropylcarbamoyl)benzenesulfonamide (Intermediate L)

[00271] To a solution of *N*-(isopropylcarbamoyl)-4-nitrobenzenesulfonamide (6.50 g, 22.6 mmol) in methanol (100 mL) was added Pd/C (650 mg, 10%). The mixture was stirred under hydrogen (45 psi) at 20 °C for 12 hrs. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 2:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.92 (s, 1 H), 7.51 (d, 2 H), 6.59 (d, 2H), 6.14 (d, 2H), 6.06 (s,1H), 3.60 (m,1H), 1.00 (d, 6H).

4-Amino-*N*-(methylcarbamoyl) benzenesulfonamide (Intermediate M)



M

Step 1 – Isocyanatomethane

[00272] To a suspension of sodium azide (10.2 g, 157 mmol) in toluene (360 mL) was added acetyl chloride (12 g, 152 mmol) dropwise at 0 °C. The resulting mixture was stirred for 30 min at 0° C, then the reaction mixture was heated at 100 °C and stirred for 3 hrs. On completion, the reaction was cooled to 20 °C and the solution of isocyanatomethane was used in next step directly.

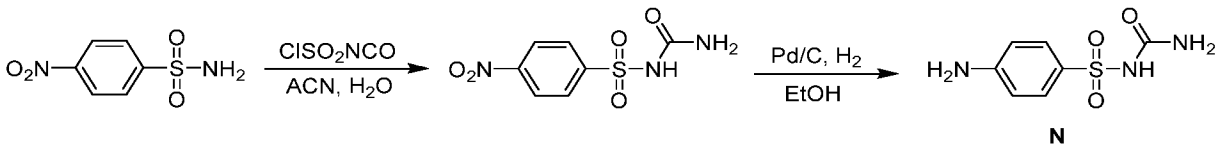
Step 2 - *N*-(Methylcarbamoyl)-4-nitrobenzenesulfonamide

[00273] To a solution of 4-nitrobenzenesulfonamide (17.9 g, 88.8 mmol) in *N,N*-dimethylformamide (50 mL) was added copper (I) chloride (3.52 g, 35.6 mmol). Then isocyanatomethane (360 mL toluene solution, 152.85 mmol) was added to the reaction mixture dropwise. The suspension was stirred at 30 °C for 16 hrs. On completion, the mixture was filtered and the filtrate was diluted with water (100 mL) and was extracted with ethyl acetate (3 x 200 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was triturated with ethyl acetate (20 mL) to give the title compound. ^{1}H NMR (400M, CD_3OD): δ = 8.45 (d, *J* = 8.0 Hz, 2H), 8.25 (d, *J* = 8.8 Hz, 2H), 2.67 (s, 3H).

Step 3 - 4-Amino-*N*-(methylcarbamoyl) benzenesulfonamide (Intermediate M)

[00274] To a solution of *N*-(methylcarbamoyl)-4-nitrobenzenesulfonamide (4.00 g, 15.4 mmol) in methanol (200 mL) was added Pd/C (0.5 g, 10%). The reaction mixture was stirred under hydrogen (30 Psi) at 20 °C for 3.5 hrs. Then the reaction mixture was filtered, and the filtrate was concentrated. The residue was triturated with dichloromethane (20 mL) to give the title compound. ^{1}H NMR (300MHz, DMSO-d_6): δ = 7.51 (d, *J* = 11.6 Hz, 2H), 6.58 (d, *J* = 11.6 Hz, 2H), 6.27 (br, d, *J* = 6.0 Hz, 1H), 6.05 (br, 2H), 2.50 (s, 3H).

4-Amino-*N*-carbamoylbenzenesulfonamide (Intermediate N)



N

Step 1 – *N*-Carbamoyl-4-nitrobenzenesulfonamide

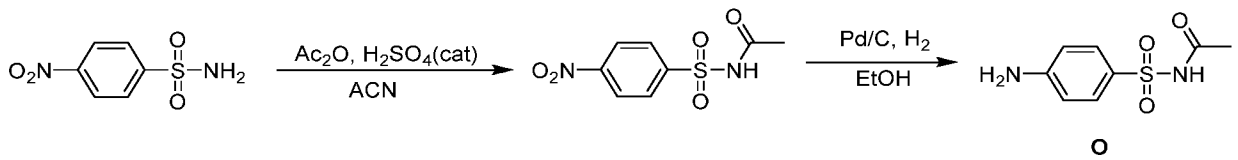
[00275] To a solution of 4-nitrobenzenesulfonamide (7.00 g, 34.6 mmol) in acetonitrile (80 mL) was added sulfurisocyanatidic chloride (5.00 g, 35.3 mmol, CAS#1189-71-5) at 20 °C. The reaction mixture was stirred at 20 °C for 1 h. On completion, the reaction mixture was quenched

with water (5 mL), then the mixture was stirred at 20 °C for another 1 h during which a solid precipitate formed. The solid was collected by filtration, washed with water (20 mL), and dried to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.99 (br. s., 1H), 8.51 - 8.38 (m, 2H), 8.20 - 8.09 (m, 2H), 6.94 - 5.81 (m, 2H).

Step 2 – 4-Amino-*N*-carbamoylbenzenesulfonamide (Intermediate N)

[00276] To a solution of *N*-carbamoyl-4-nitrobenzenesulfonamide (4.00 g, 16.31 mmol) in ethanol (50 mL) was added Pd/C (0.4 g, 10%). The reaction mixture was stirred under a hydrogen balloon at 20 °C for 3 hrs. On completion, the reaction mixture was filtered, and the filtrate was concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.14 (s, 1H), 7.51 (d, *J*=8.7 Hz, 2H), 6.60 (d, *J*=8.8 Hz, 2H), 3.78 (br. s., 2H)

N-((4-Aminophenyl)sulfonyl)acetamide (Intermediate O)



O

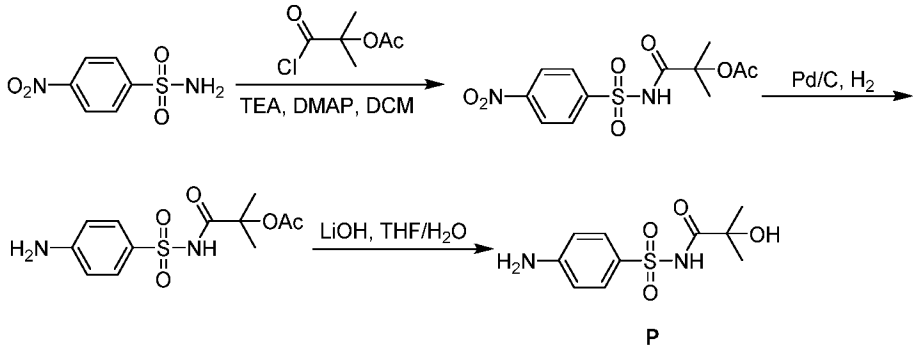
Step 1 - *N*-((4-Nitrophenyl)sulfonyl)acetamide

[00277] To a solution of 4-nitrobenzenesulfonamide (4.00 g, 19.8 mmol) and acetic anhydride (6.10 g, 59.3 mmol) in acetonitrile (60 mL) was added concentrated sulfuric acid (38.8 mg, 0.401 mmol). The mixture was stirred at 80 °C for 3 hrs. On completion, the mixture was diluted with ethyl acetate (100 mL), washed with water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate, and concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.46 (br. s., 1H), 8.44 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 1.96 (s, 3H).

Step 2 - *N*-((4-Aminophenyl)sulfonyl)acetamide (Intermediate O)

[00278] To a solution of *N*-((4-nitrophenyl)sulfonyl)acetamide (3.80 g, 14.8 mmol) in ethanol (60 mL) was added Pd/C (0.4 g, 10%). The mixture was stirred under hydrogen balloon at 20 °C for 12 hrs. On completion, the mixture was filtered, and the filtrate was concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.52 (d, *J* = 8.5 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.14 (s, 2H), 1.87 (s, 3H).

N-((4-Aminophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (Intermediate P)



Step 1 - 2-Methyl-1-(4-nitrophenylsulfonamido)-1-oxopropan-2-yl acetate

[00279] To a solution of 4-nitrobenzenesulfonamide (7.00 g, 34.6 mmol) in anhydrous dichloromethane (100 mL) was added triethylamine (10.5 g, 104 mmol) and DMAP (423 mg, 3.46 mmol) at 0 °C. Then (2-chloro-1,1-dimethyl-2-oxo-ethyl) acetate (11.4 g, 69.2 mmol) was added and the mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was quenched with hydrochloric acid (1 M, 50 mL) and water (50 mL), then extracted with dichloromethane (3 x 80 mL). The combined organic phase was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 4:1), then triturated with dichloromethane:petroleum ether (2:1) to give the title compound. LCMS: (ES+) m/z $(M+H)^+$ = 352.9, tR = 1.074. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.44 (d, *J* = 11.6 Hz, 2H), 8.10 (d, *J* = 11.6 Hz, 2H), 2.01 (s, 3H), 1.35 (s, 6H).

Step 2 - 1-(4-Aminophenylsulfonamido)-2-methyl-1-oxopropan-2-yl acetate

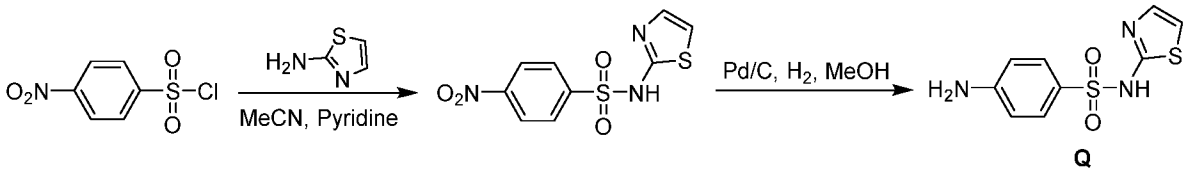
[00280] To a solution of [1,1-dimethyl-2-[(4-nitrophenyl)sulfonylamino]-2-oxo-ethyl] acetate (7.00 g, 21.2 mmol) in methanol (300 mL) was added palladium on carbon (1.00 g, 10%). The mixture was stirred at 20 °C under hydrogen (50 psi) for 16 hrs. On completion, the mixture was filtered and the filtrate was concentrated to give the title compound. LCMS: (ES+) m/z $(M+H)^+$ = 301.0, tR = 0.829. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 (brs, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.57 (d, *J* = 8.8 Hz, 2H), 6.11 (brs, 2H), 1.99 (s, 3H), 1.33 (s, 6H).

Step 3 - *N*-((4-Aminophenyl)sulfonyl)-2-hydroxy-2-methylpropanamide (Intermediate P)

[00281] To a solution of [2-[(4-aminophenyl)sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate (6.00 g, 20.0 mmol) in a mixture of tetrahydrofuran (80.0 mL) and water (20.0 mL) was added lithium hydroxide hydrate (2.4 g, 100 mmol). The mixture was stirred at 20 °C for 16 hrs.

On completion, the mixture was acidified to pH = 3 with hydrochloric acid (1 M, 120 mL), then concentrated. The residue was triturated with water (40 mL) and acetone (5 mL) to give the title compound. LCMS: (ES+) m/z $(M+H)^+$ = 281.1, tR = 0.512. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.84 (brs, 1H), 7.54 (d, *J* = 11.6 Hz, 2H), 6.58 (d, *J* = 11.6 Hz, 2H), 6.14 (brs, 2H), 5.49 (s, 1H), 1.16 (s, 6H).

4-Amino-*N*-thiazol-2-yl-benzenesulfonamide (Intermediate Q)



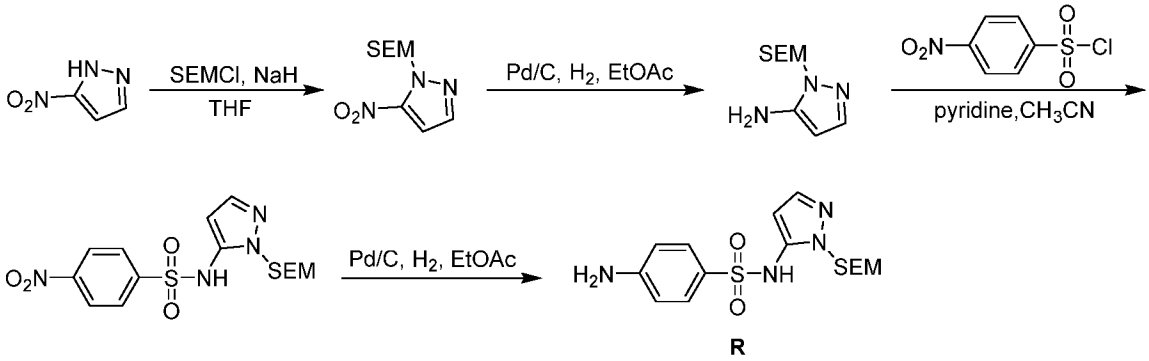
Step 1 - 4-Nitro-*N*-thiazol-2-yl-benzenesulfonamide

[00282] To a mixture of 4-nitrobenzenesulfonyl chloride (15.0 g, 67.7 mmol) and thiazol-2-amine (6.78 g, 67.7 mmol) in acetonitrile (100 mL) was added pyridine (16.1 g, 203 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in 20 mL methanol and 50 mL dichloromethane. Then the mixture was filtrated to give a filter cake. The filter cake was dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.37 (d, *J* = 8.8 Hz, 2H), 8.08 - 7.99 (m, 2H), 7.41 - 7.25 (m, 1H), 6.97 - 6.82 (m, 1H).

Step 2 - 4-Amino-*N*-thiazol-2-yl-benzenesulfonamide (Intermediate Q)

[00283] To a mixture of 4-nitro-*N*-thiazol-2-yl-benzenesulfonamide (6.00 g, 21.0 mmol) in methanol (50 mL) was added Pd/C (1.00 g, 21.0 mmol). The mixture was then stirred at 30 °C for 24 hrs under hydrogen atmosphere (30 psi). On completion, the mixture was filtered and concentrated *in vacuo* to give the title compound. The solid was used to the next step directly without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.43 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 4.5 Hz, 1H), 6.75 (d, *J* = 4.5 Hz, 1H), 6.56 (d, *J* = 8.8 Hz, 2H).

4-Amino-*N*-[2-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]benzenesulfonamide (Intermediate R)



Step 1 – 5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole

[00284] To a suspension of sodium hydride (5.52 g, 229 mmol) in tetrahydrofuran (50.0 mL) was added a solution of 3-nitro-1*H*-pyrazole (20.0 g, 176 mmol) in tetrahydrofuran (150 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h. Then 2-(chloromethoxy) ethyl-trimethyl-silane (38.3 g, 229 mmol) was added to the reaction mixture dropwise. The reaction mixture was stirred for 2 hrs. On completion, the mixture was poured into ice water (300 mL), then extracted with ethyl acetate (3 x 200 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by chromatography (petroleum ether:ethyl acetate = 30:1 to 5:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68 (s, 1H), 6.98 (s, 1H), 5.50 (s, 2H), 3.61 (t, 2H), 0.92 (t, 2H), 0.01 (s, 9H).

Step 2 – 1-(2-Trimethylsilylethoxymethyl) pyrazol-3-amine

[00285] To a solution of 5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (18.0 g, 73.97 mmol) in ethyl acetate (350 mL) was added Pd/C (2.50 g, 10%). The mixture was stirred under hydrogen atmosphere (30 psi) at 20 °C for 12 hrs. On completion, the mixture was filtered, and the filtrate was concentrated to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 5.48 (d, *J* = 2 Hz, 1H), 5.10 (s, 1H), 3.47 (t, *J* = 7.6 Hz, 2H), 0.82 (t, *J* = 8.0 Hz, 2H), 0.032 (s, 9H).

Step 3 – 4-Nitro-*N*-[2-(2-trimethylsilylethoxymethyl) pyrazol-3-yl]benzenesulfonamide

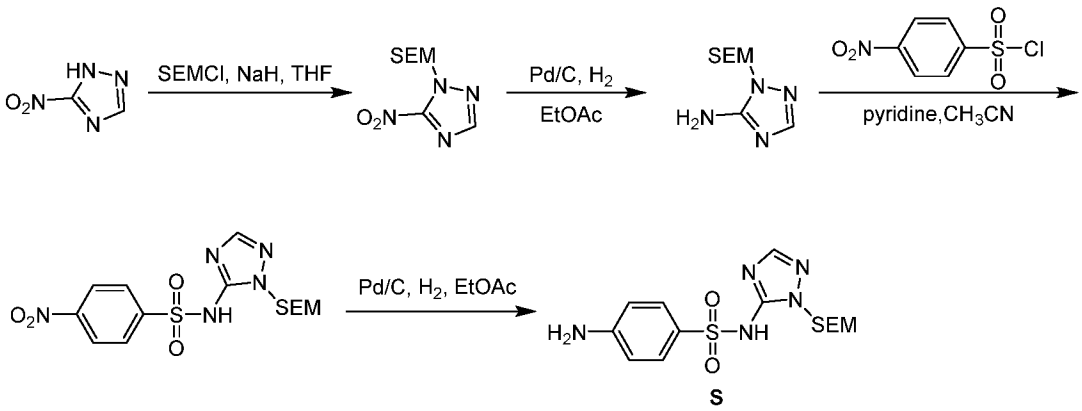
[00286] To a solution of 2-(2-trimethylsilylethoxymethyl)pyrazol-3-amine (4.00 g, 18.75 mmol) and 4-nitrobenzenesulfonyl chloride (4.99 g, 22.5 mmol) in acetonitrile (20 mL) was added pyridine (4.45 g, 56.25 mmol). The reaction mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was concentrated. The residue was purified by chromatography

(petroleum ether:ethyl acetate = 20:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.4 Hz, 2H), 7.46 (s, 1H), 6.40 (s, 1H), 5.38 (s, 2H), 3.49 (t, 2H), 0.85 (t, 2H), 0.01 (s, 9H).

Step 4 – 4-Amino-*N*-[2-(2-trimethylsilylethoxymethyl)pyrazol-3-yl]benzenesulfonamide (Intermediate R)

[00287] To a solution of 4-nitro-*N*-[2-(2-trimethylsilylethoxymethyl) pyrazol-3-yl] benzenesulfonamide (6.80 g, 17.1 mmol) in ethyl acetate (100 mL) was added Pd/C (1.00 g, 10%). The mixture was stirred under hydrogen atmosphere (30 Psi) at 20 °C for 6 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 9.6 Hz, 2H), 7.44 (d, *J* = 2.8 Hz, 1H), 6.51 (d, *J* = 9.6 Hz, 2H), 6.35 (d, *J* = 2.8 Hz, 1H), 5.40 (s, 2H), 3.49 (t, 2H), 0.86 (t, 2H), 0.01 (s, 9H).

4-Amino-*N*-[2-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzenesulfonamide (Intermediate S)



Step 1 - 5-Nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazole

[00288] To a solution of 5-nitro-1*H*-1,2,4-triazole (5.00 g, 43.8 mmol, CAS# 24807-55-4) in tetrahydrofuran (100 mL) was added sodium hydride (2.63 g, 65.8 mmol) at 0 °C under N_2. After the reaction mixture was stirred at 0 °C for 60 min, (2-(chloromethoxy)-ethyl)-trimethylsilane (11.0 g, 65.8 mmol) was added. The reaction mixture was stirred at 0-5 °C for another 2 hrs. On completion, the reaction mixture was quenched with ice-water and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound.

Step 2 - 2-((2-(Trimethylsilyl)ethoxy)methyl)-2*H*-1,2,4-triazol-3-amine

[00289] To a solution of 5-nitro-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazole (7.00 g, 28.7 mmol) in methanol (140 mL) was added Pd/C (1.00 g, 10%). The reaction mixture was stirred under H_2 (50 psi) at 25 °C for 10 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated. The crude product was purified by silica gel chromatography (dichloromethane:methanol = 100:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.13 (s, 1H), 5.32 (s, 2H), 5.23 (t, 2H), 3.54 (t, 2H), 0.85 (t, 2H), 0.03 (s, 9H).

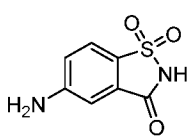
Step 3 - 4-Nitro-*N*-[2-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzenesulfonamide

[00290] To a mixture of 2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-amine (5.20 g, 24.3 mmol) in acetonitrile (100 mL) was added 4-nitrobenzenesulfonyl chloride (5.38 g, 24.3 mmol) in one portion at 25 °C. Then pyridine (5.76 g, 72.8 mmol) was added to the reaction mixture at 25 °C, and the reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction was concentrated *in vacuo*. The residue was purified by silica gel chromatography (dichloromethane:methanol = 20:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.69 (br s, 1H), 8.50 (s, 1H), 8.44-8.38 (m, 2H), 8.19-8.13 (m, 2H), 5.33 (s, 2H), 3.48-3 (t, 2H), 0.81 (t, 2H), 0.13 (s, 9H).

Step 4 - 4-Amino-*N*-[2-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl]benzenesulfonamide

[00291] To a solution of 4-nitro-*N*-(2-((2-(trimethylsilyl)ethoxy)methyl)-2H-1,2,4-triazol-3-yl) benzenesulfonamide (4.00 g, 10.0 mmol) in methanol (100 mL) was added palladium-charcoal (900 mg, 10%) under N_2. The reaction mixture was stirred under H_2 (50 psi) at 15 °C for 20 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated. The crude product was triturated with a mixture solvent of dichloromethane and petroleum ether (1:10) and filtered to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.67 (s, 1H), 8.39 (s, 1H), 7.50 (d *J* = 8.4Hz, 2H), 6.53 (t, 2H), 5.96 (s, 2H), 3.50 (t, 2H), 0.82 (t, 2H), 0.06 (s, 9H).

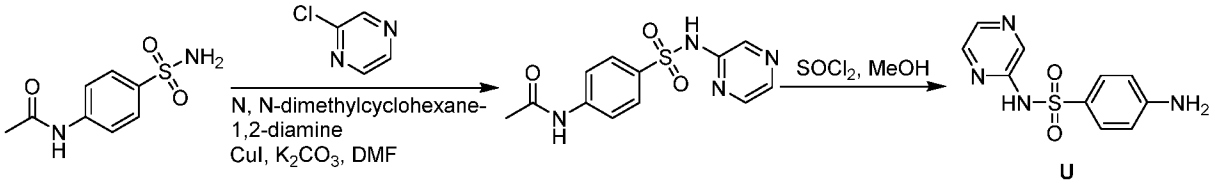
5-amino-1,1-dioxo-1,2-benzothiazol-3-one (Intermediate T)



T

[00292] 5-amino-1,1-dioxo-1,2-benzothiazol-3-one was purchased from a commercial source. CAS# 22094-61-7.

4-Amino-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate U)



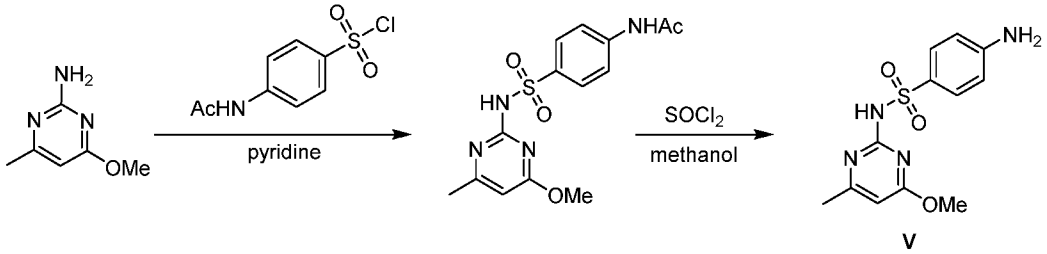
Step 1 - *N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]acetamide

[00293] To a solution of *N*-(4-sulfamoylphenyl)acetamide (4.70 g, 21.9 mmol, CAS# 121-61-9), 2-chloropyrazine (5.03 g, 43.8 mmol) and *N*,*N*-dimethylcyclohexane-1,2-diamine (3.12 g, 21.9 mmol) in *N*,*N*-dimethylformamide (100 mL) was added copper iodide (20.8 g, 109 mmol) and potassium carbonate (21.2 g, 153 mmol) under a nitrogen atmosphere. The mixture was stirred at 100 °C for 16 hrs. On completion, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography to give the title compound (crude). LCMS: (ES^+) m/z $(M+H)^+$ = 293.0, tR= 0.989.

Step 2- 4-Amino-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate U)

[00294] To a solution of *N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]acetamide (8.00 g, 27.3 mmol) in methanol (50 mL) was added $SOCl_2$ (9.77 g, 82.1 mmol) dropwise under a nitrogen atmosphere. The mixture was stirred at 100 °C for 16 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was purified with pre-HPLC (condition:0.225% FA-MeCN; column: Phenomenex Synergi Max-RP 250*80mm*10 μm) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.08 (br. s., 1H), 8.33 (br. s., 1H), 8.20 (d, *J* = 10.0 Hz, 2H), 7.57 (d, *J* = 8.7 Hz, 2H), 6.59 (d, *J* = 8.8 Hz, 2H).

4-Amino-*N*-(4-methoxy-6-methyl-pyrimidin-2-yl)benzenesulfonamide (Intermediate V)



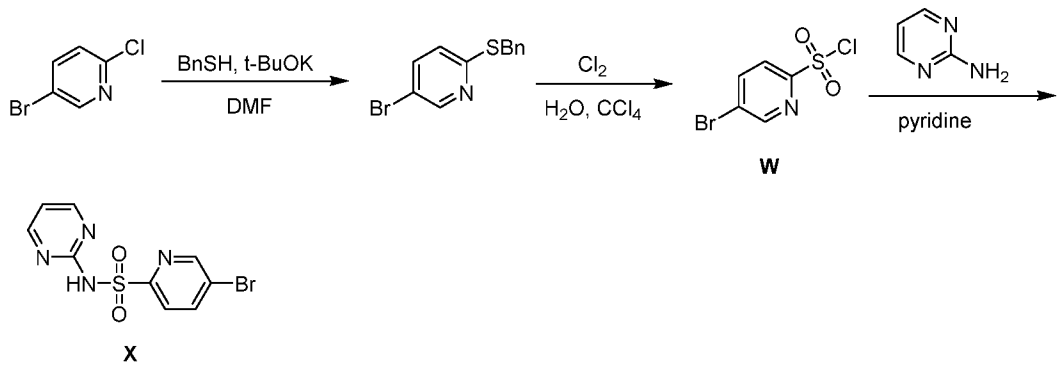
Step 1 - *N*-[4-[(4-methoxy-6-methyl-pyrimidin-2-yl)sulfamoyl]phenyl]acetamide

[00295] To a suspension of 4-methoxy-6-methyl-pyrimidin-2-amine (4.00 g, 28.8 mmol) in pyridine (40 mL) was added 4-acetamidobenzenesulfonyl chloride (7.05 g, 30.2 mmol, CAS#121-60-8). The reaction mixture was stirred at 60 °C for 12 hr. On completion, the reaction mixture was concentrated and the residue was diluted with water, the solid was filtered, washed with dichloromethane (30 mL), and dried under vacuum to give the title compound. LCMS: (ES^-) m/z $(M-H)^-$ = 335.1, tR = 1.011.

Step 2 – 4-Amino-*N*-(4-methoxy-6-methyl-pyrimidin-2-yl)benzenesulfonamide (Intermediate V)

[00296] To a solution of *N*-[4-[(4-methoxy-6-methyl-pyrimidin-2-yl)sulfamoyl] phenyl]acetamide in methanol (50 mL) was added $SOCl_2$ (4.24 g, 35.7 mmol) at 0 °C. The reaction mixture was stirred at 70 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 295.1, tR = 0.265.

5-Bromopyridine-2-sulfonyl chloride (Intermediate W) and 5-Bromo-*N*-pyrimidin-2-yl-pyridine-2-sulfonamide (Intermediate X)



Step 1 - 2-Benzylsulfanyl-5-bromo pyridine

[00297] To a solution of sodium *tert*-butoxide (4.99 g, 51.9 mmol) in anhydrous *N*,*N*-dimethylformamide (100 mL) was added phenylmethanethiol (6.45 g, 51.9 mmol) dropwise at 0 °C. The mixture was stirred at 30 °C for 30 min and then cooled to 0 °C again. To the cooled mixture was added 5-bromo-2-chloro-pyridine (10.0 g, 51.9 mmol) dissolved in anhydrous *N*,*N*-dimethylformamide (150 mL) dropwise, while the temperature was kept below 5 °C. Afterwards, the mixture was heated to 80 °C and stirred at for 1.5 hrs. On completion, the reaction mixture

was concentrated *in vacuo* to remove most of the solvent. The resulting mixture was poured into water (250 mL) and extracted with ethyl acetate (3 x 150 mL). The combined organic phases were washed with brine, dried over anhydrous sodium sulfate, concentrated *in vacuo*, and the residue was purified by column chromatography (petroleum ether:ethyl acetate = 40:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.58 (d, *J* = 2.1 Hz, 1H), 7.83 (dd, *J* = 2.4, 8.5 Hz, 1H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.33 - 7.27 (m, 3H), 7.26 - 7.20 (m, 1H), 4.41 (s, 2H).

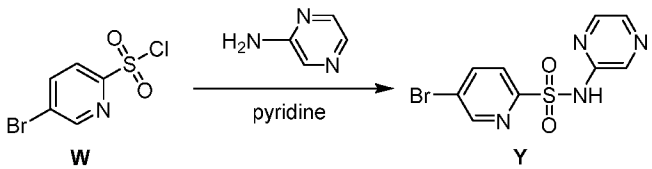
Step 2 - 5-Bromopyridine-2-sulfonyl chloride (Intermediate W)

[00298] To a solution of 2-benzylsulfanyl-5-bromo-pyridine (10.0 g, 35.7 mmol) in tetrachloromethane (200 mL) and water (50 mL) was vigorously bubbled chlorine (15 psi) for 15 mins, during which the temperature was kept below 0 °C. The mixture was then stirred for another 15 mins, maintaining the temperature between 0 °C to 5 °C. On completion, the mixture was degassed under vacuum and purged with nitrogen gas several times. Ice water and dichloromethane were then added and the organic phase was separated, dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a residue. The residue was purified by flash silica gel chromatography (ethylacetate:petroleum = 8:1) to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.88 (d, *J* = 1.8 Hz, 1H), 8.21 (dd, *J* = 2.3, 8.4 Hz, 1H), 8.04 - 8.00 (m, 1H).

Step 3 - 5-Bromo-*N*-pyrimidin-2-yl-pyridine-2-sulfonamide (Intermediate X)

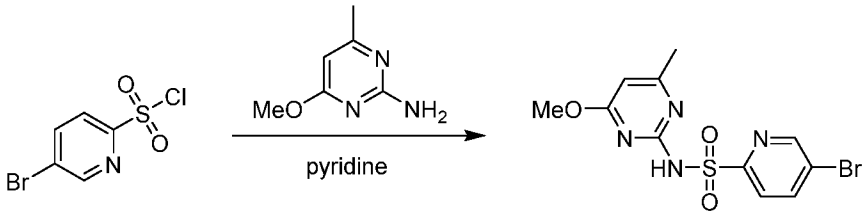
[00299] To a solution of 5-bromopyridine-2-sulfonyl chloride (4.20 g, 16.3 mmol) in pyridine (30 mL) was added pyrimidin-2-amine (1.56 g, 16.3 mmol). The reaction was stirred at 15 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was triturated with dichloromethane:methanol = 5:1 to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.34 (br. s., 1H), 8.82 (d, *J* = 2.0 Hz, 1H), 8.45 (d, *J* = 4.9 Hz, 2H), 8.36 (dd, *J* = 2.3, 8.4 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 4.9 Hz, 1H).

5-Bromo-*N*-pyrazin-2-yl-pyridine-2-sulfonamide (Intermediate Y)



[00300] To a solution of 5-bromopyridine-2-sulfonyl chloride (3.00 g, 11.70 mmol, Intermediate W) in pyridine (25 mL) was added pyrazin-2-amine (1.11 g, 11.7 mmol). The reaction mixture was stirred at 15 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was triturated with dichloromethane:methanol = 5:1 to give the title compound which was used without further purification. LCMS: (ES^+) m/z $(M+H)^+$ = 317.0, tR= 0.722. ^1H NMR (400MHz, DMSO-d_6) δ = 11.99 (br. s., 1H), 8.85 (d, *J* = 2.0 Hz, 1H), 8.43 (d, *J* = 1.1 Hz, 1H), 8.39 (dd, *J* = 2.3, 8.3 Hz, 1H), 8.24 (d, *J* = 2.6 Hz, 1H), 8.14 (dd, *J* = 1.4, 2.6 Hz, 1H), 8.08 (d, *J* = 8.4 Hz, 1H).

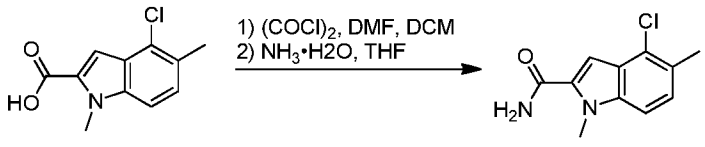
5-Bromo-*N*-(4-methoxy-6-methyl-pyrimidin-2-yl)pyridine-2-sulfonamide (Intermediate Z)



W Z

[00301] To a solution of 5-bromopyridine-2-sulfonyl chloride (1.00 g, 3.90 mmol, Intermediate W) in pyridine (10 mL) was added 4-methoxy-6-methyl-pyrimidin-2-amine (542 mg, 3.90 mmol). The reaction mixture was stirred at 15 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was triturated with dichloromethane:methanol = 5:1 to give the title compound which was used directly without further purification. LCMS: (ES^+) m/z $(M+H)^+$ = 360.8, tR= 0.965. ^1H NMR (400MHz, DMSO-d_6) δ = 12.96 (br. s., 1H), 8.75 (d, *J* = 1.6 Hz, 1H), 8.26 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 3.43 (s, 3H), 2.23 (s, 3H).

4-chloro-1,5-dimethyl-indole-2-carboxamide (Intermediate AA)



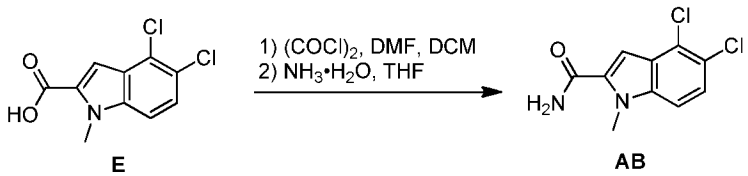
D AA

[00302] To a solution of 4-chloro-1,5-dimethyl-indole-2-carboxylic acid (1.00 g, 4.47 mmol, Intermediate D) in a mixture of *N,N*-dimethylformamide (10 μL) and dichloromethane (50 mL) was added oxalyl chloride (851 mg, 6.71 mmol) dropwise and the reaction mixture was stirred at

15 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give 4-chloro-1,5-dimethyl-indole-2-carbonyl chloride (1.20 g, crude) as white solid.

[00303] A solution of 4-chloro-1,5-dimethyl-indole-2-carbonyl chloride (1.20 g, 4.96 mmol) in dichloromethane (20 mL) was added into a mixture of ammonium hydroxide (18.2 g, 519 mmol) in tetrahydrofuran (20 mL) and the reaction mixture was stirred at 15 °C for 15 min. On completion, the reaction mixture was concentrated *in vacuo* to remove dichloromethane and tetrahydrofuran. The residue was filtered and the filter cake was washed with water (3 x 10 mL). The white solid was dried *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (brs, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 1H), 7.16 (s, 1H), 4.05 (s, 3H), 2.44 (s, 3H).

4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide (Intermediate AB)

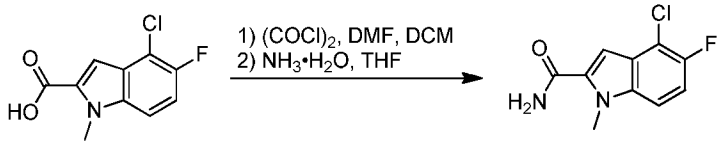


E AB

[00304] To a solution of 4,5-dichloro-1-methyl-1*H*-indole-2-carboxylic acid (1.00 g, 1.00 equiv., Intermediate E) in anhydrous dichloromethane (50 mL) was added anhydrous *N,N*-dimethylformamide (20 uL) and oxalyl chloride (780 mg, 6.15 mmol) at 0 °C. The mixture was warmed to 15 °C and stirred for 1 hr. On completion, the mixture was concentrated *in vacuo* to give 4,5-dichloro-1-methyl-1*H*- indole-2-carbonyl chloride (1.30 g, crude) as a yellow solid. The crude product was used in the next step directly.

[00305] To a solution of ammonium hydroxide (18.2 g, 519 mmol) in tetrahydrofuran (20 mL) was added 4,5-dichloro-1-methyl-1*H*-indole-2-carbonyl chloride (1.30 g, crude) in anhydrous dichloromethane (20 mL). The reaction mixture was stirred at 15 °C for 15 min. On completion, the mixture was concentrated *in vacuo*. The solid was washed with water (10 mL) 3 times and filtered. The filter cake was evaporated to dryness to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.17 (brs, 1H), 7.60 (d, J = 13.6 Hz, 1H), 7.56 (s, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.23 (s, 1H), 4.02 (s, 3H).

4-Chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide (Intermediate AC)

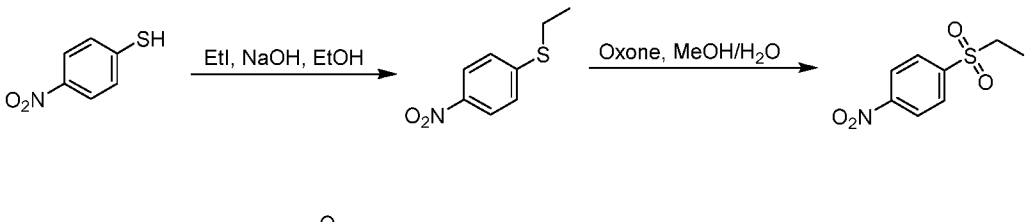


F AC

[00306] To a solution of 4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxylic acid (1.00 g, 4.39 mmol) in anhydrous dichloromethane (10.0 mL) was added anhydrous *N,N*-dimethylformamide (20.0 µL) and oxalyl chloride (1.45 g, 11.4 mmol) dropwise at 0 °C. The reaction mixture was warmed to 15 °C and stirred for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (1.10 g, crude) as a yellow solid. The crude product was used in the next step directly.

[00307] To a solution of ammonium hydroxide (5 mL) in anhydrous tetrahydrofuran (50.0 mL) was added 4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carbonyl chloride (1.10 g, crude) in anhydrous dichloromethane (10.0 mL). The mixture was stirred at 15 °C for 1 hour. On completion, the mixture was concentrated. The residue was triturated with water / methanol (60 mL / 10 mL) to give the title compound. LCMS: (ES+) m/z (M+H)+ = 226.8, tR = 0.637. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.14 (s, 1H), 7.60 - 7.54 (m, 2H), 7.31 (t, J = 9.2 Hz, 1H), 7.24 (s, 1H), 4.02 (s, 3H).

4-(Ethylsulfonyl)aniline (Intermediate AD)



AD

Step 1 - Ethyl(4-nitrophenyl)sulfane

[00308] To a solution of 4-nitrobenzenethiol (2.00 g, 12.9 mmol) in ethanol (20.0 mL) was added sodium hydroxide (773 mg, 19.3 mmol). After stirred for 30 min, iodoethane (4.02 g, 25.8 mmol) was added. The reaction mixture was stirred at 15 °C for 2 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated. The residue was dissolved in

ethyl acetate (40 mL), washed with water (2 x 20 mL) and brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude was purified by silica gel chromatography (petroleum ether: ethyl acetate = 20:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.13 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H), 3.06 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.6 Hz, 3H).

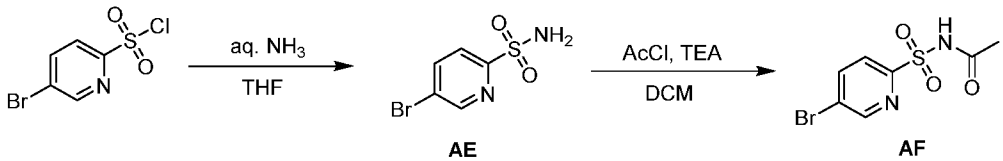
Step 2 - 1-(Ethylsulfonyl)-4-nitrobenzene

[00309] To a solution of ethyl(4-nitrophenyl)sulfane (800 mg, 4.37 mmol) in methanol (16.0 mL) was added a solution of Oxone (3.32 g, 21.9 mmol) in water (16.0 mL). The reaction mixture was stirred at 15 °C for 4 hrs. On completion, saturated sodium sulfite (20 mL) solution was added to the mixture. The organic solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (40 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.43 (d, *J* = 8.8 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 3.22 - 3.13 (m, 2H), 1.33 (t, *J* = 7.6 Hz, 3H).

Step 3 - 4-(Ethylsulfonyl)aniline (Intermediate AD)

[00310] To a solution of 1-(ethylsulfonyl)-4-nitrobenzene (600 mg, 2.79 mmol) in methanol (30.0 mL) was added Pd/C (200 mg, 10%). The mixture was stirred at 15 °C for 16 hrs under hydrogen gas atmosphere with a balloon. On completion, the mixture was filtered and the filtrate was concentrated to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 4.22 (brs, 2H), 3.12 - 3.01 (m, 2H), 1.26 (t, *J* = 7.6 Hz, 3H).

5-Bromopyridine-2-sulfonamide (Intermediate AE) and *N*-[(5-Bromo-2-pyridyl)sulfonyl]-acetamide (Intermediate AF)



Step 1 - 5-Bromopyridine-2-sulfonamide

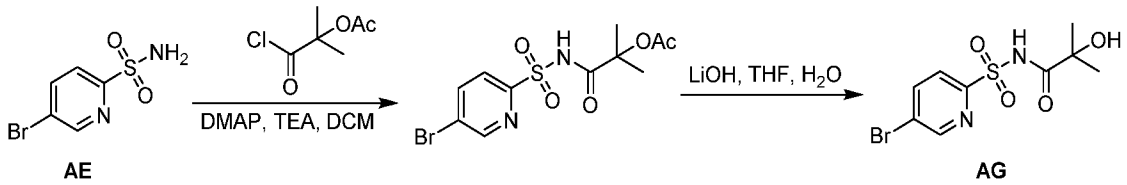
[00311] To a solution of 5-bromopyridine-2-sulfonyl chloride (4.00 g, 15.6 mmol) in tetrahydrofuran (40 mL) was added a solution of ammonium hydroxide (18.2 g, 519 mmol) in tetrahydrofuran (10 mL). The reaction mixture was stirred at 10 °C for 4 hrs. On completion, the

reaction mixture was concentrated *in vacuo* to remove the tetrahydrofuran, during which a fine white solid was formed. The mixture was filtered and the filter cake was washed with ice water and dried *in vacuo* to give the title compound.

Step 2 - *N*-[(5-Bromo-2-pyridyl)sulfonyl]acetamide (Intermediate AF)

[00312] To a solution of 5-bromopyridine-2-sulfonamide (200 mg, 0.843 mmol) in anhydrous dichloromethane (15 mL) was added triethylamine (170 mg, 1.69 mmol). Then acetyl chloride (99.3 mg, 1.27 mmol) was added dropwise. The reaction mixture was stirred at 10 °C for 16 hours. On completion, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 x 25 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound (190 mg, crude) as a yellow solid which was used in the next step without further purification. LCMS: (ES^+) m/z $(M+H)^+$ = 279.0, tR = 0.373.

N-[(5-Bromo-2-pyridyl)sulfonyl]-2-hydroxy-2-methyl-propanamide (Intermediate AG)



Step 1 - [2-[(5-Bromo-2-pyridyl)sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate

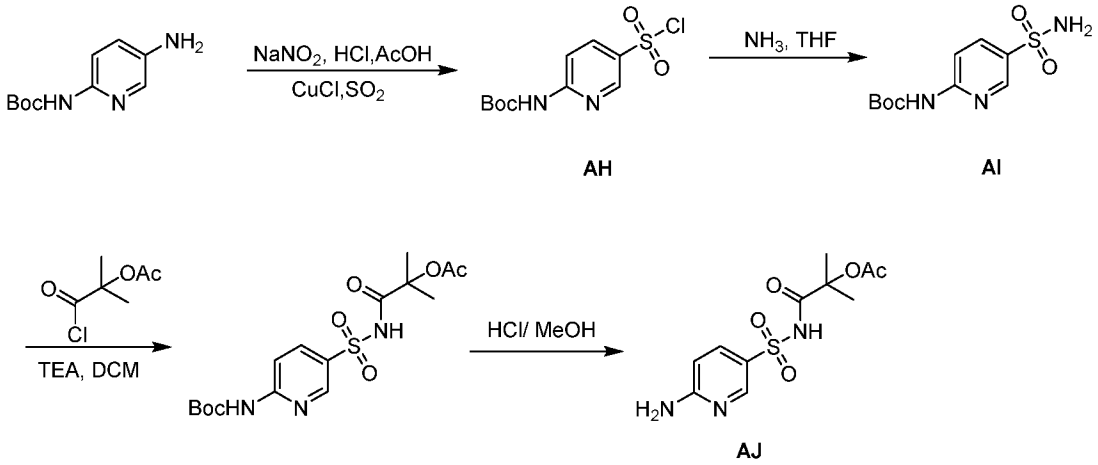
[00313] To a solution of 5-bromopyridine-2-sulfonamide (800 mg, 3.37 mmol) in anhydrous dichloromethane (60 mL) was added *N*,*N*-dimethylpyridin-4-amine (205 mg, 1.69 mmol), triethylamine (1.02 g, 10.1 mmol) and (2-chloro-1,1-dimethyl-2-oxo-ethyl) acetate (832 mg, 5.06 mmol) was added. The reaction mixture was stirred at 10 °C for 15 hours. On completion, the reaction mixture was quenched with water (20 mL) and was extracted with dichloromethane (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give a residue. The residue was purified by silica gel column chromatography (dichloromethane / methane = 10:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 367.0, tR= 0.796.

Step 2 - *N*-[(5-Bromo-2-pyridyl)sulfonyl]-2-hydroxy-2-methyl-propanamide (Intermediate AG)

[00314] To a solution of [2-[(5-bromo-2-pyridyl)sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate (500 mg, 1.37 mmol) in tetrahydrofuran (8 mL) and water (2 mL) was added lithium hydroxide (131 mg, 5.48 mmol). The mixture was stirred at 15 °C for 16 hrs. On completion, the

reaction mixture was acidified with 4 M hydrochloric acid to pH = 7. Then the reaction mixture was concentrated *in vacuo* give the title compound. The crude product was used in the next step without further purification. LCMS: (ES^+) m/z $(M+H)^+$ = 323.0, tR= 0.717.

<u>*Tert*-butyl *N*-(5-chlorosulfonyl-2-pyridyl)carbamate (Intermediate AH), *Tert*-butyl *N*-(5-sulfamoyl-2-pyridyl)carbamate (Intermediate AI), and [2-[(6-Amino-3-pyridyl)sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate (Intermediate AJ)</u>



<u>Step 1 - *Tert*-butyl *N*-(5-chlorosulfonyl-2-pyridyl)carbamate (Intermediate AH)</u>

[00315] To a solution of sodium nitrite (2.77 g, 40.1 mmol) in a mixture of water (20 mL) and acetonitrile (120 mL) at 0 °C was added concentrated hydrochloric acid (18.3 g, 502 mmol) dropwise, keeping the internal temperature between 0-10 °C. After the resulting reaction mixture was stirred at 0 °C for 30 min, a solution of *tert*-butyl *N*-(5-amino-2-pyridyl)carbamate (7.00 g, 33.4 mmol) was added in portions during a period of 30 min. The reaction mixture was then stirred at 0 °C for 30 min followed by addition of acetic acid (25 mL), cuprous chloride (33.1 mg, 0.334 mmol) and copper chloride (2.25 g, 16.7 mmol). Sulfur dioxide (15 psi) gas was then bubbled through the resulting mixture for 5 min. After the reaction mixture was stirred at 0 °C for 30 min, it was poured into ice water and filtered and the filter cake was washed with water and dried *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 3:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 293, tR= 1.509.

<u>Step 2 - *Tert*-butyl *N*-(5-sulfamoyl-2-pyridyl)carbamate (Intermediate AI)</u>

[00316] To a solution of ammonium hydroxide (30.3 g, 866 mmol) in THF (10 mL) was added a solution of *tert*-butyl *N*-(5-chlorosulfonyl-2-pyridyl)carbamate (1.50 g, 5.12 mmol) in anhydrous tetrahydrofuran (20 mL) dropwise. The resulting mixture was stirred at 15 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran, then the resulting mixture was filtered and the filter cake was purified by silica gel chromatography (petroleum ether:ethyl acetate =1:1) to give the title compound. ^{1}H NMR (300MHz, DMSO-d_6) δ = 10.31 (s, 1H), 8.61 (s, 1H), 8.11 (d, J = 8.9 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.44 (s, 2H), 1.49 (s, 9H).

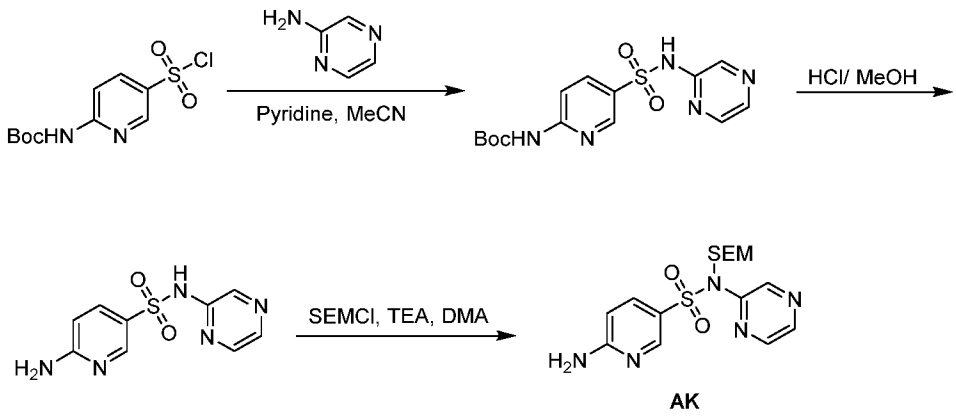
Step 3 - [2-[[6-(*Tert*-butoxycarbonylamino)-3-pyridyl]sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate

[00317] To a solution of *tert*-butyl *N*-(5-sulfamoyl-2-pyridyl)carbamate (300 mg, 1.10 mmol), *N,N*-dimethyl pyridin-4-amine (26.8 mg, 0.220 mmol) and triethylamine (445 mg, 4.40 mmol) in dichloromethane (20.0 mL) was added dropwise (2-chloro-1,1-dimethyl-2-oxo-ethyl) acetate (217 mg, 1.32 mmol) and the reaction mixture was stirred at 15 °C for 0.5 hr. After removal of the solvent *in vacuo*, 30 mL water was added and the aqueous phase was extracted with dichloromethane (3 x 30 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The resulting solid was purified by silica gel chromatography (dichloromethane:methanol = 10:1) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 402, tR= 0.739.

Step 4 - [2-[(6-Amino-3-pyridyl)sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate (Intermediate AJ)

[00318] To a solution of [2-[[6-(*tert*-butoxycarbonylamino)-3-pyridyl]sulfonylamino]-1,1-dimethyl-2-oxo-ethyl] acetate (400 mg, 996 µmol) in methanol (10 mL) was added hydrogen chloride / methanol (4 M, 10 mL) and the reaction mixture was stirred at 40 °C for 2 hrs. After removal of the solvent *in vacuo*, the title compound (360 mg, crude) was obtained as white solid. LCMS: (ES$^+$) m/z $(M+H)^+$ = 302, tR= 0.562.

6-Amino-*N*-pyrazin-2-yl-*N*-(2-trimethylsilylethoxymethyl)pyridine-3-sulfonamide (Intermediate AK)



Step 1 - *Tert*-butyl *N*-[5-(pyrazin-2-ylsulfamoyl)-2-pyridyl]carbamate

[00319] To a solution of *tert*-butyl *N*-(5-chlorosulfonyl-2-pyridyl)carbamate (1.50 g, 3.07 mmol) in pyridine (20 mL) and acetonitrile (10 mL) was added pyrazin-2-amine (350 mg, 3.68 mmol) and the reaction mixture was stirred at 10 °C for 6 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a black brown solid. The solid was triturated with methanol (100 mL), filtrated and the filter cake was washed with methanol. Then the filter cake was dried *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 352, tR = 1.033. ^1H NMR (400MHz, DMSO-d_6) = 11.65 (br. s., 1H), 10.44 (s, 1H), 10.02 (s, 1H), 8.76 (d, *J* = 2.5 Hz, 1H), 8.33 (s, 1H), 8.27 - 8.21 (m, 2H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.85 - 7.82 (m, 1H), 1.47 (s, 9H).

Step 2 - 6-amino-*N*-pyrazin-2-yl-pyridine-3-sulfonamide

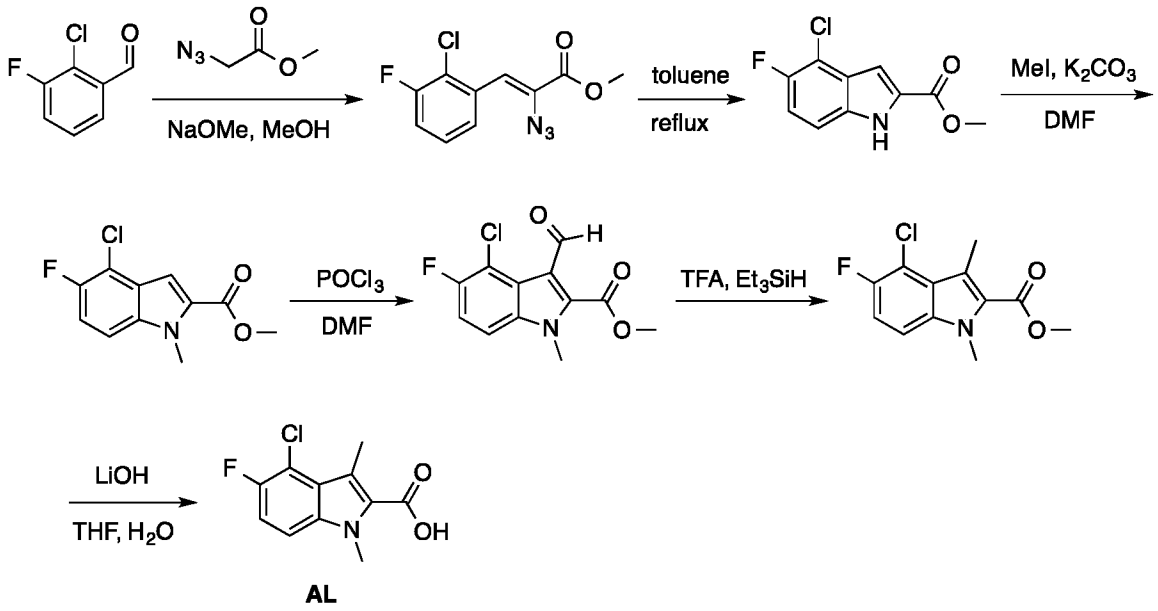
[00320] To a solution of *tert*-butyl *N*-[5-(pyrazin-2-ylsulfamoyl)-2-pyridyl]carbamate (800 mg, 2.28 mmol) in methanol (20 mL) was added hydrogen chloride / methanol (4 M, 20 mL) and the reaction mixture was stirred at 50 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (700 mg, crude) as yellow solid. LCMS: (ES^+) m/z $(M+H)^+$ = 252, tR = 0.121.

Step 3 - 6-Amino-*N*-pyrazin-2-yl-*N*-(2-trimethylsilylethoxymethyl)pyridine-3-sulfonamide (Intermediate AK)

[00321] To a solution of 6-amino-*N*-pyrazin-2-yl-pyridine-3-sulfonamide (600 mg, 2.09 mmol) and triethylamine (1.06 g, 10.4 mmol) in *N,N*-dimethylacetamide (15 mL) was added 2-(trimethylsilyl)ethoxymethyl chloride (418 mg, 2.51 mmol) dropwise and the reaction mixture was stirred at 10 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to

give a crude product, which was purified by silica gel chromatography (dichloromethane:methanol = 50:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 382, tR = 1.862.

4-Chloro-5-fluoro-1,3-dimethyl-1*H*-indole-2-carboxylic acid (Intermediate AL)



AL

Step 1 - Methyl (Z)-2-azido-3-(2-chloro-3-fluoro-phenyl)prop-2-enoate

[00322] To a solution of sodium methoxide (17.4 g, 322 mmol) in anhydrous methanol (200 mL) was added 2-chloro-3-fluoro-benzaldehyde (17.0 g, 107 mmol) in several portions at -20 °C under nitrogen, then methyl 2-azidoacetate (41.5 g, 322 mmol) was added to the solution dropwise at -20 °C under nitrogen. The reaction was stirred at 20 °C for 12 hrs. On completion, the mixture was poured into water (500 mL) and extracted with ethyl acetate (3 × 200 mL). The combined organic phase was washed with saturated brine (3 × 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. ^1H NMR (400MHz, $CDCl_3$) δ = 8.02 (d, *J* = 8.2 Hz, 1H), 7.35 - 7.26 (m, 2H), 7.15 (dt, *J* = 1.4, 8.4 Hz, 1H), 3.97 (s, 3H).

Step 2 - Methyl 4-chloro-5-fluoro-1*H*-indole-2-carboxylate

[00323] Methyl (Z)-2-azido-3-(2-chloro-3-fluoro-phenyl)prop-2-enoate (15.0 g, 58.6 mmol) in toluene (200 mL) was stirred at reflux for 12 hrs. On completion, the mixture was

concentrated *in vacuo*. The residue purified by silica gel chromatography (petroleum ether:ethyl acetate = 100:1 to 1:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 9.05 (br. s., 1H), 7.32 - 7.28 (m, 1H), 7.27 – 7.14 (m, 1H), 3.98 (s, 3H).

Step 3 - Methyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate

[00324] To a solution of methyl 4-chloro-5-fluoro-*1H*-indole-2-carboxylate (850 mg, 3.73 mmol) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (1.55 g, 11.2 mmol) and methyl iodide (2.12 g, 14.9 mmol) in one portion at 15 °C under nitrogen. The mixture was stirred at 50 °C for 12 hrs. On completion, the residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic phase was washed with brine (3 × 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.68 (dd, *J* = 3.8, 9.2 Hz, 1H), 7.42 (t, *J* = 9.5 Hz, 1H), 7.23 (s, 1H), 4.05 (s, 3H), 3.89 (s, 3H).

Step 4 - Methyl 4-chloro-5-fluoro-3-formyl-1-methyl-1*H*-indole-2-carboxylate

[00325] To anhydrous *N,N*-dimethylformamide (422 mg, 5.77 mmol) was added phosphorus oxychloride (237 mg, 1.55 mmol) at 0 °C, then methyl 4-chloro-5-fluoro-1-methyl-indole-2-carboxylate (250 mg, 1.03 mmol) in *N,N*-dimethylformamide (5 mL) was added. The reaction mixture was stirred at 20 °C for 1 h, then at 90 °C for 4 hrs. On completion, the mixture was quenched with water (20 mL), basified with aqueous sodium hydroxide (2 M), extracted with ethyl acetate (3 x 10 mL), the combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo*. The residue was purified by silica gel chromatography (dichloromethane:ethyl acetate = 80:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 270, tR = 0.788.

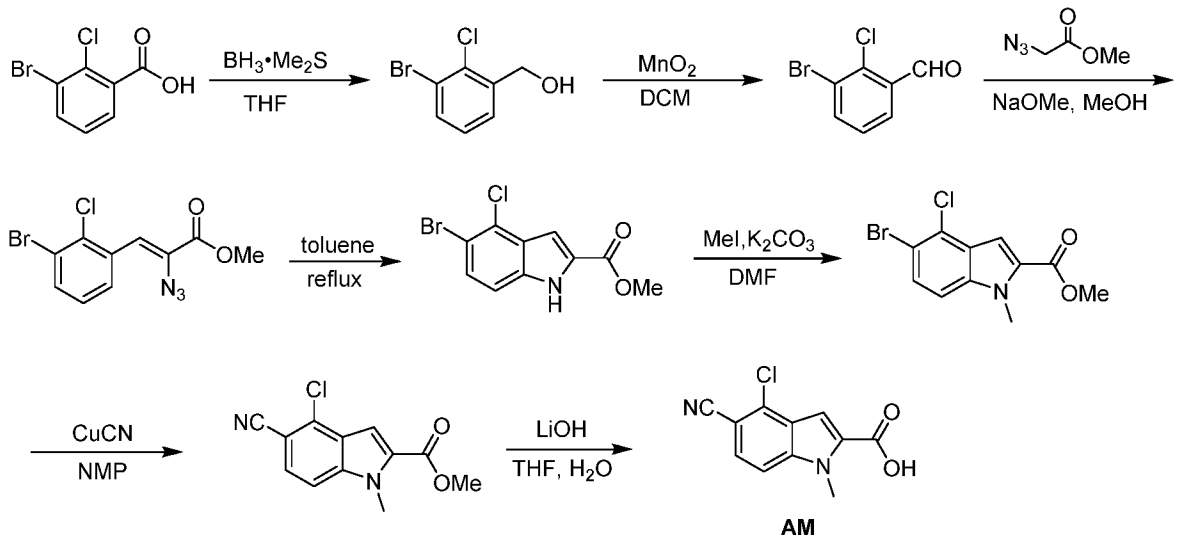
Step 5 - Methyl 4-chloro-5-fluoro-1,3-dimethyl-1*H*-indole-2-carboxylate

[00326] To a solution of methyl 4-chloro-5-fluoro-3-formyl-1-methyl-1*H*-indole-2-carboxylate (71.0 mg, 0.263 mmol) in trifluoroacetic acid (2 mL) was added triethylsilane (122 mg, 1.05 mmol). The reaction mixture was stirred at 18 °C for 2 hrs. On completion, the mixture was quenched by saturated aqueous sodium carbonate and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 256, tR = 0.937.

Step 6 - 4-Chloro-5-fluoro-1,3-dimethyl-1*H*-indole-2-carboxylic acid (Intermediate AL)

[00327] To a solution of methyl 4-chloro-5-fluoro-1,3-dimethyl-1*H*-indole-2-carboxylate (60.0 mg, 0.235 mmol) in tetrahydrofuran (10 mL) and water (2 mL) was added lithium hydroxide (56.0 mg, 2.35 mmol). The reaction mixture was stirred at 30 °C for 48 hrs. On completion, the mixture was concentrated to remove the organic solvent; the aqueous phase was acidified by aqueous hydrochloride (2 mL, 1 M). The solid was collected by filtration and dried *in vacuo* to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 242, tR= 0.826.

4-Chloro-5-cyano-1-methyl-indole-2-carboxylic acid (Intermediate AM)



AM

Step 1 - (3-Bromo-2-chloro-phenyl)methanol

[00328] A solution of 3-bromo-2-chloro-benzoic acid (5.00 g, 20.6 mmol) in anhydrous tetrahydrofuran (100 mL) was heated to reflux at 70 °C under a nitrogen atmosphere. Then BH_3-Me_2S (10 M, 2.47 mL) was added dropwise to the reaction mixture. The reaction mixture was stirred at 70 °C for 12 hrs. On completion, the reaction mixture was quenched with methanol (10 mL), washed with water (100 mL) and extracted with ethyl acetate (3 x 300 mL), the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. The crude product was used in the next step directly. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.57 (d, *J*=7.8 Hz, 1H), 7.46 (d, *J*=7.5 Hz, 1H), 7.16 (t, *J*=7.8 Hz, 1H), 4.79 (s, 2H), 2.23 (br. s., 1H)

Step 2 - 3-Bromo-2-chloro-benzaldehyde

[00329] To a solution of (3-bromo-2-chloro-phenyl)methanol (1.00 g, 4.52 mmol) in dichloromethane (10 mL) was added manganese dioxide (3.14 g, 36.2 mmol) with stirring at 25 °C under a nitrogen atmosphere for 48 hrs. On completion, the reaction mixture was filtered. The filter cake was washed with dichloromethane (5 mL) and then filtered again. The combined filtrates were concentrated *in vacuo* to give the title compound. The crude product was used in the next step directly. ^{1}H NMR (400MHz, $CDCl_3$) δ = 10.40 (s, 1H), 7.89 - 7.72 (m, 2H), 7.25 - 7.18 (m, 1H)

Step 3 - Methyl (Z)-2-azido-3-(3-bromo-2-chloro-phenyl)prop-2-enoate

[00330] To a solution of sodium methoxide (740 mg, 13.7 mmol) in methanol (10 mL) was added methyl 2-azidoacetate (1.86 g, 13.7 mmol) and 3-bromo-2-chloro-benzaldehyde (1.00 g, 4.56 mmol) in methanol (10 mL) dropwise at -20 °C under a nitrogen atmosphere. After, the mixture was stirred at -20 °C for 2 hrs; it was warmed up to 25 °C under a nitrogen atmosphere for 12 hrs. On completion, the suspension was poured onto ice water and the azido derivative was collected by filtration and washed with cold water. The solid was dissolved in dichloromethane (200 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residual was purified by silica gel chromatography [petroleum ether: ethyl acetate = 10:1] to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.09 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.62 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.29 (s, 1H), 7.19 (t, *J* = 8.0 Hz, 1H), 3.97 (s, 3H).

Step 4 - methyl 5-bromo-4-chloro-1*H*-indole-2-carboxylate

[00331] A solution of methyl (Z)-2-azido-3-(3-bromo-2-chloro-phenyl)prop-2-enoate (880 mg, 2.78 mmol) in toluene (10 mL) was heated at 120 °C under a nitrogen atmosphere. The reaction was stirred at 120 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The residue was then triturated with toluene (2 mL) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.50 (br. s., 1H), 7.57 - 7.50 (m, 1H), 7.37 (d, *J*=8.8 Hz, 1H), 7.11 (br. s., 1H), 3.89 (s, 3H)

Step 5 - Methyl 5-bromo-4-chloro-1-methyl-indole-2-carboxylate

[00332] To a solution of methyl 5-bromo-4-chloro-1*H*-indole-2-carboxylate (360 mg, 1.25 mmol) and potassium carbonate (518 mg, 3.75 mmol) in *N,N*-dimethylformamide (10 mL) was added dropwise methyl iodide (532 mg, 3.75 mmol). The reaction was stirred at 60 °C under a

nitrogen atmosphere for 24 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound. The crude product was used for the next step without purification. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.54 (d, *J*=8.8 Hz, 1H), 7.44 (s, 1H), 7.37 (d, *J*=8.5 Hz, 1H), 4.11 (s, 3H), 4.00 - 3.92 (m, 3H)

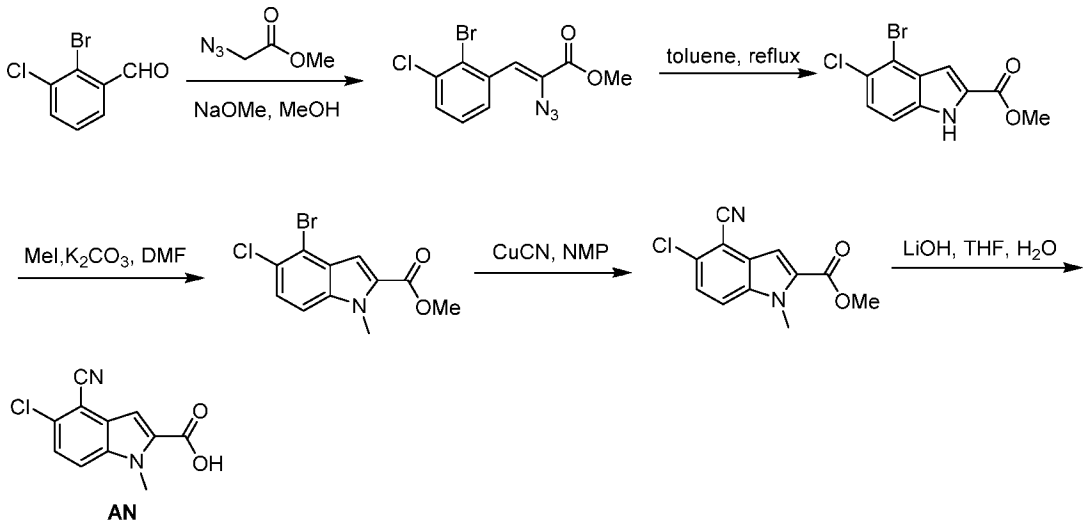
Step 6 - Methyl 4-chloro-5-cyano-1-methyl-indole-2-carboxylate

[00333] To a solution of methyl 5-bromo-4-chloro-1-methyl-indole-2-carboxylate (500 mg, 1.65 mmol) in 1-methylpyrrolidin-2-one (5 mL) was added cuprous cyanide (443 mg, 4.95 mmol) at 25 °C. The reaction mixture was stirred at 120 °C for 12 hrs. On completion, the reaction mixture was cooled to 25 °C, poured into water (100 mL), and extracted with ethyl acetate (3 x 100 mL). The organic layers were combined and washed with brine (10 mL), then concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 249.0, tR = 2.143. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.59 - 7.52 (m, 1H), 7.46 (s, 1H), 7.41 - 7.36 (m, 1H), 4.13 (s, 3H), 3.97 (s, 3H)

Step 7 - 4-Chloro-5-cyano-1-methyl-indole-2-carboxylic acid (Intermediate AM)

[00334] To a solution of methyl 4-chloro-5-cyano-1-methyl-indole-2-carboxylate (200 mg, 0.806 mmol) in tetrahydrofuran (3 mL) and water (1 mL) was added lithium hydroxide (41.0 mg, 0.965 mmol) at 15 °C. Then, the reaction mixture was stirred at 15 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo*, diluted with water (5 mL), and washed with ethyl acetate (3 x 5 mL). Then, the combined aqueous layer was acidified with HCl (1 M, 5mL) to pH = 1, filtered and dried *in vacuo* to give the title compound) which was used without further purification. LCMS: (ES$^+$) m/z $(M+1)^+$ = 235.1, tR = 0.734.

5-Chloro-4-cyano-1-methyl-indole-2-carboxylic acid (Intermediate AN)



AN

Step 1 - Methyl-2-azido-3-(2-bromo-3-chloro-phenyl)prop-2-enoate

[00335] To a solution of sodium methoxide (665 mg, 12.3 mmol) in anhydrous methanol (10 mL) was added 2-bromo-3-chloro-benzaldehyde (900 mg, 4.10 mmol) in several portions at -20 °C under nitrogen, then methyl 2-azidoacetate (1.59 g, 12.3 mmol) was added to the solution dropwise at -20 °C under nitrogen. The mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic phase was washed with saturated brine (3 x 200 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound (600 mg, 46% yield) as a yellow solid. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.93 (d, *J* = 7.8 Hz, 1H), 7.45 - 7.41 (m, 1H), 7.32 - 7.28 (m, 1H), 7.24 (s, 1H), 3.96 (s, 3H).

Step 2 - Methyl 4-bromo-5-chloro-1*H*-indole-2-carboxylate

[00336] Methyl-2-azido-3-(2-bromo-3-chloro-phenyl)prop-2-enoate (80.0 mg, 0.253 mmol) in toluene (20 mL) was stirred at 80 °C for 12 hrs. On completion, the mixture was concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 9.05 (br. s., 1H), 7.41 - 7.31 (m, 2H), 7.26 (dd, *J* = 0.9, 2.4 Hz, 1H), 3.98 (s, 3H).

Step 3 - Methyl 4-bromo-5-chloro-1-methyl-indole-2-carboxylate

[00337] To a solution of methyl 4-bromo-5-chloro-1*H*-indole-2-carboxylate (50.0 mg, 0.173 mmol) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (71.9 mg, 0.520 mmol) and methyl iodide (73.8 mg, 0.519 mmol) in one portion at 15 °C under nitrogen. The mixture was stirred at 50 °C for 12 hrs. On completion, the residue was poured into water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.73 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.14 (s, 1H), 4.05 (s, 3H), 3.89 (s, 3H).

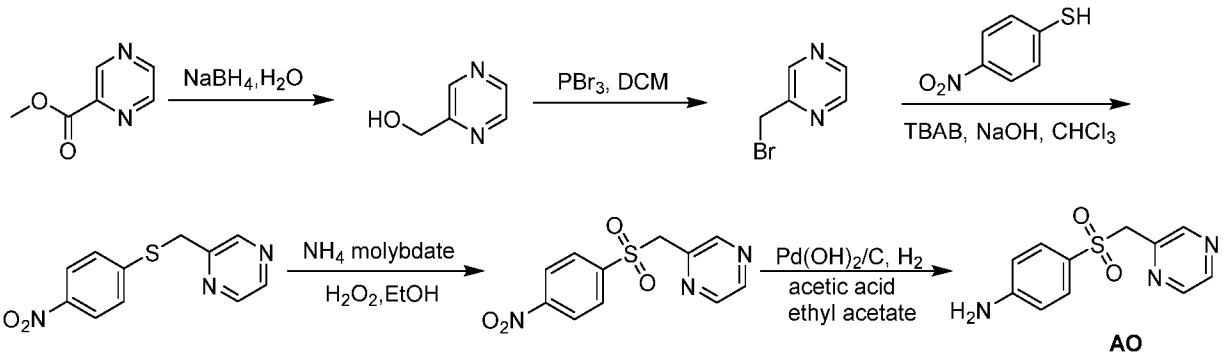
Step 4 - Methyl 5-chloro-4-cyano-1-methyl-indole-2-carboxylate

[00338] To a solution of methyl 4-bromo-5-chloro-1-methyl-indole-2-carboxylate (10.0 mg, 33.1 μmol) in 1-methyl-2-pyrrolidinone (NMP) (3 mL) was added copper cyanide (5.92 mg, 0.0661 mmol) at 15 °C. The reaction was heated at 120 °C for 12 hrs. On completion, ethyl acetate (10 mL) and 5% sodium carbonate (10 mL) were added. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.58 (dd, *J* = 0.8, 9.0 Hz, 1H), 7.46 - 7.40 (m, 2H), 4.14 (s, 3H), 3.98 (s, 3H).

Step 5 - 5-Chloro-4-cyano-1-methyl-indole-2-carboxylic acid (Intermediate AN)

[00339] To a solution of methyl 5-chloro-4-cyano-1-methyl-indole-2-carboxylate (190 mg, 0.764 mmol) in a mixture of tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide (27.5 mg, 1.15 mmol) in one portion at 15 °C, the mixture was stirred at 15 °C for 12 hrs. The mixture was concentrated *in vacuo*. The residue was adjusted to pH = 0.3 with 3 M HCl (3 mL). The resulting solid was filtered and dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.05 (d, *J*=9.0 Hz, 1H), 7.59 (d, *J*=9.0 Hz, 1H), 7.16 (s, 1H), 4.10 (s, 3H).

4-(Pyrazin-2-ylmethylsulfonyl)aniline (Intermediate AO)



Step 1 - Pyrazin-2-ylmethanol

[00340] To a solution of methyl pyrazine-2-carboxylate (15.0 g, 108 mmol) in water (250 mL) was added sodium borohydride (20.5 g, 543 mmol) in one portion and the reaction mixture was stirred vigorously at 15 °C for 16 hrs. On completion, methanol (100 mL) was added dropwise into the reaction mixture. After stirring at 15 °C for 0.5 hr, the mixture was concentrated *in vacuo* to remove methanol and the aqueous phase was extracted with dichloromethane (6 x 80 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound.

Step 2 - 2-(Bromomethyl)pyrazine

[00341] To a solution of pyrazin-2-ylmethanol (750 mg, 6.81 mmol) in dichloromethane (10 mL) was added phosphorus tribromide (2.77 g, 10.2 mmol) dropwise and the reaction mixture was stirred at 15 °C for 16 hrs. On completion, methanol (20 mL) was added to the reaction mixture. Then the mixture was concentrated *in vacuo* and the resulting solid was purified by silica gel chromatography (dichloromethane:methanol = 50:1) to give the title compound. ^{1}H NMR (300MHz, CD_3OD) δ = 8.86 (s, 1H), 8.74 (br. s., 1H), 8.63 (d, *J* = 2.6 Hz, 1H), 4.72 (s, 2H).

Step 3 - 2-[(4-Nitrophenyl)sulfanylmethyl]pyrazine

[00342] To a solution of 4-nitrobenzenethiol (1.08 g, 6.94 mmol), 2-(bromomethyl)pyrazine (2.00 g, 6.94 mmol) and tetrabutylammonium bromide (TBAB) (850 mg, 2.64 mmol) in chloroform (10 mL) was added aqueous sodium hydroxide (2 M, 3.47 mL) and the reaction mixture was stirred at 15 °C for 17 hrs. On completion, the reaction mixture was separated and

the organic phase was washed with water (50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (dichloromethane:methanol = 50:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.78 - 8.66 (m, 1H), 8.59 - 8.45 (m, 2H), 8.18 - 8.08 (m, 2H), 7.51 - 7.43 (m, 2H), 4.42 (s, 2H).

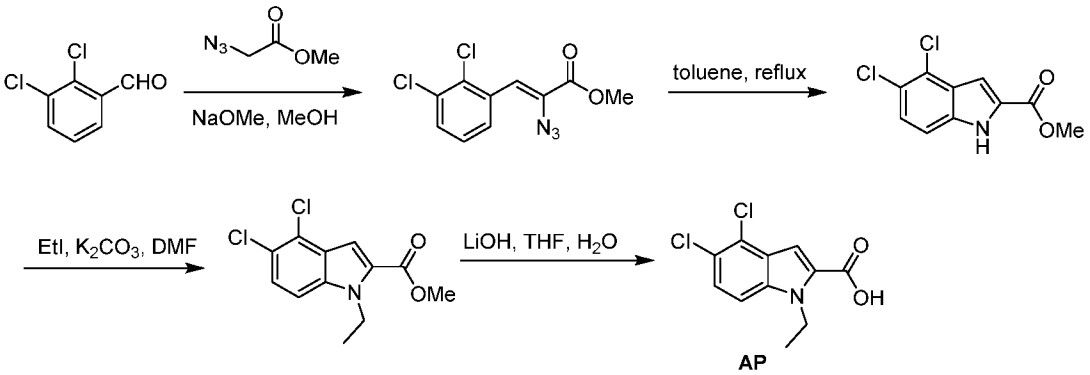
Step 4 - 2-[(4-Nitrophenyl)sulfanylmethyl]pyrazine

[00343] A solution of ammonium molybdate (282 mg, 0.242 mmol) in hydrogen peroxide (2.00 mL) was prepared at 0 °C. To a solution of 2-[(4-nitrophenyl)sulfanylmethyl]pyrazine (240 mg, 0.970 mmol) in ethanol (4 mL) was added dropwise the above mixture at 0 °C. Then the reaction mixture was warmed to 15 °C and stirred for 16 hrs. On completion, aqueous saturated sodium sulfite solution (20 mL) was added into the reaction mixture. After stirring for 10 min, the mixture was extracted with dichloromethane (2 x 80 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 280.1, tR = 0.764.

Step 5 - 4-(Pyrazin-2-ylmethylsulfonyl)aniline (Intermediate AO)

[00344] To a solution of 2-[(4-nitrophenyl)sulfonylmethyl]pyrazine (50.0 mg, 0.179 mmol) and acetic acid (10.5 mg, 0.179 mmol) in ethyl acetate (10 mL) was added Pearlman's catalyst (20.0 mg, 0.142 mmol) and the reaction mixture was stirred under hydrogen (50 psi) at 50 °C for 16 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 250, tR = 1.154.

4,5-Dichloro-1-ethyl-indole-2-carboxylic acid (Intermediate AP)



Step 1 - Methyl (Z)-2-azido-3-(2,3-dichlorophenyl)prop-2-enoate

[00345] To a solution of sodium methoxide (926 mg, 17.1 mmol) in methanol (10 mL) was added 2,3-dichlorobenzaldehyde (1.00 g, 5.71 mmol) and methyl 2-azidoacetate (1.84 g, 14.2 mmol) at -50 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 2 hours, then warmed to 15 °C and stirred for 14 hours. On completion, the suspension was poured into ice and the azido derivative was collected by filtration and washed with cold water. The filter cake was dried over *in vacuo* to give the crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 6:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97 (dd, *J* = 0.9, 8.0 Hz, 1H), 7.36 (dd, *J* = 1.3, 8.0 Hz, 1H), 7.19 - 7.15 (m, 1H), 3.88 (s, 3H).

Step 2 - Methyl 4,5-dichloro-1*H*-indole-2-carboxylate

[00346] Methyl (*Z*)-2-azido-3-(2,3-dichlorophenyl)prop-2-enoate (600 mg, 2.21 mmol) was dissolved in toluene (15 mL), the mixture was stirred at 120 °C for 16 hours. On completion, the reaction mixture was concentrated *in vacuo* to afford a residue. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 12:1 to 5:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.52 (br. s., 1H), 7.45 (s, 2H), 7.13 (d, *J*=1.9 Hz, 1H), 3.91 (s, 3H).

Step 3 - Methyl 4,5-dichloro-1-ethyl-indole-2-carboxylate

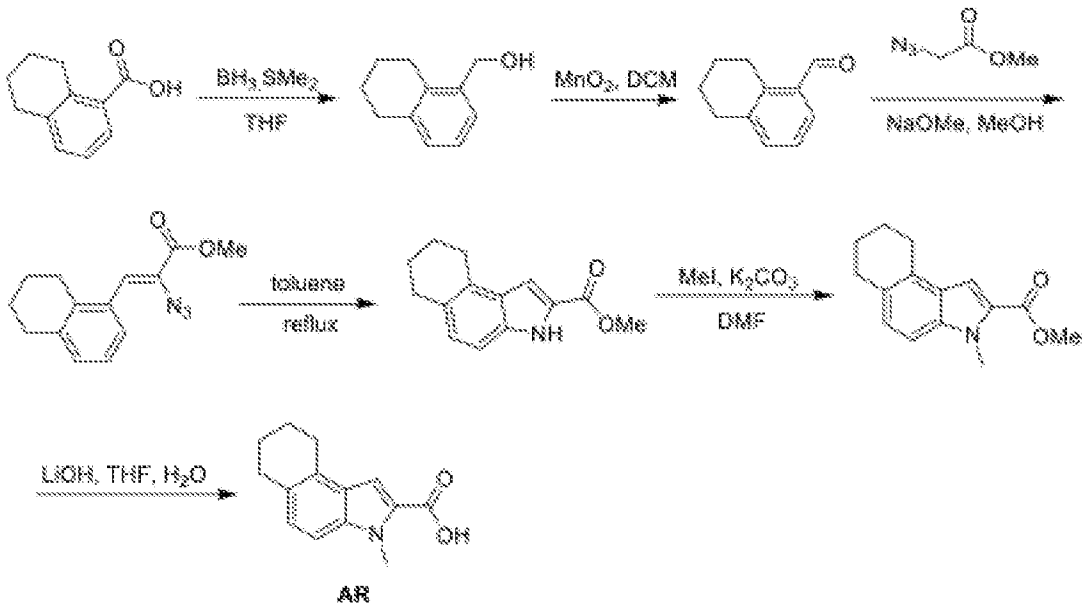
[00347] To a solution of methyl 4,5-dichloro-1*H*-indole-2-carboxylate (450 mg, 1.84 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (637 mg, 4.61 mmol) and iodoethane (1.15 g, 7.37 mmol). The resulting mixture was warmed to 60 °C and stirred for 16 hours. On completion, the reaction mixture was concentrated *in vacuo* to afford a residue. The residue was diluted with water (10 mL) and extracted with dichloromethane (10 mL × 3). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30 - 7.25 (m, 2H), 7.20 - 7.14 (m, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 3.86 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H).

Step 4 - 4,5-Dichloro-1-ethyl-indole-2-carboxylic acid (Intermediate AP)

[00348] To a solution of methyl 4,5-dichloro-1-ethyl-indole-2-carboxylate (440 mg, 1.62 mmol) in tetrahydrofuran (8 mL) and water (2 mL) was added lithium hydroxide (116 mg, 4.86 mmol). The resulting mixture was stirred at 15 °C for 16 hours. On completion, the reaction

mixture was concentrated *in vacuo* and the residue was acidified with 2 M hydrochloric acid to pH = 3, during which a fine precipitate was formed. The precipitate was filtered and the filter cake was washed with water and dried *in vacuo* to give the title compound (400 mg, crude) as a white solid which was used without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.68 (d, *J*=9.0 Hz, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.18 (s, 1H), 4.62 (q, *J*=6.8 Hz, 1H), 1.28 (t, *J*=7.0 Hz, 1H).

3-methyl-6,7,8,9-tetrahydrobenzo[*e*]indole-2-carboxylic acid (Intermediate AR)



Step 1 - Tetralin-5-ylmethanol

[00349] A solution of tetralin-5-carboxylic acid (10.0 g, 56.7 mmol) in anhydrous tetrahydrofuran (100 mL) was heated to reflux at 100 °C under a nitrogen atmosphere, to which borane dimethyl sulfide complex solution (10 M, 6.81 mL) was added dropwise. The mixture was stirred at 100 °C for 17 hrs. On completion, methanol (100 mL) and subsequently 2 M HCl (50 mL) was added. The mixture was stirred at 100 °C for 2 hrs. The mixture was washed with water (200 mL) and extracted with ethyl acetate (2 x 150 mL), the combined organic layer dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate=10:1) to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.17 (d, *J* = 7.5

Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.4 Hz, 1H), 4.99 (t, *J* = 5.4 Hz, 1H), 4.44 (d, *J* = 5.4 Hz, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.1 Hz, 2H), 1.83 - 1.63 (m, 4H).

Step 2 - Tetralin-5-carbaldehyde

[00350] To a solution of tetralin-5-ylmethanol (7.20 g, 44.3 mmol) in dichloromethane (100 mL) was added manganese dioxide (19.2 g, 221 mmol) under a nitrogen atmosphere. The mixture was stirred at 20 °C for 6 hrs. On completion, the mixture was filtered; the filtrate was concentrated *in vacuo* to afford a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.23 (s, 1H), 7.65 (dd, *J* = 1.1, 7.4 Hz, 1H), 7.41 - 7.35 (m, 1H), 7.35 - 7.29 (m, 1H), 3.15 (t, *J* = 6.1 Hz, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 1.79 - 1.69 (m, 4H).

Step 3 - Methyl (*Z*)-2-azido-3-tetralin-5-yl-prop-2-enoate

[00351] To a solution of sodium methoxide (3.24 g, 59.9 mmol) in methanol (100 mL) was added dropwise a solution of tetralin-5-carbaldehyde (3.20 g, 19.9 mmol) and methyl 2-azidoacetate (7.74 g, 66.7 mmol) in methanol (100 mL) at -50 °C. After the reaction mixture was stirred at -50 °C for 2 hr, it was warmed to 25 °C during 2 hrs. The reaction mixture was then stirred at RT for 14 hr. On completion, the mixture was poured into ice water (300 mL) and extracted with dichloromethane (3 x 200 mL), the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to afford the title compound (2.6 g, crude) as yellow solid.

Step 4 - Methyl 6,7,8,9-tetrahydro-3*H*-benzo[*e*]indole-2-carboxylate

[00352] A solution of methyl (*Z*)-2-azido-3-tetralin-5-yl-prop-2-enoate (2.40 g, 9.33 mmol) in toluene (5 mL) was stirred at 110 °C for 16 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.80 (br. s., 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.11 - 7.06 (m, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 2.87 (t, *J* = 5.7 Hz, 2H), 2.74 (t, *J* = 5.6 Hz, 2H), 1.87 - 1.73 (m, 4H).

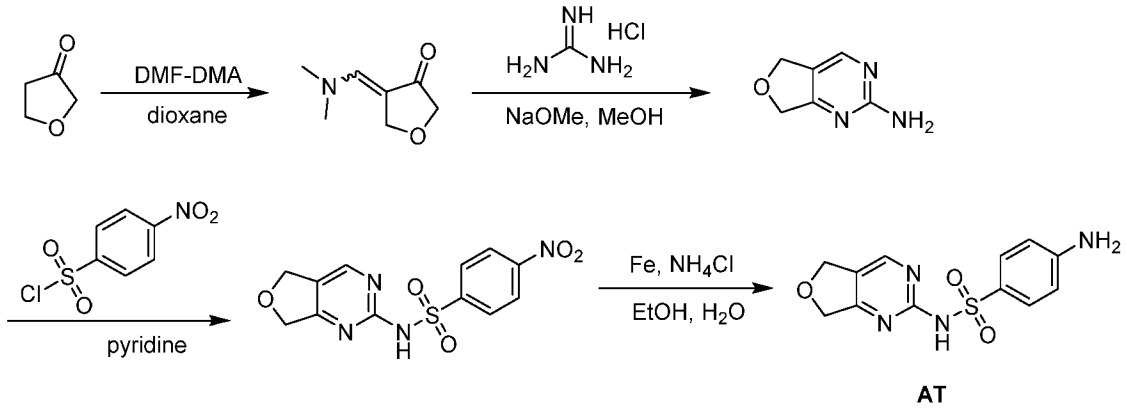
Step 5 - Methyl 3-Methyl-6,7,8,9-tetrahydrobenzo[*e*]indole-2-carboxylate

[00353] To a mixture of methyl 6,7,8,9-tetrahydro-3*H*-benzo[*e*]indole-2-carboxylate (1.10 g, 4.80 mmol) and potassium carbonate (2.65 g, 19.2 mmol) in *N*,*N*-dimethylformamide (15 mL) was added methyl iodide (4.09 g, 28.8 mmol) under a nitrogen atmosphere, the mixture was stirred at 60 °C for 16 hrs. On completion, the reaction mixture was filtered, the filtrate was extracted with ethyl acetate (3 x 20 mL), the combined organic layers were dried over anhydrous sodium sulfate, concentrated *in vacuo* to afford the title compound (crude).

Step 6 - 3-Methyl-6,7,8,9-tetrahydrobenzo[*e*]indole-2-carboxylic acid (Intermediate AR)

[00354] To a mixture of methyl 3-methyl-6,7,8,9-tetrahydrobenzo[*e*]indole-2-carboxylate (1.10 g, 4.52 mmol) in anhydrous tetrahydrofuran (10 mL) and water (5 mL) was added lithium hydroxide (324 mg, 13.5 mmol). The mixture was stirred at 25 °C for 16 hrs. On completion, the mixture was concentrated *in vacuo* to afford a residue which was washed with water, acidified with 4 M HCl, and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.80 (br. s., 1H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.14 (s, 1H), 7.01 (d, *J* = 8.5 Hz, 1H), 3.98 (s, 3H), 2.87 (t, *J* = 5.5 Hz, 2H), 2.76 (t, *J* = 5.5 Hz, 2H), 1.86 - 1.72 (m, 4H).

4-Amino-*N*-(5,7-dihydrofuro[3,4-*d*]pyrimidin-2-yl)benzenesulfonamide (Intermediate AT)



AT

Step 1 - 4-((Dimethylamino)methylene)dihydrofuran-3(2*H*)-one

[00355] To a solution of 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (48.4 g, 407 mmol) in dioxane (150 mL) was added tetrahydrofuran-3-one (7.00 g, 81.3 mmol). The reaction mixture was stirred at 110 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo*. The

residue was triturated with petroleum ether to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.15 (s, 1H), 5.00 (s, 2H), 3.86 (s, 2H), 3.01 (s, 6H).

Step 2 - 5,7-Dihydrofuro[3,4-*d*]pyrimidin-2-amine

[00356] To a solution of sodium methoxide (4.04 g, 74.8 mmol) in methanol (100 mL) was added guanidine hydrochloride (2.03 g, 21.3 mmol) and 4-(dimethylaminomethylene)tetrahydrofuran-3-one (3.00 g, 21.3 mmol). The reaction mixture was stirred at 65 °C for 2 hrs. On completion, the solid was collected by filtration, washed with water and brine, and dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.18 (s, 1H), 6.82 - 6.45 (m, 2H), 4.91 (s, 2H), 4.70 (s, 2H).

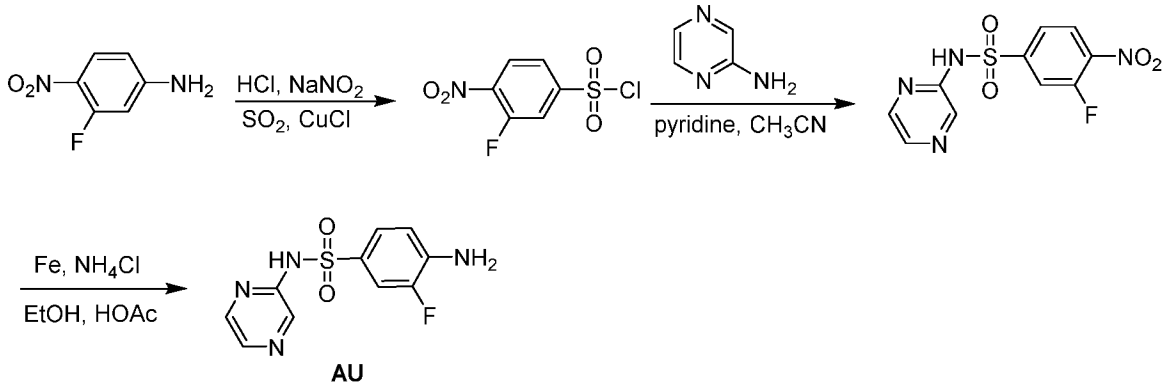
Step 3 - *N*-(5,7-dihydrofuro[3,4-d]pyrimidin-2-yl)-4-nitrobenzenesulfonamide

[00357] To a solution of 5,7-dihydrofuro[3,4-*d*]pyrimidin-2-amine (1.00 g, 7.29 mmol) in pyridine (10 mL) was added 4-nitrobenzene-1-sulfonyl chloride (1.62 g, 7.29 mmol, CAS#98-74-8). The reaction mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was concentrated; the residue was triturated with methanol to give the title compound.

Step 4 - 4-Amino-*N*-(5,7-dihydrofuro[3,4-*d*]pyrimidin-2-yl)benzenesulfonamide (Intermediate AT)

[00358] To a mixture of *N*-(5,7-dihydrofuro[3,4-*d*]pyrimidin-2-yl)-4-nitrobenzenesulfonamide (1.00 g, 3.10 mmol) and iron (1.13 g, 20.2 mmol) in ethanol (20 mL) was added ammonium chloride (134 mg, 2.51 mmol) and water (6 mL). The reaction mixture was stirred at 78 °C for 2 hrs. On completion, the mixture was filtered and the filtrate was concentrated. The residue was triturated with ethanol to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 442, tR = 0.859.

4-Amino-3-fluoro-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate AU)



AU

Step 1 - 3-Fluoro-4-nitro-benzenesulfonyl chloride

[00359] 3-fluoro-4-nitro-aniline (5.00 g, 32.0 mmol) was dissolved in hydrochloric acid (12 M, 40.8 g, 403 mmol) solution. The reaction mixture was cooled to 0 °C with an ice bath and sodium nitrite (2.65 g, 38.4 mmol) was added portion-wise at 0 °C. The mixture was stirred at 0 °C for 1.5 hrs. At the same time, sulfur dioxide (15 psi) was bubbled through a mixture of cuprous chloride (31.7 mg, 0.320 mmol) and copper chloride (2.15 g, 16.0 mmol) in a mixture of acetic acid (40 mL) and water (10 mL) for 10 min until the solution appeared slightly blue. Then the sulfur dioxide solution was added to the diazonium salt mixture at 0 °C. After complete addition, the cooling bath was removed and the mixture was stirred at 15 °C for 1 hrs. On completion, the reaction solution was poured onto ice. The aqueous layer was extracted with ethyl acetate (3 x 100 mL), and the combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 100:1 to 50:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.30 (q, J = 6.8 Hz, 8.4 Hz; 1H), 8.03(d, J = 0.8 Hz 1H), 8.01 (t, J = 6 Hz 1H).

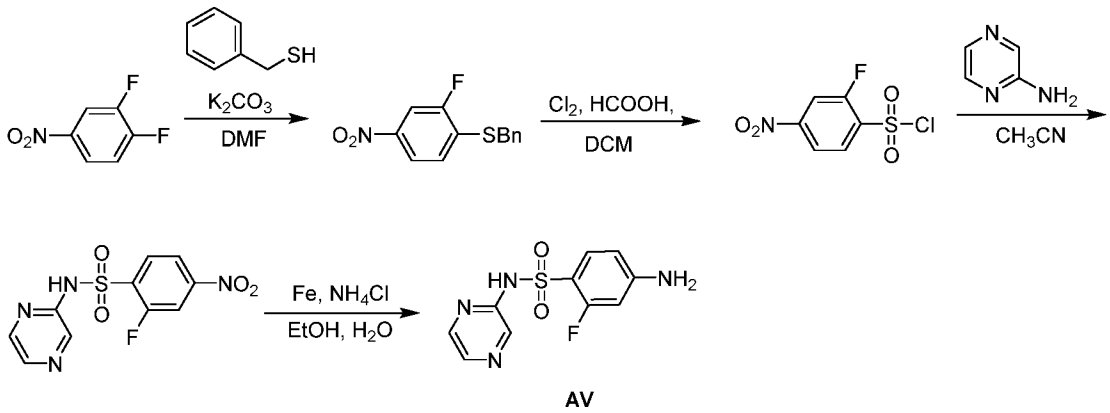
Step 2 - 3-Fluoro-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide

[00360] To a mixture of 3-fluoro-4-nitro-benzenesulfonyl chloride (2.20 g, 9.18 mmol) and pyridine (19.6 g, 248 mmol) in acetonitrile (10 mL) was added pyrazin-2-amine (1.05 g, 11.0 mmol) portion-wise at 15 °C. The mixture was stirred at 15 °C for 16 hrs. On completion, the reaction was concentrated *in vacuo* to give a residue. The residue was diluted in methanol (10 mL) and the solution was stirred at 15 °C for 20 min. The mixture was filtered to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 299.0; tR = 1.007.

Step 3 - 4-Amino-3-fluoro-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate AU)

[00361] To a solution of 3-fluoro-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide (300 mg, 1.01 mmol) and ammonium chloride (162 mg, 3.03 mmol) in a mixture of ethanol (10 mL) and acetic acid (60.6 mg, 1.01 mmol) at 15 °C. Then the reaction was warmed to 80 °C and Fe (169 mg, 3.03 mmol) was added to the reaction mixture. The reaction mixture was stirred at 80 °C for 16 hrs. On completion, the reaction was filtrated and concentrated *in vacuo*. The residue was purified by silica gel chromatography (dichloromethane:methanol = 100:1 to 10:1) to give the title compound. ^{1}H NMR (300MHz, DMSO-d_6) δ = 11.20 (br. s., 1H), 8.32 (br. s., 1H), 8.21 (d, *J*=7.2 Hz, 2H), 7.59 - 7.27 (m, 2H), 6.79 (t, *J*=8.2 Hz, 1H), 6.15 (br. s., 2H).

4-Amino-2-fluoro-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate AV)



AV

Step 1 - 1-Benzylsulfanyl-2-fluoro-4-nitro-benzene

[00362] To a solution of 1,2-difluoro-4-nitro-benzene (1.00 g, 6.29 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (1.74 g, 12.5 mmol) and phenylmethanethiol (780 mg, 6.29 mmol), while keeping the internal temperature below 15 °C. Upon the addition the reaction mixture was allowed to stir for 3 hrs at 15 °C. On completion, the reaction mixture was poured into ice water (30 mL). A yellow solid was formed and the solid was collected by filtration. The filter cake was washed with petroleum ether:ethyl acetate = 50:1 three times to give the title compound (1.40 g, crude) as a light yellow solid. The crude product was used directly in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.86 - 7.79 (m, 2H), 7.32 - 7.16 (m, 5H), 4.17 (s, 2H).

Step 2 - 2-Fluoro-4-nitro-benzenesulfonyl chloride

[00363] To a solution of 1-benzylsulfanyl-2-fluoro-4-nitro-benzene (6.00 g, 22.8 mmol) in formic acid (8 mL) and dichloromethane (40 mL) was vigorously bubbled chlorine for 15 min, during which the temperature was kept between -5 to 0 °C. The resulting mixture was stirred at 0 °C for another 15 min. On completion, ice water and dichloromethane were added and the organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated to give the crude product. The crude product was purified by flash silica gel chromatography (petroleum ether:ethyl acetate = 8:1) to give title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.21 - 8.11 (m, 3H).

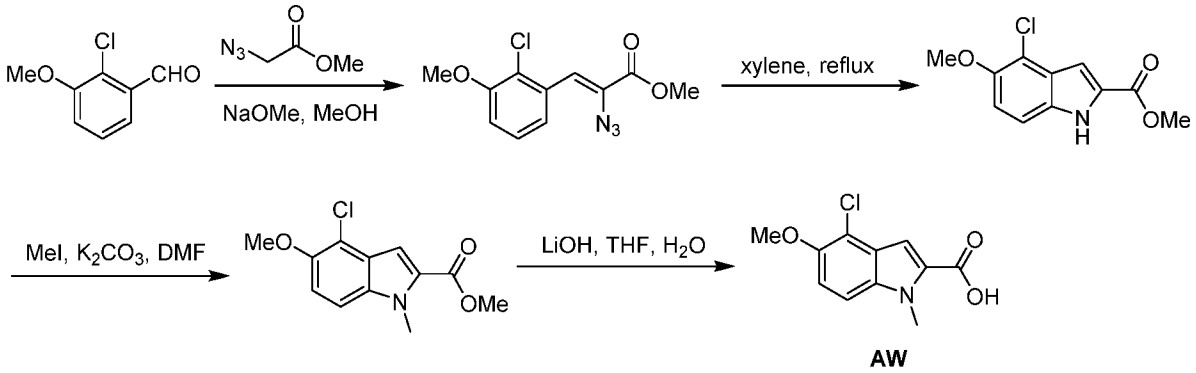
Step 3 - 2-Fluoro-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide

[00364] To a solution of 2-fluoro-4-nitro-benzenesulfonyl chloride (1.90 g, 7.93 mmol) in pyridine (20 mL) was added pyrazin-2-amine (754 mg, 7.93 mmol) at 15 °C. The reaction was stirred at 15 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was purified by prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5μ; Mobile phase: 0.225% formic acid-acetonitrile) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.39 (d, *J* = 1.1 Hz, 1H), 8.35 - 8.30 (m, 1H), 8.29 - 8.22 (m, 3H), 8.14 (dd, *J* = 1.3, 2.5 Hz, 1H).

Step 4 - 4-Amino-2-fluoro-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate AV)

[00365] To a solution of 2-fluoro-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide (390 mg, 1.31 mmol) in water (20 mL) and ethanol (50 mL) was added ammonium chloride (280 mg, 5.24 mmol) and iron powder (219 mg, 3.93 mmol). The mixture was stirred at 80 °C for 3 hrs. On completion, the reaction mixture was filtered through a sand core funnel matted with diatomaceous earth, and the filtrate was concentrated *in vacuo* to give the title compound, which was used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.44 (br. s, 1H), 8.35 - 8.29 (m, 1H), 8.19 (s, 2H), 7.35 (br. s, 2H), 6.46 - 6.38 (m, 3H).

4-Chloro-5-methoxy-1-methyl-indole-2-carboxylic acid (Intermediate AW)



AW

Step 1 - Methyl-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate

[00366] To a solution of sodium methoxide (2.38 g, 43.9 mmol) in methanol (40 mL) was added 2-chloro-3-methoxy-benzaldehyde (2.50 g, 14.6 mmol) and methyl 2-azidoacetate (4.73 g, 36.7 mmol) at -50 °C under nitrogen atmosphere. The mixture was stirred at the same temperature for 2 hrs, then warmed to 15 °C and stirred for 14 hrs. On completion, the suspension was poured into ice and the azido derivative was collected by filtration and washed with cold water. The filter cake was dried over *in vacuo* to give the crude product. The crude product was purified by silica gel chromatography (petroleum ether:ethyl acetate = 6:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.77 (dd, *J* = 1.0, 8.0 Hz, 1H), 7.35 (s, 1H), 7.31 - 7.26 (m, 1H), 6.95 (dd, *J* = 1.3, 8.3 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H).

Step 2 - Methyl-4-chloro-5-methoxy-1*H*-indole-2-carboxylate

[00367] Methyl-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (2.00 g, 7.47 mmol) was dissolved in xylene (200 mL) and the mixture was stirred at 180 °C for 30 min. On completion, the reaction mixture was concentrated *in vacuo* to afford a residue. The residue was triturated with (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.16 (br. s., 1H), 7.40 (dd, *J* = 0.6, 9.0 Hz, 1H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.04 (d, *J* = 1.5 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H).

Step 3 - Methyl 4-chloro-5-methoxy-1-methyl-indole-2-carboxylate

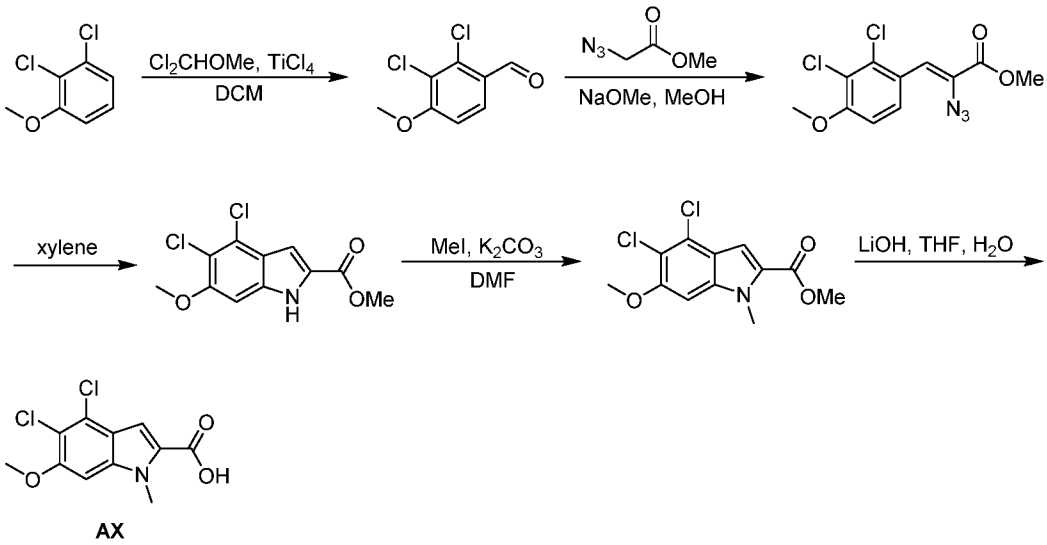
[00368] To a solution of methyl 4-chloro-5-methoxy-1*H*-indole-2-carboxylate (920 mg, 3.84 mmol) in *N,N*-dimethylformamide (15 mL) was added potassium carbonate (1.33 g, 9.60 mmol) and iodomethane (2.18 g, 15.4 mmol). The resulting mixture was warmed to 60 °C and stirred for 3 hrs. On completion, the reaction mixture was concentrated *in vacuo* to afford a residue. The

residue was diluted with water (30 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.57 (d, *J* = 9.2 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.10 (s, 1H), 4.00 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H).

Step 4 - 4-Chloro-5-methoxy-1- methyl-indole-2-carboxylic acid (Intermediate AW)

[00369] To a solution of methyl 4-chloro-5-methoxy-1-methyl-indole-2-carboxylate (950 mg, 3.74 mmol) in tetrahydrofuran (16 mL) and water (4 mL) was added lithium hydroxide (268 mg, 11.2 mmol). The resulting mixture was stirred at 15 °C for 3 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was acidified with 2 M hydrochloric acid to pH = 3, during which a fine precipitate was formed. The precipitate was filtered and the filter cake was washed with water and dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.19 (br. s., 1H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 7.08 (s, 1H), 4.02 (s, 3H), 3.88 (s, 3H).

4,5-Dichloro-6-methoxy-1-methyl-indole-2-carboxylic acid (Intermediate AX)



AX

Step 1 - 2,3-Dichloro-4-methoxy-benzaldehyde

[00370] To a solution of 1,2-dichloro-3-methoxy-benzene (5.00 g, 28.2 mmol) in dichloromethane (30 mL) was added $TiCl_4$ (9.11 g, 48.0 mmol) dropwise at 0 °C under nitrogen. Then dichloro(methoxy)methane (3.25 g, 28.2 mmol) was added to the solution dropwise at 0 °C under nitrogen, and the solution was stirred at 15 °C for 5 hrs. The residue was poured into water

(200 mL). The aqueous phase was extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with brine (3 x 200 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 100:1 to 10:1) to give the title compound. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.36 (s, 1H), 7.95 - 7.85 (d, *J* = 8.8 Hz, 1H), 7.03 - 6.93 (d, *J* = 8.4 Hz, 1H), 4.01 (s, 3H)

Step 2 - Methyl (*Z*)-2-azido-3-(2,3-dichloro-4-methoxy-phenyl)prop-2-enoate

[00371] To a solution of sodium methoxide (7.90 g, 146 mmol) in methanol (300 mL) was added 2,3-dichloro-4-methoxy-benzaldehyde (10.0 g, 48.8 mmol) several portions at -20 °C under nitrogen, then ethyl 2-azidoacetate (18.9 g, 146.3 mmol) was added to the solution dropwise at -20 °C under nitrogen. The mixture was stirred at 20 °C for 12 hrs. The mixture was poured into water (500 mL) and extracted with ethyl acetate (3 x 500 mL). The combined organic phase was washed with saturated brine (3 x 500 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 100:1 to 1:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.19 (d, *J*=8.8 Hz, 1H), 7.29 (d, *J*=3.5 Hz, 1H), 6.93 (d, *J*=9.0 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H).

Step 3 - Methyl 4,5-dichloro-6-methoxy-1*H*-indole-2-carboxylate

[00372] Methyl (Z)-2-azido-3-(2,3-dichloro-4-methoxy-phenyl)prop-2-enoate (500 mg, 1.66 mmol) was added to xylene (100 mL) in one portion at 15 °C, the solution was stirred at 120 °C for 12 hrs. The mixture was concentrated *in vacuo*. The residue was washed with (petroleum ether:ethyl acetate = 10:1, 50 mL) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.31 (br. s., 1H), 7.07 (d, *J*=1.3 Hz, 1H), 7.01 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H).

Step 4 - Methyl 4,5-Dichloro-6-methoxy-1-methyl-indole-2-carboxylate

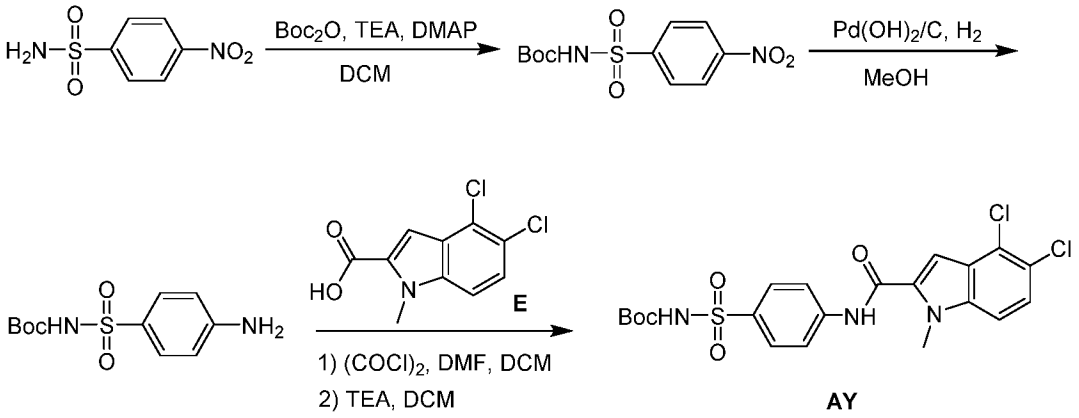
[00373] To a solution of methyl 4,5-dichloro-6-methoxy-1*H*-indole-2-carboxylate (220 mg, 0.803 mmol) in *N,N*-dimethylformamide (5 mL) was added potassium carbonate (333 mg, 2.41 mmol) and methyl iodide (342 mg, 2.41 mmol) in one portion at 15 °C under nitrogen. The mixture was stirred at 50 °C for 12 hrs. The mixture was then poured into water (10 mL). The aqueous phase was extracted with ethyl acetate (3 x 20 mL) the combined organic phase was

washed with brine (3 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 7.31 (s, 1H), 7.15 (s, 1H), 4.03 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H).

Step 5 - 4,5-Dichloro-6-methoxy-1-methyl-indole-2-carboxylic acid (Intermediate AX)

[00374] To a solution of methyl 4,5-dichloro-6-methoxy-1-methyl-indole-2-carboxylate (200 mg, 0.694 mmol) in a mixture solvent of tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide (49.8 mg, 2.08 mmol) in one portion at 15 °C under nitrogen. The mixture was stirred at 15 °C for 12 hrs. The mixture was concentrated *in vacuo*, the residue was adjusted to pH = 0.3 with 3 M hydrochloric acid (3 mL). The solid was filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ= 12.90 (br. s., 1H), 7.29 (s, 1H), 7.10 (s, 1H), 4.02 (s, 3H), 3.98 (s, 3H).

***Tert*-butyl-*N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonyl-carbamate (Intermediate AY)**



Step 1 - *Tert*-butyl *N*-(4-nitrophenyl)sulfonylcarbamate

[00375] To a solution of 4-nitrobenzenesulfonamide (5.00 g, 24.7 mmol) in anhydrous dichloromethane (40 mL) was added triethylamine (5.00 g, 49.4 mmol) and catalytic amount of *N,N*-dimethylpyridin-4-amine. The mixture was cooled to 0 °C and di-*tert*-butyl dicarbonate (5.67 g, 25.9 mmol) was added over 10 min. Then the mixture was warmed to 18 °C and stirred for 50 min. On completion, the reaction mixture was quenched with ice water (40 mL). Afterwards, the organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give a residue. The residue was purified by column

chromatography (petroleum ether:ethyl acetate = 3:1 to 1:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.44 - 8.40 (m, 2H), 8.28 - 8.24 (m, 2H), 1.43 (s, 9H).

Step 2 - *Tert*-butyl-*N*-(4-aminophenyl)sulfonylcarbamate

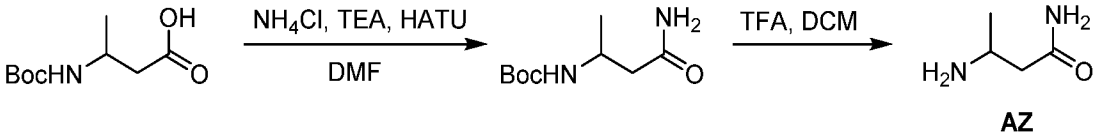
[00376] To a solution of *tert*-butyl-*N*-(4-nitrophenyl)sulfonylcarbamate (4.90 g, 16.2 mmol) in methanol (50 mL) was added $Pd(OH)_2$/C (10%, 490 mg) under nitrogen gas atmosphere. The suspension was degassed *in vacuo* and purged with hydrogen gas several times. Then the mixture was stirred under hydrogen gas (50 psi) at 40 °C for 16 hrs. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to afford the title compound (4.10 g, crude) as a white solid. The crude product was used for the next step directly without further purification. ^{1}H NMR (400MHz, CD_3OD-d_4) δ = 7.66 - 7.62 (m, 2H), 6.72 - 6.68 (m, 2H), 1.39 (s, 9H).

Step 3 - *Tert*-butyl *N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonyl-carbamate (Intermediate AY)

[00377] To a solution of 4,5-dichloro-1-methyl-indole-2-carboxylic acid (1.80 g, 7.37 mmol) in anhydrous dichloromethane (40 mL) was added a catalytic amount of *N,N*-dimethylformamide. Then the solution was cooled to 0 °C and oxalyl chloride (2.81 g, 22.1 mmol) was added dropwise. The mixture was then warmed to 15 °C and stirred for 2 hrs. On completion, the mixture was concentrated *in vacuo* to give the desired acid chloride. The acid chloride was used directly for the next step without further purification.

[00378] To a solution of *tert*-butyl *N*-(4-aminophenyl)sulfonylcarbamate (2.07 g, 7.60 mmol) in anhydrous dichloromethane (30 mL) was added triethylamine (2.20 g, 21.72 mmol). Then the mixture was cooled to 0 °C and 4,5-dichloro-1-methyl-indole-2-carbonyl chloride (1.90 g, 7.24 mmol) dissolved in anhydrous dichloromethane (30 mL) was added. The mixture was allowed to reach 15 °C in 1 hour and stirred at 15 °C for 4 hrs. On completion, the reaction mixture was washed with 0.5 M hydrochloric acid (20 mL) and ice water (2 x 20 mL) and the organic phase was collected, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound which was used without further purification. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.59 (br. s., 1H), 10.84 (s, 1H), 8.04 (d, *J* = 8.5 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.51 (br. s., 2H), 5.76 (s, 1H), 4.05 (br. s., 3H), 1.31 (s, 9H)

(±)-3-aminobutanamide (Intermediate AZ)



AZ

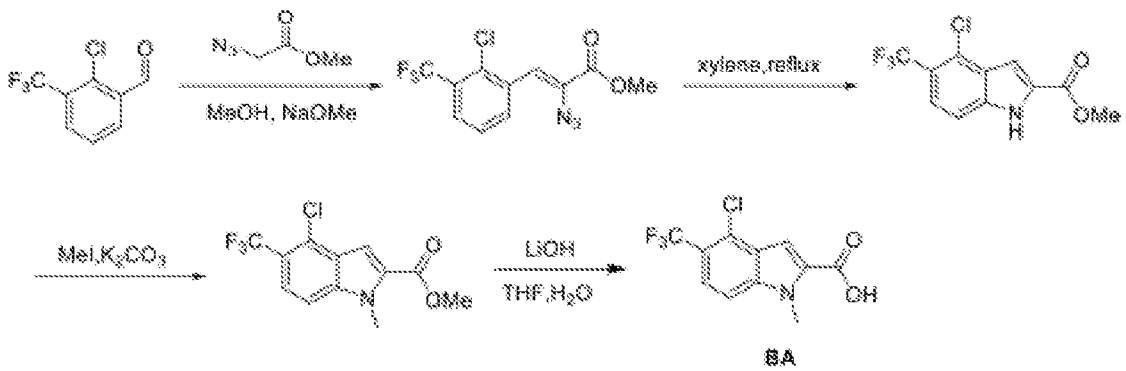
Step 1 - (±)-*Tert*-butyl *N*-(3-amino-1-methyl-3-oxo-propyl)carbamate

[00379] To a mixture of (±)-3-(*tert*-butoxycarbonylamino)butanoic acid (1.00 g, 4.92 mmol) in *N,N*-dimethylformamide (8 mL) was added ammonium chloride (526 mg, 9.84 mmol), 2-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) (2.81 g, 7.38 mmol) and triethylamine (1.49 g, 14.7 mmol). Then the mixture was stirred at 15 °C for 12 hours. On completion, the mixture was concentrated *in vacuo*. The residue was washed with water (20 mL), extracted with ethyl acetate (3 x 30 mL). The organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo*. The crude product was purified by prep-column chromatography (petroleum ether:ethyl acetate = 2:1 to dichloromethane:methanol = 10:1) to give the title compound. ^{1}H NMR (400MHz, CD_3OD) δ = 4.02 - 3.96 (m, 1H), 2.43 (dd, *J* = 6.4, 13.9 Hz, 1H), 2.27 (dd, *J* = 7.0, 14.1 Hz, 1H), 1.45 (s, 9H), 1.25 - 1.13 (m, 3H).

Step 2 - (±)-3-aminobutanamide (Intermediate AZ)

[00380] To a mixture of (±)-*tert*-butyl *N*-(3-amino-1-methyl-3-oxo-propyl)carbamate (100 mg, 0.494 mmol) in dichloromethane (3 mL) was added trifluoroacetic acid (3.06 g, 26.8 mmol). Then the mixture was stirred at 15 °C for 3 hours. On completion, the mixture was concentrated *in vacuo* to give the title compound, which was used without further purification.

4-Chloro-1-methyl-5-(trifluoromethyl)indole-2-carboxylic acid (Intermediate BA)



BA

Step 1 - Methyl (Z)-2-azido-3-[2-chloro-3-(trifluoromethyl)phenyl]prop-2-enoate

[00381] To a solution of 2-chloro-3-(trifluoromethyl)benzaldehyde (1.00 g, 4.79 mmol) in methanol (30 mL) was added sodium methoxide (1.33 g, 24.7 mmol) in one portion at -20 °C, then methyl 2-azidoacetate (1.86 g, 14.4 mmol) was added to the reaction dropwise and the reaction mixture was stirred at 30 °C for 4 hrs. On completion, 50 mL water was added to the solution, the reaction was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with water (2 x 50 mL), dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo*. The resulting solid was purified by column chromatography (petroleum ether:ethyl acetate = 500:1 to 100:1) to give the title compound.

Step 2 - Methyl 4-chloro-5-(trifluoromethyl)-1*H*-indole-2-carboxylate

[00382] Methyl (*Z*)-2-azido-3-[2-chloro-3-(trifluoromethyl) phenyl] prop-2-enoate (300 mg, 0.982 mmol) was added into xylene (20 mL), the reaction was stirred at 140 °C for 12 hrs. On completion, the reaction was concentrated *in vacuo*, the residue was purified by column chromatography (petroleum ether:ethyl acetate = 500:1 to 50:1) to give the title compound.

Step 3 - Methyl 4-Chloro-1-methyl-5-(trifluoromethyl)indole-2-carboxylate

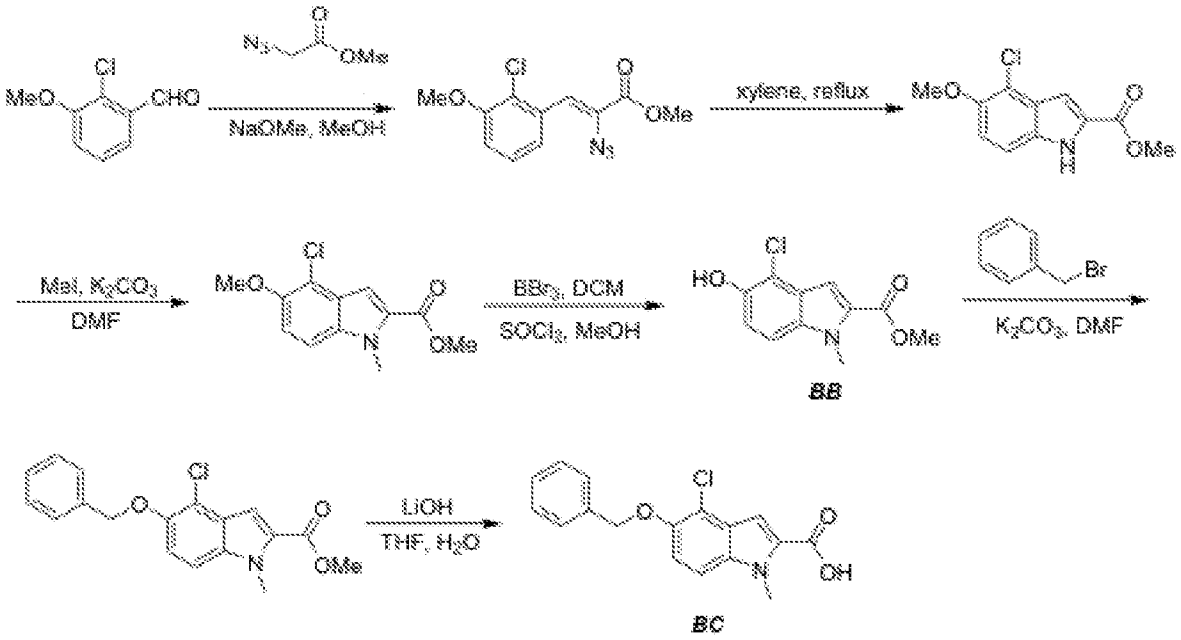
[00383] To a solution of methyl 4-chloro-5-(trifluoromethyl)-1*H*-indole-2-carboxylate (100 mg, 0.360 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (149 mg, 1.08 mmol) and methyl iodide (153 mg, 1.08 mmol) in turn at 30 °C, and the reaction was stirred at 30 °C for 1 hr. On completion, 10 mL water was added into the solution, the reaction was extracted with ethyl acetate (2 x 20 mL), washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.86 - 7.81 (m, 1H), 7.76 - 7.71 (m, 1H), 7.40 (s, 1H), 4.10 (s, 3H), 3.91 (s, 3H)

Step 4 - 4-Chloro-1-methyl-5-(trifluoromethyl)indole-2-carboxylic acid (Intermediate BA)

[00384] To a solution of methyl 4-chloro-1-methyl-5-(trifluoromethyl)indole-2-carboxylate (90.0 mg, 0.309 mmol) in tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide (22.0 mg, 0.926 mmol) in one portion, the reaction was stirred at 30 °C for 1 hr. On completion, the reaction was concentrated *in vacuo*, the residue was adjusted to pH = 3 with 1 M hydrochloric acid (5 mL), then extracted with ethyl acetate (2 x 20 mL), washed with water (2 x

20 mL), dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.83 - 7.77 (m, 1H), 7.73 - 7.68 (m, 1H), 7.34 (s, 1H), 4.09 (s, 1H).

Methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate (Intermediate BB) and 5-Benzyloxy-4-chloro-1-methyl-indole-2-carboxylic acid (Intermediate BC)



Step 1 - Methyl-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate

[00385] To a solution of sodium methoxide (9.50 g, 175 mmol) in methanol (100 mL) was added dropwise a solution of 2-chloro-3-methoxy-benzaldehyde (10.0 g, 58.6 mmol) and methyl 2-azidoacetate (22.7 g, 175 mmol) in methanol (100 mL) at -40 °C. After the reaction mixture was stirred at -50 °C for 2 hr, it was warmed to 20 °C during 2 hrs. The reaction mixture was then stirred at 20 °C for 14 hrs. On completion, the mixture was poured into ice water (300 mL) and extracted with dichloromethane (2 x 200 mL), the combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.81 - 7.73 (m, 1H), 7.36 (s, 1H), 7.32 - 7.25 (m, 2H), 6.95 (dd, *J* = 1.2, 8.2 Hz, 1H), 3.96 (s, 3H), 3.94 (s, 3H).

Step 2 - Methyl 4-chloro-5-methoxy-1*H*-indole-2-carboxylate

[00386] A solution of methyl-2-azido-3-(2-chloro-3-methoxy-phenyl)prop-2-enoate (10.0 g, 37.3 mmol) in xylene (150 mL) was stirred at 160 °C for 5 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was triturated with a mixture of petroleum ether (100 mL), dichloromethane (5 mL) and methanol (5 mL) to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.96 (br. s., 1H), 7.34 - 7.25 (m, 2H), 7.12 (d, *J* = 8.9 Hz, 1H), 3.98 (s, 3H), 3.97 (s, 3H).

Step 3 - Methyl 4-chloro-5-methoxy-1-methyl-indole-2-carboxylate

[00387] To a mixture of methyl 4-chloro-5-methoxy-1*H*-indole-2-carboxylate (7.34 g, 30.6 mmol) and potassium carbonate (16.9 g, 122 mmol) in *N,N*-dimethylformamide (80 mL) was added methyl iodide (21.7 g, 153 mmol), and the mixture was stirred at 60 °C for 16 hrs. On completion, the reaction mixture was filtered; the filtrate was washed with water (100 mL), extracted with ethyl acetate (2 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.34 (d, *J* = 0.6 Hz, 1H), 7.27 (dd, *J* = 0.8, 9.0 Hz, 1H), 7.16 - 7.12 (m, 1H), 4.07 (s, 3H), 3.97 (s, 3H), 3.95 - 3.93 (m, 3H).

Step 4 - Methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate (Intermediate BB)

[00388] To a solution of methyl 4-chloro-5-methoxy-1-methyl-indole-2-carboxylate (3.00 g, 11.8 mmol) in dichloromethane (40 mL) was added a solution of boron tribromide (23.7 g, 94.6 mmol) in dichloromethane (40 mL) dropwise at -50 °C. The mixture was stirred at -50 °C for 2 hrs and then was allowed to warm to 20 °C and stirred 15 hrs. On completion, methanol (15 mL) was added dropwise into the mixture at 0 °C. The mixture was concentrated *in vacuo*, washed with water (20 mL), extracted with ethyl acetate (3 x 30 mL). The combined organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to give 3 g of a mixture of methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate and 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylic acid as a yellow solid. To this crude solid in methanol (40 mL) was added $SOCl_2$ (8.20 g, 68.9 mmol) dropwise at 100 °C. The resulting mixture was stirred at 100 °C for 15 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was triturated in petroleum ether (50 mL) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 9.69 (s, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.11 - 7.05 (m, 2H), 3.99 (s, 3H), 3.86 (s, 3H).

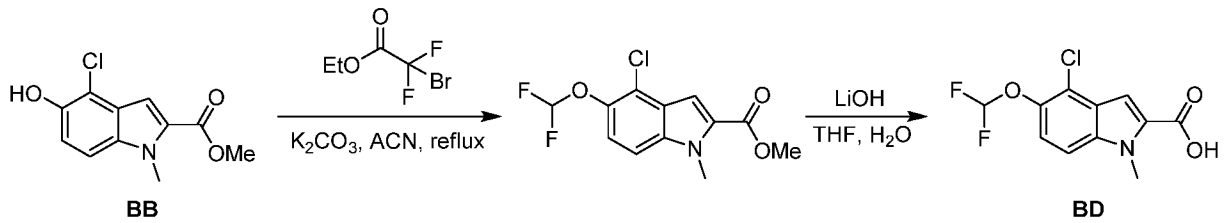
Step 5 - Methyl 5-benzyloxy-4-chloro-1-methyl-indole-2-carboxylate

[00389] To a suspension of methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate (100 mg, 0.417 mmol) and bromomethylbenzene (107 mg, 0.625 mmol) in *N,N*-dimethylformamide (3 mL) was added potassium carbonate (115 mg, 0.834 mmol), and the mixture was stirred at 50 °C for 15 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was washed with saturated sodium bicarbonate solution (20 mL) and extracted with ethyl acetate (3 X 30 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.58 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 2H), 7.41 - 7.39 (m, 2H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.35 - 7.31 (m, 1H), 7.14 (s, 1H), 5.24 (s, 2H), 4.02 (s, 3H), 3.87 (s, 3H).

Step 6 - 5-Benzyloxy-4-chloro-1-methyl-indole-2-carboxylic acid (Intermediate BC)

[00390] To a mixture of methyl 5-benzyloxy-4-chloro-1-methyl-indole-2-carboxylate (210 mg, 0.636 mmol) in a mixture of tetrahydrofuran (6 mL) and water (3 mL) was added lithium hydroxide (53.4 mg, 1.27 mmol) and the reaction mixture was stirred at 20 °C for 15 hrs. On completion, 1 M HCl (5 mL) was added into the mixture and the mixture was concentrated *in vacuo* to afford a residue. The residue was wash with water (20 mL) and extracted with ethyl acetate (2 x 20 mL), and the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.60 (d, *J* = 9.0 Hz, 1H), 7.55 (d, *J* = 7.3 Hz, 2H), 7.50 - 7.44 (m, 2H), 7.43 (d, *J* = 5.9 Hz, 1H), 7.15 (s, 1H), 4.07 (s, 3H).

4-Chloro-5-(difluoromethoxy)-1-methyl-indole-2-carboxylic acid (Intermediate BD)



BB BD

Step 1 - Methyl 4-chloro-5-(difluoromethoxy)-1-methyl-indole-2-carboxylate

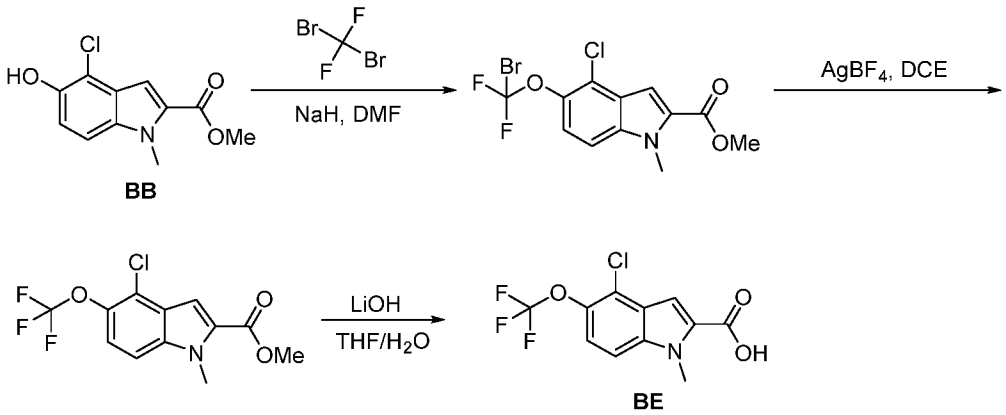
[00391] To a solution of methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate (200 mg, 0.834 mmol) and potassium carbonate (115 mg, 0.834 mmol) in acetonitrile (2 mL) was added ethyl 2-bromo-2,2-difluoro-acetate (338 mg, 1.67 mmol), and the mixture was heated to 100 °C

and stirred at 100 °C for 4 hrs. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was washed with water (30 mL) and extracted with ethyl acetate (3 x 30 mL), the combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue was purified with silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to afford the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.73 - 7.69 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 7.37-7.02 (t, *J* = 64.0 Hz 1H), 4.08 - 4.04 (m, 3H), 3.89 (s, 3H).

Step 2 - 4-Chloro-5-(difluoromethoxy)-1-methyl-indole-2-carboxylic acid (Intermediate BD)

[00392] To a mixture of methyl 4-chloro-5-(difluoromethoxy)-1-methyl-indole-2-carboxylate (140 mg, 0.483 mmol) in a mixture of tetrahydrofuran (6 mL) and water (3 mL) was added lithium hydroxide (40.5 mg, 0.966 mmol). The mixture was stirred at 20 °C for 15 hrs. On completion, 1 M HCl (5 mL) was added into the mixture, and the mixture was concentrated *in vacuo* to afford a residue. The residue was washed with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound.

4-Chloro-1-methyl-5-(trifluoromethoxy)indole-2-carboxylic acid (Intermediate BE)



Step 1 - Methyl 5-[bromo(difluoro)methoxy]-4-chloro-1-methyl-indole-2-carboxylate

[00393] To a solution of methyl 4-chloro-5-hydroxy-1-methyl-indole-2-carboxylate (800 mg, 3.34 mmol) in *N,N*-dimethylformamide (20 mL) was added NaH (200 mg, 5.01 mmol) in several portions at 0°C. The reaction was stirred at 0 °C for 0.5 hr, then dibromo(difluoro)methane (7.00 g, 33.4 mmol) was added to the solution at 0 °C, and the reaction was stirred at 30 °C for 2 hrs. On completion, the reaction was quenched with water (20 mL), then extracted with ethyl acetate

(2 x 50 mL), washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 100:1 to 50:1) to give the title compound. LCMS: (ES^+) m/z$(M+H)^+$ = 367,tR = 0.986.

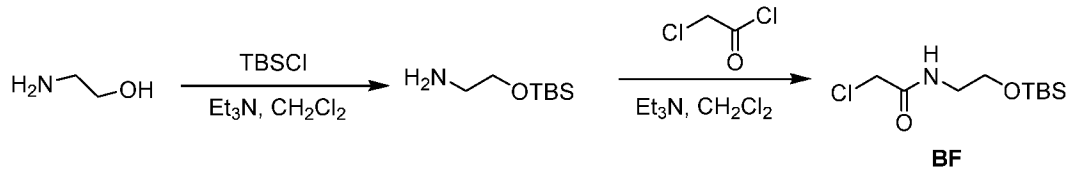
Step 2 - Methyl 4-chloro-1-methyl-5-(trifluoromethoxy)indole-2-carboxylate

[00394] To a solution of methyl 5-[bromo(difluoro)methoxy]-4-chloro-1-methyl-indole-2-carboxylate (240 mg, 0.651 mmol) in 1,2-dichloroethane (5 mL) was added $AgBF_4$ (1.27 g, 6.51 mmol) in one portion at 30 °C, and the reaction was stirred at 80 °C for 3 hrs. On completion, the reaction was diluted with 20 mL water, extracted with dichloromethane (2 x 20 mL), washed with water (2 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether: ethyl acetate = 500:1 to 50:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 308, tR = 0.973.

Step 3 - 4-Chloro-1-methyl-5-(trifluoromethoxy)indole-2-carboxylic acid (Intermediate BE)

[00395] To a solution of methyl 4-chloro-1-methyl-5-(trifluoromethoxy)indole-2-carboxylate (80 mg, 0.260 mmol) in tetrahydrofuran (5 mL) and water (5 mL) was added lithium hydroxide (18.7 mg, 0.780 mmol) in one portion, and the reaction was stirred at 30 °C for 1 hr. On completion, the reaction was concentrated *in vacuo*, and the residue was adjusted to pH = 3 with 1 M hydrochloric acid (5 mL). The residue was then extracted with ethyl acetate (2 x 20 mL), washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound. ^1H NMR (400MHz, DMSO-d_6) δ = 7.77 - 7.72 (m, 1H), 7.49 (dd, *J* = 1.3, 9.1 Hz, 6.1 Hz, 1H), 7.26 (s, 1H), 4.08 (s, 3H).

***N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-chloroacetamide (Intermediate BF)**



BF

Step 1 - 2-((*Tert*-butyldimethylsilyl)oxy)ethanamine

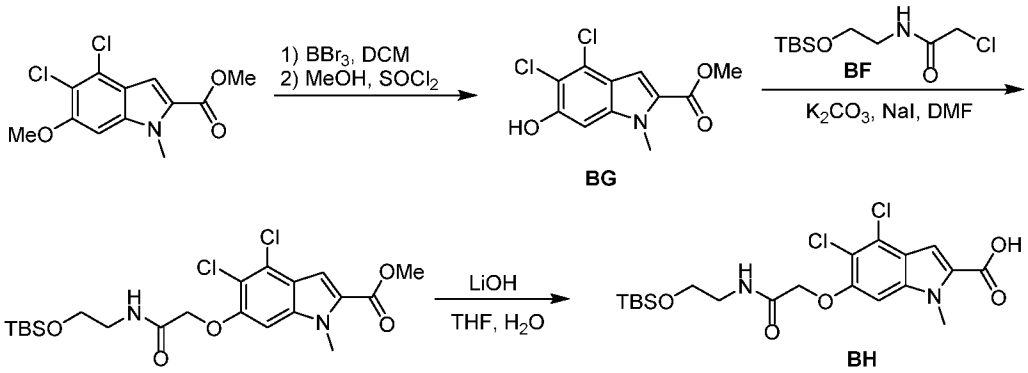
[00396] To a solution of 2-aminoethanol (5.00 g, 81.8 mmol) and triethylamine (16.5 g, 163 mmol) in dichloromethane (80 mL) was added TBSCl (12.3 g, 81.8 mmol) at 0 °C. After

addition, the mixture was allowed to warm to 20 °C slowly. After the mixture was stirred at 20 °C for 12 hrs, the reaction mixture was concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography eluting with dichloromethane to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.60 (t, *J* = 5.8 Hz, 2H), 2.68 (t, *J* = 5.8 Hz, 2H), 0.87 (s, 9H), 0.04 (s, 6H).

Step 2 - *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-chloroacetamide (Intermediate BF)

[00397] To a solution of 2-((*tert*-butyldimethylsilyl)oxy)ethanamine (12.0 g, 59.5 mmol) and triethylamine (12.0 g, 119 mmol) in dichloromethane (300 mL) was added 2-chloroacetyl chloride (6.72 g, 59.5 mmol) and the reaction mixture was stirred at 20 °C for 12 hrs. The reaction mixture was washed with water, dried over anhydrous sodium sulfate, filtered and concentrated to afford the crude product. The crude product was purified by column chromatography (petroleum ether:ethyl acetate = 8:1 to 3:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.02 (br. s., 1H), 4.06 (s, 2H), 3.71 (t, *J* = 5.2 Hz, 2H), 3.43 (q, *J* = 5.4 Hz, 2H), 0.91 (s, 9H), 0.08 (s, 6H).

Methyl 4,5-dichloro-6-hydroxy-1-methyl-indole-2-carboxylate (Intermediate BG) and Methyl 6-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethylamino]-2-oxo-ethoxy]-4,5-dichloro- 1-methyl-indole-2-carboxylate (Intermediate BH)



Step 1- Methyl 4,5-dichloro-6-hydroxy-1-methyl-indole-2-carboxylate

[00398] To a solution of methyl 4,5-dichloro-6-methoxy-1-methyl-indole-2-carboxylate (1.60 g, 5.55 mmol, synthesized via steps 1-4 of Intermediate AX described above) in dichloromethane (20 mL) was added boron tribromide (2.78 g, 11.1 mmol, 1.07 mL) at 0 °C, and then the mixture was stirred at 30 °C for 16 hours. On completion, dichloromethane (20 mL) was added to the

mixture and was then poured into water (30 mL). Then the mixture was filtered, the filtrate was extracted with dichloromethane (3 x 30 mL), and the combined organic phase was combined with the filter cake and concentrated to yield 4,5-dichloro-6-hydroxy-1-methyl-indole-2-carboxylic acid (2.00 g) as a gray solid.

[00399] To a solution of 4,5-dichloro-6-hydroxy-1-methyl-indole-2-carboxylic acid (1.44 g, 5.54 mmol) in methanol (20 mL) was added thionyl chloride (725 mg, 6.09 mmol) at 20-30 °C, and then the mixture was stirred at 50 °C for 16 hours. On completion, methanol (10 mL) was added to the mixture and was then filtered to get the filter cake. The filter cake was dried to afford the title compound. ^{1}H NMR (400 MHz, DMSO-d6) δ = 10.71 (br. s., 1H), 7.10 (s, 1H), 6.98 (s, 1H), 3.91 (s, 3H), 3.86 - 3.80 (m, 3H).

Step 2 - Methyl 6-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethylamino]-2-oxo-ethoxy]-4,5-dichloro-1-methyl-indole-2-carboxylate

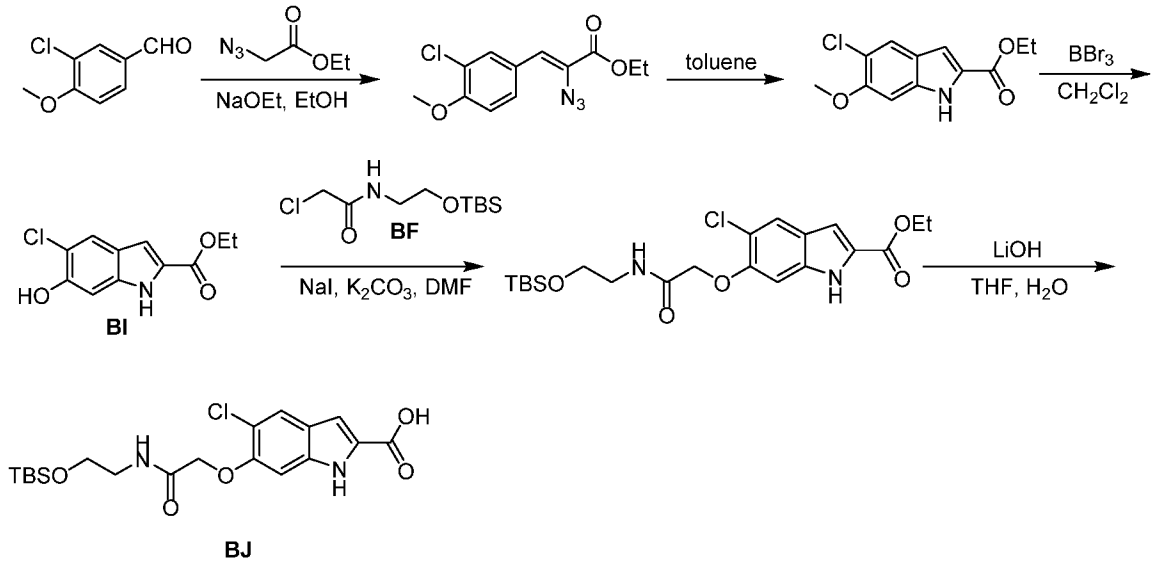
[00400] To a solution of methyl 4,5-dichloro-6-hydroxy-1-methyl-indole-2-carboxylate (500 mg, 1.82 mmol) in DMF (5.00 mL) was added *N*-[2-[*tert*-butyl(dimethyl)silyl]oxyethyl]-2-chloro-acetamide (504 mg, 2.00 mmol, Intermediate BF), NaI (13.6 mg, 91.0 μmol) and K_2CO_3 (251 mg, 1.82 mmol). The reaction mixture was stirred at 100 °C for 12 hours. On completion, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.02 (s, 1H), 7.32 (s, 1H), 6.73 (s, 1H), 4.62 (s, 2H), 4.04 (s, 3H), 3.92 (s, 3H), 3.77 (t, *J* = 5.0 Hz, 2H), 3.55 – 3.51 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H).

Step 3 - Methyl 6-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethylamino]-2-oxo-ethoxy]-4,5-dichloro-1-methyl-indole-2-carboxylate

[00401] To a solution of methyl 6-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethylamino]-2-oxo-ethoxy]-4,5-dichloro-1-methyl-indole-2-carboxylate (750 mg, 1.53 mmol) in a mixture of H_2O (1.00 mL) and THF (7.00 mL) was added and LiOH (147 mg, 6.13 mmol). The reaction mixture was stirred at 20 °C for 12 hours. On completion, the reaction solution was diluted with water (50 mL) and acidified with citric acid solution (0.1 mol/L) to pH = 6~7 at 0 °C. A white precipitate formed which was filtered. The filter cake was dissolved in DCM/MeOH (5:1, 150 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title

compound. LCMS (ES^+): 475.2 m/z $(M+H)^+$, tR = 0.980 min. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.75 (t, J = 5.7 Hz, 1H), 7.31 (s, 1H), 7.06 (s, 1H), 4.72 (s, 2H), 4.00 (s, 3H), 3.65 (t, J = 5.8 Hz, 2H), 3.45 – 3.08 (m, 2H), 0.83 (s, 9H), 0.02 (s, 6H).

Ethyl 5-chloro-6-hydroxy-1*H*-indole-2-carboxylate (Intermediate BI) and 6-(2-((2-((*Tert*-butyldimethylsilyl)oxy)ethyl)amino)-2-oxoethoxy)-5-chloro-1*H*-indole-2-carboxylic acid (Intermediate BJ)



Step 1 - Ethyl 2-azido-3-(3-chloro-4-methoxyphenyl)acrylate

[00402] Sodium ethoxide (2.02 g, 87.9 mmol) was added to ethanol (50 mL) at 0 °C. After gas evolution ceased, 3-chloro-4-methoxybenzaldehyde (5.00 g, 29.3 mmol) and ethyl 2-azidoacetate (11.9 g, 87.9 mmol, 12.9 mL) in ethanol (50 mL) was added dropwise at -40 °C. The mixture was then stirred at 20 °C for 12 hours. The residue was adjusted to pH = 7 with dilute hydrochloric acid solution (1 M) at 0 °C, and then ethanol was removed under reduced pressure. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:0 to 10:1) to give the title compound. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.96 (d, J = 2.3 Hz, 1H), 7.68 (dd, J = 8.6, 2.0 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 6.80 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.95 (s, 3H), 1.40 (t, J = 7.2 Hz, 3H).

Step 2 - Ethyl 5-chloro-6-methoxy-1*H*-indole-2-carboxylate

[00403] Ethyl 2-azido-3-(3-chloro-4-methoxyphenyl)acrylate (4.87 g, 17.3 mmol) in toluene (80 mL) was heated to 110 °C and allowed to stir for 9 hrs. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1 to 1:1) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.87 (br. s., 1H), 7.73 (s, 1H), 7.06 (d, *J* = 1.8 Hz, 1H), 7.01 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.87 (s, 3H), 1.32 (t, *J* = 7.2 Hz, 3H).

Step 3 - Ethyl 5-chloro-6-hydroxy-1*H*-indole-2-carboxylate (Intermediate BI)

[00404] To a solution of ethyl 5-chloro-6-methoxy-1*H*-indole-2-carboxylate (3.10 g, 12.2 mmol) in dichloromethane (60 mL) was added boron tribromide (9.18 g, 36.6 mmol, 3.53 mL) in dichloromethane (10 mL) at 0-15 °C for 5 hours. The reaction mixture was quenched by addition of ethanol (20 mL) at 0 °C and then concentrated under reduced pressure. The residue was diluted with ethyl acetate (60 mL) and washed with water (30 mL). The organic phase was separated and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1 to 1:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.59 (br. s., 1H), 10.11 (s, 1H), 7.63 (s, 1H), 7.01 (s, 2H), 4.30 (q, *J* = 7.2 Hz, 2H), 1.31 (t, *J* = 7.0 Hz, 3H).

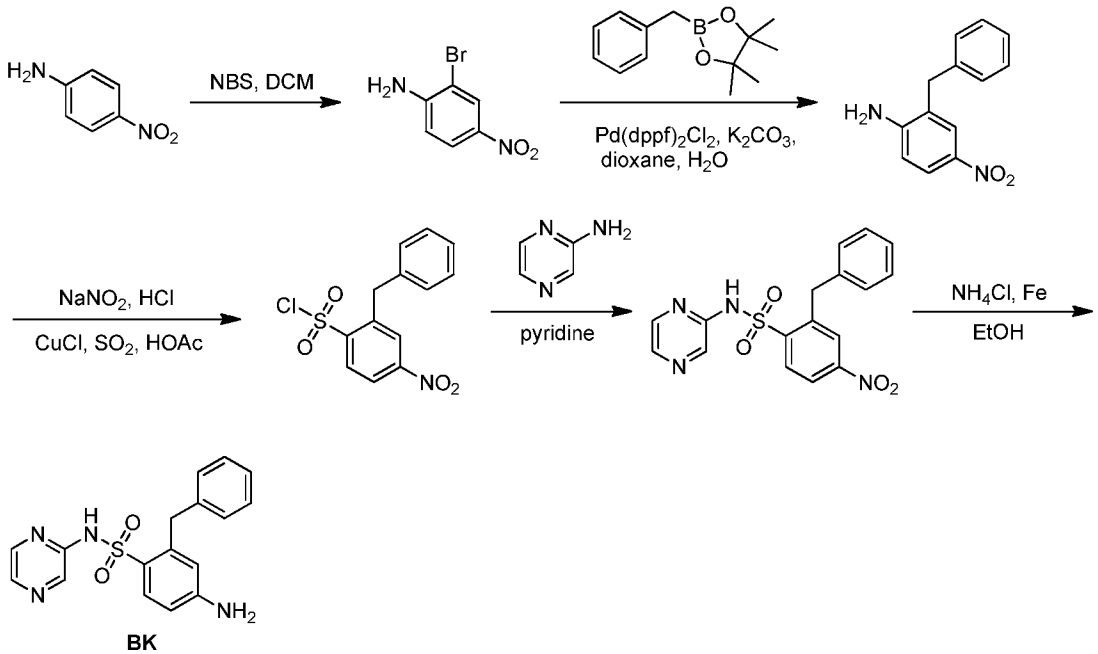
Step 4 - Ethyl 6-[2-[2-[*tert*-butyl(dimethyl)silyl]oxyethylamino]-2-oxo-ethoxy]-5-chloro-1*H*-indole-2-carboxylate

[00405] A mixture of ethyl 5-chloro-6-hydroxy-1*H*-indole-2-carboxylate (370 mg, 1.54 mmol), *N*-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-2-chloroacetamide (428 mg, 1.70 mmol), potassium carbonate (213 mg, 1.54 mmol) and sodium iodide (11.5 mg, 0.0772 mmol) in *N,N*-dimethylformamide (15 mL) was stirred at 90 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1 to 1:1) to give the title compound (0.65 g, crude) as a red solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.49 (br. s., 1H), 7.69 (s, 1H), 7.30 (br. s, 1H), 7.11 (d, *J* = 1.4 Hz, 1H), 6.93 (s, 1H), 4.58 (s, 2H), 4.39 (q, *J* = 7.0 Hz, 2H), 3.74 (t, *J* = 5.0 Hz, 2H), 3.51 (q, *J* = 5.4 Hz, 2H), 0.87 (s, 9H), 0.05 (s, 6H).

Step 5 - 6-(2-((2-((*Tert*-butyldimethylsilyl)oxy)ethyl)amino)-2-oxoethoxy)-5-chloro-1*H*-indole-2-carboxylic acid (Intermediate BJ)

[00406] A mixture of ethyl 6-(2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-2-oxoethoxy)-5-chloro-1*H*-indole-2-carboxylate (1.30 g, 1.57 mmol) and lithium hydroxide (300 mg, 12.5 mmol) in water (1 mL) and tetrahydrofuran (10 mL) was stirred at 20 °C for 24 hours. The reaction mixture was adjusted to pH = 6-7 with citric acid (0.1 M) at 0 °C, and then diluted with water (100 mL). A yellow solid formed, which was filtered and washed with water. The filter cake was dissolved in dichloromethane:methanol = 5:1 (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 11.40 (br. s., 1H), 7.75 (t, *J* = 5.6 Hz, 1H), 7.64 (s, 1H), 7.00 (s, 1H), 6.73 (s, 1H), 4.54 (s, 2H), 3.63 (t, *J* = 6.0 Hz, 2H), 3.29 (q, *J* = 5.8 Hz, 2H), 0.85 (s, 9H), 0.03 (s, 6H).

4-Amino-2-benzyl-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate BK)



BK

Step 1 - 2-Bromo-4-nitro-aniline

[00407] To a solution of 4-nitroaniline (25.0 g, 181 mmol) in dichloromethane (50 mL) was added *N*-bromosuccinimide (NBS) (35.4 g, 199 mmol) at 0 °C and the reaction mixture was stirred at 15 °C for 16 hrs. On completion, the reaction mixture was washed with water (200 mL). The organic layer was dried over anhydrous sodium sulfate, filtrated, and concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography

(dichloromethane:methanol = 20:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.39 (d, *J* = 2.5 Hz, 1H), 8.05 (dd, *J* = 2.5, 8.9 Hz, 1H), 6.75 (d, *J* = 8.9 Hz, 1H), 4.83 (br. s, 1H).

Step 2 - 2-Benzyl-4-nitro-aniline

[00408] To a mixture of 2-bromo-4-nitro-aniline (200 mg, 0.921 mmol), 2-benzyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (241 mg, 1.11 mmol) and potassium carbonate (254 mg, 1.84 mmol) in a mixture of water (2 mL) and dioxane (4 mL) was added Pd(dppf)Cl_2 (67.4 mg, 0.0921 mmol) and the reaction mixture was stirred at 100 °C for 1 hr under nitrogen. On completion, the reaction mixture was concentrated *in vacuo* to give a solid. The resulting solid was purified by silica gel chromatography (petroleum ether:ethyl acetate = 20:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 229.0, tR = 1.411. ^{1}H NMR (400MHz, DMSO-d_6) δ = 7.88 (dd, *J* = 9.0 Hz, 1H), 7.70 (d, *J* = 2.6 Hz, 1H), 7.39 - 7.29 (m, 2H), 7.28 - 7.18 (m, 3H), 6.69 (d, *J* = 9.0 Hz, 1H), 6.58 (s, 2H), 3.85 (s, 2H).

Step 3 - 2-Benzyl-4-nitro-benzenesulfonyl chloride

[00409] To a solution of 2-benzyl-4-nitro-aniline (1.30 g, 5.70 mmol) in concentrated hydrochloric acid (15 mL) was added a solution of sodium nitrite (392 mg, 5.70 mmol) in water (1 mL) dropwise and the reaction mixture was stirred at 0 °C for 0.5 hr. Then sulfur dioxide (15 psi) was bubbled through a mixture of cuprous chloride (112 mg, 1.14 mmol) in acetic acid (15 mL) for 10 min until the solution appeared slightly blue. Then the above diazonium solution was added dropwise into the sulfur dioxide solution at 0 °C and stirred for 0.5 hr. The mixture was poured into water (300 mL) and ethyl acetate (200 mL) was added. The aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography (petroleum ether:ethyl acetate = 50:1) to give the title compound.

Step 4 - 2-Benzyl-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide

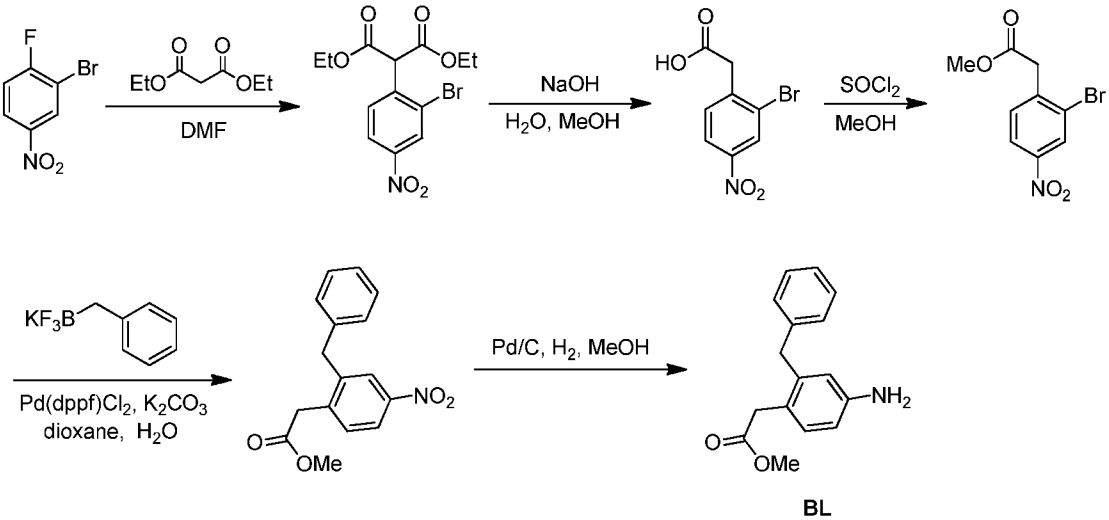
[00410] To a solution of 2-benzyl-4-nitro-benzenesulfonyl chloride (800 mg, 2.57 mmol) in pyridine (20 mL) was added pyrazin-2-amine (800 mg, 2.57 mmol) and the reaction mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a yellow solid. The resulting solid was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:5) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 371.0, tR =

0.716. ^{1}H NMR (300MHz, CD_3OD) δ = 8.43 (d, *J* = 8.9 Hz, 1H), 8.20 (dd, *J* = 2.3, 8.9 Hz, 1H), 8.06 (s, 1H), 8.01 (br. s., 1H), 7.98 (s, 1H), 7.91 (d, *J* = 2.1 Hz, 1H), 7.31 - 7.17 (m, 3H), 7.11 (d, *J* = 6.0 Hz, 2H), 4.64 (s, 2H).

Step 5 - 4-Amino-2-benzyl-*N*-pyrazin-2-yl-benzenesulfonamide (Intermediate BK)

[00411] To a solution of 2-benzyl-4-nitro-*N*-pyrazin-2-yl-benzenesulfonamide (300 mg, 0.809 mmol) and ammonium chloride (433 mg, 8.10 mmol) in ethanol (5 mL) was added iron (452 mg, 8.10 mmol) in portions at 80 °C and the reaction mixture was stirred at 80 °C for 5 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The resulting solid was triturated with dichloromethane (20 mL) and methanol (5 mL), filtrated and concentrated *in vacuo* to give a red solid, which was purified by silica gel chromatography (dichloromethane:methanol = 10:1) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 341.1, tR = 1.381. ^{1}H NMR (400MHz, DMSO-d_6) δ = 11.30 (br. s., 1H), 8.18 (s, 1H), 8.16 (s, 2H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.26 - 7.16 (m, 3H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.45 (dd, *J* = 2.3, 8.7 Hz, 1H), 6.16 (d, *J* = 2.1 Hz, 1H), 5.95 (s, 2H), 4.25 (s, 2H).

Methyl 2-(4-amino-2-benzylphenyl)acetate (Intermediate BL)



BL

Step 1 - Diethyl 2-(2-bromo-4-nitrophenyl)malonate

[00412] To a mixture of diethyl propanedioate (9.46 g, 59.1 mmol) in *N*,*N*-dimethylformamide (100 mL) was added sodium hydride (1.82 g, 45.5 mmol) in portions at 0 °C (ice-water bath) under nitrogen. The mixture was stirred at 0 °C for 30 mins, then 2-bromo-1-fluoro-4-nitro-benzene (10.0 g, 45.5 mmol) was added in portions. The resultant mixture was

warmed to 20 °C and stirred for 16 hrs. On completion, to the mixture was added ammonium chloride solution (150 mL), and the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed by brine (200 mL), dried over sodium sulfate, and concentrated *in vacuo* to give the crude residue, which was purified by column chromatography (petroleum ether:ethyl acetate = 20:1 to 5:1) to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.48 (d, *J* = 2.7 Hz, 1H), 8.20 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 5.29 (s, 1H), 4.29 - 4.18 (m, 4H), 1.32 - 1.27 (m, 6H).

Step 2 – 2-(2-Bromo-4-nitrophenyl)acetic acid

[00413] To a solution of diethyl 2-(2-bromo-4-nitro-phenyl)propanedioate (2.00 g, 5.55 mmol) in ethanol (11.0 mL) was added the solution of sodium hydroxide (888 mg, 22.2 mmol) in water (11.0 mL) drop-wise at 20 °C. The mixture was stirred for 16 hrs. On completion, the mixture was concentrated *in vacuo* to remove the ethanol. The aqueous phase was extracted with ethyl acetate (3 x 30 mL) and this organic phase was discarded. Then to the aqueous phase was added hydrochloric acid (2 M, 2 mL) to adjust the pH to 4-5. The mixture was extracted with dichloromethane (3 x 150 mL), and the combined organic phase was dried over sodium sulfate and concentrated *in vacuo* to give title compound, which was used without further purification, as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.41 (d, *J* = 2.4 Hz, 1H), 8.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H).

Step 3 – Methyl 2-(2-bromo-4-nitrophenyl)acetate

[00414] A mixture of 2-(2-bromo-4-nitro-phenyl)acetic acid (1.30 g, 5.00 mmol) in thionyl chloride (20.0 mL) was heated to 100 °C and stirred for 3 hrs. After the complete consumption of the acid, the solvent was concentrated *in vacuo* to give an oil. To the oil was added methanol (30.00 mL) slowly at 0 °C, and the resulting solution was warmed to 20 °C and stirred for 13 hrs. On completion, the mixture was concentrated *in vacuo* to give a yellow solid which was triturated with petroleum ether:ethyl acetate (30:1, 31 mL) for 30 mins. The mixture was filtered and the solid was collected to give the title compound. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.47 (d, *J* = 2.1 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 2H), 3.76 (s, 3H).

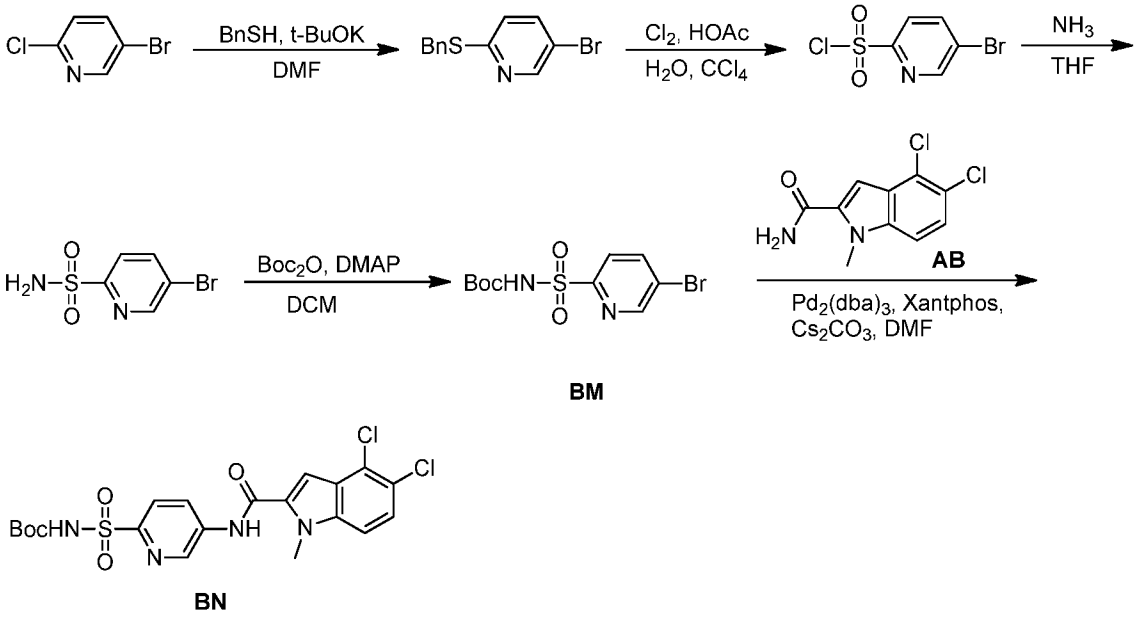
Step 4 – Methyl 2-(2-benzyl-4-nitrophenyl) acetate

[00415] Methyl 2-(2-bromo-4-nitro-phenyl)acetate (400 mg, 1.46 mmol), [benzyl(trifluoro)-boranyl]potassium (347 mg, 1.75 mmol), $Pd(dppf)Cl_2$ (107 mg, 0.146 mmol) and potassium carbonate (303 mg, 2.19 mmol) in dioxane (8.00 mL) and water (4.00 mL) was de-gassed with nitrogen three times at 20 °C and then heated to 100 °C for 3 hrs. On completion, to the mixture was added water (10 mL), and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine (30 mL), dried over sodium sulfate, and concentrated *in vacuo* to give a crude, which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ = 8.11 (dd, *J* = 2.8 Hz, 1H), 8.17 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 2H), 3.76 (s, 3H).

Step 5 – Methyl 2-(4-amino-2-benzylphenyl)acetate (Intermediate BL)

[00416] To a solution of methyl 2-(2-benzyl-4-nitro-phenyl)acetate (400 mg, 1.40 mmol) in methanol (5.00 mL) was added palladium on carbon (10%, 100 mg) under nitrogen. The suspension was degassed under vacuum and purged with hydrogen gas several times. The mixture was stirred under hydrogen gas (40 psi) at 20 °C for 3 hrs. On completion, the mixture was filtered, and the filtrate was concentrated *in vacuo* to give the title compound. ^1H NMR (300 MHz, DMSO-d_6) δ = 7.30 - 7.27 (m, 2H), 7.25 - 7.09 (m, 3H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.39 (d, *J* = 8.4, 2.4 Hz, 1H), 6.34 (d, *J* = 2.0 Hz, 1H), 4.94 (br. s, 2H), 3.80 (s, 2H), 3.52 (s, 3H), 3.45 (s, 2H).

***Tert*-butyl *N*-[(5-bromo-2-pyridyl)sulfonyl]carbamate (Intermediate BM) and *Tert*-butyl *N*-[[5-[(4,5-dichloro-1-methyl-indole-2-carbonyl)-amino]-2-pyridyl]-sulfonyl]-carbamate (Intermediate BN)**



Step 1 - 2-Benzylsulfanyl-5-bromo-pyridine

[00417] To a solution of potassium *tert*-butoxide (9.04 g, 80.5 mmol) in anhydrous *N,N*-dimethylformamide (150 mL) was added benzenemethanethiol (10.7 g, 86.5 mmol) drop-wise at 30 °C. The mixture was stirred at 30 °C for 30 minutes and then 5-bromo-2-chloro-pyridine (10.0 g, 52.0 mmol) was added portion-wise. Afterwards, the mixture was stirred at 90 °C for 15.5 hours. On completion, the reaction was diluted with water (400 mL) and extracted with ethyl acetate (4 x 300 mL). The combined organic layer was washed with brine (2 x 20 mL), dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography eluting with petroleum ether to give the title compound. LCMS: (ES^+) m/z $(M+H)^+ = 282.0$, tR = 0.985.

Step 2 - 5-Bromopyridine-2-sulfonyl chloride

[00418] To a mixture of 2-benzylsulfanyl-5-bromo-pyridine (5.50 g, 19.6 mmol) in carbon tetrachloride (100 mL) and water (20 mL) was vigorously bubbled chlorine (gas) (15 psi) for 15 minutes, during which the temperature was kept below 0 °C. Then, the mixture was stirred for another 15 minutes keeping the temperature between -10-0 °C. On completion, the organic layer

was washed with sodium sulfite (50 mL) and brine (50 mL), dried over sodium sulfate and concentrated *in vacuo*. The residue was purified by silica gel chromatography with petroleum ether: ethyl acetate = 100:1 to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.67 (d, *J* = 2.4 Hz,, 1H), 8.18 (dd, *J* = 2.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H).

Step 3 - 5-Bromopyridine-2-sulfonamide

[00419] To a solution of 5-bromopyridine-2-sulfonyl chloride (200 mg, 0.780 mmol) in tetrahydrofuran (5 mL) was added ammonia/tetrahydrofuran (4 M, 2.00 mL) at 0 °C under a nitrogen. The resulting mixture was stirred at 0-10 °C for 10 min. On completion, the reaction was concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.86 (d, *J* = 2.0 Hz, 1H), 8.34 (dd, *J* = 2.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.43 - 7.36 (m, 3H).

Step 4 - *Tert*-butyl *N*-[(5-bromo-2-pyridyl)sulfonyl]carbamate (Intermediate BM)

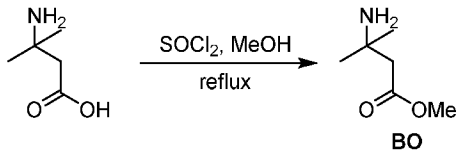
[00420] To a mixture of 5-bromopyridine-2-sulfonamide (1.00 g, 4.22 mmol) and DMAP (210 mg, 1.72 mmol) in dichloromethane (20 mL) was added di-*tert*-butyl dicarbonate ester (2.19 g, 10.0 mmol) in one portion at 25 °C under nitrogen. The mixture was stirred at 25 °C for 16 hours. On completion, the reaction was concentrated *in vacuo*. The crude product was purified by silica gel chromatography with petroleum ether:ethyl acetate = 100:1 to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.92 (s, 1H), 8.41 (d, *J* = 10.8 Hz, 1H), 8.02 (d, *J* = 10.8 Hz, 1H), 1.52 (s, 9H).

Step 5 - *Tert*-butyl *N*-[[5-[(4,5-dichloro-1-methyl-indole-2-carbonyl)-amino]-2-pyridyl]-sulfonyl]-carbamate (Intermediate BN)

[00421] To a mixture of *tert*-butyl *N*-[(5-bromo-2-pyridyl)sulfonyl]carbamate (300 mg, 0.890 mmol) and 4,5-dichloro-1-methyl-indole-2-carboxamide (216 mg, 0.890 mmol) in *N,N*-dimethylformamide (20 mL) was added cesium carbonate (580 mg, 1.78 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenylphosphane (51.5 mg, 0.089 mmol), and $Pd_2(dba)_3$ (81.5 mg, 0.089 mmol) in one portion at 25 °C under nitrogen. The mixture was stirred at 25 °C for 30 min, then heated to 100 °C and stirred for 15.5 hours. On completion, the reaction was concentrated *in vacuo*. The residue was purified by silica gel chromatography with dichloromethane:methanol = 10:1 to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ

= 11.71 (br s, 1H), 10.95 (br s, 1H), 9.02 (s, 1H), 8.40 (s, 1H), 8.01 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 9.6 Hz, 2H), 4.06 (s, 3H), 1.24 (s, 9H).

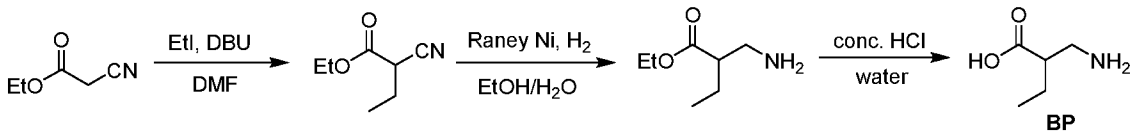
Methyl 3-amino-3-methyl-butanoate (Intermediate BO)



BO

[00422] To a mixture of 3-amino-3-methyl-butanoic acid (1.00 g, 8.54 mmol, CAS# 625-05-8) in methanol (10 mL) was added thionyl chloride (3.05 g, 25.6 mmol). Then the mixture was stirred at 80 °C for 12 hours. The mixture was concentrated *in vacuo* to give the title compound, which was used without further purification.

(±)-2-(Aminomethyl)butanoic acid (Intermediate BP)



BP

Step 1- (±)-Ethyl 2-cyanobutanoate

[00423] To a solution of ethyl 2-cyanoacetate (10.0 g, 88.4 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (13.4 g, 88.4 mmol) in *N,N*-dimethylformamide (80 mL) was added iodoethane (13.7 g, 88.4 mmol) dropwise and the reaction mixture was stirred at 20 °C for 16 hrs. On completion, the reaction mixture was poured into 500 mL water. The aqueous phase was extracted with ethyl acetate (3 x 300 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo*. The resulting oil was distilled *in vacuo* (80 °C, 5 mm Hg) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 4.32 - 4.25 (m, 2H), 3.48 (dd, J = 6.1, 7.5 Hz, 1H), 2.07 - 1.99 (m, 2H), 1.34 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.5 Hz, 3H).

Step 2- (±)-Ethyl 2-(aminomethyl)butanoate

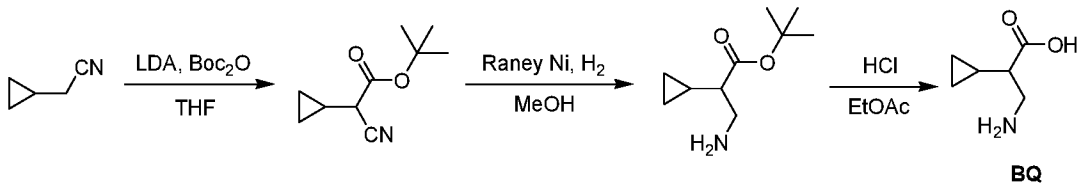
[00424] To a solution of (±)-ethyl 2-cyanobutanoate (3.00 g, 21.2 mmol) in a mixture of ethanol (30 mL) and water (5 mL) was added Raney Nickel (910 mg, 10.6 mmol) and the reaction mixture was stirred under hydrogen (50 psi) at 25 °C for 16 hrs. On completion, the

reaction mixture was carefully filtered to remove the Raney Nickel and the filtrate was concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography (dichloromethane:methanol = 20:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 146.3, tR = 0.891. ^1H NMR (400MHz, $CDCl_3$) δ = 4.22 - 4.12 (m, 2H), 2.97 - 2.88 (m, 1H), 2.85 - 2.77 (m, 1H), 2.35 (ddt, *J* = 4.9, 5.9, 8.2 Hz, 1H), 1.69 - 1.48 (m, 2H), 1.27 (t, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.5 Hz, 3H).

Step 3 - (±)-2-(Aminomethyl)butanoic acid (Intermediate BP)

[00425] To a solution of (±)-ethyl 2-(aminomethyl)butanoate (500 mg, 3.44 mmol) in water (1.00 mL) was added concentrated hydrochloric acid (12 M, 1.00 mL) and the reaction mixture was stirred at 100 °C for 16 hrs. On completion, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo* to give the title compound (700 mg, crude) as a black/brown oil used without further purification. LCMS: (ES^+) m/z $(M+H)^+$ = 118.0, tR= 0.326.

(±)-3-Amino-2-cyclopropylpropanoic acid hydrochloride (Intermediate BQ)



BQ

Step 1 – (±)-*Tert*-butyl 2-cyano-2-cyclopropylacetate

[00426] To a solution of 2-cyclopropylacetonitrile (1.46 g, 18.0 mmol) and Boc_2O (4.32 g, 19.8 mmol) in tetrahydrofuran (18 mL) was added LDA (2 M, 18.0 mL) dropwise at -70 °C under nitrogen. The reaction mixture was slowly warmed to 25 °C and stirred for 3 hrs. On completion, to the mixture was added citric acid solution (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to give a crude product, which was purified by column chromatography (petroleum ether:ethyl acetate = 20:1) to give the title compound. ^1H NMR (400 MHz, $CDCl_3$) δ 3.06 (d, *J* = 7.6 Hz, 1H), 1.44 (s, 9H), 1.27-1.31 (m, 1H), 0.44-0.66 (m, 4H).

Step 2 – (±)-*Tert*-butyl 3-amino-2-cyclopropylpropanoate

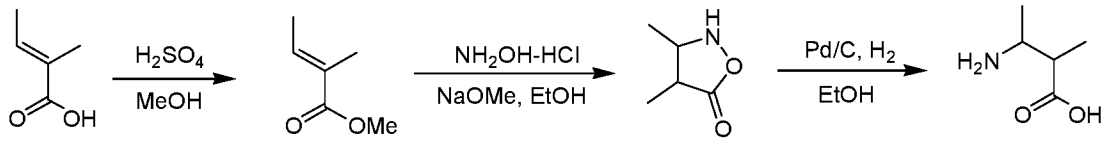
[00427] To a solution of (±)-*tert*-butyl 1-cyanocyclopropanecarboxylate (1.0 g, 5.98 mmol) in methanol (10 mL) was added Raney Nickel (50.0 mg) under nitrogen and the reaction mixture

was stirred under hydrogen gas (40 psi) at 25 °C for 3 hrs. On completion, the mixture was filtered and the filtrate was concentrated *in vacuo* to give a crude residue which was purified by column chromatography (dichloromethane:methanol = 50:1 to 20:1) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.53-2.64 (m, 2H), 1.37-1.40 (m, 1H), 1.24 (s, 9H), 0.00-0.29 (m, 5H).

Step 3 – (±)-3-Amino-2-cyclopropylpropanoic acid hydrochloride (Intermediate BQ)

[00428] To a mixture of (±)-*tert*-butyl 3-amino-2-cyclopropyl-propanoate (150 mg, 0.810 mmol) in ethyl acetate (1 mL) was added HCl/EtOAc (4 M, 5.00 mL) in one portion at 25 °C and the reaction mixture was stirred at 25 °C for 3 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.70 (br. s, 1H), 8.14 (br. s, 3H), 2.94 - 3.09 (m, 2H), 1.98 - 2.03 (m, 1H), 0.52 - 0.54 (m, 2H), 0.86 - 0.87 (m, 1H), 0.32 - 0.35 (m, 2H).

(±)-3-Amino-2-methyl-butanoic acid (Intermediate BR)



BR

Step 1 - Methyl (E)-2-methylbut-2-enoate

[00429] To a solution of (*E*)-2-methylbut-2-enoic acid (20.0 g, 199 mmol) in methanol (60 mL) was added concentrated sulfuric acid (4 mL) dropwise and the reaction mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was poured into 200 mL water and 100 mL dichloromethane was added. The aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined layer was washed with aqueous saturated sodium bicarbonate, dried over anhydrous sodium sulfate, and filtrated. The filtrate was concentrated *in vacuo* at 0 °C to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 6.87 (dq, *J* = 1.2, 7.0 Hz, 1H), 3.75 (s, 3H), 1.85 (s, 3H), 1.81 (d, *J* = 7.0 Hz, 3H).

Step 2 - (±)-3,4-Dimethylisoxazolidin-5-one

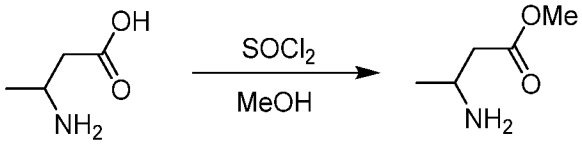
[00430] To a solution of methyl (*E*)-2-methylbut-2-enoate (1.00 g, 8.76 mmol) and hydroxylamine hydrochloride (3.04 g, 43.8 mmol) in ethanol (20 mL) was added sodium

methoxide (1.71 g, 43.8 mmol) and the reaction mixture was stirred at 80 °C for 2 hrs. On completion, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 3.39 (q, *J* = 6.5 Hz, 1H), 2.67 - 2.58 (m, 1H), 1.15 (d, *J* = 6.7 Hz, 3H), 1.09 (d, *J* = 7.3 Hz, 3H).

Step 3 - (±)-3-Amino-2-methyl-butanoic acid (Intermediate BR)

[00431] To a solution of (±)-3,4-dimethylisoxazolidin-5-one (1.00 g, 8.69 mmol) in ethanol (30 mL) was added Pd/C (100 mg, 50%) and the reaction mixture was stirred at 25 °C for 16 hrs under hydrogen (50 psi). On completion, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 3.23 (t, *J* = 6.6 Hz, 1H), 2.38 (t, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 7.3 Hz, 3H).

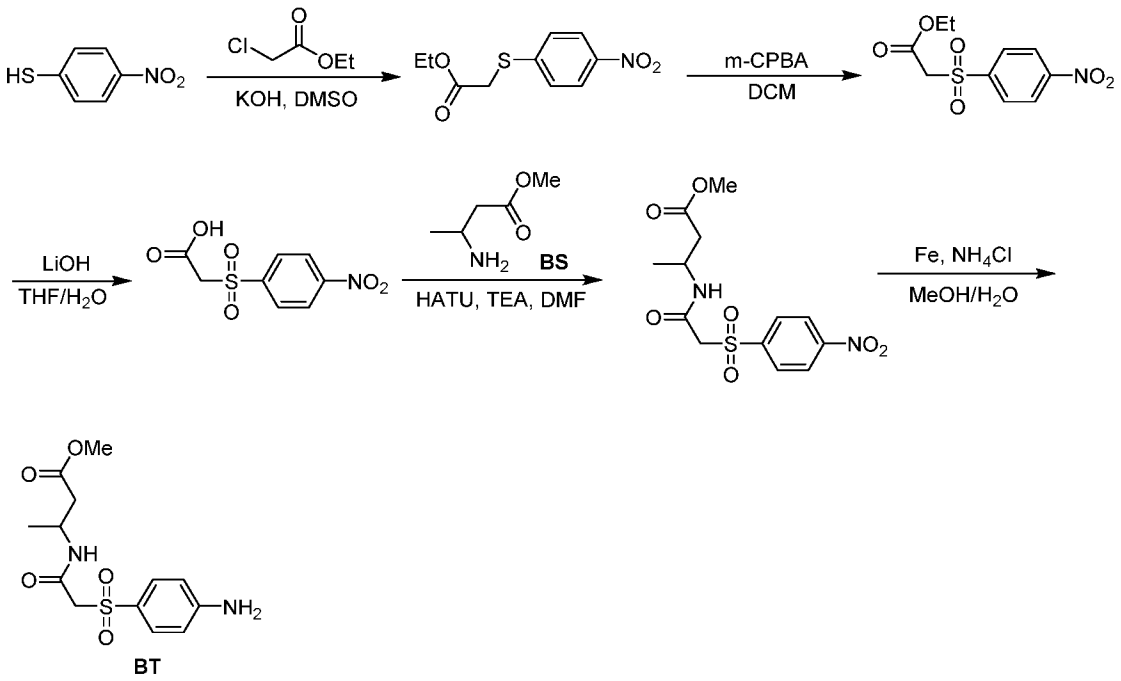
Methyl 3-aminobutanoate (Intermediate BS)



BS

[00432] To a solution of (±)-3-aminobutanoic acid (500 mg, 4.85 mmol) in methanol (10 mL) was added thionyl chloride (1.15 g, 9.70 mmol) the mixture was stirred at 80 °C for 12 hrs. On completion, the reaction was concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.37 (br. s., 3H), 3.60 (s, 3H), 3.44 (m, *J* = 6.4, 1H), 2.82 (dd, *J* = 16.4, 1H), 2.59 (dd, *J* = 16.3, 1H), 1.22 (d, *J* = 6.5 Hz, 3H).

(±)-Methyl 3-[[2-(4-aminophenyl)sulfonylacetyl]amino]butanoate (Intermediate BT)



Step 1 - Ethyl 2-(4-nitrophenyl)sulfanylacetate

[00433] To a solution of 4-nitrobenzenethiol (12.0 g, 77.3 mmol) in dimethyl sulfoxide (80 mL) was added ethyl 2-chloroacetate (12.3 g, 100 mmol) and potassium hydroxide (8.68 g, 154 mmol), and the mixture was stirred at 20 °C for 12 hrs. On completion, the reaction was poured into hydrochloric acid (1 M, 50 mL) at 0 °C, and some precipitate formed. The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 242.1, tR= 0.793. ^1H NMR (400MHz, $CDCl_3$) δ = 8.15 (d, *J* = 8.8 Hz, 2H), 7.41 (*J* = 8.8 Hz, 2H), 4.24 – 4.20 (m, 2H), 3.76 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H).

Step 2 - Ethyl 2-(4-nitrophenyl)sulfonylacetate

[00434] To a solution of ethyl 2-(4-nitrophenyl)sulfanylacetate (1.50 g, 6.22 mmol) in dichloromethane (100 mL) was added 3-chloroperoxybenzoic acid (5.37 g, 31.1 mmol) at 0 °C, and the mixture was stirred at 20 °C for 12 hrs. On completion the reaction was poured into sodium hydroxide (1 M, 10 mL) at 0 °C. The mixture was extracted with dichloromethane (3 x

20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 3:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.42 (d, *J* = 8.8 Hz, 2H), 8.17 (*J* = 8.8 Hz, 2H), 4.20 (s, 2H), 4.18 – 4.15 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H).

Step 3 -2-(4-Nitrophenyl)sulfonylacetic acid

[00435] To a solution of ethyl 2-(4-nitrophenyl)sulfonylacetate (700 mg, 2.56 mmol) in tetrahydrofuran (80 mL) was added lithium hydroxide (245 mg, 10.2 mmol) in water (80 mL), and the mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was quenched with hydrochloric acid (1 M, 15 mL), extracted with ethyl acetate (3 x 60 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.45 (d, *J* = 8.8 Hz, 2H), 8.20 (*J* = 8.8 Hz, 2H), 4.70 (s, 2H).

Step 4 - (±)-Methyl 3-[[2-(4-nitrophenyl)sulfonylacetyl]amino]butanoate

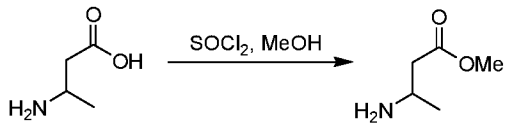
[00436] To a solution of 2-(4-nitrophenyl)sulfonylacetic acid (400 mg, 1.63 mmol) and methyl 3-aminobutanoate (210 mg, 1.79 mmol) in DMF (3 mL) was added triethylamine (495 mg, 4.89 mmol) and HATU (1.24 g, 3.26 mmol), and the mixture was stirred at 20 °C for 12 hrs. On completion the mixture was diluted with saturated ammonium chloride (10 mL), extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1 to 1:1) to give the title compound (340 mg, crude) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 - 8.44 (m, 2 H), 8.14 (d, *J* = 8.78 Hz, 2 H), 4.24 - 4.35 (m, 1 H), 4.05 (s, 2 H), 3.69 - 3.74 (m, 3 H), 2.54 (d, *J* = 5.27 Hz, 2 H), 1.25 (d, *J* = 6.53 Hz, 3 H).

Step 5 - (±)- Methyl 3-[[2-(4-aminophenyl)sulfonylacetyl]amino]butanoate (Intermediate BT)

[00437] To a solution of (±)-methyl 3-[[2-(4-nitrophenyl)sulfonylacetyl]amino]butanoate (430 mg, 1.25 mmol) in methanol (8 mL) and water (8 mL) was added iron (2.79 g, 5.00 mmol) and ammonium chloride (267 mg, 5.00 mmol). The mixture was stirred at 80 °C for 4 hours. On completion, the mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 3:1 to dichloromethane:methanol = 10:1) to give the title compound (200 mg, crude) as yellow oil. ^{1}H

NMR (400MHz, $CDCl_3$) δ = 7.63 (d, *J* = 8.8 Hz, 2H), 7.10 (*J* = 7.6 Hz, 1H), 7.68 (*J* = 8.8 Hz, 2H), 4.33 – 4.30 (m, 1H), 4.27 (s, 2H), 3.90 (s, 2H), 3.72 (s, 3H), 2.49 – 2.52 (m, 2H), 1.24 (d, *J* = 6.4 Hz, 3H).

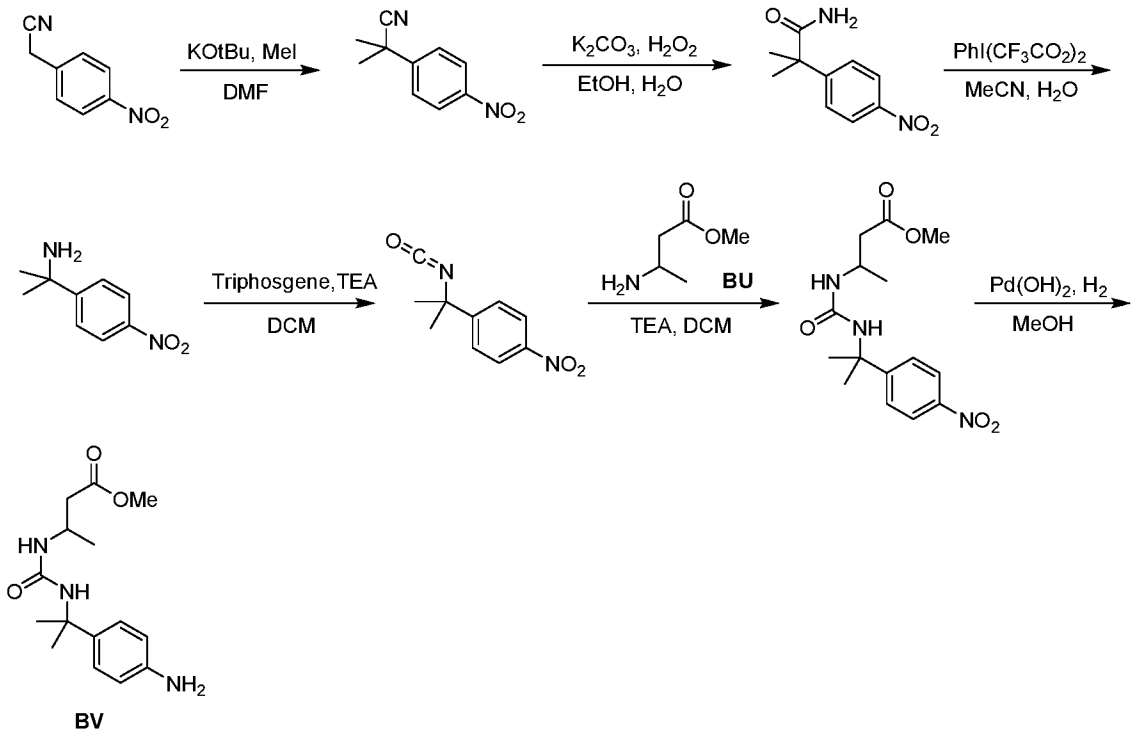
(±)-Methyl 3-aminobutanoate (Intermediate BU)



BU

[00438] To a solution of (±)-3-aminobutanoic acid (800 mg, 7.76 mmol) in methanol (20 mL) was added thionyl chloride (4.92 g, 41.3 mmol, 3 mL) and the reaction mixture was stirred at 80 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound which was used in the next step directly. ^1H NMR (400MHz, DMSO-d_6) δ = 8.20 (br. s., 3H), 3.65 (s, 3H), 3.48 - 3.43 (m, 1H), 2.83 - 2.74 (m, 1H), 2.65 - 2.56 (m, 1H), 1.24 (d, *J* = 6.7 Hz, 3H).

(±)-Methyl 3-[[1-(4-aminophenyl)-1-methyl-ethyl]carbamoylamino]butanoate (Intermediate BV)



BV

Step 1 - 2-Methyl-2-(4-nitrophenyl)propanenitrile

[00439] To a mixture of potassium *tert*-butoxide (10.9 g, 97.1 mmol) in *N,N*-dimethylformamide (300 mL) was added 2-(4-nitrophenyl)acetonitrile (15.0 g, 92.5 mmol) at 0 °C and the reaction mixture was stirred for 1 hr. Then methyl iodide (13.7 g, 97.1 mmol, 6.05 mL) was added dropwise and the reaction mixture was stirred at 0 °C for 1 hr. After an additional 1 hr at 25 °C, to this purple solution was added additional potassium *tert*-butoxide (11.9 g, 106 mmol) and the mixture was stirred at 25 °C for 1 hr. Then methyl iodide (15.1 g, 106 mmol, 6.62 mL) was added and the reaction mixture was stirred at 25 °C for 12 hrs. On completion, the reaction mixture was poured into 1000 mL water and the aqueous phase was extracted with ethyl acetate (3 x 500 mL). The combined layer was dried over anhydrous sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The resulting black oil was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.31 - 8.24 (m, 2H), 7.72 - 7.65 (m, 2H), 1.79 (s, 6H).

Step 2 - 2-Methyl-2-(4-nitrophenyl)propanamide

[00440] To a solution of potassium carbonate (1.74 g, 12.6 mmol) in a mixture of ethanol (30 mL) and water (30 mL) was added hydrogen peroxide (118 g, 3.47 mol, 100 mL). Then 2-methyl-2-(4-nitrophenyl)propanenitrile (6.00 g, 31.5 mmol) was added in portions and the reaction mixture was stirred at 25 °C for 16 hrs. On completion, 50 mL sodium sulfite solution was added to the reaction mixture and stirred at 25 °C for 0.5 hr. The resulting mixture was concentrated *in vacuo* and 100 mL water was added. The mixture was filtrated and the filter cake was washed with water (3 x 50 mL). The solid was purified by silica gel chromatography (dichloromethane: methanol = 20:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.28 - 8.13 (m, 2H), 7.63 - 7.51 (m, 2H), 5.82 (br. s., 1H), 5.54 (br. s, 1H), 1.63 (d, J = 1.8 Hz, 6H).

Step 3 - 2-(4-Nitrophenyl)propan-2-amine

[00441] To a solution of 2-methyl-2-(4-nitrophenyl)propanamide (5.40 g, 25.9 mmol) in a mixture of acetonitrile (40 mL) and water (40 mL) was added [phenyl-(2,2,2-trifluoroacetyl)oxy-iodanyl] 2,2,2-trifluoroacetate (12.2 g, 28.5 mmol) and the reaction mixture was stirred at 25 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* to removal acetonitrile. The mixture was basified with aqueous saturated sodium bicarbonate (20 mL) to pH

= 9. The aqueous phase was extracted with dichloromethane (3 x 100 mL). The combined layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give a black red oil, which was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 164.1, tR= 1.067. ^1H NMR (400MHz, $CDCl_3$) δ = 8.23 - 8.17 (m, 2H), 7.75 - 7.69 (m, 2H), 1.55 (s, 6H).

Step 4 - 1-(1-isocyanato-1-methyl-ethyl)-4-nitro-benzene

[00442] To a solution of 2-(4-nitrophenyl)propan-2-amine (500 mg, 2.77 mmol) and triethylamine (561 mg, 5.55 mmol, 0.769 mL) in dichloromethane (10 mL) was added triphosgene (329 mg, 1.11 mmol) in portions and the reaction mixture was stirred at 25 °C for 10 min. On completion, the reaction mixture was used for the next step directly.

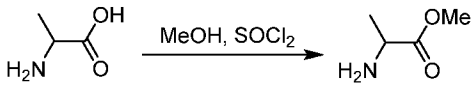
Step 5 - (±)-Methyl 3-[[1-methyl-1-(4-nitrophenyl)ethyl]carbamoylamino]butanoate

[00443] To a solution of 1-(1-isocyanato-1-methyl-ethyl)-4-nitro-benzene (570 mg, 2.76 mmol) in dichloromethane (10 mL) was added triethylamine (1.12 g, 11.0 mmol) and (±)-methyl 3-aminobutanoate (424 mg, 2.76 mmol) in turn. The reaction mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* and the resulting solid was purified by silica gel chromatography (petroleum ether: ethyl acetate = 1:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 324.1, tR= 1.211. ^1H NMR (400MHz, $CDCl_3$) δ = 8.21 - 8.14 (m, 1H), 7.61 - 7.55 (m, 1H), 5.09 (s, 1H), 4.88 (d, *J* = 8.8 Hz, 1H), 4.16 - 3.97 (m, 1H), 3.66 (s, 3H), 2.55 - 2.30 (m, 2H), 1.65 (s, 6H), 1.14 (d, *J* = 6.8 Hz, 3H).

Step 6 - (±)-Methyl 3-[[1-(4-aminophenyl)-1-methyl-ethyl]carbamoylamino]butanoate (Intermediate BV)

[00444] To a solution of (±)-methyl 3-[[1-methyl-1-(4-nitrophenyl)ethyl]carbamoylamino]butanoate (400 mg, 1.24 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ (100 mg, 50%) and the reaction mixture was stirred at 50 °C under hydrogen (50 psi) for 16 hrs. On completion, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo* to give the title compound. ^1H NMR (400MHz, $CDCl_3$) δ = 7.28 - 7.22 (m, 2H), 7.03 (d, *J* = 8.3 Hz, 1H), 6.71 - 6.62 (m, 3H), 4.97 (s, 1H), 4.54 - 4.43 (m, 1H), 3.63 (s, 3H), 2.54 (d, *J* = 5.5 Hz, 1H), 2.37 - 2.34 (m, 1H), 1.58 (d, *J* = 9.7 Hz, 6H), 0.99 (d, *J* = 6.8 Hz, 3H).

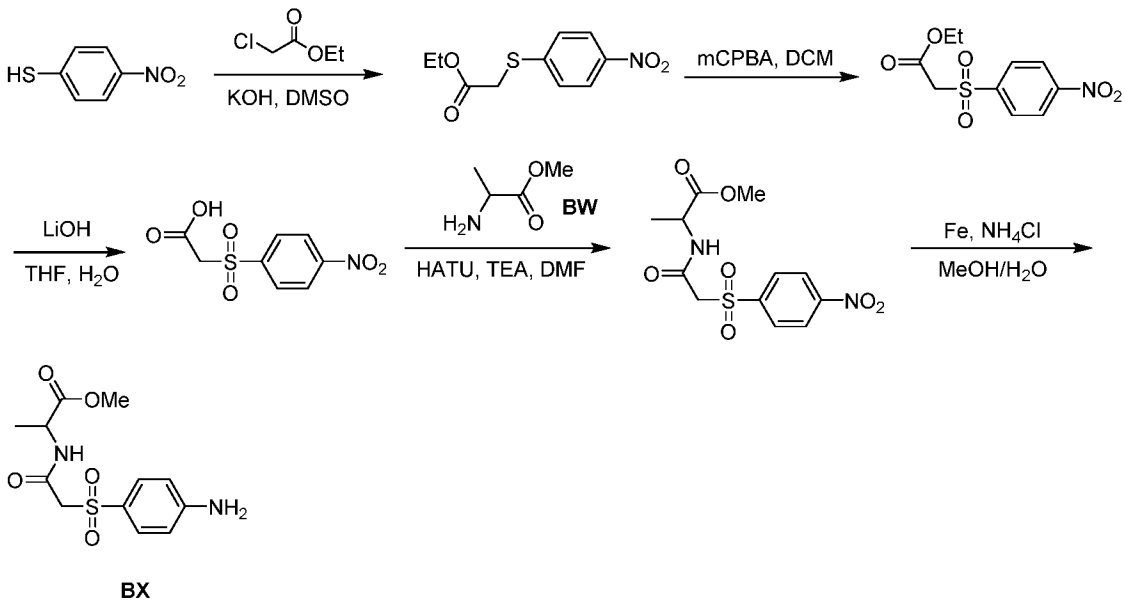
2-(±)-Aminopropanoate (Intermediate BW)



BW

[00445] To a mixture of (±)-2-aminopropanoic acid (500 mg, 5.61 mmol) in methanol (15.0 mL) was added thionyl chloride (2.00 g, 16.8 mmol) dropwise at 25 °C under nitrogen. The mixture was stirred at 62 °C for 16 hrs. On completion, the reaction was concentrated *in vacuo*. The crude was dissolved in methanol (40.0 mL) and the mixture was filtrated and the solid was dried *in vacuo* to give the title compound.

(±)-Methyl 2-[[2-(4-aminophenyl)sulfonylacetyl]amino]propanoate (Intermediate BX)



BX

Step 1 - Ethyl 2-(4-nitrophenyl)-sulfanylacetate

[00446] To a solution of 4-nitrobenzenethiol (12.0 g, 77.3 mmol) in dimethyl sulfoxide (80.0 mL) was added ethyl 2-chloroacetate (12.3 g, 101 mmol) and potassium hydroxide (8.68 g, 155 mmol), and the mixture was stirred at 20 °C for 12 hrs. On completion, the reaction mixture was transferred into hydrochloric acid (1 M, 50 mL) at 0 °C, and some precipitate formed. The mixture was extracted with ethyl acetate (3 x 20 mL) and dried over sodium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 242.1, tR = 0.793.

Step 2 - Ethyl 2-(4-nitrophenyl)sulfonylacetate

[00447] To a mixture of ethyl 2-(4-nitrophenyl)sulfanylacetate (1.50 g, 6.22 mmol) in dichloromethane (90.0 mL) was added *meta*-chloroperoxybenzoic acid (5.36 g, 31.1 mmol) portion-wise at 0 °C under nitrogen. The mixture was stirred at 25 °C 16 hrs. On completion, the reaction was washed with potassium hydroxide (1 M, 100 mL) and extracted with dichloromethane (3 x 80 mL). The organic layers were combined and washed with saturated aqueous sodium sulfite, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography with petroleum ether:ethyl acetate = 10:1 to 5:1 to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.48 - 8.42 (m, 2H), 8.22 - 8.16 (m, 2H), 4.23 - 4.17 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H).

Step 3 - 2-(4-Nitrophenyl)sulfonylacetic acid

[00448] To a mixture of ethyl 2-(4-nitrophenyl)-sulfonylacetate (1.95 g, 7.14 mmol) in tetrahydrofuran (25.0 mL) and water (25.0 mL) was added lithium hydroxide hydrate (513 mg, 21.4 mmol) in one portion at 25 °C under nitrogen. The mixture was stirred at 25 °C for 0.5 hrs. On completion, the reaction was acidified by hydrochloric acid (2 M, 15 mL) to pH = 3-4 and extracted with ethyl acetate (12 X 30 mL). The residue was washed with sodium sulfite and dried over sodium sulfate, concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.50 - 8.42 (m, 2H), 8.26 - 8.17 (m, 2H), 4.68 (s, 2H).

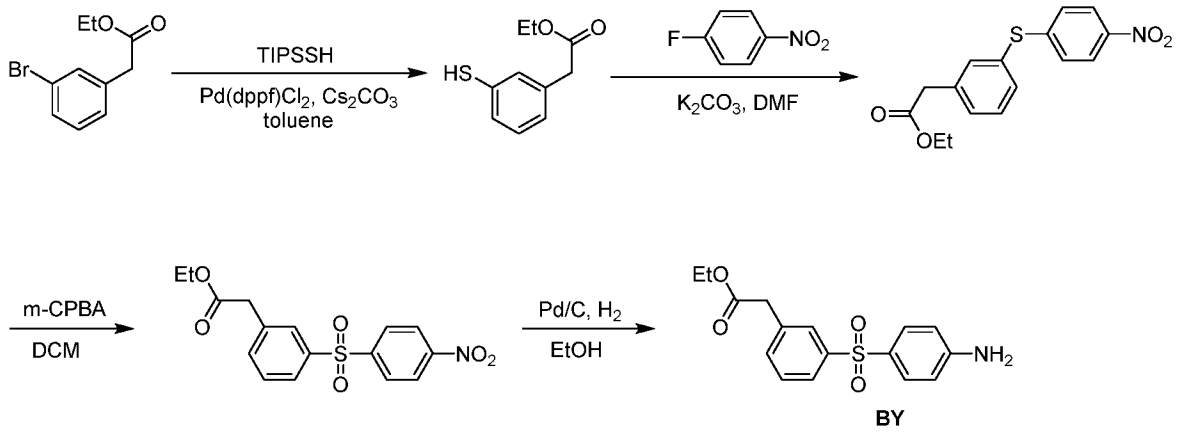
Step 4 - (±)-Methyl 2-[[2-(4-nitrophenyl)sulfonylacetyl]amino]propanoate

[00449] To a mixture of 2-(4-nitrophenyl)sulfonylacetic acid (527 mg, 2.15 mmol) and (±)-methyl 2-aminopropanoate (300 mg, 2.15 mmol) in *N,N*-dimethylformamide (20.0 mL) was added triethylamine (870 mg, 8.60 mmol) and HATU (1.63 g, 4.30 mmol) in one portion at 25 °C under nitrogen. The mixture was stirred at 25 °C for 12 hrs. On completion, the reaction was washed by water (40 mL), extracted with ethyl acetate (3 x 500 mL) and the organic layers were combined and concentrated *in vacuo*. The residue was purified by silica gel chromatography with petroleum ether:ethyl acetate = 10:1 to 5:1 to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.33 (d, *J* = 6.5 Hz, 1H), 8.16 - 8.08 (m, 2H), 7.94 - 7.86 (m, 2H), 4.18 - 4.10 (m, 1H), 4.05 - 3.99 (m, 2H), 3.51 - 3.38 (m, 3H), 1.11 - 1.05 (m, 3H).

Step 5 - (±)-Methyl 2-[[2-(4-aminophenyl)sulfonylacetyl]amino]propanoate (Intermediate BX)

[00450] To a mixture of methyl 2-[[2-(4-nitrophenyl)sulfonylacetyl]amino]propanoate (690 mg, 2.09 mmol) in methanol (20.0 mL) and water (15.0 mL) was added ammonium chloride (447 mg, 8.36 mmol) and iron powder (467 mg, 8.36 mmol) in one portion at 25 °C under nitrogen. The mixture was heated to 80 °C and stirred for 1 hr. On completion, the reaction was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography with dichloromethane:methanol = 50:1 to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.50 (d, J = 6.9 Hz, 1H), 7.43 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.14 (s, 2H), 4.20 (quin, J = 7.2 Hz, 1H), 4.08 (s, 2H), 3.61 (s, 3H), 1.20 (d, J = 7.2 Hz, 3H).

Ethyl 2-(3-((4-aminophenyl)sulfonyl)phenyl)acetate (Intermediate BY)



Step 1 - Ethyl 2-(3-mercaptophenyl)acetate

[00451] A mixture of ethyl 2-(3-bromophenyl)acetate (1.00 g, 4.11 mmol), triisopropyl(sulfanyl)silane (TIPSSH) (783 mg, 4.11 mmol), Pd(dppf)Cl_2 (150 mg, 0.206 mmol) and cesium carbonate (2.01 g, 6.17 mmol) in toluene (30 mL) was stirred at 120 °C for 5 hours. On completion, the mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (petroleum ether:ethyl acetate = 100:1) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 197.1, tR = 0.797.

Step 2 - Ethyl 2-(3-((4-nitrophenyl)thio)phenyl)acetate

[00452] A mixture of ethyl 2-(3-sulfanylphenyl)acetate (500 mg, 2.55 mmol), 1-fluoro-4-nitro-benzene (359 mg, 2.55 mmol) and potassium carbonate (704 mg, 5.10 mmol) in *N,N*-

dimethylformamide (10 mL) was stirred at 20 °C for 1 hour. The mixture was quenched with water (30 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was purified by chromatography (petroleum ether:ethyl acetate = 20:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ= 8.15 (d, *J* = 8.8 Hz, 2H), 7.52 (s, 1H), 7.51 - 7.48 (m, 2H), 7.47 - 7.42 (m, 1H), 7.34 - 7.28 (m, 2H), 4.09 (q, *J* = 7.0 Hz, 2H), 3.76 (s, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

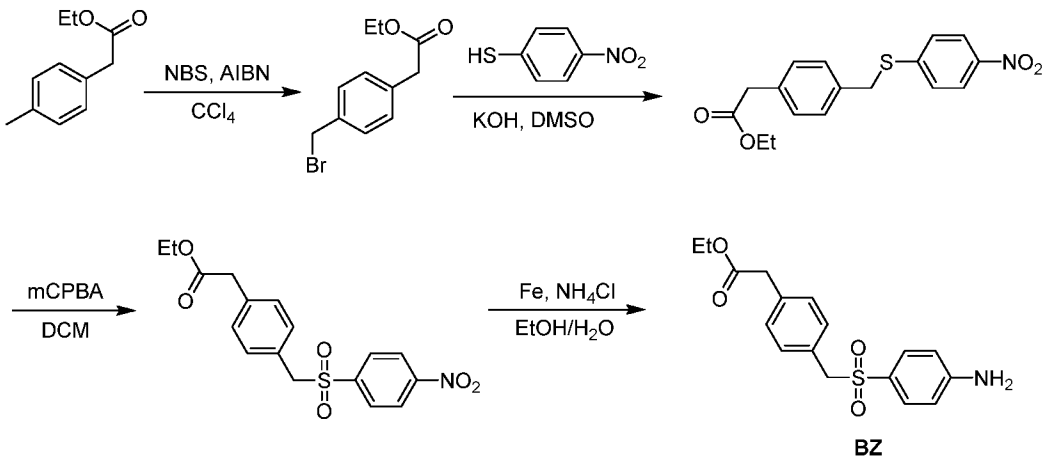
Step 3 - Ethyl 2-(3-((4-nitrophenyl)sulfonyl)phenyl)acetate

[00453] To the solution of ethyl 2-[3-(4-nitrophenyl)sulfanylphenyl]acetate (500 mg, 1.58 mmol) in dichloromethane (20 mL) was added 3-chloroperoxybenzoic acid (1.60 g, 7.90 mmol), and the mixture was stirred at 20 °C for 12 hours. On completion, the mixture was quenched with saturated sodium sulfite solution (20 mL), the organic layer was separated, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 4:1) to give the title product (300 mg, 54% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d6) δ = 8.41 (d, *J* = 8.8 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H), 7.97 (s, 1H), 7.93 (d, *J* = 6.8 Hz, 1H), 7.67 - 7.59 (m, 2H), 4.08 (q, *J* = 7.1 Hz, 2H), 3.84 (s, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

Step 4 - Ethyl 2-(3-((4-aminophenyl)sulfonyl)phenyl)acetate (Intermediate BY)

[00454] To the solution of ethyl 2-[3-(4-nitrophenyl)sulfonylphenyl]acetate (200 mg, 0.572 mmol) in ethanol (10 mL) was added Pd/C (50.0 mg, 10%), and the mixture was stirred at 20 °C under hydrogen balloon for 1 hour. On completion, the mixture was filtered. The filtrate was concentrated *in vacuo* to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 320.1, tR = 0.689.

Ethyl 2-[3-[(4-aminophenyl)sulfonylmethyl]phenyl]acetate (Intermediate BZ)



Step 1 - Ethyl 2-[4-(bromomethyl)phenyl]acetate

[00455] To a solution of ethyl 2-(*p*-tolyl)acetate (200 mg, 1.12 mmol) in perchloromethane (20 mL) was added *N*-bromosuccinimide (NBS) (239 mg, 1.34 mmol) and AIBN (18.4 mg, 0.112 mmol) in one portion, and the reaction was stirred at 50 °C for 12 hrs. On completion, 20 mL water was added to the solution. The reaction was extracted with dichloromethane (3 x 30 mL), washed with water (3 x 30 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 257, tR = 0.799.

Step 2 - Ethyl 2-[4-[(4-nitrophenyl)sulfanylmethyl]phenyl]acetate

[00456] To a solution of ethyl 2-[4-(bromomethyl)phenyl]acetate (150 mg, 0.583 mmol) in dimethyl sulfoxide (10 mL) was added potassium hydroxide (98.2 mg, 1.75 mmol) and 4-nitrobenzenethiol (272 mg, 1.75 mmol) in one portion, and the reaction was stirred at 30 °C for 12 hrs. On completion, 20 mL of water was added into the solution, then it was extracted with ethyl acetate (3 x 20 mL), washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 332, tR = 0.881.

Step 3 - Ethyl 2-[4-[(4-nitrophenyl)sulfonylmethyl]phenyl]acetate

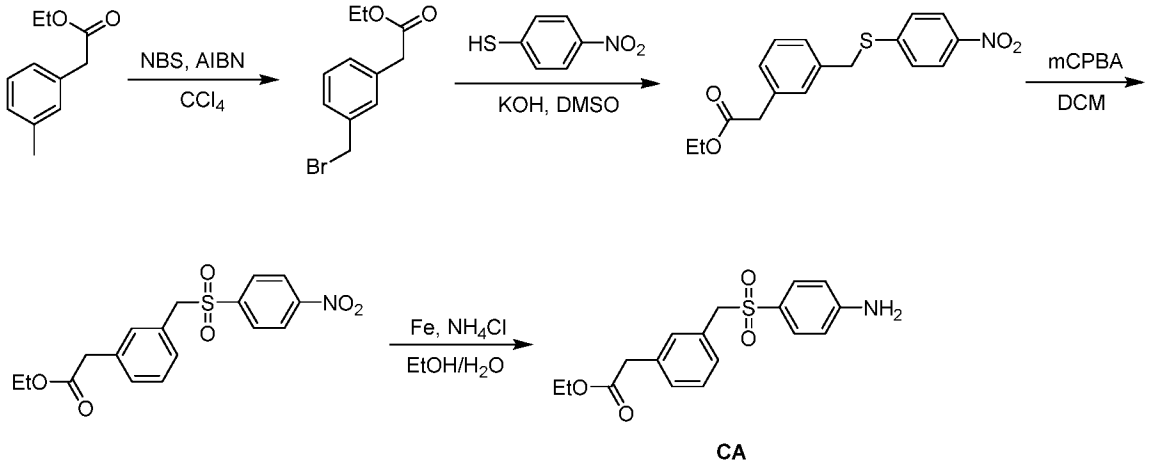
[00457] To a solution of ethyl 2-[4-[(4-nitrophenyl)sulfanylmethyl]phenyl]acetate (100 mg, 0.302 mmol) in dichloromethane (19 mL) was added *m*-chloroperbenzoic acid (52.1 mg, 0.302 mmol) in several potions, and the reaction was stirred at 30 °C for 12 hrs. On completion, 20 mL of water was added to the solution, the reaction was extracted with dichloromethane (3 x 20 mL),

washed with water (3 x 20 mL) dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 390, tR = 0.615.

Step 4 - Ethyl 2-[3-[(4-aminophenyl)sulfonylmethyl]phenyl]acetate (Intermediate BZ)

[00458] To a solution of ethyl 2-[3-[(4-nitrophenyl)sulfonylmethyl]phenyl]acetate (100 mg, 0.275 mmol) in a mixture of ethanol (20 mL) and water (4 mL) was added ammonium chloride (129 mg, 2.42 mmol) and iron (135 mg, 2.42 mmol) and the reaction was stirred at 80 °C for 1 hr. On completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography with dichloromethane:methanol = 50:1 to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 354, tR = 0.884.

Ethyl 2-[3-[(4-aminophenyl)sulfonylmethyl]phenyl]acetate (Intermediate CA)



CA

Step 1 - Ethyl 2-[3-(bromomethyl)phenyl]acetate

[00459] To a solution of ethyl 2-(*m*-tolyl)acetate (5.00 g, 28.1 mmol) in carbon tetrachloride (20 mL) was added *N*-bromosuccinimide (5.99 g, 33.7 mmol) and AIBN (460 mg, 2.81 mmol) in one portion, and the reaction was stirred at 50 °C for 12 hours. On completion, 20 mL of water was added to the solution. The reaction was extracted with dichloromethane (3 x 30 mL), washed with water (3 x 30 mL), dried over anhydrous sodium sulfate and concentrated *in vacuo* to give the a residue, and the residue was purified by column chromatography with petroleum ether:ethyl acetate = 500:1 to 100:1) to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.47 - 7.35 (m, 2H), 7.33 - 7.25 (m, 2H), 7.31 (d, *J* = 8.3 Hz, 1H), 4.50 (s, 2H), 4.17 - 4.13 (m, 2H), 3.62 (s, 2H), 1.28 - 1.26 (m, 3H).

Step 2 - Ethyl 2-[4-[(3-nitrophenyl)sulfanylmethyl]phenyl]acetate

[00460] To a solution of ethyl 2-[3-(bromomethyl)phenyl]acetate (3.00 g, 11.7 mmol) in dimethyl sulfoxide (10 mL) was added potassium hydroxide (98.2 mg, 1.75 mmol) and 4-nitrobenzenethiol (5.43 g, 35.0 mmol) in one portion, and the reaction was stirred at 30 °C for 12 hours. On completion, 20 mL of water was added into the solution. The solution was extracted with ethyl acetate (3 x 20 mL), washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 500:1 to 100:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 354.00, tR = 0.884.

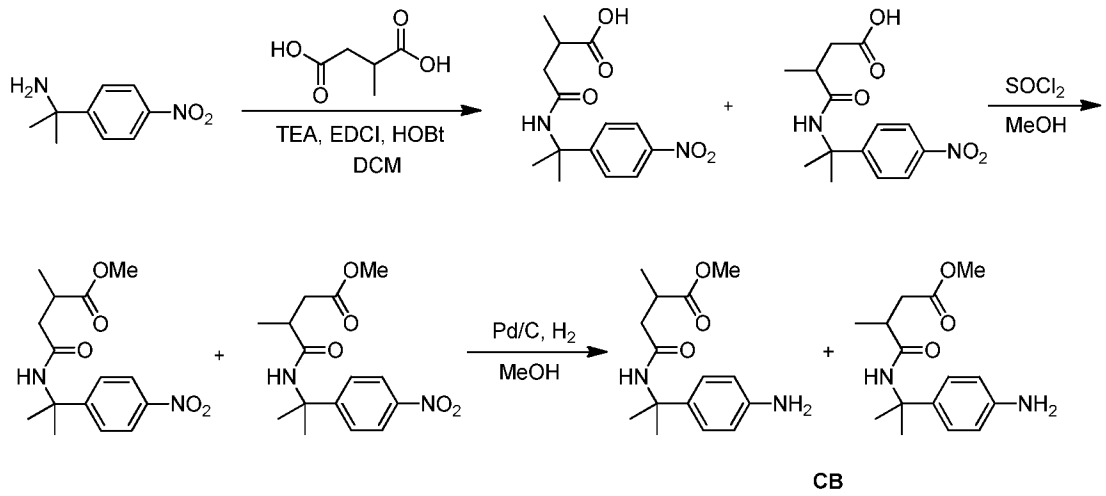
Step 3 - Ethyl 2-[3-[(4-nitrophenyl)sulfonylmethyl]phenyl]acetate

[00461] To a solution of ethyl 2-[3-[(4-nitrophenyl)sulfanylmethyl]phenyl]acetate (350 mg, 1.06 mmol) in dichloromethane (20 mL) was added 3-chlorobenzoperoxoic acid (2.15 g, 10.6 mmol) in one portion at 30 °C, and the reaction was stirred at 30 °C for 12 hours. On completion, 20 mL of aqueous sodium sulfite solution was added into the solution. The reaction was extracted with dichloromethane (3 x 20 mL), washed with water (3 x 20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 386.00, tR = 0.830.

Step 4 - Ethyl 2-[3-[(4-aminophenyl)sulfonylmethyl]phenyl]acetate (Intermediate CA)

[00462] To solution of ethyl 2-[3-[(4-nitrophenyl)sulfonylmethyl]phenyl]acetate (300 mg, 0.826 mmol) in a mixture of ethanol (20 mL) and water (4 mL) was added iron (184 mg, 3.30 mmol) and ammonium chloride (177 mg, 3.30 mmol) in one portion at 30 °C, and the reaction was stirred at 80 °C for 2 hours. On completion, the reaction was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (dichloromethane:methanol = 500:1 to 100:1) to give the title compound.

Methyl 4-((2-(4-aminophenyl)propan-2-yl)amino)-2-methyl-4-oxobutanoate and methyl 4-((2-(4-aminophenyl)propan-2-yl)amino)-3-methyl-4-oxobutanoate (Intermediate CB)



CB

Step 1 - 2-Methyl-4-((2-(4-nitrophenyl)propan-2-yl)amino)-4-oxobutanoic acid and 3-methyl-4-((2-(4-nitrophenyl)propan-2-yl)amino)-4-oxobutanoic acid

[00463] To a solution of 2-(4-nitrophenyl)propan-2-amine (272 mg, 1.51 mmol), (±)-2-methylbutanedioic acid (200 mg, 1.51 mmol) and triethylamine (306 mg, 3.02 mmol) in dichloromethane (2 mL) was added EDCI (318 mg, 1.66 mmol) and HOBt (224 mg, 1.66 mmol). The mixture was stirred at 25 °C for 16 hrs. On completion, the reaction was quenched with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 20:1) to give the title product (350 mg, crude) as yellow solid. The product contained a geometric isomer of 3-methyl-4-((2-(4-nitrophenyl)propan-2-yl)amino)-4-oxobutanoic acid which was brought on with the title compound to the next step. ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.07 (d, *J* = 8.4 Hz, 2H), 7.46 (dd, *J* = 2.5, 9.0 Hz, 2H), 6.43 (d, *J* = 17.6 Hz, 1H), 3.08 (q, *J* = 7.3 Hz, 1H), 2.72 - 2.60 (m, 1H), 2.40 - 2.21 (m, 1H), 1.64 (d, *J* = 2.0 Hz, 3H), 1.54 (d, *J* = 4.0 Hz, 3H), 1.18 - 1.10 (m, 3H).

Step 2 - Methyl 2-methyl-4-((2-(4-nitrophenyl)propan-2-yl)amino)-4-oxobutanoate and methyl 3-methyl-4-((2-(4-nitrophenyl)propan-2-yl)amino)-4-oxobutanoate

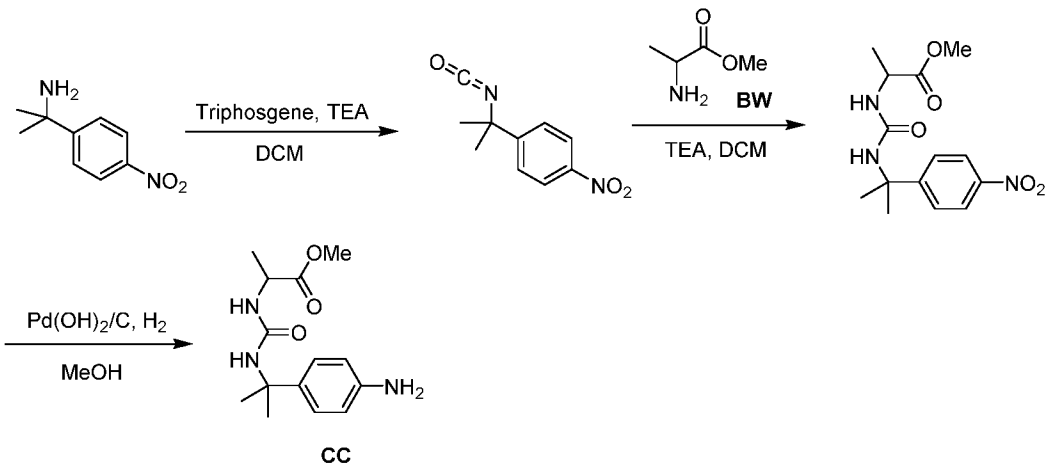
[00464] To a solution of (±)-2-methyl-4-[[1-methyl-1-(4-nitrophenyl)ethyl]amino]-4-oxo-butanoic acid and its geometric isomer (300 mg, 1.02 mmol) in methanol (5 mL) was added

thionyl chloride (146 mg, 1.22 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was concentrated. The residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate = 2:1) to give the title compounds as a mixture of isomers. LCMS: (ES^+) m/z $(M+H)^+$ = 309.1, tR= 0.688.

Step 3 - Methyl 4-((2-(4-aminophenyl)propan-2-yl)amino)-2-methyl-4-oxobutanoate and methyl 4-((2-(4-aminophenyl)propan-2-yl)amino)-3-methyl-4-oxobutanoate (Intermediate CB)

[00465] To a solution of (±)-methyl 2-methyl-4-[[1-methyl-1-(4-nitrophenyl)ethyl]amino]-4-oxo-butanoate (200 mg, 0.649 mmol) and its geometric isomer in methanol (15 mL) was added Pd/C (50.0 mg, 10%). The mixture was stirred at 20 °C under a hydrogen balloon for 2 hrs. On completion, the mixture was filtered, and the filtrate was concentrated to give the title compounds as a mixture of isomers. LCMS: (ES^+) m/z $(M+Na)^+$ = 301.1, tR = 0.955.

(±)-Methyl 2-[[1-(4-aminophenyl)-1-methyl-ethyl]carbamoylamino]propanoate (Intermediate CC)



CC

Step 1 - 1-(1-isocyanato-1-methyl-ethyl)-4-nitro-benzene

[00466] To a solution of 2-(4-nitrophenyl)propan-2-amine (400 mg, 2.22 mmol) and triethylamine (449 mg, 4.44 mmol, 0.615 mL) in dichloromethane (10 mL) was added triphosgene (263 mg, 0.888 mmol) in portions and the reaction mixture was stirred at 25 °C for 10 min. On completion, the reaction mixture was used for the next step directly.

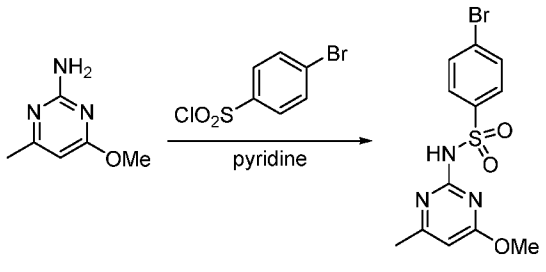
Step 2- (±)-Methyl 2-[[1-methyl-1-(4-nitrophenyl)ethyl]carbamoylamino]propanoate

[00467] To a solution of 1-(1-isocyanato-1-methyl-ethyl)-4-nitro-benzene (450 mg, 2.18 mmol) and triethylamine (882 mg, 8.72 mmol, 1.21 mL) in dichloromethane (20 mL) was added (±)-methyl 2-aminopropanoate (422 mg, 2.40 mmol) and the reaction mixture was stirred at 25 °C for 0.5 hr. On completion, the reaction mixture was concentrated *in vacuo* and the resulting solid was purified by silica gel chromatography (petroleum ether:ethyl acetate = 1:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 310.1, tR = 1.103. ^1H NMR (400MHz, DMSO-d_6) δ = 8.14 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 6.68 (s, 1H), 6.27 (d, *J* = 7.8 Hz, 1H), 4.05 (q, *J* = 7.4 Hz, 1H), 3.61 (s, 3H), 1.54 (d, *J* = 8.0 Hz, 6H), 1.23 (d, *J* = 7.3 Hz, 3H).

Step 3 - (±)-Methyl 2-[[1-(4-aminophenyl)-1-methyl-ethyl]carbamoylamino]propanoate (Intermediate CC)

[00468] To a solution of (±)-methyl 2-[[1-methyl-1-(4-nitrophenyl)ethyl]carbamoylamino]propanoate (300 mg, 0.969 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ (100 mg, 10%) and the reaction mixture was stirred under hydrogen (30 psi) at 40 °C for 4 hrs. On completion, the reaction mixture was filtrated and the filtrate was concentrated *in vacuo* to give the title compound. ^1H NMR (400MHz, $CDCl_3$) δ = 7.32 - 7.27 (m, 2H), 6.73 - 6.67 (m, 2H), 4.84 (s, 1H), 4.63 (d, *J* = 7.5 Hz, 1H), 4.37 (q, *J* = 7.3 Hz, 1H), 3.66 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H), 1.18 (d, *J* = 7.2 Hz, 3H).

4-Bromo-*N*-(4-methoxy-6-methylpyrimidin-2-yl)benzene-1-sulfonamide (Intermediate CD)

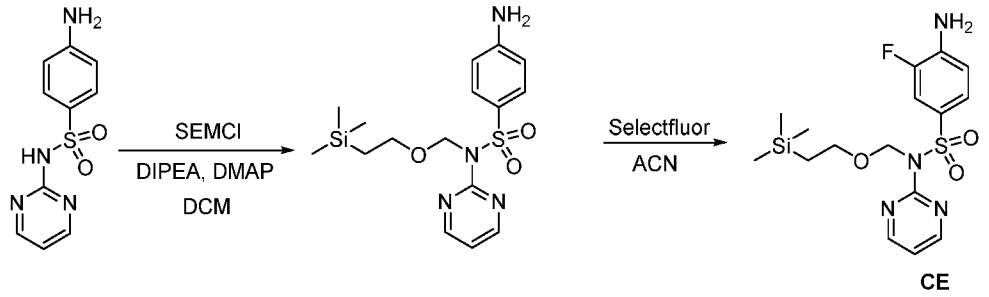


CD

[00469] 4-Bromobenzene-1-sulfonyl chloride (0.92 g, 3.59 mmol) was added portion-wise to a stirred solution of 4-methoxy-6-methylpyrimidin-2-amine (0.50 g, 3.59 mmol, CAS#7749-47-5) in pyridine (20 mL) at 0°C. The mixture was stirred at RT for 20 hrs. The solvent was removed *in vacuo* and the remaining material partitioned between water (30 mL) and DCM (30 mL). The aqueous layer was extracted again with DCM (2 x 30 mL) then the combined organics

evaporated to give a material that was purified by flash column chromatography (heptane:EtOAc 70:30 to 0:100) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 359.9.

4-Amino-3-fluoro-*N*-(pyrimidin-2-yl)-*N*-{[2-(trimethylsilyl) ethoxy]methyl}benzene-1-sulfonamide (Intermediate CE)



Step 1 - 4-amino-*N*-(pyrimidin-2-yl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzene-1-sulfonamide

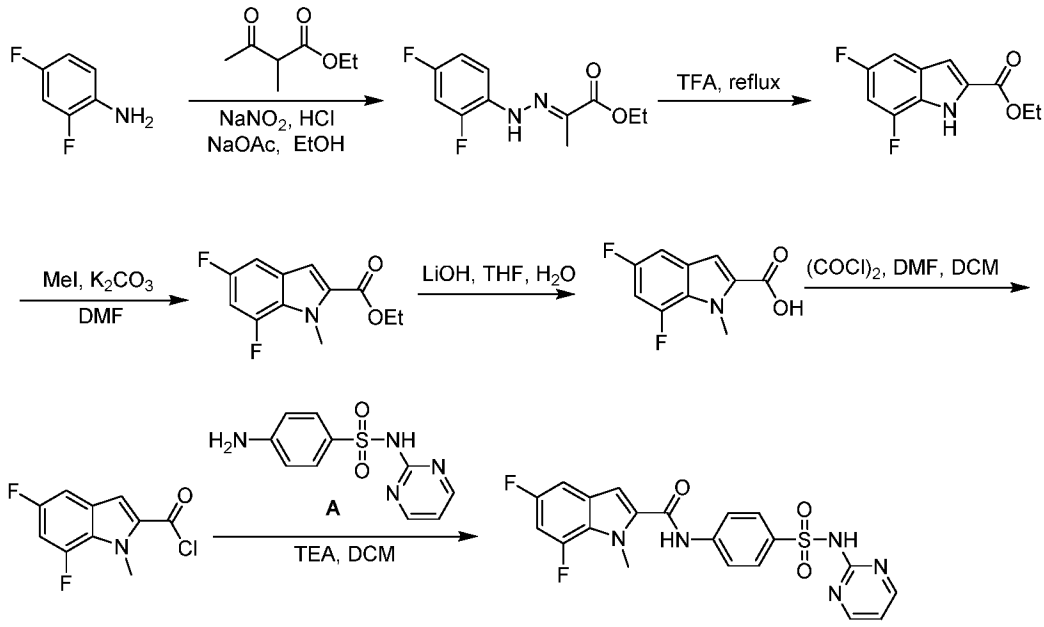
[00470] DIPEA (2.78 mL, 15.98 mmol), DMAP (0.20 g, 1.6 mmol) and SEMCl (2.83 mL, 15.98 mmol) were added sequentially at RT to a stirred solution of 4-amino-*N*-(pyrimidin-2-yl)benzenesulfonamide (4.00 g, 15.98 mmol, CAS# 68-35-9) in DCM (100 mL). The resulting mixture was stirred at RT for 20 hrs. The solvent was removed *in vacuo* and the remaining material was purified by flash column chromatography (heptane:EtOAc = 100:0 to 0:100) to afford the title compound. LCMS: (ES^+) m/z $(M+Na)^+$ = 403.1.

Step 2 - 4-Amino-3-fluoro-*N*-(pyrimidin-2-yl)-*N*-{[2-(trimethylsilyl) ethoxy]methyl}benzene-1-sulfonamide

[00471] Selectfluor (628 mg, 1.77 mmol) was added portion-wise over 10 minutes to a solution of 4-amino-*N*-(pyrimidin-2-yl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzene-1-sulfonamide (500 mg, 1.31 mmol) in MeCN (dry, 10 mL) at 0 °C and the resulting mixture was stirred at RT for 3 hrs. The reaction mixture was diluted with water (30 mL) then extracted into DCM (2 x 30 mL). The combined organic layers were evaporated to give a material that was purified by flash column chromatography (heptane:EtOAc 100:0 to 50:50) to afford the title compound. LCMS: (ES^+) m/z $(M+Na)^+$ = 421.0.

Examples 1-8 (Method 1)

5, 7-difluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide (Example 1)



Step 1 – Ethyl - (2*E*)-2-[(2,4-difluorophenyl)hydrazono]propanoate

[00472] To a solution of 2,4-difluoroaniline (10.0 g, 77.4 mmol) in a mixture of ethanol (50 mL) and water (30 mL) was added concentrated hydrochloric acid (20 mL) at -5 °C. A solution of sodium nitrite (5.88 g, 85.2 mmol) in water (20 mL) was added dropwise, during which the temperature was kept below 0 °C. Then a solution of ethyl 2-methyl-3-oxo-butanoate (11.2 g, 77.4 mmol) and sodium acetate (22.5 g, 275 mmol) in a mixture of ethanol (100 mL) and water (50 mL) was added dropwise, during which the temperature was kept below 0 °C. The mixture was stirred at 0 °C for 2 hours. On completion, the reaction mixture was poured onto ice water and extracted with EtOAc. The combined organic layers were collected, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (petroleum ether:EtOAc = 20:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.27 (t, *J* = 7.15 Hz, 3 H) 2.23 (s, 3 H) 4.16 - 4.22 (m, 2 H) 6.77 - 6.89 (m, 1 H) 7.55 - 7.63 (m, 1 H) 7.66 - 7.71 (m, 1 H).

Step 2 – Ethyl 5,7-Difluoro-1*H*-indole-2-carboxylate

[00473] Ethyl (2*E*)-2-[(2,4-difluorophenyl)hydrazono]propanoate (5.00 g, 20.6 mmol) was dissolved in trifluoroacetic acid (30 mL). The mixture was stirred at 100 °C for 16 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with ice water (30 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with aqueous saturated sodium bicarbonate (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 30:1 to 20:1) to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.56 (br. s., 1H), 7.33 (dd, *J* = 2.2, 9.1 Hz, 1H), 7.22 (d, *J* = 2.3 Hz, 1H), 7.21 - 7.14 (m, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H).

Step 3 – Ethyl-5,7-difluoro-1-methyl-indole-2-carboxylate

[00474] To a solution of ethyl-5,7-difluoro-1*H*-indole-2-carboxylate (350 mg, 1.55 mmol) in *N,N*-dimethylformamide (15 mL) was added potassium carbonate (471 mg, 3.41 mmol) and methyl iodide (880 mg, 6.20 mmol). The mixture was stirred at 60 °C for 16 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was diluted with water (30 mL) and extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give the title compound. The crude product was used directly in the next step without further purification. ^{1}H NMR (300MHz, DMSO-d_6) δ = 7.33 (dd, *J* = 2.2, 8.9 Hz, 1H), 7.27 (d, *J* = 2.1 Hz, 1H), 7.26-7.17 (m, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.17 (d, *J* = 1.3 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H).

Step 4 - 5,7-Difluoro-1-methyl-indole-2-carboxylic acid

[00475] To a solution of ethyl-5,7-difluoro-1-methyl-indole-2-carboxylate (300 mg, 1.25 mmol) in a mixture of water (2 mL) and tetrahydrofuran (8 mL) was added lithium hydroxide (90 mg, 3.76 mmol). The mixture was stirred at 20 °C for 16 hours. On completion, the reaction mixture was concentrated *in vacuo* and the residue was acidified with 2 M of hydrochloric acid to pH = 3. During which, a fine precipitate was formed. The suspension was filtered and the filter cake was washed with water and dried *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.28 (br. s., 1H), 7.33 (dd, *J* = 2.3, 8.9 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.20 (ddd, *J* = 2.3, 9.7, 13.1 Hz, 1H), 4.19 (d, *J* = 1.5 Hz, 3H).

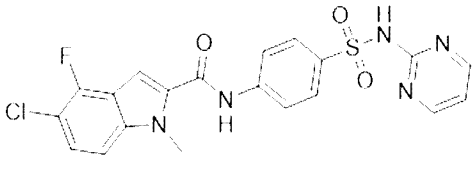
Step 5 - 5,7-Difluoro-1-methyl-indole-2-carbonyl chloride

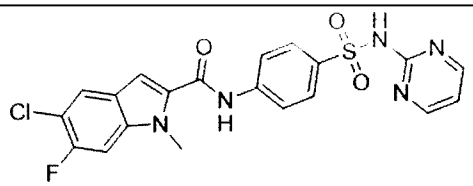
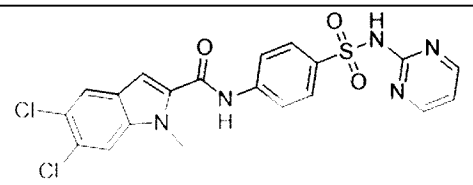
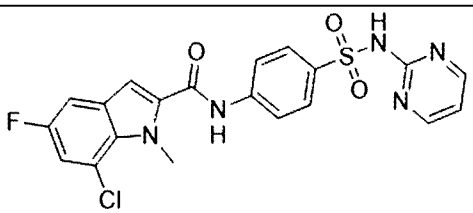
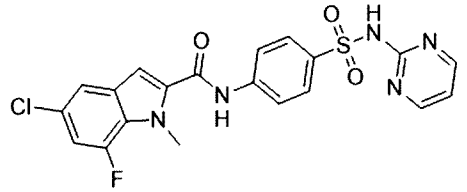
[00476] To a solution of 5,7-difluoro-1-methyl-indole-2-carboxylic acid (100 mg, 0.473 mmol) in anhydrous dichloromethane (10 mL) was added a catalytic amount of *N*,*N*-dimethylformamide. The solution was then cooled to 0 °C and oxalyl chloride (180 mg, 1.42 mmol) was added under nitrogen atmosphere. The mixture was warmed to 20 °C and stirred for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (crude). The crude product was used directly in the next step without further purification.

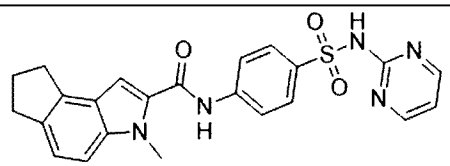
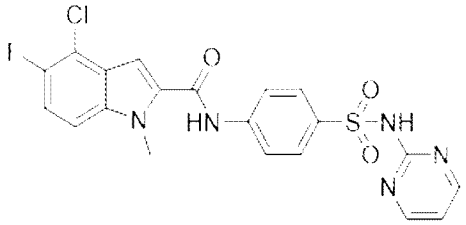
Step 6 - 5,7-difluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide

[00477] To a solution of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A) (115 mg, 0.462 mmol) in anhydrous dichloromethane (10 mL) was added triethylamine (117 mg, 1.15 mmol). A solution of 5,7-difluoro-1-methyl-indole-2-carbonyl chloride (106 mg, 0.462 mmol) dissolved in anhydrous dichloromethane (5 mL) was added dropwise to the reaction mixture at 0 °C. The mixture was then warmed to 20 °C and stirred for 16 hours. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (Condition: 0.1% TFA-MeCN; Column: YMC-Actus C_{18} 150 mm × 30 mm × 5 µm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 443.9, tR = 1.445. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.72 (br. s., 1 H), 10.81 (s, 1 H), 8.52 (d, *J* = 4.77 Hz, 2 H), 7.93 - 8.03 (m, 4 H), 7.40 (dd, *J* = 9.03, 2.01 Hz, 1 H), 7.34 (s, 1 H), 7.16 - 7.24 (m, 1 H), 7.06 (t, *J* = 4.77 Hz, 1 H), 4.14 (s, 3 H).

Method 1 Table: Compounds Synthesized via Method 1 using the appropriate amine starting material

Example #	Structure/Name	Amine Starting Material	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
2[a]	 5-chloro-4-fluoro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-	4-chloro-3-fluoro-aniline	460.0	10.63 (br.s., 1H), 8.32 (m, 2H), 7.87 (s., 4H), 7.55 - 7.51 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.46 - 7.40 (dd, J = 8.1, 8.2 Hz, 1H), 6.75 (br. s., 1H), 4.04 (s, 3H).

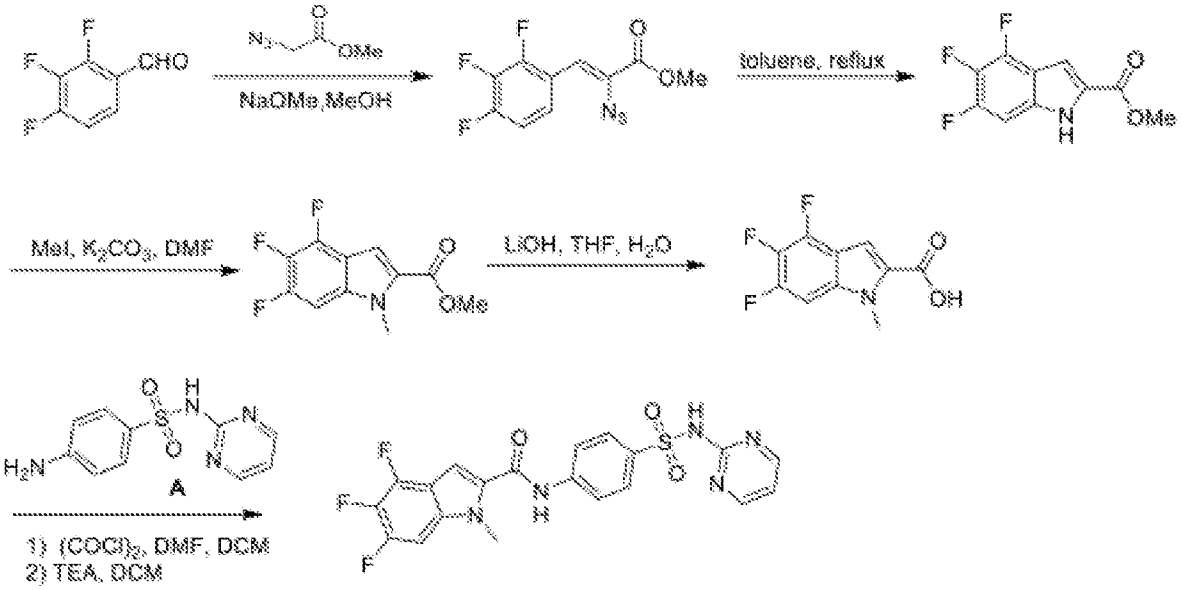
Example #	Structure/Name	Amine Starting Material	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	1*H*-indole-2-carboxamide			
3[a]	 5-chloro-6-fluoro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide	4-chloro-3-fluoro-aniline	459.9	10.67 (s, 1H), 8.40 (d, *J* = 4.9 Hz, 2H), 7.98 (d, *J* = 7.4 Hz, 1H), 7.95 - 7.86 (m, 4H), 7.77 (d, *J* = 10.5 Hz, 1H), 7.36 (s, 1H), 6.87 (t, *J* = 4.8 Hz, 1H), 3.98 (s, 3H)
4[b]	 5,6-dichloro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide	3,4-dichloro-aniline	476.0	10.75 (s, 1H), 8.46 (d, *J* = 4.9 Hz, 2H), 8.05 (s, 1H), 8.01 (s, 1H), 7.98 - 7.91 (m, 4H), 7.35 (s, 1H), 6.97 (br. s., 1H), 4.00 (s, 3H)
5	 7-chloro-5-fluoro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole 2-carboxamide	2-chloro-4-fluoro-aniline	460.1	10.88 (s, 1H), 8.51 (d, J = 4.8 Hz, 2H), 8.05 - 7.89 (m, 4H), 7.56 (d, J = 8.5 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.30 (s, 1H), 7.10 - 6.98 (m, 1H), 4.26 (s, 3H)
6	 5-chloro-7-fluoro-1-methyl-*N*-{4-	4-chloro-2-fluoro-aniline	460.0	11.86 (brs, 1H), 10.83 (s, 1H), 8.51 (d, J=4.8 Hz, 2H), 8.08 - 7.87 (m, 4H), 7.67 (d, J=1.5 Hz, 1H), 7.34 (d, J=1.5 Hz, 1H), 7.29 (dd, J=1.5, 12.5 Hz, 1H), 7.04 (t, J=4.9 Hz,

Example #	Structure/Name	Amine Starting Material	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide			1H), 4.14(s,3 H)
7	 3-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-3*H*,6*H*,7*H*,8*H*-cyclopenta[*e*]indole-2-carboxamide	indan-5-amine[c]	448.0	10.51 (s, 1H), 8.32 (d, J = 4.8 Hz, 2H), 7.86 (s, 4H), 7.34 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H),7.21 (d, J = 8.4 Hz, 1H), 6.74 (s, 1H), 4.00 (s, 3H), 3.07 (t, J = 7.2 Hz, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.19-2.11 (m, 2H)
8[d]	 4-chloro-5-fluoro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide	3-chloro-4-fluoro-aniline	460.0	11.70 (brs. 1H), 10.77 (s, 1H), 8.51 (d, J = 4.8 Hz, 2H), 8.04 - 7.94 (s, 4H), 7.66 (dd, J = 3.7, 9.1 Hz, 1H), 7.48 (s, 1H), 7.39 (t, J = 9.5 Hz, 1H), 7.05 (t, J = 4.8 Hz, 1H), 4.04 (s, 3H)

[a]Gave a mixture of regioisomers after Step 2: 5-Chloro-4-fluoro-1*H*-indole-2-carboxylate and ethyl 5-chloro-6-fluoro-1*H*-indole-2-carboxylate. Isomers were separated after Step 3 by SFC to afford the 1-ethyl 5-chloro-4-fluoro-1-methyl-indole-2-carboxylate (230 mg, 14 % yield) and 1-ethyl 5-chloro-6-fluoro-1-methyl-indole-2-carboxylate (450 mg, 28 % yield). These compounds were carried on separately to form the final products. [b]A mixture of regioisomers was obtained after Step 2, which were separated by silica gel chromatography (petroleum ether:EtOAc = 300:1 to 50:1) to afford ethyl 5,6-dichloro-1*H*-indole-2-carboxylate (120 mg, 13% yield, carried on further to product) and ethyl-4,5-dichloro-1*H*-indole-2-carboxylate (60.0 mg, 6.4% yield). [c]Indan-5-amine was converted to ethyl 3,6,7,8-tetrahydrocyclopenta[*e*]indole-2-carboxylate used in Step 3 via the three step synthesis described for Intermediate C. [d]A mixture of regioisomers was obtained after Step 2 and was carried on as a mixture through the last step. The final product was first purified by prep-HPLC (acetonitrile/water, 0.05% TFA) and then the regioisomers were separated by SFC.

Examples 9-11 (Method 2)

4,5,6-Trifluoro-1-methyl-N-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide (Example 9)



Step 1 - Methyl (Z)-2-azido-3-(2,3,4-trifluorophenyl)prop-2-enoate

[00478] To a solution of sodium methoxide (2.53 g, 46.8 mmol) in methanol (20.0 mL) was added a solution of 2,3,4-trifluorobenzaldehyde (2.50 g, 15.6 mmol) and methyl 2-azidoacetate (6.05 g, 46.8 mmol) in methanol (20 mL) dropwise at -50 °C. After the reaction mixture was stirred at -50 °C for 2 hrs, it was warmed to 25 °C and stirred at 25 °C for 14 hrs. On completion, the suspension was poured into ice-water, then filtrated and the filter cake was washed with water (40 mL). The resulting solid was purified by silica gel chromatography (petroleum ether:ethyl acetate = 50:1) to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.10 (m, 1H), 7.04 (m, 2H), 3.96 (s, 3H).

Step 2 - Methyl 4,5,6-trifluoro-1*H*-indole-2-carboxylate

[00479] A solution of methyl (*Z*)-2-azido-3-(2,3,4-trifluorophenyl)prop-2-enoate (1.18 g, 4.59 mmol) in toluene (40.0 mL) was stirred at 110 °C for 18 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 5:1) to give the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.48 (s, 1H), 7.26 (m, 2H), 3.89 (s, 3H).

Step 3 - Methyl 4,5,6-trifluoro-1-methyl-indole-2-carboxylate

[00480] To a solution of methyl-4,5,6-trifluoro-1*H*-indole-2-carboxylate (420 mg, 1.83 mmol) in *N,N*-dimethylformamide (8.00 mL) was added potassium carbonate (759 mg, 5.50 mmol) and methyl iodide (1.04 g, 7.33 mmol). The reaction mixture was stirred at 50 °C for 4 hrs. On completion, the reaction mixture was diluted with water (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ =7.27 (s, 1H), 6.87 (m, 1H), 3.95 (s, 3H), 3.84 (s, 3H).

Step 4 - 4,5,6-Trifluoro-1-methyl-indole-2-carboxylic acid

[00481] To a solution of methyl-4,5,6-trifluoro-1-methyl-indole-2-carboxylate (430 mg, 1.77 mmol) in a mixture of water (5 mL) and tetrahydrofuran (10 mL) was added lithium hydroxide (127 mg, 5.30 mmol). The reaction mixture was stirred at 25 °C for 7 hrs. On completion, the reaction mixture was concentrated *in vacuo* and the residue was acidified with 2 M aqueous HCl to pH = 3. Then the resulting mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over anhydrous sodium sulfate, filtrated and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 (s, 1H), 7.02 (m, 1H), 4.05 (s, 3H).

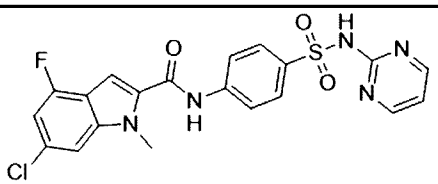
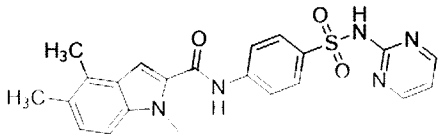
Step 5 - 4,5,6-Trifluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide

[00482] To a solution of 4,5,6-trifluoro-1-methyl-indole-2-carboxylic acid (150 mg, 0.654 mmol) in a mixture of dichloromethane (10.0 mL) and *N,N*-dimethylformamide (5.00 µL) was added oxalyl chloride (124 mg, 0.981 mmol) dropwise at 0 °C. The mixture reaction was stirred at 25 °C for 1.5 hr. On completion, the reaction mixture was concentrated *in vacuo* to give 4,5,6-trifluoro-1-methyl-indole-2-carbonyl chloride (191 mg, crude) as light yellow solid and for the next step directly.

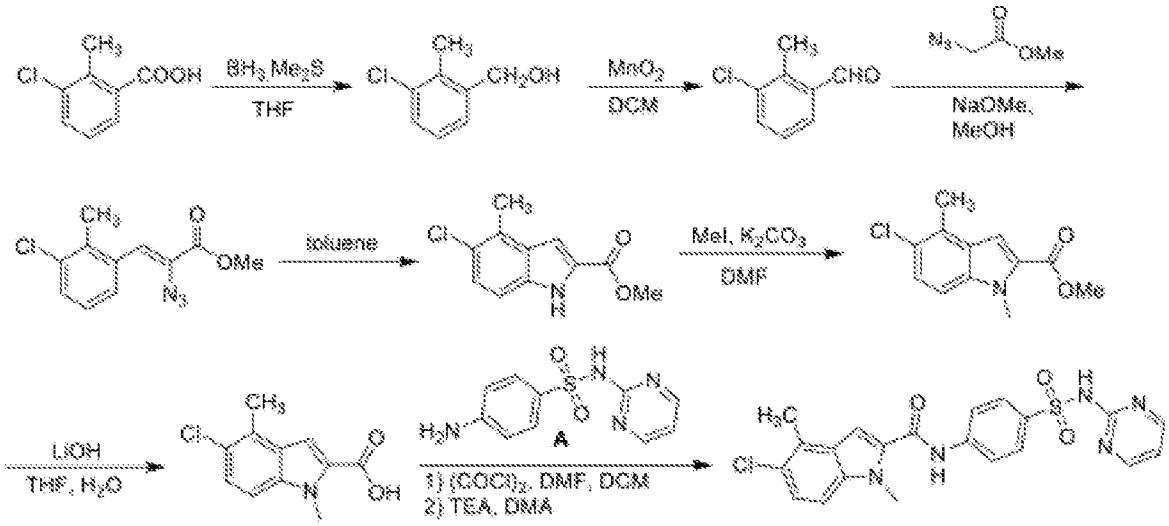
[00483] To a solution of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A) (180 mg, 0.719 mmol) and triethylamine (264 mg, 2.62 mmol) in dichloromethane (10 mL) was added a solution of 4,5,6-trifluoro-1-methyl-indole-2-carbonyl chloride (162 mg, 0.654 mmol) in dichloromethane (5 mL) dropwise. The reaction was stirred at 25 °C for 1.5 hr. On completion, the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by prep-

HPLC (0.05% ammonia-MeCN, Phenomenex Gemini C18 250*50 10μ) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 462.0, tR = 1.365. ^1H NMR (400 MHz, DMSO-d_6) δ =10.67 (s, 1H), 8.43 (d, *J* = 4.8 Hz 2H), 7.96-7.90 (m, 4H), 7.74-7.69 (m, 1H), 7.53 (s, 1H), 6.92 (s, 1H), 3.99 (s, 3H).

Method 2 Table: Compounds Synthesized via Method 2 using the appropriate aldehyde starting material

Example #	Structure	Aldehyde Starting Material	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
10	 6-chloro-4-fluoro-1-methyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide	4-chloro-2-fluoro-benzaldehyde	460.0	11.76 (br. s., 1H), 10.72 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 2H), 8.02 - 7.91 (m, 4H), 7.68 (s, 1H), 7.48 (s, 1H), 7.12 (dd, *J* = 10.0, 1.4Hz, 1H), 7.04 (t, *J* = 4.9 Hz, 1H), 4.01 (s, 3H)
11	 1,4,5-trimethyl-*N*-{4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1*H*-indole-2-carboxamide	2, 3-dimethylbenzaldehyde	436.1	10.60 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 2H), 7.97 (s, 4H), 7.43 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 7.09 - 6.98 (m, 1H), 3.97 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H)

Example 12 (Method 3): 5-Chloro-1,4-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl] indole-2-carboxamide



Step 1 - 3-Chloro-2-methyl-phenyl)methanol

[00484] To a solution of 3-chloro-2-methyl-benzoic acid (500 mg, 2.93 mmol) in anhydrous tetrahydrofuran (10 mL) was added BH_3-Me_2S (10 M, 2.93 mL) dropwise at 30 °C under nitrogen. The solution was stirred at 80 °C for 12 hours. On completion, the reaction mixture was concentrated *in vacuo*. The residue was poured into water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 20 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 100:1 to 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.34 (d, *J*=7.9 Hz, 1H), 7.32 - 7.25 (m, 1H), 7.21 - 7.05 (m, 1H), 4.73 (s, 2H), 2.41 (s, 3H).

Step 2 - 3-Chloro-2-methyl-benzaldehyde

[00485] To a solution of (3-chloro-2-methyl-phenyl)methanol (400 mg, 2.55 mmol) in dichloromethane (20 mL) was added manganese dioxide (2.22 g, 25.5 mmol) in one portion at 20 °C under nitrogen. The mixture was stirred at 30-40 °C for 12 hours. On completion, the mixture was filtered and concentrated, the residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 500:1 to 200:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ =

10.28 (s, 1H), 7.73 - 7.71 (d, *J* = 7.6 Hz, 1H), 7.61 - 7.60 (d, *J* = 6.8 Hz, 1H), 7.33 - 7.29 (m, 1H), 2.72 (s, 3H).

Step 3 - Methyl (Z)-2-azido-3-(3-chloro-2-methylphenyl) prop-2-enoate

[00486] To a solution of sodium methoxide (2.34 g, 43.2 mmol) in methanol (140 mL) was added 3-chloro-2-methyl-benzaldehyde (5.80 g, 43.3 mmol) and methyl 2-azidoacetate (16.8 g, 129 mmol,) dropwise at -20 °C under nitrogen. The mixture was stirred at 20 °C for 11 hours. On completion, the mixture was poured into ice-water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined organic phase was washed with saturated brine (2 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 500:1 to 5:1) to give the title compound. ^{1}H NMR (300MHz, $CDCl_3$) δ = 8.98 (br. s., 1H), 7.37 - 7.10 (m, 3H), 3.98 (s, 3H), 2.60 (s, 3H).

Step 4 - Methyl 5-chloro-4-methyl-1*H*-indole-2-carboxylate

[00487] Methyl (Z)-2-azido-3-(2-chloro-3-methyl-phenyl) prop-2-enoate (8.20 g, 32.6 mmol) in toluene (50 mL) was stirred at 80 °C for 11 hours. On completion, the mixture was concentrated *in vacuo*. The residue purified by silica gel chromatography (petroleum ether:ethyl acetate = 100:1 to 1:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 9.05 (br. s., 1H), 7.41 - 7.36 (m, 1H), 7.33 (dd, *J* = 6.9, 8.2 Hz, 2H), 4.05 (s, 3H), 2.67 (s, 3H).

Step 5 - Methyl 5-chloro-1,4-dimethyl-1*H*-indole-2-carboxylate

[00488] To a solution of methyl 5-chloro-4-methyl-1*H*-indole-2-carboxylate (660 mg, 2.95 mmol) in *N,N*-dimethylformamide (10 mL) was added potassium carbonate (1.22 g, 8.85 mmol) in one portion at 20 °C, then methyl iodide (1.68 g, 11.8 mmol) was added to the solution at 30 °C under nitrogen. The mixture was stirred at 40 °C and stirred for 11 hours. On completion, the mixture was concentrated *in vacuo*, the residue was poured into ice-water (20 mL) and the aqueous phase was extracted with ethyl acetate (3 x 20 mL). The combined organic phase was washed with saturated brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to afford the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.33 – 7.28 (m, 2H), 7.17 - 7.14 (d, *J* = 11.6 Hz, 1H), 3.08 (s, 3H), 3.93 (s, 3H), 2.57 (s, 3H).

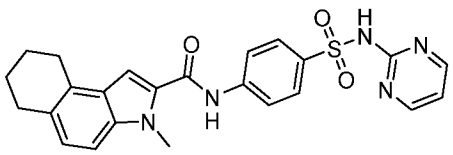
Step 6 - 5-Chloro-1,4-dimethyl-1*H*-indole-2-carboxylic acid

[00489] To a solution of methyl 5-chloro-1,4-dimethyl-indole-2-carboxylate (640 mg, 2.69 mmol) in a mixture of tetrahydrofuran (6 mL) and water (6 mL) was added lithium hydroxide (129 mg, 5.39 mmol) in one portion at 25 °C under nitrogen. The mixture was stirred at 25 °C for 11 hours. On completion, the mixture was concentrated *in vacuo*, the residue was adjusted to pH = 3 with 3 M hydrochloric acid. The solid was filtered and dried *in vacuo* to give the title compound.

Step 7 - 5-Chloro-1,4-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide

[00490] To a solution of 5-chloro-1,4-dimethyl-indole-2-carboxylic acid (300 mg, 1.34 mmol) in dichloromethane (1 mL) was added oxalyl chloride (1.70 g, 13.4 mmol) and *N,N*-dimethylformamide (10 µL) dropwise at 0 °C under nitrogen. The mixture was stirred at 30 °C for 1 hour. On completion, the reaction was concentrated *in vacuo* to afford 5-chloro-1, 4-dimethyl-indole-2-carbonyl chloride (324 mg, 99% yield) as yellow solid which was brought on directly to the next step. To a solution of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A) (402 mg, 1.61 mmol) in DMA (10 mL) was added triethylamine (813 mg, 8.03 mmol) dropwise at 0 °C under nitrogen. Then 5-chloro-1,4-dimethyl-indole-2-carbonyl chloride (324 mg, 1.34 mmol) was added to the solution at 0 °C under nitrogen. The mixture was stirred at 0 °C for 1 hour. On completion, the reaction was concentrated *in vacuo*, the residue was purified by recrystallized from (dichloromethane:methanol = 1:1, 50 mL) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 456.1, tR= 0.875. ^1H NMR (400MHz, DMSO-d_6) δ = 11.75 (br. s., 2H), 10.69 (s., 1H), 8.51 (d, *J* = 4.3 Hz, 2H), 7.97 (s, 4H), 7.47 (s., 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.05 (s., 1H), 3.99 (br. s., 3H), 2.55 (br. s., 3H).

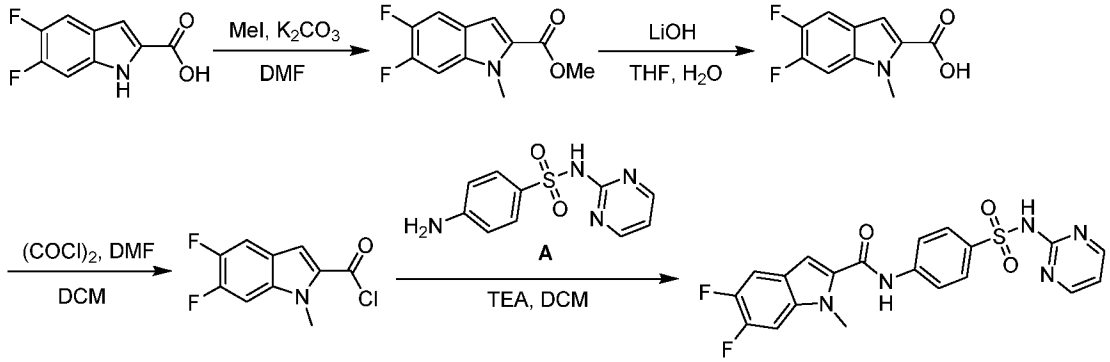
Example 13: 3-Methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]-6,7,8,9-tetrahydrobenzo[*e*]-indole-2- carboxamide



[00491] 3-Methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]-6,7,8,9-tetrahydrobenzo[*e*]-indole-2- carboxamide was synthesized via Method 3 using tetralin-5-carboxylic acid as the starting material. The acid was transformed as detailed in the preparation for Intermediate AR. LCMS: (ES^+) m/z $(M+H)^+$ = 462.1, tR= 1.038. ^1H NMR (400MHz, DMSO-d_6) δ = 10.57 (s, 1H), 8.49

(d, *J* = 4.9 Hz, 2H), 7.96 (s, 4H), 7.36 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 7.07 - 6.96 (m, 2H), 3.98 (s, 3H), 2.93 (t, *J* = 5.7 Hz, 2H), 2.79 (t, *J* = 5.6 Hz, 2H), 1.91 - 1.76 (m, 4H).

Example 14 (Method 4): 5,6-Difluoro-1-methyl-*N*-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide



Step 1 - Methyl 5,6-Difluoro-1-methyl-indole-2-carboxylate

[00492] To a mixture of 5,6-difluoro-1*H*-indole-2-carboxylic acid (1.00 g, 5.07 mmol, CAS# 169674-35-5) in *N,N*-dimethylformamide (15 mL) was added potassium carbonate (2.80 g, 20.3 mmol) and iodomethane (4.32 g, 30.4 mmol). The reaction mixture was then stirred at 60 °C for 12 hours. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was purified by silica gel chromatography (petroleum ether:ethyl acetate = 10:1) to give the title compound. ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.42 (dd, *J* = 7.8, 10.2 Hz, 1H), 7.25 (s, 1H), 7.17 (dd, *J* = 6.6, 10.7 Hz, 1H), 4.05 (s, 3H), 3.93 (s, 3H).

Step 2 - 5,6-Difluoro-1-methyl-indole-2-carboxylic acid

[00493] To a mixture of methyl 5,6-difluoro-1-methyl-indole-2-carboxylate (970 mg, 4.31 mmol) in a mixture of tetrahydrofuran (30 mL) and water (10 mL) was added lithium hydroxide (542 mg, 12.9 mmol). The reaction mixture was then stirred at 30 °C for 12 hours. On completion, the solvent was removed and the residue was acidified with 2 M HCl, then extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated to yield the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 13.08 (br. s., 1H), 7.75 (dd, *J* = 6.9, 11.7 Hz, 1H), 7.69 (dd, *J* = 8.2, 10.9 Hz, 1H), 7.21 (d, *J* = 0.8 Hz, 1H), 4.00 (s, 3H).

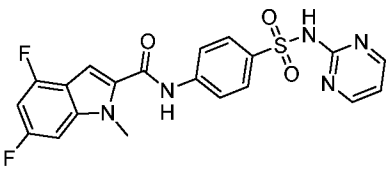
Step 3 - 5,6-Difluoro-1-methyl-indole-2-carbonyl chloride

[00494] To a solution of 5,6-difluoro-1-methyl-indole-2-carboxylic acid (200 mg, 0.947 mmol) in anhydrous dichloromethane (15 mL) was added one drop of DMF. Then, the solution was cooled to 0 °C and oxalyl chloride (240 mg, 1.89 mmol) in anhydrous dichloromethane (15 mL) was added under an atmosphere of nitrogen. The reaction mixture was allowed to come to 30 °C and stirred for 1 hour. On completion, the mixture was concentrated *in vacuo* to yield the title compound (crude), which was used in the next step directly without further purification.

Step 4 - 5,6-Difluoro-1-methyl-*N*-(4-(*N*-(pyrimidin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide

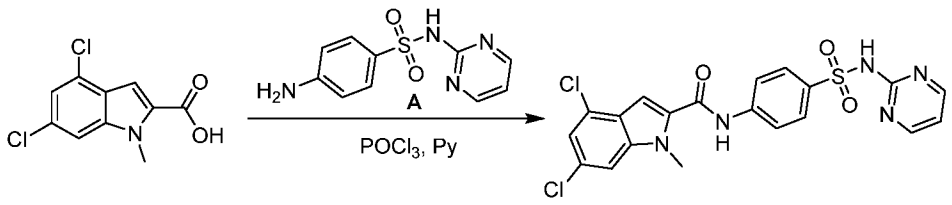
[00495] To a mixture of 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A) (251 mg, 1.01 mmol) in DMA (2 mL) was added triethylamine (277 mg, 2.74 mmol). The mixture was stirred at 0 °C for 0.5 hour. Then a solution of 5,6-difluoro-1-methyl-indole-2-carbonyl chloride (210 mg, 0.914 mmol) in anhydrous dichloromethane (3 mL) was added dropwise at 0 °C. The mixture was then warmed to 30 °C and allowed to stir for 12 hrs. On completion, the mixture was concentrated *in vacuo* to get a residue. The residue was purified by prep-HPLC (0.05% ammonia-acetonitrile) to yield the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 444.0, tR = 1.354. ^1H NMR (400MHz, DMSO-d_6) δ = 10.67 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 2H), 8.01-7.91 (m, 4H), 7.82-7.72 (m, 2H), 7.37 (s, 1H), 7.04 (t, *J* = 4.8 Hz, 1H), 3.98 (s, 3H).

Example 15: 4,6-Difluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide



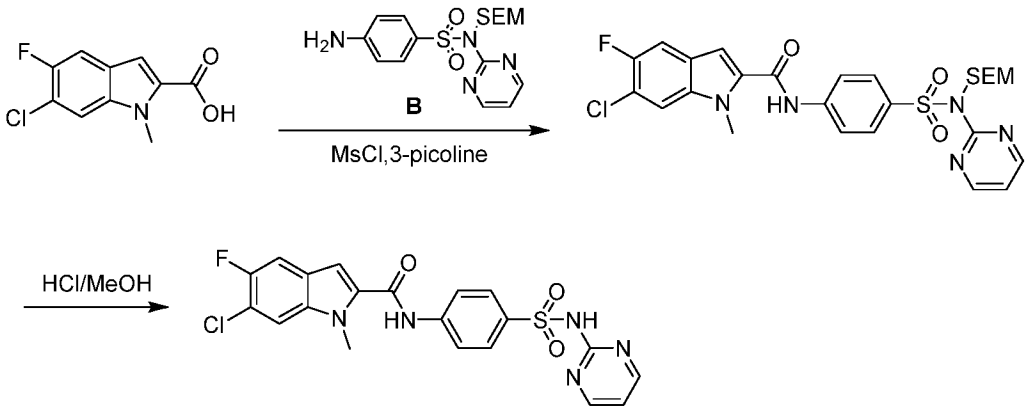
[00496] 4,6-Difluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide was synthesized via Method 4 using 4,6-difluoro-1*H*-indole-2-carboxylic acid (CAS# 247564-66-5) as the starting material. LCMS: (ES^+) m/z $(M+H)^+$ = 444.0, tR = 0.942. ^1H NMR (400MHz, DMSO-d_6) δ = 11.78 (brs, 1H), 10.72 - 10.61 (s, 1H), 8.4.9 (d, *J* = 4.9Hz, 2H), 7.96 (m, 4H), 7.48 (s, 1H), 7.43 (dd, *J* = 10Hz, 1H), 7.02 (m, 2H), 4.00 (s, 3H).

Example 16: 4,6-Dichloro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl] indole-2-carboxamide



[00497] 4,6-Dichloro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl] indole-2-carboxamide was synthesized via Method 4, starting with 4,6-dichloro-1*H*-indole-2-carboxylic acid (CAS# 101861-63-6) in the first step. In the third step, instead of treating the acid with oxalyl chloride, to a mixture of 4,6-dichloro-1-methyl-indole-2-carboxylic acid (100 mg, 0.410 mmol) and 4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide (Intermediate A) (103 mg, 0.409 mmol) in pyridine (2 mL) was added phosphorus oxychloride (94 mg, 0.615 mmol) at 0 °C. The mixture was then stirred at 30 °C for 3 hours. On completion, the reaction solution was concentrated. The residue was purified by prep-HPLC (acetonitrile/water, 0.05% TFA) to give 4,6-dichloro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl] indole-2-carboxamide. LCMS: (ES^+) m/z $(M+H)^+$ = 476.0, tR = 0.897. ^1H NMR (400MHz, DMSO-d_6) δ = 11.71 (br. s., 1H), 11.03 - 10.59 (m, 1H), 8.52 (d, *J* = 4.8 Hz, 2H), 7.99 (s, 4H), 7.83 (s, 1H), 7.47 (s, 1H), 7.35 (d, *J* = 1.3 Hz, 1H), 7.07 (br. s., 1H), 4.03 (s, 3H).

Example 17 (Method 5): 6-Chloro-5-fluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl) phenyl]indole-2-carboxamide



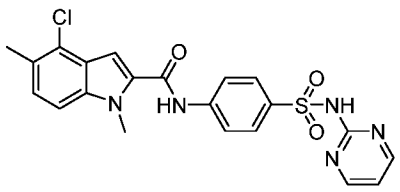
Step 1 - 6-Chloro-5-fluoro-*N*-[4-[pyrimidin-2-yl(2-trimethylsilylethoxymethyl)sulfamoyl] phenyl]-1-methylindole-2-carboxamide

[00498] To a solution of 6-chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (373 mg, 1.75 mmol, synthesized via Method 1, Steps 1-4) and 3-picoline (0.104 mL) in acetonitrile (15 mL) was added MsCl (200 mg, 1.75 mmol) with stirring at 0 °C for 0.5 hour. Then a solution of 4-amino-*N*-pyrimidin-2-yl-*N*-(2-trimethylsilylethoxymethyl) benzenesulfonamide (Intermediate B) (799 mg, 2.10 mmol) in acetonitrile (1 mL) was added dropwise into the mixture. The mixture was stirred at 25 °C for 11.5 hours. On completion, the mixture was filtrated and concentrated to give 6-chloro-5-fluoro-*N*-[4-[pyrimidin-2-yl(2-trimethylsilylethoxymethyl)sulfamoyl]phenyl]-1-methylindole-2-carboxamide. LCMS: (ES^+) m/z $(M+H)^+$ = 590.1, tR = 1.082.

Step 2 - 6-Chloro-5-fluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl) phenyl] indole-2-carboxamide

[00499] To a mixture of 6-chloro-5-fluoro-*N*-[4-[pyrimidin-2-yl(2-trimethylsilylethoxymethyl)sulfamoyl]phenyl]-1-methylindole-2-carboxamide (990 mg, 1.68 mmol) in methanol (5 mL) was added hydrochloric acid/methanol (3 mL). Then the mixture was stirred at 30 °C for 12 hours. On completion, the mixture was concentrated to give the crude product. Then the residue was triturated with 10 mL methanol. The mixture was then filtered to give 6-Chloro-5-fluoro-1-methyl-*N*-[4-(pyrimidin-2-ylsulfamoyl) phenyl] indole-2-carboxamide. LCMS: (ES^+) m/z $(M+H)^+$ = 460.0, tR= 0.894. ^1H NMR (400MHz, DMSO-d_6) δ = 11.82 (brs. 1H), 10.73 (s, 1H), 8.52 (d, *J* = 4.9 Hz, 2H), 8.05 - 7.89 (m, 5H), 7.77 (d, *J* = 9.8 Hz, 1H), 7.36 (s, 1H), 7.06 (t, *J* = 4.9 Hz, 1H), 4.05 - 3.93 (m, 3H).

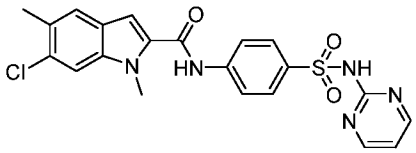
Example 18: 4-Chloro-1,5-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide



[00500] 4-Chloro-1,5-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide was synthesized via Method 5 using 3-chloro-4-methyl-aniline to make 4-Chloro-1,5-dimethyl-indole-2-carboxylic acid as the coupling partner. After Step 2 of Method 1 to form the ester, 2 regioisomers, ethyl 4-chloro-5-methyl-1*H*-indole-2-carboxylate and ethyl 6-chloro-5-methyl-1*H*-indole-2-carboxylate, were obtained and were carried on as a mixture through the last step. After

the final step, the crude product was purified by prep-HPLC (acetonitrile/water, 0.05% TFA) and SFC to separate the regioisomers. LCMS: (ES^+) m/z $(M+H)^+$ = 456.0, tR = 0.946. ^1H NMR (400MHz, DMSO-d_6) δ = 11.59 (brs. 1 H), 10.72 (s, 1H), 8.52 (d, *J* = 4.9 Hz, 2H), 8.03 - 7.94 (s, 4H), 7.55 - 7.47 (m, 1H), 7.42 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.05 (t, *J* = 4.8 Hz, 1H), 4.01 (s, 3H).

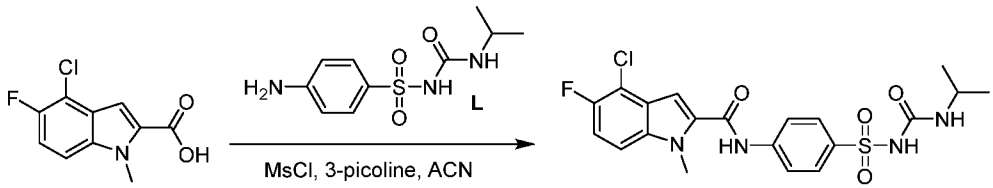
Example 19: 6-Chloro-1,5-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide



[00501] 6-Chloro-1,5-dimethyl-*N*-[4-(pyrimidin-2-ylsulfamoyl)phenyl]indole-2-carboxamide was synthesized via Method 5 with 3-chloro-4-methylaniline to form 6-Chloro-1,5-dimethyl-indole-2-carboxylic acid as the coupling partner. LCMS: (ES^+) m/z $(M+H)^+$ = 456.0, tR = 0.923. ^1H NMR (400MHz, DMSO-d_6) δ = 11.72 (brs, 1H), 10.66 (s, 1H), 8.51 (d, *J* = 4.9 Hz, 2H), 8.03 - 7.92 (s, 4H), 7.74 (s, 1H), 7.67 (s, 1H), 7.30 (s, 1H), 7.05 (t, *J* = 4.8 Hz, 1H), 3.97 (s, 3H).

Examples 20-69 (Method 6)

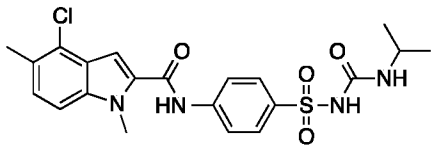
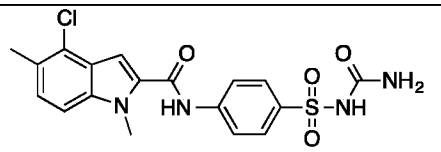
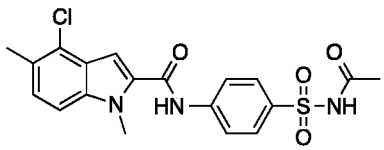
4-Chloro-5-fluoro-*N*-[4-(isopropylcarbamoylsulfamoyl)phenyl]-1-methyl-indole-2-carboxamide (Example 20)

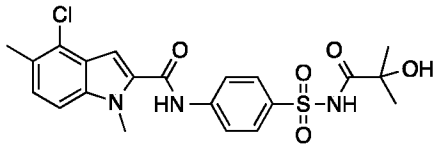
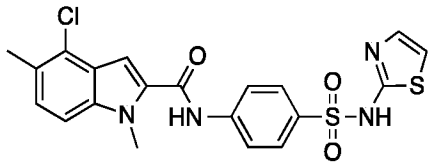
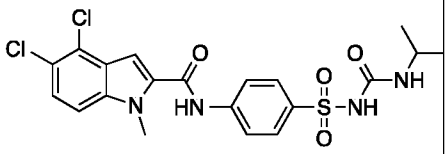
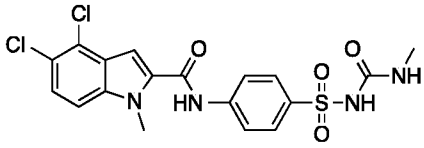


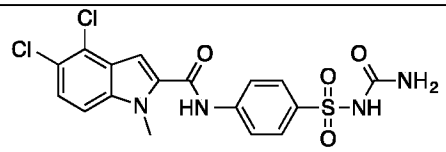
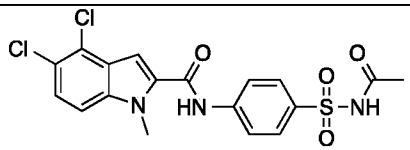
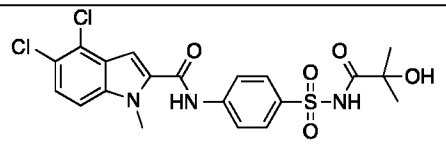
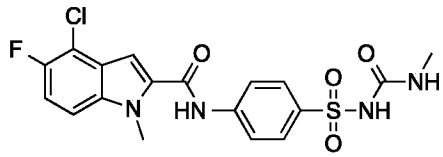
[00502] To a solution of 1-(4-aminophenyl)sulfonyl-3-isopropyl-urea (Intermediate L) (135 mg, 0.527 mmol) and 4-chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (120 mg, 0.527 mmol) in acetonitrile (MeCN) (20 mL) was added 3-picoline (147 mg, 1.58 mmol) and methanesulfonyl chloride (80 mg, 0.701 mmol) dropwise at 0 °C. The mixture was stirred at 20 °C for 12 hrs. On completion, the solution was concentrated *in vacuo*, the residue was purified by prep-HPLC (condition: 0.225% FA-MeCN, column: Boston Green ODS 150*30 5μ), to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 467.1, tR = 0.873. ^1H NMR (400MHz, DMSO-

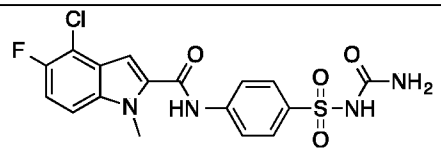
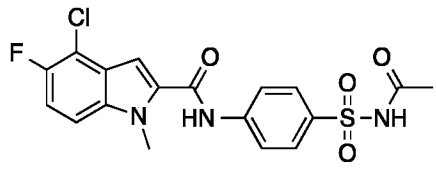
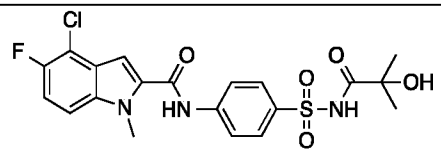
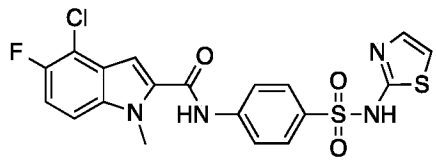
d_6) δ = 10.79 (s, 1H), 8.02 - 7.95 (m, 2H), 7.93 - 7.85 (m, 2H), 7.68 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.51 (s, 1H), 7.45 - 7.35 (m, 1H), 6.24 (br. s., 1H), 4.06 (s, 3H), 3.59 (dd, *J* = 6.3, 13.6 Hz, 1H), 1.01 (d, *J* = 6.5 Hz, 6H).

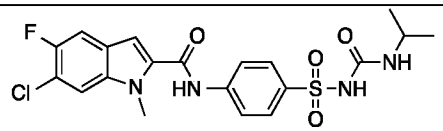
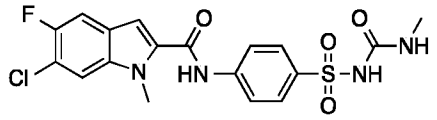
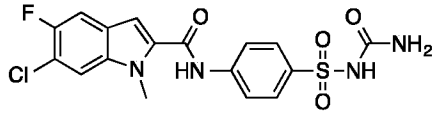
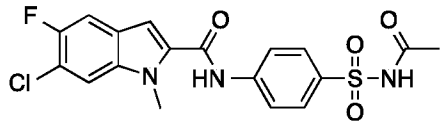
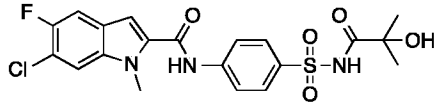
Method 6 Table: Compounds Synthesized via Method 6 using the appropriate acid and amine intermediate

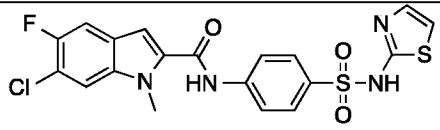
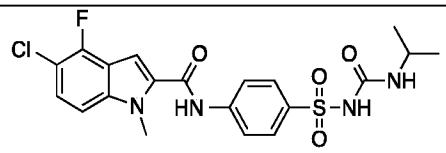
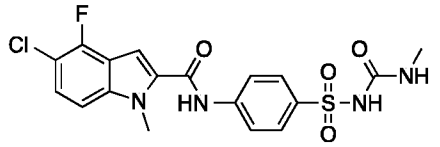
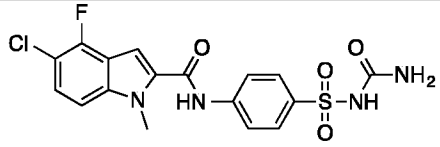
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
21	 4-chloro-*N*-(4-(*N*-(isopropylcarbamoyl)sulfamoyl) phenyl)-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**L**	463.1	10.75 (s, 1H), 10.33 (br. s., 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.92 - 7.83 (m, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.44 (s, 1H), 7.31 (d, *J* = 8.7 Hz, 1H), 6.27 (d, *J* = 7.2 Hz, 1H), 4.03 (s, 3H), 3.59 (qd, *J* = 6.6, 13.5 Hz, 1H), 2.44 (s, 3H), 1.01 (d, *J* = 6.5 Hz, 6H)
22	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-4-chloro-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**N**	421.0	10.75 (s, 1H), 8.00 (d, *J*=8.7 Hz, 2H), 7.88 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=8.3 Hz, 1H), 7.44 (s, 1H), 7.31 (d, *J*=8.5 Hz, 1H), 4.04 (s, 3H), 2.45 (s, 3H)
23	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-4-chloro-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**O**	420.1	12.03 (br. s., 1H), 10.79 (s, 1H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.45 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 2.45 (s, 3H), 1.93 (s, 3H)

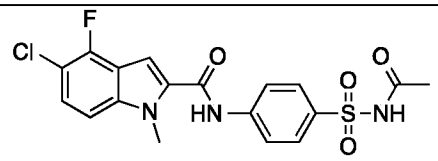
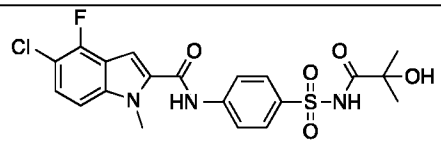
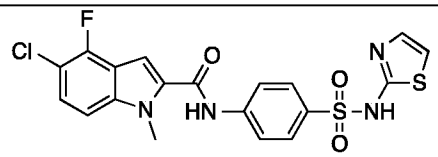
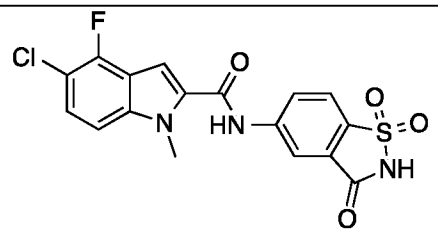
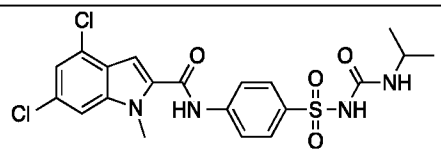
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
24	 4-chloro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phenyl)-1,5-dimethyl-1*H*-indole-2-carboxamide	D	P	464.1	11.37 (brs, 1H), 10.77 (brs, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.43 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 5.59 (brs, 1H), 4.02 (s, 3H), 2.44 (s, 3H), 1.18 (s, 6H)
25	 4-chloro-1,5-dimethyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	D	Q	461.1	12.72 (brs, 1H), 10.68 (brs, 1H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.45 (d, *J* = 33.2 Hz, 1H), 7.30 (s, 1H), 7.26 (t, *J* = 4.8 Hz, 2H), 6.83 (d, *J* = 4.4 Hz, 1H), 4.01 (s, 3H), 2.43 (s, 3H)
26	 4,5-dichloro-*N*-(4-(*N*-(isopropylcarbamoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	E	L	483.1	10.85 (s, 1H), 10.37 (br. s., 1H), 8.04 - 7.98 (m, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.55 - 7.47 (m, 2H), 6.38 (d, *J* = 7.5 Hz, 1H), 4.06 (s, 3H), 3.59 (qd, *J* = 6.7, 13.5 Hz, 1H), 1.01 (d, *J* = 6.5 Hz, 6H)
27	 4,5-dichloro-1-methyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	E	M	455.0	10.84 (s, 1H), 10.68 (s, 1H), 8.03 - 7.98 (m, 2H), 7.93 - 7.88 (m, 2H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.50 (s, 1H), 6.39 (d, *J* = 4.4 Hz, 1H), 4.06 (s, 3H)

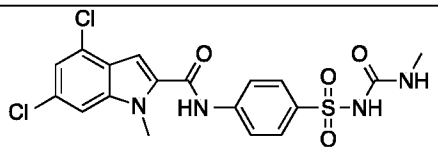
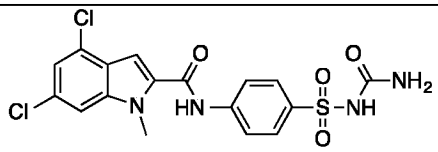
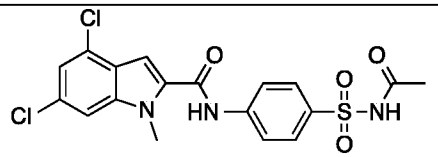
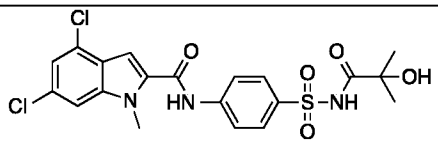
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
28	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	**E**	**N**	439.0	10.84 (s, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.56 - 7.48 (m, 2H), 4.06 (s, 3H)
29	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	**E**	**O**	440.0	10.83 (s, 1H), 8.03 - 7.96 (m, 2H), 7.90 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.47 (m, 2H), 4.06 (s, 3H), 1.90 (s, 3H)
30	 4,5-dichloro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**E**	**P**	484.0	11.38 (br. s., 1H), 10.87 (s, 1H), 8.06 - 8.00 (m, 2H), 7.97 - 7.91 (m, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.55 - 7.47 (m, 2H), 5.58 (br. s., 1H), 4.05 (s, 3H), 1.19 (s, 6H)
31	 4-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**F**	**M**	439.0	10.65 (brs., 1H), 7.85 (d, *J* = 8.4Hz, 2H), 7.78 (d, *J* = 8.8Hz, 2H), 7.66 (dd, *J* = 9.2, 3.6Hz, 1H), 7.48 (s, 1H), 7.39 (t, *J* = 9.6Hz, 1H), 6.00 (brs., 1H), 4.06 (s, 3H), 2.45 (d, *J* = 4.0Hz, 3H)

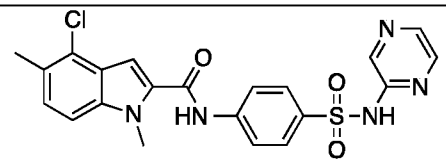
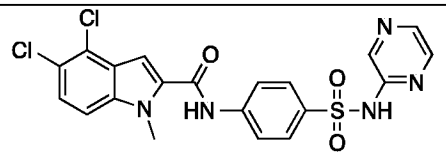
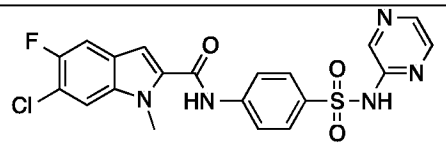
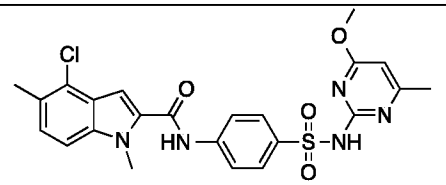
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
32	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**F**	**N**	424.9	10.82 (s, 1H), 10.65 - 10.35 (m, 1H), 8.09 - 7.97 (m, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.68 (dd, *J* = 3.9, 9.0 Hz, 1H), 7.51 (s, 1H), 7.40 (t, *J* = 9.5 Hz, 1H), 4.06 (s, 3H)
33	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**F**	**O**	424.1	12.03 (br. s., 1H), 10.77 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.64 (dd, *J* = 4.3, 9.0 Hz, 1H), 7.54 (dd, *J* = 2.3, 9.5 Hz, 1H), 7.38 (s, 1H), 7.22 (dt, *J* = 2.4, 9.2 Hz, 1H), 4.03 (s, 3H), 1.93 (s, 3H)
34	 4-chloro-5-fluoro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**F**	**P**	468.0	11.39 (brs, 1H), 10.83 (brs, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 4.0 Hz, 1H), 7.50 (s, 1H), 7.40 (d, *J* = 9.6 Hz, 1H), 5.56 (brs, 1H), 4.05 (s, 3H), 2.44 (s, 3H), 1.19 (s, 6H)
35	 4-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**F**	**Q**	464.9	12.76 (br. s., 1H), 10.73 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.87 - 7.76 (m, 2H), 7.67 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.48 (s, 1H), 7.39 (t, *J* = 9.5 Hz, 1H), 7.25 (d, *J* = 4.5 Hz, 1H), 6.82 (d, *J* = 4.6 Hz, 1H), 4.13 - 3.99 (m, 3H)

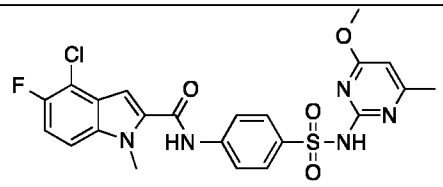
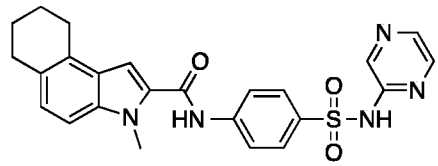
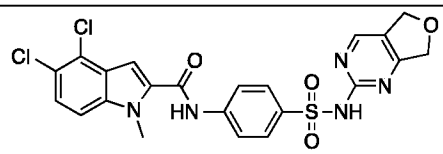
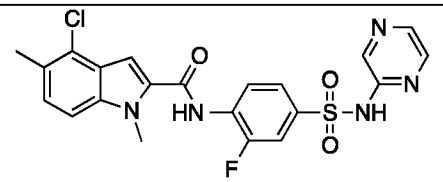
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
36	 6-chloro-5-fluoro-*N*-(4-(*N*-(isopropylcarbamoyl)sulfamoyl) phenyl)-1-methyl-1*H*-indole-2-carboxamide	G	L	467.1	10.75 (s, 1H), 7.97 (m, 3H), 7.88 (m, 2H), 7.76 (m, 1H), 7.37 (s, 1H), 6.30 (br.s., 1 H), 4.00 (s, 3H), 3.60 (m, 1 H), 1.00 (d, 6 H)
37	 6-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	G	M	439.1	10.78 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.95 (d, *J* = 6.0 Hz, 1H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 10.0 Hz, 1H), 7.39 (s, 1H), 6.43 (d, *J* = 4.4 Hz, 1H), 4.01 (s, 3H), 2.53 (d, *J* = 4.8 Hz, 3H)
38	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-6-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	G	N	425.0	10.79 (s, 1H), 10.54 (br. s., 1H), 8.04 - 7.97 (m, 2H), 7.96 (d, *J* = 6.3 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.78 (d, *J* = 9.7 Hz, 1H), 7.39 (s, 1H), 4.09 - 3.95 (m, 3H)
39	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-6-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	G	O	424.1	12.04 (s, 1H), 10.84 (s, 1H), 8.03 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.68 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.51 (s, 1H), 7.41 (t, *J* = 9.2 Hz, 1H), 4.06 (s, 3H), 1.93 (s, 3H)
40	 6-chloro-5-fluoro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phe	G	P	468.0	11.37 (brs, 1H), 10.79 (brs, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.91 (s, 1H), 7.78 (d, *J* = 10.0 Hz,

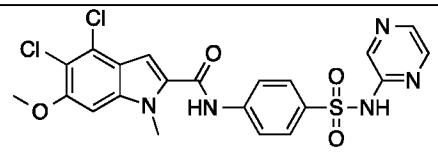
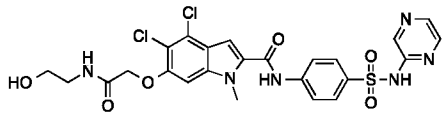
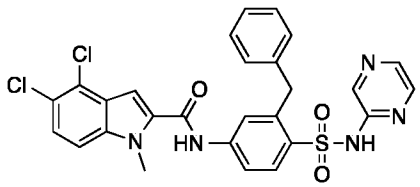
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	nyl)-1-methyl-1*H*-indole-2-carboxamide				1H), 7.38 (s, 1H), 5.55 (brs, 1H), 4.00 (s, 3H), 2.44 (s, 3H), 1.18 (s, 6H)
41	 6-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**G**	**Q**	464.9	12.71 (br. s., 1H), 10.70 (s, 1H), 8.04 - 7.87 (m, 3H), 7.83 - 7.72 (m, 3H), 7.36 (s, 1H), 7.25 (d, *J* = 4.6 Hz, 1H), 6.82 (d, *J* = 4.5 Hz, 1H), 4.01 (s, 3H)
44	 5-chloro-4-fluoro-*N*-(4-(*N*-(isopropylcarbamoyl)sulfamoyl) phenyl)-1-methyl-1*H*-indole-2-carboxamide	**I**	**L**	467.1	10.75 (s, 1H), 7.97 (m, 3H), 7.88 (m, 2H), 7.76 (m, 1H), 7.37 (s, 1H), 6.30 (br.s., 1 H), 4.00 (s, 3H), 3.60 (m, 1 H), 1.00 (d, *J* = 8.4 Hz, 6 H)
45	 5-chloro-4-fluoro-1-methyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**I**	**M**	439.0	10.77 (brs., 1H), 7.99 (d, *J* = 8.8Hz, 2H), 7.89 (d, *J* = 10.2Hz, 2H), 7.52~7.55 (m, 2H), 7.44 (t, *J* = 8.8Hz, 1H), 8.36~8.37 (m, 1H), 4.05 (s, 3H), 2.52 (d, *J* = 3.6Hz, 3H)
46	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-5-chloro-4-fluoro-1-methyl-1*H*-indole-2-carboxamide	**I**	**N**	425.1	10.79 (s, 1H), 10.54 (br. s., 1H), 8.02 (d, *J* = 8.9 Hz, 3H), 7.91 (d, *J* = 8.9 Hz, 3H), 7.58 - 7.52 (m, 3H), 7.49 - 7.42 (m, 1H), 4.06 (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
47	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-5-chloro-4-fluoro-1-methyl-1*H*-indole-2-carboxamide	I	O	424.0	12.05 (br. s., 1H), 10.81 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H), 7.58 - 7.52 (m, 2H), 7.45 (t, *J* = 9.0 Hz, 1H), 4.05 (s, 3H), 1.93 (s, 3H)
48	 5-chloro-4-fluoro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	I	P	468.1	11.38 (brs, 1H), 10.79 (brs, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.54 (s, 1H), 7.52 (s, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 5.56 (brs, 1H), 4.04 (s, 3H), 1.19 (s, 6H)
49	 5-chloro-4-fluoro-1-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	I	Q	464.9	12.73 (brs, 1H), 10.70 (brs, 1H), 7.94 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.53-7.42 (m, 3H), 7.26 (d, *J* = 4.8 Hz, 1H), 6.83 (d, *J* = 4.4 Hz, 1H), 4.03 (s, 3H)
50	 5-chloro-*N*-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl)-4-fluoro-1-methyl-1*H*-indole-2-carboxamide	I	T	408.0	11.05 (s, 1H), 8.48 (s, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.97(d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, *J* = 16.0 Hz, 1H), 4.07 (s, 3H)
53		K	L	483.2	10.62 (s, 1H), 7.83 (m, 5H), 7.45 (s, 1H), 7.34 (s, 1H), 6.00 (br.s., 1 H),

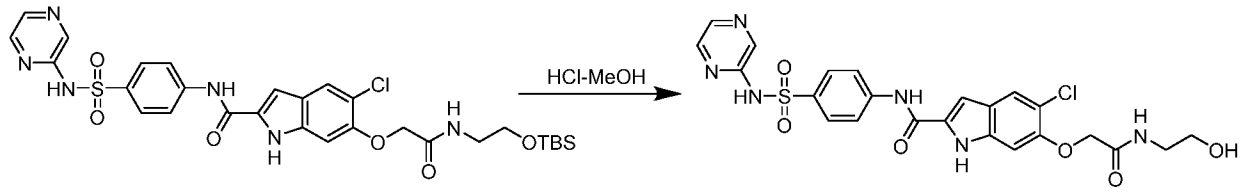
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	4,6-dichloro-*N*-(4-(*N*-(isopropylcarbamoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide				4.02 (s, 3H), 3.60 (m, 1 H), 0.97 (d, *J* = 6.3 Hz 6 H)
54	 4,6-dichloro-1-methyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**K**	**M**	455.0	10.77 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.84 (s, 1H), 7.49 (s, 1H), 7.36 (s, 1H), 6.28 (brs, 1H), 4.05 (s, 3H), 2.53 (d, *J* = 4.8 Hz, 3H)
55	 *N*-(4-(*N*-carbamoylsulfamoyl)phenyl)-4,6-dichloro-1-methyl-1*H*-indole-2-carboxamide	**K**	**N**	441.0	10.83 (s, 1H), 10.54 (s, 1H), 8.05 - 7.98 (m, 2H), 7.93 - 7.87 (m, 2H), 7.84 (m, 1H), 7.50 (d, *J* = 0.6 Hz, 1H), 7.36 (d, *J* = 1.6 Hz, 1H), 4.04 (s, 3H)
56	 *N*-(4-(*N*-acetylsulfamoyl)phenyl)-4,6-dichloro-1-methyl-1*H*-indole-2-carboxamide	**K**	**O**	440.0	12.03 (s, 1H), 10.83 (s, 1H), 8.05 - 7.98 (m, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.82 (s, 1H), 7.49 (s, 1H), 7.35 (d, *J* = 1.0 Hz, 1H), 4.03 (s, 3H), 1.92 (s, 3H)
57	 4,6-dichloro-*N*-(4-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**K**	**P**	484.0	11.38 (brs, 1H), 10.83 (brs, 1H), 8.01 (d, *J* = 9.2 Hz, 2H), 7.93 (d, *J* = 9.2 Hz, 2H), 7.82 (s, 1H), 7.49 (s, 1H), 7.34 (s, 1H), 5.57 (brs, 1H), 4.03 (s, 3H), 1.19 (s, 6H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
58	 4-chloro-1,5-dimethyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	D	U	456.0	11.53 (br. s., 1H), 10.71 (s, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 12.5 Hz, 2H), 7.99 - 7.92 (m, 4H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 4.01 (s, 3H), 2.44 (s, 3H)
59	 4,5-dichloro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	E	U	475.9	11.52 (s, 1H), 10.79 (s, 1H), 8.28 (s, 1H), 8.19 - 8.10 (m, 2H), 7.98 - 7.90 (m, 4H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 8.9 Hz, 1H), 7.47 (d, *J* = 0.5 Hz, 1H), 4.04 (s, 3H)
60	 6-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	G	U	460.0	10.81 - 10.63 (m, 1H), 8.32 (s, 1H), 8.19 (d, *J* = 9.5 Hz, 2H), 8.00 - 7.87 (m, 5H), 7.77 (d, *J* = 9.8 Hz, 1H), 7.35 (s, 1H), 4.11 - 3.85 (m, 3H)
61	 4-chloro-*N*-(4-(*N*-(4-methoxy-6-methylpyrimidin-2yl)sulfamoyl)phenyl)-1,5-dimethyl-1*H*-indole-2-carboxamide	D	V	500.1	10.64 (br. s., 1H), 7.90 (d, *J* = 9.8 Hz, 4H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.42 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 6.17 (br. s., 1H), 4.02 (s, 3H), 3.75 (s, 3H), 2.44 (s, 3H), 2.22 ppm (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
62	 4-chloro-5-fluoro-*N*-(4-(*N*-(4-methoxy-6-methylpyrimidin-2-yl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**F**	**V**	504.1	10.70 (br. s., 1H), 7.91 (m, 4H), 7.67 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.49 (s, 1H), 7.39 (t, *J* = 9.4 Hz, 1H), 6.17 (br. s., 1H), 4.05 (s, 3H), 3.75 (s, 3H), 2.22 (s, 3H)
64	 3-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-6,7,8,9-tetrahydro-3*H*-benzo[*e*]indole-2-carboxamide	**AR**	**U**	462.1	11.49 (br. s., 1H), 10.60 (s, 1H), 8.37 (s, 1H), 8.24 (s, 2H), 8.03 - 7.90 (m, 4H), 7.35 (s, 1H), 7.31 (d, *J*=8.5 Hz, 1H), 7.03 (d, *J*=8.5 Hz, 1H), 3.97 (s, 3H), 2.92 (t, *J*=5.5 Hz, 2H), 2.78 (t, *J*=5.5 Hz, 2H), 1.90 - 1.76 (m, 4H)
65	 4,5-dichloro-*N*-(4-(*N*-(5,7-dihydrofuro[3,4-*d*]pyrimidin-2-yl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**E**	**AT**	518.0	11.77 (br. s., 1H), 10.80 (s, 1H), 8.44 (s, 1H), 7.99 (m, 4H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.48 (s, 1H), 4.97 (s, 2H), 4.86 - 4.73 (m, 2H), 4.04 (s, 3H)
66	 4-chloro-*N*-(2-fluoro-4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**AU**	474.1	11.78 (s, 1H), 10.53 (s, 1H), 8.37 (s, 1H), 8.25 (s, 2H), 7.94-7.82 (m, 3H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.42 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 3.99 (s, 3H), 2.42 (s, 3H)

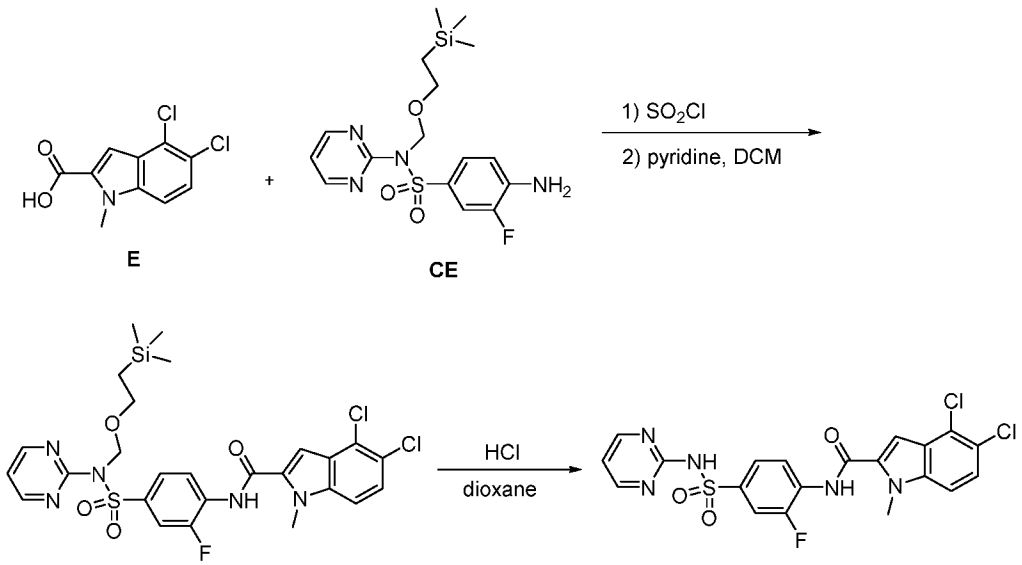
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
67	 4,5-dichloro-6-methoxy-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**AX**	**U**	506.0	11.86 - 11.19 (m, 1H), 10.69 (s, 1H), 8.37 (d, *J* = 1.0 Hz, 1H), 8.27 - 8.18 (m, 2H), 8.03 - 7.89 (m, 4H), 7.43 (s, 1H), 7.32 (s, 1H), 4.03 (s, 3H), 3.98 (s, 3H)
68	 4,5-dichloro-6-(2-((2-hydroxyethyl)amino)-2-oxoethoxy)-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**BH**	**U**	593.0	3.26 (d, *J* = 6.0 Hz, 2H), 3.48 (q, *J* = 5.6 Hz, 2 H), 4.00 (s, 3H), 4.74 (s, 2H), 4.77 (t, *J* = 5.4 Hz, 1H), 7.32 (s, 1H), 7.40 (s, 1H), 7.50 (br. s., 1H), 7.75 (s, 3H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.92 (t, *J* = 5.6 Hz, 1H), 10.46 (s, 1H)
69	 *N*-(3-benzyl-4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	**E**	**BK**	566.1	11.70 (br. s., 1H), 10.68 (s, 1H), 8.19 - 8.07 (m, 4H), 7.94 (dd, *J* = 1.6, 8.7 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 1.8 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.39 (s, 1H), 7.27 - 7.20 (m, 2H), 7.20 - 7.14 (m, 1H), 7.12 (d, *J* = 6.9 Hz, 2H), 4.44 (s, 2H), 3.99 (s, 3H)

Example 70: 5-Chloro-6-(2-((2-hydroxyethyl)amino)-2-oxoethoxy)-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide



[00503] A solution of 6-(2-((2-((*tert*-butyldimethylsilyl)oxy)ethyl)amino)-2-oxoethoxy)-5-chloro-*N*- (4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide (50.0 mg, 0.0759 mmol, synthesized via Method 6 with intermediate acid BJ and amine U) in HCl/methanol (4 M, 3 mL) was stirred at 20 °C for 10 min. The reaction mixture was concentrated under vacuum to afford a residue. This was purified by pre-HPLC (Column: YMC-Actus ODS-AQ 150*30 5μ; Condition: water (0.1% TFA-MeCN) and lyophilized to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 545.1, tR = 0.659. ^1H NMR (300 MHz, DMSO-d_6) δ = 11.829 (s, 1H), 10.542 (s, 1H), 8.375 (s, 1H), 8.239 (s, 2H), 8.005-7.914 (m, 5H), 7.64 (s, 1H), 7.838 (s, 1H), 7.417 (s, 1H), 7.021 (s, 1H), 4.775 (s, 1H), 4.611 (s, 2H), 3.476-3.464 (m, 2H), 3.272-3.229 (s, 2H).

Example 71: 4,5-Dichloro-*N*-{2-fluoro-4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1-methyl-1*H*-indole-2-carboxamide



Step 1 - 4,5-dichloro-*N*-{2-fluoro-4-[(pyrimidin-2-yl)({[2-(trimethylsilyl)ethoxy]-methyl})-

sulfamoyl]phenyl}-1-methyl-1*H*-indole-2-carboxamide

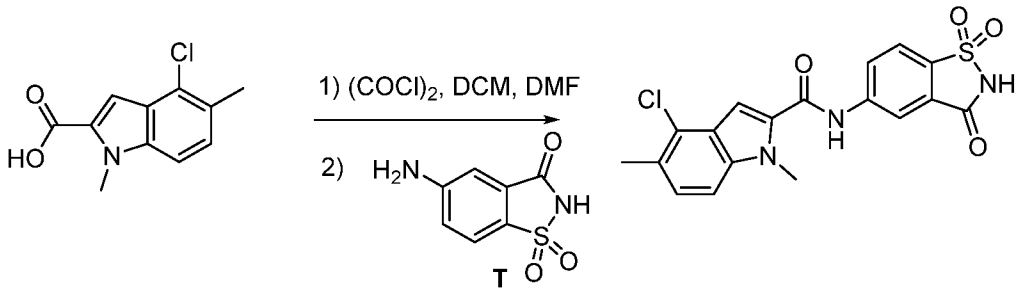
[00504] A mixture of 4,5-dichloro-1-methyl-1*H*-indole-2-carboxylic acid (77.17 mg, 0.316 mmol) and thionyl chloride (230.62 µL, 3.162 mmol) was refluxed for 3 hrs in a sealed tube. The reaction was cooled to RT and excess thionyl chloride was removed under vacuum. The resulting residue was co-distilled with toluene to remove the traces of thionyl chloride. The residue was dissolved in dry DCM (1 mL), cooled to 0°C and a solution of 4-amino-3-fluoro-*N*-(pyrimidin-2-yl)-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzene-1-sulfonamide (70 mg, 0.176 mmol) in DCM (1 mL) was added dropwise followed by the addition of pyridine (42.6 µL, 0.527 mmol). The reaction was warmed to RT. The reaction mixture was stirred at RT for 17 hrs. The mixture was then partitioned between DCM (50 mL) and water (30 mL). The organic layer was evaporated to give a material that was purified by flash column chromatography (heptane:EtOAc 80:20 to 20:80) to give the title compound. LCMS: (ES^+) m/z $(M+Na)^+$ = 646.15, 648.30.

Step 2 - 4,5-Dichloro-*N*-{2-fluoro-4-[(pyrimidin-2-yl)sulfamoyl]phenyl}-1-methyl-1*H*-indole-2-carboxamide

[00505] 4 M HCl in dioxane (2 mL) was added to a solution of 4,5-dichloro-*N*-{2-fluoro-4-[(pyrimidin-2-yl)({[2-(trimethylsilyl)ethoxy]methyl})sulfamoyl]phenyl}-1-methyl-1*H*-indole-2-carboxamide (64 mg, 0.10 mmol) in dioxane (2 mL), and the resulting mixture was stirred under nitrogen at rt for 45 minutes. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography (DCM:MeOH = 100:0 to 94:6) to obtain a material which was washed with MeOH (1 mL) and $CHCl_3$ (1 mL) followed by heptane (1 mL) and EtOAc (2 mL) to afford the title compound. LCMS: (ES^+) m/z $(M+Na)^+$ = 646.2, 648.3. ^1H NMR (DMSO, 500 MHz) δ 12.02 (1H, s), 10.59 (1H, s), 8.54 (2H, d, J=4.8 Hz), 7.94 - 7.89 (1H, m), 7.89 - 7.82 (2H, m), 7.68 (1H, d, J=8.9 Hz), 7.52 (1H, d, J=8.9 Hz), 7.49 (1H, s), 7.12 - 7.02 (1H, m), 4.03 (3H, s).

Examples 72-76 (Method 7)

4-Chloro-1,5-dimethyl-*N*-(1,1,3-trioxo-1,2-benzothiazol-5-yl)indole-2-carboxamide (Example 72)

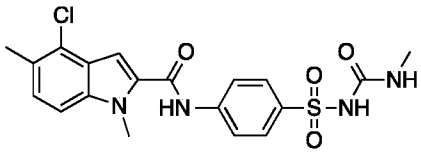
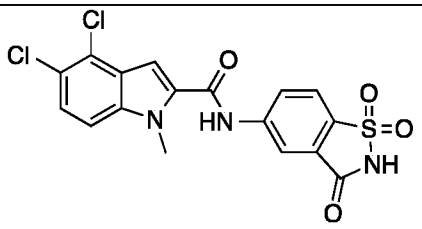
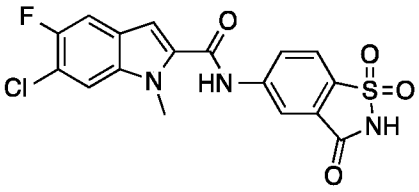


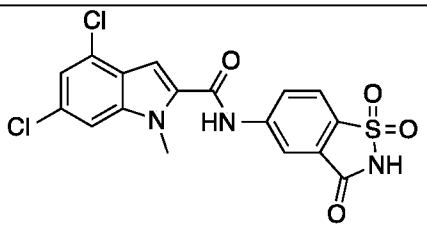
[00506] To a mixture of 4-chloro-1,5-dimethyl-1*H*-indole-2-carboxylic acid (105 mg, 0.461 mmol, Intermediate D) and catalytic amount of DMF in dichloromethane (10 mL) was added oxalyl chloride (117 mg, 0.922 mmol) dropwise at 0 °C. The mixture was then warmed to 20 °C and stirred at 20 °C for 1 hr. On completion, the mixture was concentrated *in vacuo* to afford 4-chloro-1,5-dimethyl-1*H*-indole-2-carbonyl chloride (120 mg, crude) as a light yellow solid which was used for next step directly.

[00507] To a solution of 5-amino-1,1-dioxo-1,2-benzothiazol-3-one (98.2 mg, 0.495 mmol) and pyridine (117 mg, 1.49 mmol) in DMA (2 mL) was added a solution of 4-chloro-1,5-dimethyl-indole-2-carbonyl chloride (120 mg, 0.495 mmol) in dichloromethane (3 mL) dropwise at 0 °C, then the mixture was stirred at 20 °C for 16 hrs. On completion, the mixture was concentrated *in vacuo* to a residue. The residue was purified with pre-HPLC (Instrument: GX-B; Column: Phenomenex Synergi C18 100*21.2 mm*4 μm; Mobile phase: 0.1% trifluoroacetic acid - acetonitrile) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 403.8, tR= 0.758. ^1H NMR (400MHz, DMSO-d_6) δ = 11.05 (s, 1H), 8.52 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.50 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 4.05 (s, 3H), 2.45 (s, 3H).

Method 7 Table: Compounds Synthesized via Method 7 using the appropriate acid and amine intermediates

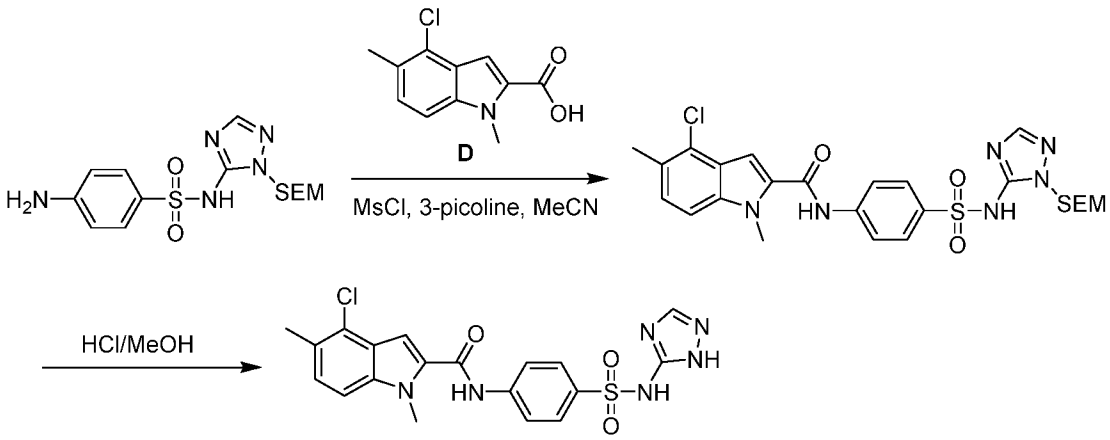
Example #	Structure/Name	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ

Example #	Structure/Name	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
73	 4-chloro-1,5-dimethyl-*N*-(4-(*N*-(methylcarbamoyl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	D	M	435.0	10.75 (s, 1H), 10.65 (s, 1H), 8.06 - 7.95 (d, *J*=8.8 Hz, 2H), 7.89 (d, *J*=8.9 Hz, 2H), 7.52 (d, *J*=8.5 Hz, 1H), 7.43 (s, 1H), 7.30 (d, *J*=8.5 Hz, 1H), 6.38 (d, *J*=4.4 Hz, 1H), 4.03 (s, 2H), 2.52 (br. s., 3H), 2.44 (s, 1H)
74	 4,5-dichloro-*N*-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl)-1-methyl-1*H*-indole-2-carboxamide	E	T	403.8	11.05 (s, 1H), 8.52 (s, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.50 (s, 1H), 7.32 (d, *J* = 8.5 Hz, 1H), 4.05 (s, 3H), 2.45 (s, 3H)
75	 6-chloro-*N*-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl)-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	G	T	407.9	11.12 (br. s., 1H), 8.49 (s, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.06 - 7.90 (m, 2H), 7.80 (d, *J* = 9.7 Hz, 1H), 7.46 (s, 1H), 4.03 (s, 3H)

Example #	Structure/Name	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
76	 4,6-dichloro-*N*-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl)-1-methyl-1*H*-indole-2-carboxamide	K	T	421.9 (-)	11.12 (s, 1H), 8.51 (d, *J* = 1.8 Hz, 1H), 8.19 (dd, *J* = 1.8, 8.5 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.55 (s, 1H), 7.37 (d, *J* = 1.6 Hz, 1H), 4.05 (s, 3H)

Examples 77-90 (Method 8)

N-(4-(*N*-(1*H*-1,2,4-Triazol-5-yl)sulfamoyl)phenyl)-4-chloro-1,5-dimethyl-1*H*-indole-2-carboxamide (Example 77)



Step 1 - 4-Chloro-1,5-dimethyl-*N*-(4-(*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide

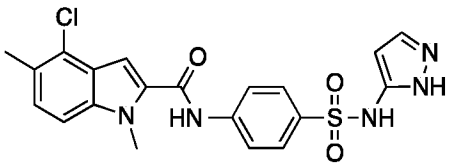
[00508] To a suspension of 4-chloro-1,5-dimethyl-1*H*-indole-2-carboxylic acid (178 mg, 0.796 mmol, Intermediate D) and 4-amino-*N*-(1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-1,2,4-triazol-5-yl)benzenesulfonamide (250 mg, 0.676 mmol, Intermediate S) in acetonitrile (20.0 mL) was added 3-picoline (222 mg, 2.39 mmol) at 0 °C. Then methanesulfonyl chloride (137 mg, 1.19 mmol) was added drop-wise. The resulting mixture was warmed to 20 °C and stirred for 16

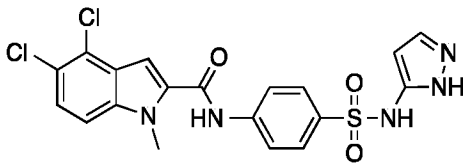
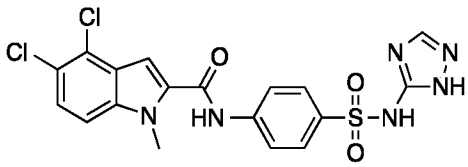
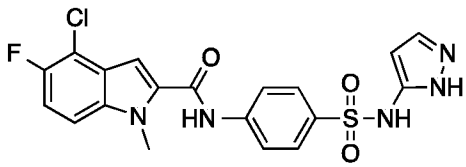
hrs. On completion, the mixture was concentrated *in vacuo* to give a crude product which was purified by column chromatography (petroleum ether:ethyl acetate = 5:1 to 2:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 575, tR = 0.969.

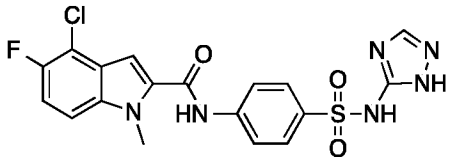
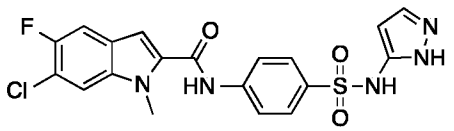
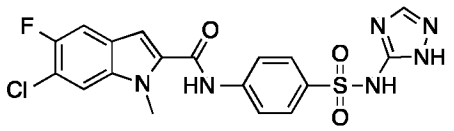
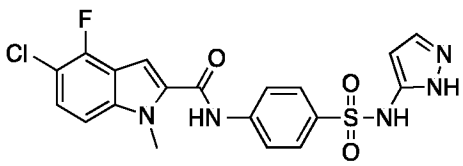
Step 2 - *N*-(4-(*N*-(1*H*-1,2,4-Triazol-5-yl)sulfamoyl)phenyl)-4-chloro-1,5-dimethy l-1*H*-indole-2-carboxamide

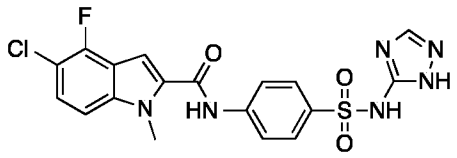
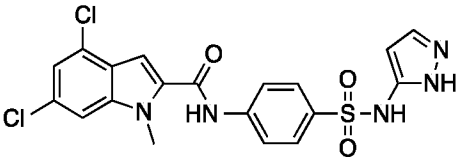
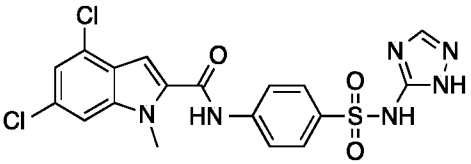
[00509] A solution of 4-chloro-1,5-dimethyl-*N*-[4-[[2-(2-trimethylsilylethoxymethyl)-1,2,4-triazol-3-yl] sulfamoyl]phenyl]indole-2-carboxamide (100 mg, 0.174 mmol) in HCl/MeOH (10.0 mL, 4 M) was stirred at 80 °C for 1 hr. On completion, the reaction mixture was concentrated *in vacuo* to give a crude product. The crude product was purified by *prep*-HPLC (Condition: 0.05%HCl-MeCN; Column: Phenomenex Synergi C18 150*30 mm*4 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 445, tR = 1.222. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.67 (br. s., 1H), 8.15 (br. s., 1H), 7.94 (d, *J* = 8.4Hz, 2H), 7.84 (d, *J* = 8.8Hz, 2H), 7.51 (d, *J* = 8.4Hz, 1H), 7.42 (s, 1H), 7.29 (d, *J* = 8.4Hz, 1H), 4.02 (s, 3H), 2.44 (s, 3H).

Method 8 Table: Compounds Synthesized via Method 8 using the appropriate acid and amine intermediates

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
78	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-4-chloro-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**R**	444.0	12.35 (br. s., 1H), 10.70 (s, 1H), 10.34 (s, 1H), 7.94 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.55 (d, *J* = 1.9 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.41 (s, 1H), 7.30 (d, *J* = 8.5 Hz, 1H), 5.97 (s, 1H), 4.02 (s, 3H), 2.44 (s, 3H)

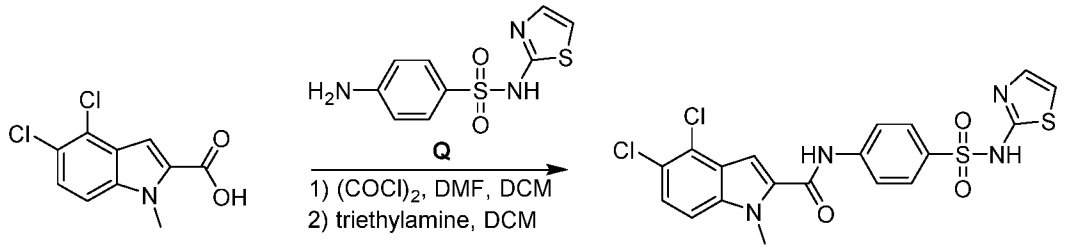
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
79	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	E	R	464.1	12.35 (br. s., 1H), 10.79 (s, 1H), 10.35 (s, 1H), 7.94 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8 Hz, 2H), 7.68 (d, J=8.8 Hz, 1H), 7.55 (d, J=2.0 Hz, 1H), 7.51 (d, J=8.8 Hz, 1H), 7.47 (s, 1H), 5.97 (s, 1H), 4.04 (s, 3H)
80	 *N*-(4-(*N*-(1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	E	S	463.1	13.07 (br s, 1H), 12.74 (br s, 1H), 10.72 (s, 1H), 8.13 (s, 1H), 7.92-7.82 (m, 4H), 7.67-7.65 (m, 1H), 7.50-7.48 (m, 1H), 7.45 (s, 1H), 4.03 (s, 3H)
81	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	F	R	448.1	12.36 (br. s., 1H), 10.77 (s, 1H), 10.36 (s, 1H), 7.97 - 7.91 (m, 2H), 7.80 - 7.74 (m, 2H), 7.67 (dd, *J* = 3.6, 9.0 Hz, 1H), 7.55 (d, *J* = 2.1 Hz, 1H), 7.48 (s, 1H), 7.43 - 7.36 (m, 1H), 5.97 (d, *J* = 2.0 Hz, 1H), 4.04 (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
82	 *N*-(4-(*N*-(1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**F**	**S**	449.1	13.07 (br s, 1H), 12.79 (br s, 1H), 10.72 (s, 1H), 8.13 (s, 1H), 7.93-7.82 (m, 4H), 7.66-7.63 (m, 1H), 7.47 (s, 1H), 7.41-7.38 (m, 1H), 4.03 (s, 3H)
83	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-6-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**G**	**R**	448.1	12.36 (br. s., 1H), 10.72 (s, 1H), 10.34 (s, 1H), 7.97 - 7.90 (m, 3H), 7.77 (m, 3H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.36 (s, 1H), 5.97 (d, *J* = 2.3 Hz, 1H), 4.01 (s, 3H)
84	 *N*-(4-(*N*-(1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-6-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**G**	**S**	449.0	13.07 (brs, 1H), 12.74 (brs, 1H), 10.67 (brs, 1H), 8.15 (brs, 1H), 7.98 - 7.69 (m, 6H), 7.36 (s, 1H), 4.01 (s, 3H)
87	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-5-chloro-4-fluoro-1-methyl-1*H*-indole-2-carboxamide	**I**	**R**	448.0	12.35 (br. s., 1H), 10.72 (s, 1H), 10.35 (s, 1H), 7.95 - 7.90 (m, 2H), 7.79 - 7.73 (m, 2H), 7.56 - 7.50 (m, 2H), 7.49 (s, 1H), 7.43 (dd, *J* = 7.2, 8.8 Hz, 1H), 5.96 (d, *J* = 2.1 Hz, 1H), 4.03 (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
88	 *N*-(4-(*N*-(1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-5-chloro-4-fluoro-1-methyl-1*H*-indole-2-carboxamide	**I**	**S**	448.9	13.07 (brs, 1H), 12.75 (brs, 1H), 10.65 (brs, 1H), 8.13 (brs, 1H), 8.13 - 7.83 (m, 4H), 7.53 – 7.40 (m, 3H), 4.03 (s, 3H)
89	 *N*-(4-(*N*-(1*H*-pyrazol-5-yl)sulfamoyl)phenyl)-4,6-dichloro-1-methyl-1*H*-indole-2-carboxamide	**K**	**R**	464.1	10.76 (s , 1H), 10.35 (s , 1H), 7.94-7.92 (*J* = 8.0 Hz, 2H), 7.83(s , 1H), 7.78-7.75 (d, *J* = 12.0 Hz, 2H), 7.55 (s, 1H), 7.46 (s, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 5.97 (s, 1H), 4.03 (s, 3H)
90	 *N*-(4-(*N*-(1*H*-1,2,4-triazol-5-yl)sulfamoyl)phenyl)-4,6-dichloro-1-methyl-1*H*-indole-2-carboxamide	**K**	**S**	463.1	13.06 (br s, 1H), 12.74 (br s, 1H), 10.69 (s, 1H), 8.12 (s, 1H), 7.91-7.81 (m, 5H), 7.45 (s, 1H), 7.34 (s, 1H), 4.02 (s, 3H)

Examples 91-95 (Method 9)

4,5-Dichloro-1-methyl-*N*-[4-(thiazol-2-ylsulfamoyl)phenyl]indole-2-carboxamide (Example 91)

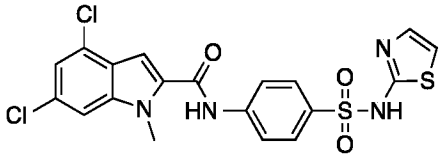
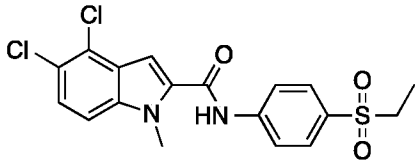
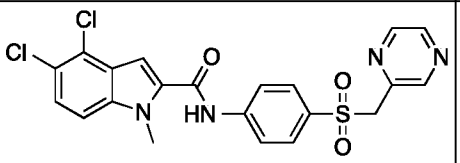
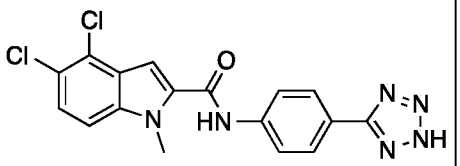


[00511] To a solution of 4,5-dichloro-1-methyl-indole-2-carboxylic acid (150 mg, 0.614 mmol, Intermediate E) in anhydrous dichloromethane (15 mL) was added a catalytic amount of *N,N*-dimethylformamide. Then, the solution was cooled to 0 °C and oxalyl chloride (234 mg, 1.84 mmol) was added. The mixture was warmed to 18 °C and stirred for 2 hrs. On completion, the mixture was concentrated *in vacuo* to give the title compound (160 mg, crude) as a white solid. The crude product was used directly in the next step without further purification.

[00512] To a solution of 4-amino-*N*-thiazol-2-yl-benzenesulfonamide (160 mg, 0.626 mmol) in 10 mL anhydrous dichloromethane was added triethylamine (158 mg, 1.57 mmol). Next, a solution of 4,5-dichloro-1-methyl-indole-2-carbonyl chloride (159 mg, 0.607 mmol) in anhydrous dichloromethane (5 mL) was added to the mixture dropwise. The reaction was stirred at 18 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC (Condition: 0.225% FA-MeCN; Column: Phenomenex Synergi Max-RP 250 × 80 mm × 10 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 480.9, tR= 1.328 ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.76 (s, 1H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.44 (m, 2H), 7.25 (d, *J* = 4.6 Hz, 1H), 6.82 (d, *J* = 4.5 Hz, 1H), 4.05 (s, 3H).

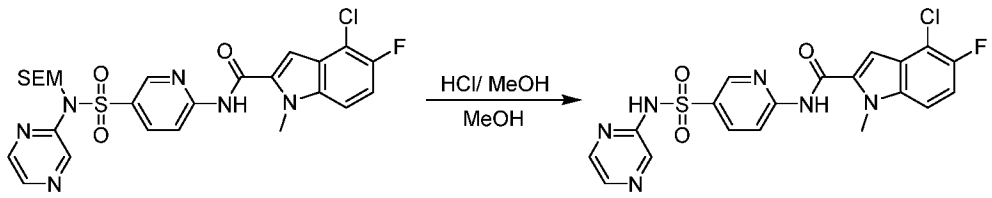
Method 9 Table: Compounds Synthesized via Method 9 using the appropriate acid and amine intermediates

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
92	 4,6-dichloro-1-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**K**	**Q**	480.9	10.72 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 2H), 7.80 (t, *J* = 8.8 Hz, 3H), 7.46 (s, 1H), 7.35 (d, *J* = 1.5 Hz, 1H), 7.21 (d, *J* = 4.5 Hz, 1H), 6.77 (d, *J* = 4.5 Hz, 1H), 4.03 (s, 3H)
93	 4,5-dichloro-*N*-(4-(ethylsulfonyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	**E**	**AD**	411.1	10.87 (brs, 1H), 8.07 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.53 (s, 1H), 7.50 (s, 1H), 4.05 (s, 3H), 3.30-3.24 (m, 2H), 1.11 (d, *J* = 7.2 Hz, 3H)
94	 4,5-dichloro-1-methyl-*N*-(4-((pyrazin-2-ylmethyl)sulfonyl)phenyl)-1*H*-indole-2-carboxamide	**E**	**AO**	475.0	10.87 (s, 1H), 8.61 (d, *J* = 1.9 Hz, 1H), 8.57 (s, 2H), 8.01 (d, *J* = 8.9 Hz, 2H), 7.74 - 7.66 (m, 3H), 7.51 (d, *J* = 8.4 Hz , 2H), 4.93 (s, 2H), 4.06 (s, 3H)
95[a]	 *N*-(4-(2*H*-tetrazol-5-yl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	**E**	4-(1*H*-tetrazol-5-yl)aniline (CAS# 46047-18-1)	387.0	10.66 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 2H), 7.94 (d, *J* = 7.4 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.47 (s, 1H), 4.07 (s, 3H)

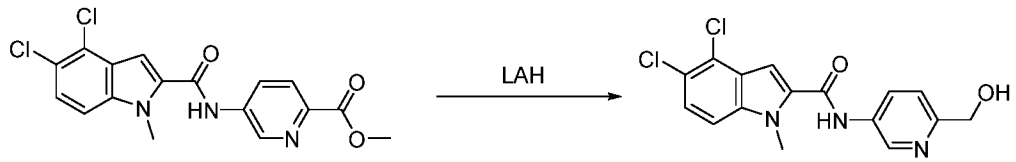
[a]Diisopropylethylamine used as the base instead of TEA in second step.

Example 96: 4-Chloro-5-fluoro-1-methyl-*N*-[5-(pyrazin-2-ylsulfamoyl)-2-pyridyl]indole-2-carboxamide



[00513] To a solution of 4-chloro-5-fluoro-1-methyl-*N*-(5-(*N*-(pyrazin-2-yl)-*N*-((2-(trimethylsilyl)ethoxy)methyl)sulfamoyl)pyridin-2-yl)-1*H*-indole-2-carboxamide (130 mg, 0.151 mmol, synthesized via Method 9 using Intermediate F and Intermediate AK as the amine) in methanol (10 mL) was added hydrogen chloride/methanol (4 M, 3 mL) and the reaction mixture was stirred at 10 °C for 14 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a crude product, which was purified by prep-HPLC (Instrument: GX-E; Column: Phenomenex Synergi C18 150*30mm*4 μm; Mobile phase: 0.05% hydrochloric acid - acetonitrile) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 461, tR = 0.866. ^1H NMR (400MHz, DMSO-d_6) δ = 11.76 (br. s., 1H), 11.49 (s, 1H), 8.94 (s, 1H), 8.48 - 8.33 (m, 3H), 8.27 (br. s., 2H), 7.72 (s, 1H), 7.67 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.40 (t, *J* = 9.5 Hz, 1H), 4.04 (s, 3H).

Example 97: 4,5-Dichloro-*N*-[6-(hydroxymethyl)-3-pyridyl]-1-methyl-indole-2-carboxamide

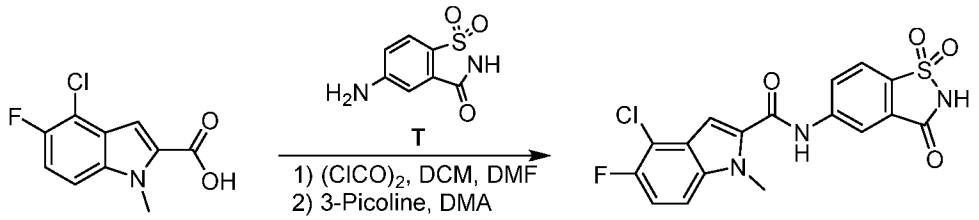


[00514] To a solution of methyl 5-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]pyridine-2-carboxylate (200 mg, 0.528 mmol, made via Method 9 with Intermediate E and methyl 5-aminopyridine-2-carboxylate) in anhydrous tetrahydrofuran (10 mL) was added lithium aluminum hydride (LAH) (40.1 mg, 1.06 mmol) in one portion at -20 °C under a nitrogen atmosphere. The resulting mixture was stirred at -20 °C for 2 hrs. On completion, water (3 mL) was added dropwise into the reaction mixture at -20 °C followed by 2 M HCl (4 mL). The solvent was removed *in vacuo* to give a residue. The residue was purified with prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5μ; Mobile phase: 0.225% formic acid-acetonitrile) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 350.1, tR = 0.754.

^{1}H NMR (400MHz, CD_3OD) d = 8.89 (d, *J* = 2.3 Hz, 1H), 8.28 (dd, *J* = 2.5, 8.4 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.54 - 7.50 (d, *J* = 8.5 Hz, 1H), 7.46 - 7.43 (d, *J* = 8.4 Hz,, 1H), 7.42 (s, 1H), 4.72 (s, 2H), 4.11 (s, 3H).

Examples 98-108 (Method 10)

4-chloro-*N*-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-5-yl)-5-fluoro-1-methyl-1*H*-indole-2-carboxamide (Example 98)

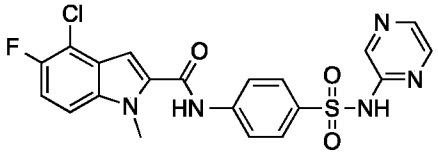
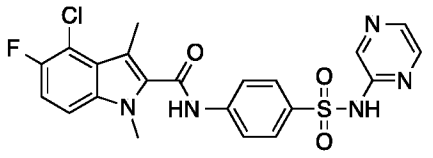
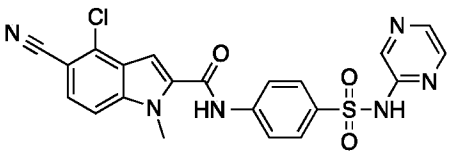
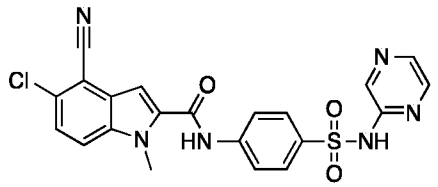


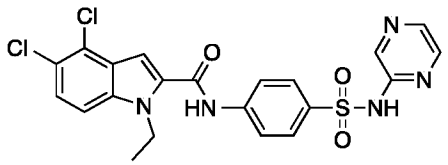
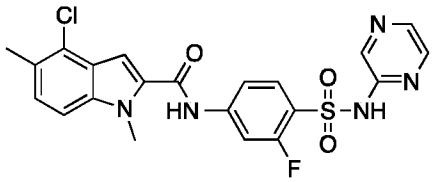
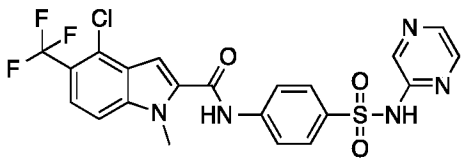
[00515] To a mixture of 4-chloro-5-fluoro-1-methyl-indole-2-carboxylic acid (62 mg, 0.272 mmol, Intermediate F) in dichloromethane (10 mL) was added *N,N*-dimethylformamide (50 µL). Then oxalyl chloride (51.8 mg, 0.408 mmol) was added to the reaction mixture. Then the reaction mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo*. The residue (68 mg, crude) was used to the next step directly without further purification.

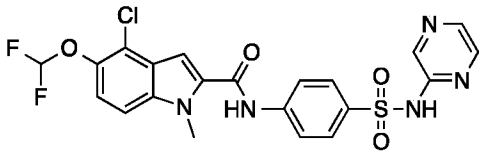
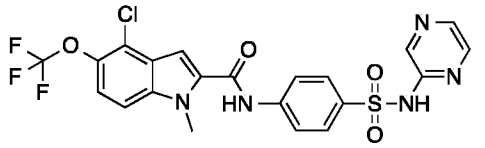
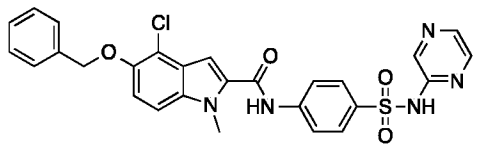
[00516] To a mixture of 5-amino-1,1-dioxo-1,2-benzothiazol-3-one (27.4 mg, 0.138 mmol) in dichloromethane (3 mL) was added 3-picoline (38.6 mg, 0.414 mmol). Then a solution of 4-chloro-5-fluoro-1-methyl-indole-2-carbonyl chloride (34 mg, 0.138 mmol) in dichloromethane (1 mL) was added to the reaction mixture dropwise at 0 °C. The mixture was stirred at 20 °C for 12 hrs. On completion, the mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC (Condition: 0.05% ammonia-MeCN; Column: Phenomenex Gemini C18 250*50mm*10 µm) to give the title compound. LCMS: (ES+) m/z $(M+H)^+$ = 408.0, tR = 0.842. ^{1}H NMR (400MHz, CD_3OD) δ = 8.37 (d, *J* = 1.8 Hz, 1H), 7.98 (dd, *J* = 1.8, 8.3 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 - 7.46 (m, 1H), 7.44 (s, 1H), 7.24 (t, *J* = 9.4 Hz, 1H), 4.10 (s, 3H).

Method 10 Table: Compounds Synthesized via Method 10 using the appropriate acid and amine intermediate

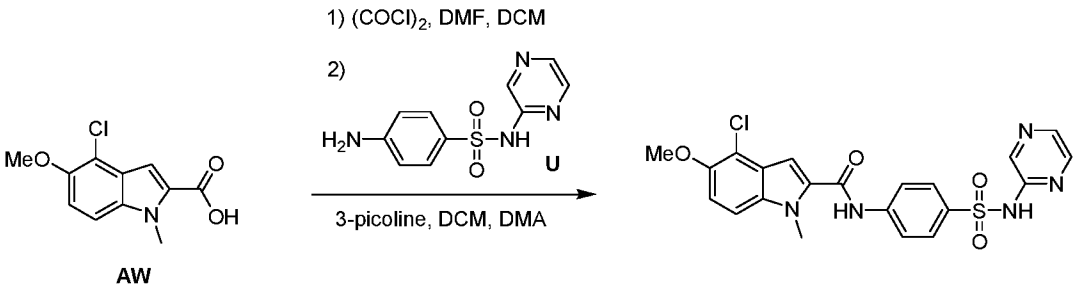
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
99	 4-chloro-5-fluoro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**F**	**U**	460.0	10.76 (s, 1H), 8.29 (s, 1H), 8.20 - 8.11 (m, 2H), 8.00 - 7.90 (m, 4H), 7.66 (dd, *J* = 3.7, 9.1 Hz, 1H), 7.47 (s, 1H), 7.39 (t, *J* = 9.4 Hz, 1H), 4.04 (s, 3H)
100	 4-chloro-5-fluoro-1,3-dimethyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**AL**	**U**	474.0	8.43 (s, 1H), 8.22 (d, *J* = 9.8 Hz, 2H), 8.05 - 8.00 (m, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.39 (dd, *J* = 3.6, 8.9 Hz, 2H), 7.24 - 7.11 (m, 2H), 3.82 (s, 3H), 2.68 (s, 3H)
101	 4-chloro-5-cyano-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**AM**	**U**	467.1	10.88 - 10.82 (m, 1H), 8.26 - 8.18 (m, 1H), 8.14 - 8.08 (m, 1H), 8.06 - 7.99 (m, 1H), 7.92 (s, 4H), 7.83 (s, 1H), 7.80 - 7.76 (m, 1H), 7.60 - 7.57 (m, 1H), 4.07 (s, 3H)
102	 5-chloro-4-cyano-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**AN**	**U**	467.0	10.65 (s, 1H), 8.28 (br. s., 1H), 8.06 (d, *J* = 8.9 Hz, 1H), 7.86 (d, *J* = 14.2 Hz, 2H), 7.80 (s, 4H), 7.63 - 7.53 (m, 3H), 4.09 (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
103	 4,5-dichloro-1-ethyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**AP**	**U**	490.1	11.52 (br. s., 1H), 10.82 (s, 1H), 8.37 (s, 1H), 8.24 (s, 2H), 8.02 - 7.94 (m, 4H), 7.71 (d, *J*=8.9 Hz, 1H), 7.50 (d, *J*=8.9 Hz, 1H), 7.48 (s, 1H), 4.60 (q, *J*=6.9 Hz, 2H), 1.32 (t, *J*=7.0 Hz, 3H)
104	 4-chloro-*N*-(3-fluoro-4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1,5-dimethyl-1*H*-indole-2-carboxamide	**D**	**AV**	474.1	11.87 (br. s., 1H), 10.87 (s, 1H), 8.37 (s, 1H), 8.24 (d, *J* = 2.5 Hz, 1H), 8.20 (s, 1H), 8.00 (t, *J* = 8.7 Hz, 1H), 7.90 (dd, *J* = 1.8, 13.2 Hz, 1H), 7.79 (dd, *J* = 1.8, 8.8 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 4.02 - 4.00 (m, 3H)
105	 4-chloro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-5-(trifluoromethyl)-1*H*-indole-2-carboxamide	**BA**	**U**	510.0	11.51 (br. s., 1H), 10.89 (s, 1H), 8.37 (s, 1H), 8.24 (s, 2H), 8.05 - 7.94 (m, 4H), 7.84 - 7.79 (m, 1H), 7.74 - 7.70 (m, 1H), 7.64 (s, 1H), 4.08 (s, 3H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
106	 4-chloro-5-(difluoromethoxy)-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**BD**	**U**	508.2	12.19 - 10.98 (m, 1H), 10.80 (s, 1H), 8.35 (d, *J* = 1.1 Hz, 1H), 8.25 - 8.18 (m, 2H), 8.03 - 7.92 (m, 4H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.50 (s, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.40 - 7.03 (t, *J* = 72.0 Hz, 1H), 4.06 - 4.01 (m, 3H)
107	 4-chloro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-5-(trifluoromethoxy)-1*H*-indole-2-carboxamide	**BE**	**U**	510.0	11.51 (br. s., 1H), 10.83 (s, 1H), 8.37 (s, 1H), 8.24 (s, 2H), 8.06 - 7.92 (m, 4H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.55 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 4.06 (s, 3H)
108	 5-(benzyloxy)-4-chloro-1-methyl-*N*-(4-(*N*-(pyrazin-2-yl)sulfamoyl)phenyl)-1*H*-indole-2-carboxamide	**BC**	**U**	548.1	10.69 (s, 1H), 8.29 (s, 1H), 8.17 (s, 1H), 8.13 (s, 1H), 7.94 (q, *J* = 9.1 Hz, 4H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.44 - 7.37 (m, 3H), 7.37 - 7.30 (m, 2H), 5.24 (s, 2H), 4.00 (s, 3H)

Example 109: 4-Chloro-5-methoxy-1-methyl-*N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]indole-2-carboxamide

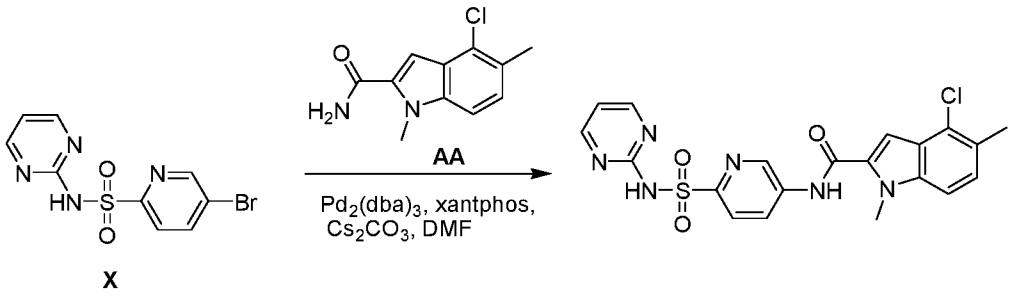


[00517] To a solution of 4-chloro-5-methoxy-1-methyl-indole-2-carboxylic acid (150 mg, 0.626 mmol) in anhydrous dichloromethane (10 mL) was added a catalytic amount of *N*,*N*-dimethylformamide. Then, the solution was cooled to 0 °C and oxalyl chloride (238 mg, 1.88 mmol) was added under nitrogen atmosphere. The mixture was warmed to 15 °C and stirred for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound (160 mg). The crude product was used directly in the next step without further purification.

[00518] To a solution of 4-amino-*N*-pyrazin-2-yl-benzenesulfonamide (155 mg, 0.619 mmol) in DMA (3 mL) was added 3-picoline (173 mg, 1.86 mmol). A solution of 4-chloro-5-methoxy-1-methyl-indole-2-carbonyl chloride (160 mg, 0.620 mmol) in anhydrous dichloromethane (5 mL) was then added dropwise at 0 °C. The mixture was then warmed to 15 °C and stirred for 3 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (Instrument: GX-B; Column: Xtimate C18 150*25 mm; Particle size: 5 μm; Mobile phase: 0.1% trifluoroacetic acid-acetonitrile) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 472.2, tR= 0.816. ^1H NMR (400MHz, DMSO-d_6) δ = 11.52 (br. s., 1H), 10.75 (s, 1H), 8.37 (s, 1H), 8.24 (s, 2H), 8.02 - 7.92 (m, 4H), 7.58 (d, *J* = 9.0 Hz, 1H), 7.37 (s, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 4.00 (s, 3H), 3.89 (s, 3H).

Examples 110-117 (Method 11)

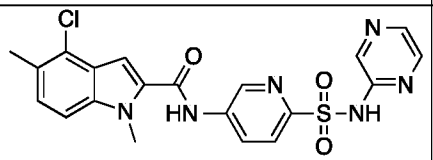
4-Chloro-1,5-dimethyl-*N*-[6-(pyrimidin-2-ylsulfamoyl)-3-pyridyl]indole-2-carboxamide (Example 110)

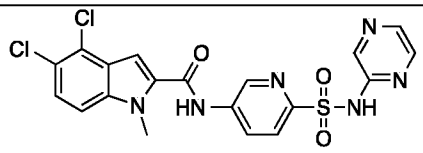
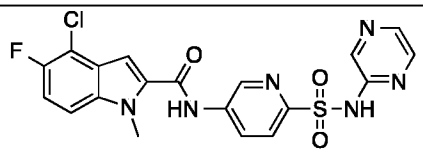
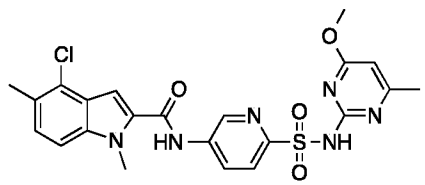
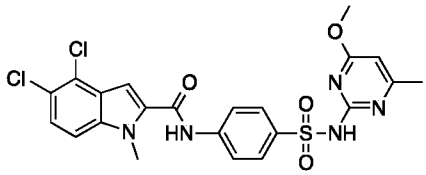


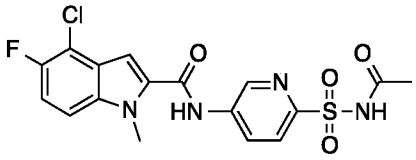
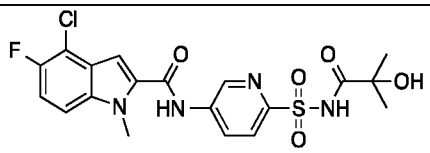
X

[00519] A mixture of 5-bromo-*N*-pyrimidin-2-yl-pyridine-2-sulfonamide (70.7 mg, 0.224 mmol), 4-chloro-1,5-dimethyl-indole-2-carboxamide (50.0 mg, 0.224 mmol), cesium carbonate (146 mg, 0.449 mmol), (5-diphenylphosphanyl-9,9-dimethyl-xanthen-4-yl)-diphenyl-phosphane (13.0 mg, 22.4 μmol) and tris(dibenzylideneacetone)dipalladium(0) (20.5 mg, 22.4 μmol) in *N,N*-dimethylformamide (5 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 100 °C for 16 hour under N_2 atmosphere. On completion, the reaction mixture was filtered through a pad of diatomaceous earth, concentrated *in vacuo* and the residue was purified by prep-HPLC (Condition: 0.05% HCl-MeCN; Column: Phenomenex Synergi C18 150*30 mm; Particle size 4 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 457.1, tR = 0.820. ^1H NMR (400MHz, DMSO-d_6) δ = 11.97 (br. s., 1H), 10.92 (s, 1H), 8.99 (d, *J* = 2.1 Hz, 1H), 8.51 (dd, *J* = 2.3, 8.7 Hz, 1H), 8.46 (d, *J* = 4.8 Hz, 2H), 8.18 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 8.7 Hz, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.04 (t, *J* = 4.8 Hz, 1H), 4.03 (s, 3H), 2.44 (s, 3H).

Method 11 Table: Compounds Synthesized via Method 11 using the appropriate amide and bromide intermediates

Example #	Structure	Inter-mediate Amide	Inter-mediate Bromide	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
111		AA	Y	457.0	11.74 (br. s., 1H), 10.92 (s, 1H), 9.01 (d, J = 2.3 Hz, 1H), 8.52 (dd, J = 2.4, 8.7 Hz, 1H), 8.45 (s,

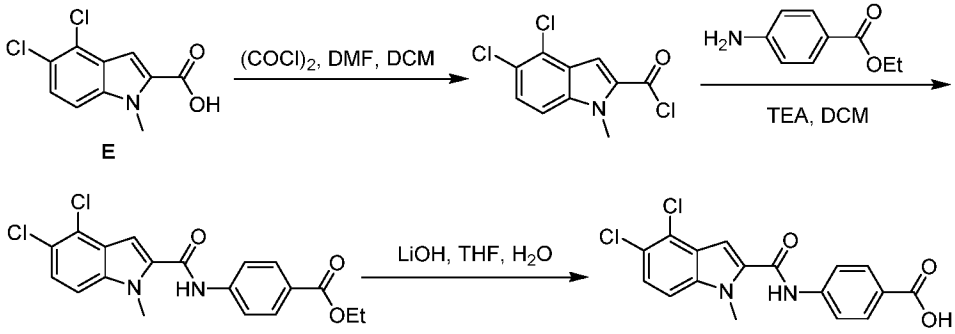
Example #	Structure	Inter-mediate Amide	Inter-mediate Bromide	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	4-chloro-1,5-dimethyl-*N*-(6-(*N*-(pyrazin-2-yl)sulfamoyl)pyridin-3-yl)-1*H*-indole-2-carboxamide				1H), 8.23 (d, J = 2.6 Hz, 1H), 8.20 - 8.16 (m, 2H), 7.53 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.31 (d, J = 8.5 Hz, 1H), 4.03 (s, 3H), 2.44 (s, 3H)
112	 4,5-dichloro-1-methyl-*N*-(6-(*N*-(pyrazin-2-yl)sulfamoyl)pyridin-3-yl)-1*H*-indole-2-carboxamide	**AB**	**Y**	477.0	11.75 (brs, 1H), 11.00 (brs, 1H), 8.99 (d, *J* = 2.0 Hz, 1H), 8.50 - 8.43 (m, 2H), 8.23 - 8.16 (m, 3H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.53 - 7.50 (m, 2H), 4.04 (s, 3H)
113	 4-chloro-5-fluoro-1-methyl-*N*-(6-(*N*-(pyrazin-2-yl)sulfamoyl)pyridin-3-yl)-1*H*-indole-2-carboxamide	**AC**	**Y**	461.0	11.75 (brs, 1H), 10.98 (brs, 1H), 9.00 (s, 1H), 8.52 - 8.49 (m, 1H), 8.43 (s, 1H), 8.23 - 8.16 (m, 3H), 7.70 - 7.66 (s, 1H), 7.51 (s, 1H), 7.41 (t, J = 9.2 Hz, 1H), 4.04 (s, 3H)
114	 4-chloro-*N*-(6-(*N*-(4-methoxy-6-methylpyrimidin-2-yl)sulfamoyl)pyridin-3-yl)-1,5-dimethyl-1*H*-indole-2-carboxamide	**AA**	**Z**	501.2	10.84 (s, 1H), 8.94 (d, *J* = 2.3 Hz, 1H), 8.43 (dd, *J* = 2.4, 8.7 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.47 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.15 (s, 1H), 4.04 (s, 3H), 3.51 (s, 3H), 2.44 (s, 3H), 2.22 (s, 3H)
115[a]		**AB**	**CD**	520.1, 522.0	12.75 (br s, 1H), 10.69 (s, 1H), 7.90 (br m, 4H), 7.67 (d, J = 8.9 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.47 (s, 1H), 6.14 (br

Example #	Structure	Inter-mediate Amide	Inter-mediate Bromide	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	4,5-dichloro-*N*-(4-(*N*-(4-methoxy-6-methylpyrimidin-2-yl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide				s, 1H), 4.04 (s, 3H), 3.74 (s, 3H), 2.21 (s, 3H).
116	 *N*-(6-(*N*-acetylsulfamoyl)pyridin-3-yl)-4-chloro-5-fluoro-1-methyl-1*H*-indole-2-carboxamide	**AC**	**AF**	425.1	12.25 (br. s., 1H), 11.03 (s, 1H), 9.10 (d, *J* = 2.3 Hz, 1H), 8.50 (dd, *J* = 2.4, 8.7 Hz, 1H), 8.13 (d, *J* = 8.8 Hz, 1H), 7.70 (dd, *J* = 3.6, 9.2 Hz, 1H), 7.55 (s, 1H), 7.42 (t, *J* = 9.5 Hz, 1H), 4.07 (s, 3H), 1.97 (s, 3H)
117	 4-chloro-5-fluoro-*N*-(6-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)pyridin-3-yl)-1-methyl-1*H*-indole-2-carboxamide	**AC**	**AG**	469.1	10.87 (br. s., 1H), 8.95 (br. s., 1H), 8.35 (d, *J* = 7.9 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.69 (dd, *J* = 3.6, 9.0 Hz, 1H), 7.53 (s, 1H), 7.41 (t, *J* = 9.4 Hz, 1H), 4.07 (s, 3H), 2.90 (s, 2H), 1.18 (s, 6H)

[a] Coupling was done at 140 °C for 2 hrs in a microwave reactor using dioxane as the solvent.

Examples 118-125 (Method 12)

4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]benzoic acid (Example 118)



Step 1 - 4,5-Dichloro-1-methyl-indole-2-carbonyl chloride

[00520] To a solution of 4,5-dichloro-1-methyl-indole-2-carboxylic acid (500 mg, 2.05 mmol) in anhydrous dichloromethane (20 mL) was added one drop of DMF. Then, the solution was cooled to 0 °C and oxalyl chloride (780 mg, 6.15 mmol) was added. The mixture was warmed to 15 °C and stirred for 1 hour. On completion, the mixture was concentrated *in vacuo* to give the title compound (540 mg, crude). The crude product was used directly in the next step without further purification.

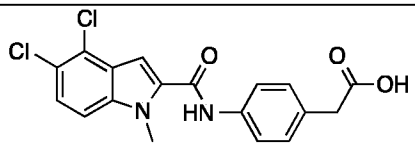
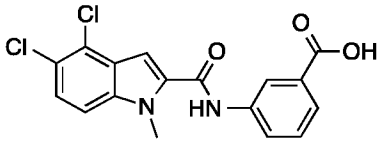
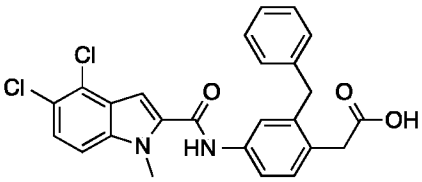
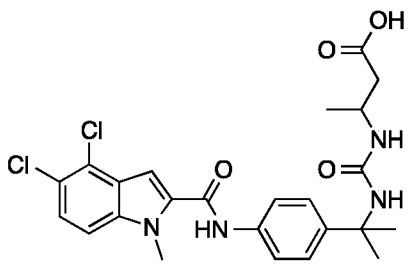
Step 2 - Ethyl 4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]benzoate

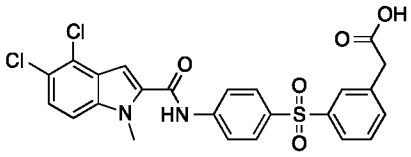
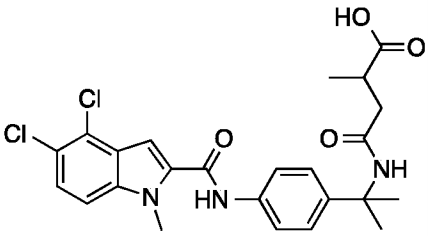
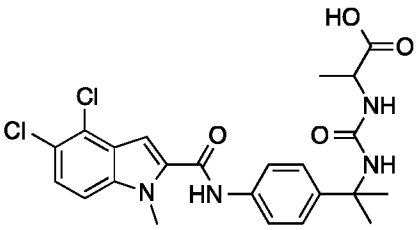
[00521] To a solution of ethyl 4-aminobenzoate (340 mg, 2.06 mmol) in anhydrous dichloromethane (10 mL) was added triethylamine (625 mg, 6.18 mmol). A solution of 4,5-dichloro-1-methyl-indole- 2-carbonyl chloride (540 mg, 2.06 mmol) dissolved in dichloromethane (10 mL) was then added dropwise at 0 °C. The resulting mixture was then warmed to 15 °C and stirred for 3 hours. On completion, the reaction mixture was washed with 0.5 M hydrochloric acid (20 mL), saturated sodium bicarbonate aqueous (2 x 20 mL). The organic phase was collected, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give the title compound. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.76 (s, 1H), 8.03 - 7.90 (m, 4H), 7.67 (d, J = 9.0 Hz, 1H), 7.53 - 7.47 (m, 2H), 4.31 (q, J = 7.0 Hz, 2H), 4.05 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H).

Step 3 - 4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]benzoic acid

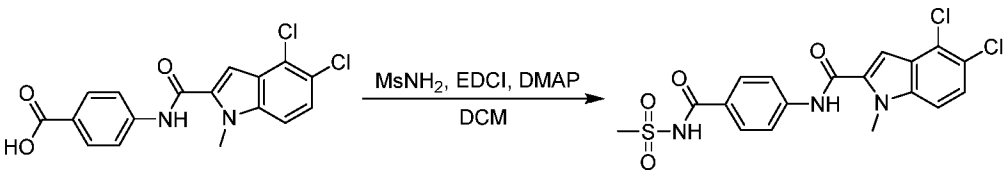
[00522] To a solution of ethyl 4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]benzoate (200 mg, 0.511 mmol) in tetrahydrofuran (8 mL) and water (2 mL) was added lithium hydroxide (37.0 mg, 1.53 mmol). The mixture was stirred at 30 °C for 16 hours. On completion, the reaction mixture was concentrated under reduced pressure and the residue was acidified with 2 M hydrochloric acid to pH = 3. The precipitate was filtered and the filter cake was washed with water, and dried *in vacuo* to give the crude product. The crude product was triturated with (petroleum ether:ethyl acetate = 10:1) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 361.0, tR = 0.971. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.79 (br. s., 1H), 10.75 (s, 1H), 8.00 - 7.91 (m, 4H), 7.68 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 8.9 Hz, 1H), 7.49 (s, 1H), 4.06 (s, 3H).

Method 12 Table: Compounds Synthesized via Method 12 using the appropriate acid and amine intermediates

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
119	 2-(4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)acetic acid	**E**	ethyl 2-(4-amino-phenyl) acetate	377.1	10.38 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.05 (s, 3H), 3.16 (s, 2H)
120	 3-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)benzoic acid	**E**	methyl 3-amino-benzoate	363.1	13.01 (brs, 1H), 10.64 (s, 1H), 8.46 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.68 (dd, *J* = 8.4, 12.4 Hz, 2H), 7.58 - 7.43 (m, 3H), 4.06 (s, 3H)
121	 2-(2-benzyl-4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)acetic acid	**E**	**BL**	489.0	10.43 (br. s, 1H), 7.65 (d, *J* = 9.2 Hz,1H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.49 (d, *J* = 9.2 Hz, 1H), 7.40 (s, 1H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.23 - 7.16 (m, 4H), 4.03 (s, 3H), 3.98 (s, 2H), 3.56 (s, 2H)
122	 3-(3-(2-(4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)propan-2-yl)ureido)butanoic acid	**E**	**BV**	505.1	10.44 (s, 1H), 7.66 (d, *J* = 8.7 Hz, 3H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.41 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 6.42 (br. s., 1H), 6.01 (br. s., 1H), 4.05 (s, 3H), 3.76 (br. s., 1H), 2.22 (br. s., 1H), 2.14 (br. s., 1H), 1.52 (d, *J* = 4.0 Hz, 6H), 1.04 (d, *J* =

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
					6.1 Hz, 3H)
123	 2-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)phenyl)acetic acid	**E**	**BY**	515.0	10.85 (s, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.97 (d, *J* = 9.0 Hz, 2H), 7.88 (s, 1H), 7.84 (m, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 4.8 Hz, 2H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.48 (s, 1H), 4.04 (s, 3H), 3.74 (s, 2H)
124	 4-((2-(4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)propan-2-yl)amino)-2-methyl-4-oxobutanoic acid	**E**	**CB**	488.1	12.10 (br. s., 1H), 10.43 (s, 1H), 8.06 (d, *J* = 10.8 Hz, 1H), 7.70 - 7.61 (m, 3H), 7.49 (d, *J* = 9.0 Hz, 1H), 7.40 (d, *J* = 2.8 Hz, 1H), 7.31 (dd, *J* = 2.1, 8.7 Hz, 2H), 4.05 (s, 3H), 2.86 - 2.73 (m, 1H), 2.70 - 2.61 (m, 1H), 2.49 - 2.39 (m, 1H), 2.26 - 2.08 (m, 1H), 1.60 - 1.47 (m, 6H), 1.09 - 1.01 (m, 3H)
125	 ((2-(4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)propan-2-yl)carbamoyl)alanine	**E**	**CC**	491.1	10.43 (s, 1H), 7.66 (d, *J* = 3.5 Hz, 1H), 7.64 (d, *J* = 3.1 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 1H), 7.40 (s, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.71 (br. s., 1H), 6.14 (br. s., 1H), 4.05 (s, 3H), 3.57 (br. s., 1H), 1.50 (d, *J* = 2.9 Hz, 6H), 1.10 (d, *J* = 6.5 Hz, 3H)

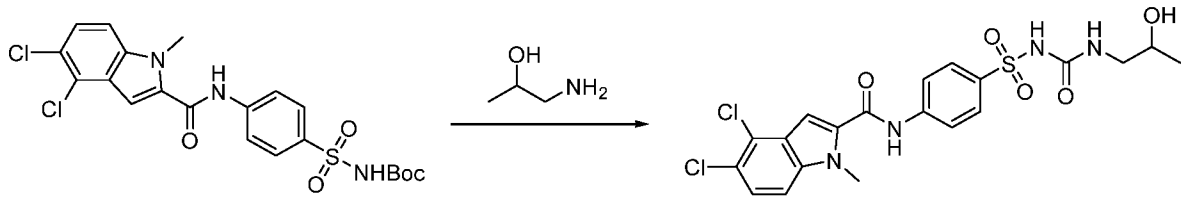
Example 126: 4,5-Dichloro-1-methyl-*N*-[4-(methylsulfonylcarbamoyl)phenyl]indole-2-carboxamide



[00523] To a solution of 4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]benzoic acid (150 mg, 0.413 mmol, synthesized via Method 12) and methanesulfonamide (39.2 mg, 0.413 mmol) in anhydrous DMF (8 mL) was added 3-(((ethylimino)methylene)amino)-*N*,*N*-dimethylpropan-1-aminium chloride (EDCI) (633 mg, 3.30 mmol) and DMAP (201 mg, 1.65 mmol). The reaction mixture was stirred at 18 °C for 16 hrs. On completion, the reaction mixture was diluted with dichloromethane (50 mL), washed with 2 M hydrochloric acid (10 mL), followed with saturated sodium bicarbonate solution (10 mL). The organic phase was collected, dried over anhydrous sodium sulfate and concentrated *in vacuo* to get a residue. The residue was purified by prep-HPLC (Condition: 0.1% TFA-MeCN, Column: Welch Ultimate AQ-C_{18} 150*30 mm; Particle size: 5 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 440.0, tR = 0.870. ^{1}H NMR (400MHz, DMSO-d_6) δ = 12.04 (br. s., 1H), 10.77 (s, 1H), 8.02 - 7.93 (m, 4H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.53 - 7.48 (m, 2H), 4.06 (s, 3H), 3.39 (s, 3H).

Examples 127-129 (Method 13)

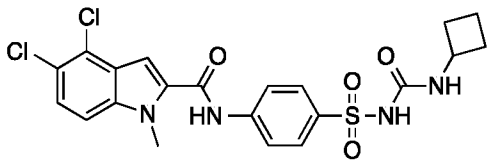
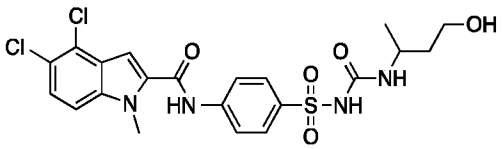
4,5-Dichloro-*N*-[4-(2-hydroxypropylcarbamoylsulfamoyl)-phenyl]-1-methyl-indole-2-carboxamide (Example 127)



[00524] To a solution of *tert*-butyl *N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonyl-carbamate (120 mg, 0.240 mmol, Intermediate AY) in toluene (5 mL) was added 1-aminopropan-2-ol (36.1 mg, 0.481 mmol). The mixture was then warmed to 100 °C and stirred at the same temperature for 30 mins. On completion, the reaction mixture was concentrated *in vacuo* directly to get a residue. The residue was purified by prep-HPLC

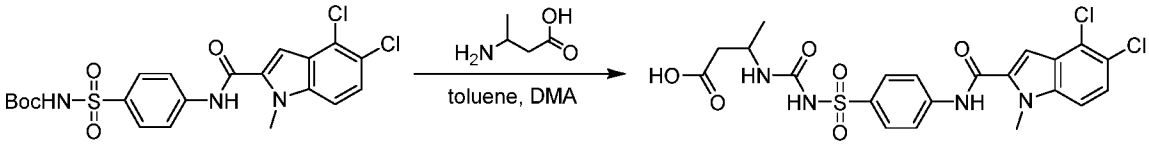
(Condition: 0.1% TFA-MeCN; Column: Welch Ultimate AQ-C18 150*30 mm; particle size: 5 µm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 499.1, tR = 0.846. ^1H NMR (400MHz, DMSO-d_6) δ = 10.84 (s, 1H), 10.40 (br. s., 1H), 8.01 (d, *J* = 8.5 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.54 - 7.50 (m, 2H), 6.35 (d, *J* = 7.8 Hz, 1H), 4.83 (t, *J* = 5.2 Hz, 1H), 4.06 (s, 3H), 3.57 - 3.50 (m, 1H), 3.28 (t, *J* = 5.0 Hz, 2H), 0.98 (d, *J* = 6.7 Hz, 3H).

Method 13 Table: Compounds Synthesized via Method 13 using the appropriate amine

Example #	Structure	Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
128	 4,5-dichloro-*N*-(4-(*N*-(cyclobutylcarbamoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	cyclobutanamine	495.1	10.83 (s, 1H), 10.46 (br. s., 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.92 - 7.87 (m, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.49 (m, 2H), 6.74 (br. s., 1H), 4.06 (s, 3H), 4.00 - 3.89 (m, 1H), 2.09 (q, *J* = 7.8 Hz, 2H), 1.90 - 1.75 (m, 2H), 1.64 - 1.46 (m, 2H)
129	 4,5-dichloro-*N*-(4-(*N*-((4-hydroxybutan-2-yl)carbamoyl)sulfamoyl)phenyl)-1-methyl-1*H*-indole-2-carboxamide	3-aminobutan-1-ol	513.2	10.67 (br. s., 1H), 7.82 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.46 (s, 1H), 6.00 (br. s., 1H), 4.56 (br. s., 1H), 4.05 (s, 3H), 3.18 (d, *J* = 7.5 Hz, 2H), 1.53 - 1.32 (m, 2H), 1.18 (d, *J* = 4.0 Hz, 1H), 0.98 (d, *J* = 6.0 Hz, 3H)

Example 130-136 (Method 14)

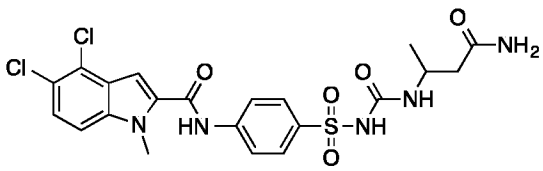
(±)-3-[[4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]-phenyl]sulfonylcarbamoylamino]butanoic acid (Example 130)

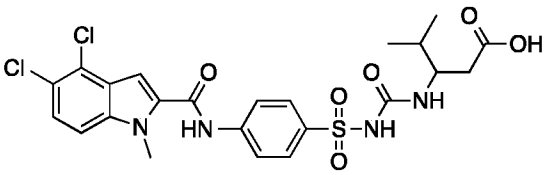
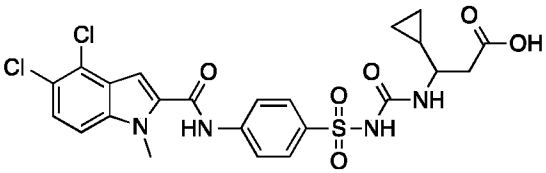
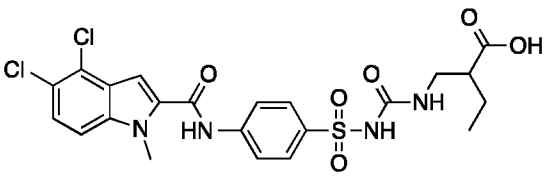


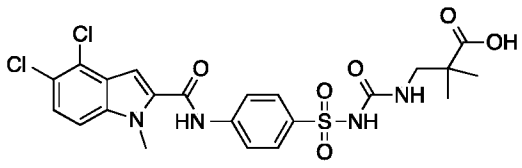
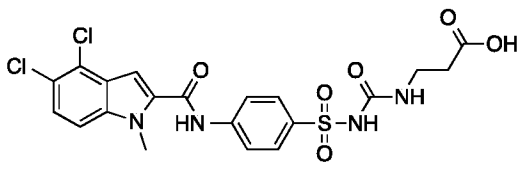
AY

[00525] A mixture of 3-aminobutanoic acid (694 mg, 6.73 mmol) in toluene (15 mL) and DMA (1 mL) was stirred at 110 °C for 1 hour under a nitrogen atmosphere. Then (±)-*tert*-butyl *N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamate (500 mg, 1.00 mmol) was added in the mixture at 110 °C. The mixture was stirred at 110 °C for 12 hours under a nitrogen atmosphere. On completion, the organic layer was concentrated *in vacuo* to give a residue. The mixture was purified by prep-HPLC (Condition: 0.225% FA-MeCN; Column: Boston Green ODS 150*30 5μ) to give the title compound. LCMS: (ES+) m/z $(M+H)^+$ = 526.9, tR= 0.858. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.82 (s, 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.55 - 7.49 (m, 2H), 4.06 (s, 3H), 3.90 - 3.80 (m, 1H), 2.37 (d, *J* = 5.6 Hz, 1H), 2.36 - 2.29 (m, 1H), 1.06 (d, *J* = 6.7 Hz, 3H).

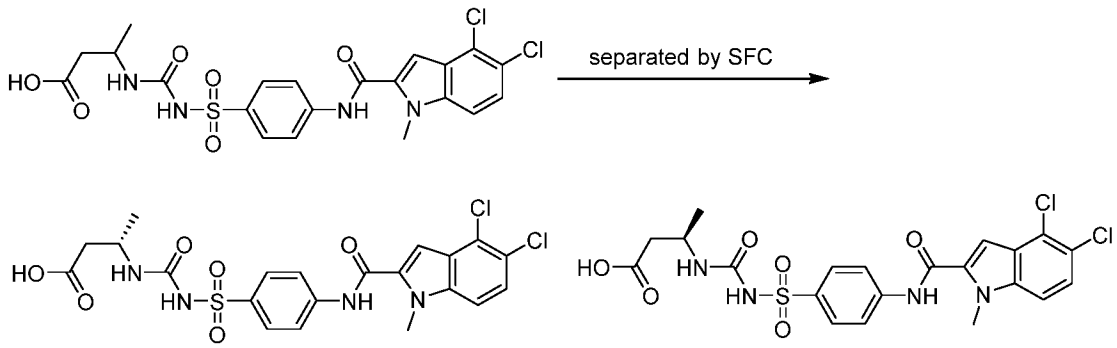
Method 14 Table: Compounds Synthesized via Method 14 using the appropriate amine

Example #	Structure	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
131	 *N*-(4-(*N*-((4-amino-4-oxobutan-2-yl)carbamoyl)sulfamoyl)phenyl)-4,5-dichloro-1-methyl-1*H*-indole-2-carboxamide	AZ	526.0	10.79 (s, 1H), 8.04 - 7.92 (m, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.56 - 7.45 (m, 2H), 7.37 (br. s., 1H), 6.87 (br. s., 1H), 4.06 (s, 3H), 3.91 - 3.77 (m, 1H), 2.28 - 2.18 (m, 1H), 2.17 - 2.05 (m, 1H), 1.01 (d, *J* = 6.5 Hz, 3H)

Example #	Structure	Inter-mediate Amine	LCMS (ES^+) m/z (M+H)$^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
132	 3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)-4-methylpentanoic acid	(±)-3-amino-4-methyl-pentanoic acid	555.1	12.25 (br. s., 1H), 10.81 (s, 1H), 10.38 (s, 1H), 8.00 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.48 (m, 2H), 6.43 (d, *J* = 8.8 Hz, 1H), 4.06 (s, 3H), 3.67 (br. s., 1H), 2.37 - 2.24 (m, 2H), 1.70 (dd, *J* = 6.9, 12.9 Hz, 1H), 0.74 (t, *J* = 6.7 Hz, 6H)
133	 3-cyclopropyl-3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)propanoic acid	(±)-3-amino-3-cyclopropyl-propanoic acid	553.1	12.28 (br. s., 1H), 10.82 (s, 1H), 10.49 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.54 - 7.48 (m, 2H), 6.65 (d, *J* = 8.4 Hz, 1H), 4.05 (s, 3H), 3.25 (br. s., 1H), 2.45 (d, *J* = 5.6 Hz, 2H), 0.97 (br. s., 1H), 0.40 - 0.26 (m, 2H), 0.20 - 0.08 (m, 2H)
134	 2-((3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)methyl)butanoic acid	**BP**	541.1	12.36 (br. s., 1H), 10.83 (s, 1H), 10.55 (br. s., 1H), 8.01 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.57 - 7.46 (m, 2H), 6.54 (t, *J* = 6.2 Hz, 1H), 4.06 (s, 3H), 3.13 (t, *J* = 6.1 Hz, 2H), 2.33 - 2.25 (m, 1H), 1.51 -

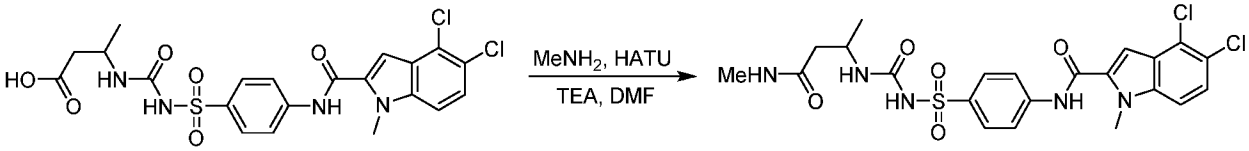
Example #	Structure	Inter-mediate Amine	LCMS (ES^+) m/z (M+H)$^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
				1.31 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H)
135	 3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)-2,2-dimethylpropanoic acid	3-amino-2,2-dimethyl-propanoic acid	541.1	12.49 (br. s., 1H), 10.83 (s, 1H), 10.53 (br. s., 1H), 8.01 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.55 - 7.48 (m, 2H), 6.51 (t, *J* = 6.1 Hz, 1H), 4.06 (s, 3H), 3.10 (d, *J* = 6.1 Hz, 2H), 0.99 (s, 6H)
136	 3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)propanoic acid	3-aminopropanoic acid	513.1	10.59 (s, 1H), 7.80 - 7.75 (m, 2H), 7.74 - 7.70 (m, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 1H), 7.46 (s, 1H), 4.06 (s, 3H), 3.08 (br. s., 2H), 2.31 - 2.24 (m, 2H)

Example 137 and 138: (3*S*)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]-phenyl] sulfonylcarbamoylamino]butanoic acid and (3*R*)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]-butanoic acid



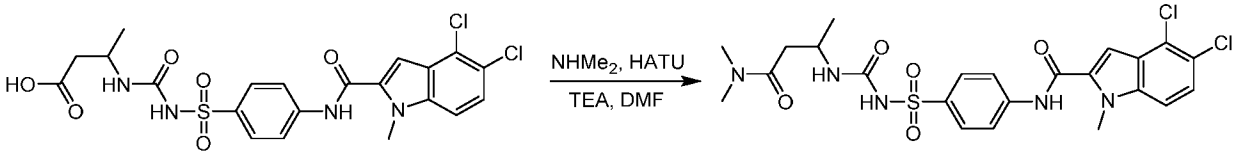
[00526] 3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]-butanoic acid (187 mg, 0.355 mmol, Example 130) was purified by chiral SFC (instrument: SFC-A; column: AS (250mm*30 mm, 10 μm); condition: Base-MeOH) to afford (3*S*)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]butanoic acid and (3*R*)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]butanoic acid. One enantiomer (Peak 1-SFC) had a tR = 3.834 and the other (Peak 2-SFC) had tR = 4.129. Peak 1: SFC tR = 3.834, LCMS: (ES+) m/z (M+H)+ = 527.1, tR = 0.883. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.81 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.9 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.56 - 7.48 (m, 2H), 6.51 (br. s., 1H), 4.06 (s, 3H), 3.89 - 3.81 (m, 1H), 2.37 (d, *J* = 5.5 Hz, 1H), 2.35 - 2.31 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H). Peak 2: SFC tR = 4.129, LCMS: (ES+) m/z (M+H)+ = 527.1, tR = 0.880. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.74 (br. s., 1H), 7.98 - 7.88 (m, 2H), 7.88 - 7.80 (m, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.46 (m, 2H), 6.35 (br. s., 1H), 4.06 (s, 3H), 3.87 - 3.78 (m, 1H), 2.39 - 2.32 (m, 1H), 2.31 - 2.21 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H).

Example 139: (±)-4,5-Dichloro-1-methyl-*N*-[4-[[1-methyl-3-(methylamino)-3-oxo-propyl]-carbamoyl sulfamoyl] phenyl]indole-2-carboxamide



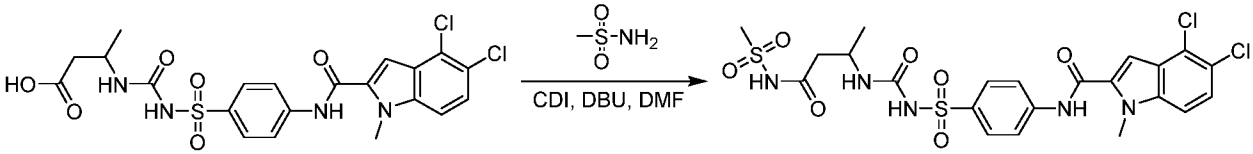
[00527] To a solution of (±)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl] sulfonylcarbamoylamino]-butanoic acid (80 mg, 0.152 mmol, Example 130) in DMA (20 mL) was added triethylamine (76 mg, 0.758 mmol), methanamine (31 mg, 0.455 mmol) and HATU (87 mg, 0.228 mmol) in one portion and the reaction mixture was stirred at 30 °C for 12 hrs. On completion, the reaction mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC (0.1%TFA-MeCN, Welch Ultimate AQ-C18 150 x 30mm x 5 μm) to give the title compound. LCMS: (ES$^+$) m/z (M+H)$^+$ = 540.0, tR = 1.374. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.82 (s, 1H), 10.55 (s, 1H), 8.00 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.83 (br. s., 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.54 - 7.48 (m, 2H), 6.72 (d, *J* = 8.3 Hz, 1H), 4.05 (s, 3H), 3.88 - 3.79 (m, 1H), 2.56 - 2.54 (m, 3H), 2.26 - 2.12 (m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H).

Example 140: 4,5-Dichloro-*N*-[4-[[3-(dimethylamino)-1-methyl-3-oxo- propyl]carbamoyl-sulfamoyl]phenyl]-1-methyl-indole-2-carboxamide



[00528] To a solution of (±)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]-butanoic acid (80 mg, 0.152 mmol, Example 130) in DMF (5 mL) was added triethylamine (77 mg, 0.758 mmol), HATU (86.5 mg, 0.228 mmol) and dimethylamine (20.5 mg, 0.455 mmol) in one portion at 30 °C. The reaction was stirred at 30 °C for 12 hrs. On completion, the reaction was concentrated *in vacuo*, and the residue was purified by prep-HPLC (0.1% TFA-MeCN, Welch Ultimate AQ-C18 150 x 30 mm x 5 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 554.0, tR = 1.416. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.69 (br. s., 1H), 7.86 (br. s., 2H), 7.80 (br. s., 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.54 - 7.44 (m, 2H), 4.05 (s, 3H), 3.80 (br. s., 1H), 2.93 (br. s., 3H), 2.78 (s, 3H), 2.60 - 2.55 (m, 1H), 2.24 (br. s., 1H), 1.01 (d, *J* = 6.7 Hz, 3H).

Example 141: (±)-4,5-Dichloro-*N*-[4-[[3-(methanesulfonamido)-1-methyl-3-oxo-propyl]-carbamoylsulfamoyl] phenyl]-1-methyl-indole-2-carboxamide

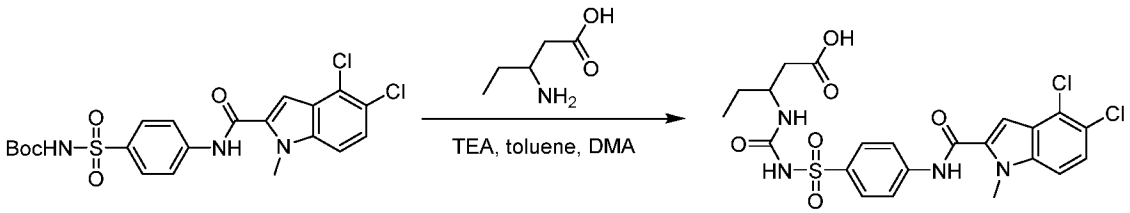


[00529] To a solution of (±)-3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamoylamino]-butanoic acid (45.0 mg, 0.0853 mmol, Example 130) in DMF (5 mL) was added carbonyl diimidazole (CDI) (27.7 mg, 0.171 mmol) at 30 °C. The solution was stirred at 30 °C for 2 hrs, then DBU (25.9 mg, 0.171 mmol) and methanesulfonamide (40.6 mg, 0.427 mmol) was added to the solution in one portion at 30 °C, and the reaction was stirred at 30 °C for 12 hrs. On completion, the reaction was concentrated *in vacuo*, and the residue was purified by prep-HPLC (water (0.1% TFA-MeCN, Welch Ultimate AQ-C18 150 × 30mm × 5 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 604, tR = 3.05. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.83 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* =

8.6 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.54 - 7.47 (m, 2H), 6.56 - 6.49 (m, 1H), 4.05 (s, 3H), 3.93 - 3.82 (m, 1H), 3.16 (s, 3H), 2.42 (br. s., 1H), 2.36 (d, *J* = 6.6 Hz, 1H), 0.99 (d, *J* = 6.5 Hz, 3H).

Examples 142-147 (Method 15)

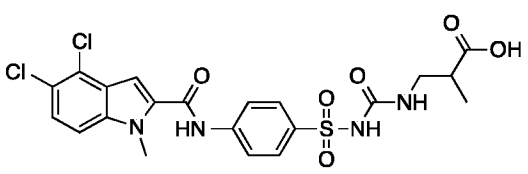
(±)-3-[[4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]-phenyl] sulfonylcarbamoylamino]pentanoic acid (Example 142)

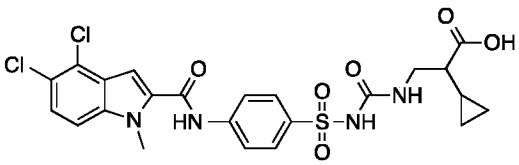
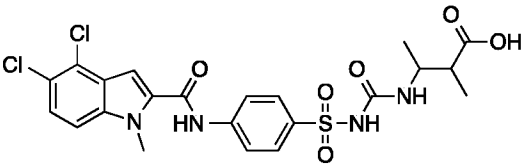
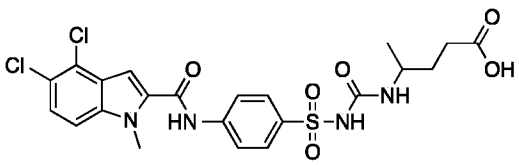


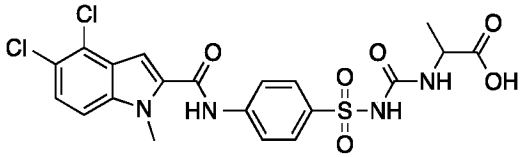
AY

[00530] To a mixture of (±)-3-aminopentanoic acid (103 mg, 0.883 mmol) in dimethyl acetamide (500 uL) and toluene (3 mL) was added triethylamine (67.0 mg, 0.662 mmol). Then *tert*-butyl *N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamate (110 mg, 0.220 mmol) was added to the mixture and the reaction mixture was stirred at 120 °C for 12 hrs. On completion, the residue was purified by prep-HPLC (0.05% ammonium hydroxide/MeCN; column: Phenomenex Gemini C18 250*50 10 µm) to give the title compound. LCMS: (ES$^+$) m/z (M+H)$^+$ = 541.2, tR = 0.910. ^{1}H NMR (400MHz, DMSO-d$_6$) δ = 10.72 - 10.54 (m, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.76 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.52 - 7.43 (m, 2H), 4.10 (s, 3H), 3.64 (br. s., 1H), 2.32 (dd, *J* = 5.0, 15.1 Hz, 1H), 2.25 - 2.12 (m, 1H), 1.50 - 1.27 (m, 2H), 0.77 (t, *J* = 7.3 Hz, 3H).

Method 15 Table: Compounds Synthesized via Method 15 using the appropriate amine

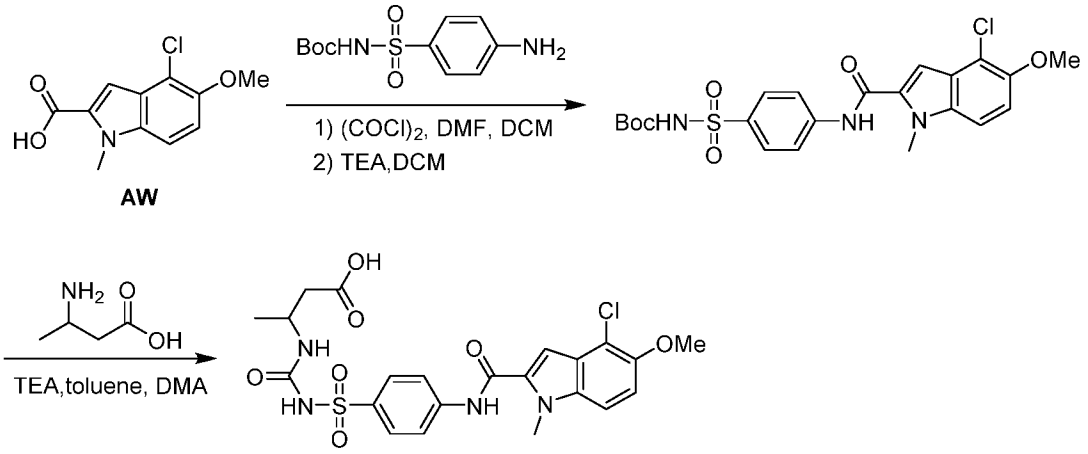
Example #	Structure	Inter-mediate Amine	LCMS (ES$^+$) m/z (M+H)$^+$	^{1}H NMR (400MHz, DMSO-d$_6$) δ
143	 3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-	3-amino-2-methyl-propanoic acid	527.2	10.82 (s, 1H), 7.99 (d, *J* = 8.8 Hz, 2H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.56 - 7.46 (m, 2H), 6.54 (br. s., 1H), 4.15 - 3.94 (m, 3H), 3.19 - 3.01 (m, 2H), 2.47 - 2.41 (m,

Example #	Structure	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
	carboxamido)phenyl)sulfonyl)ureido)-2-methylpropanoic acid			1H), 0.97 (d, *J* = 7.2 Hz, 3H)
144[a]	 2-cyclopropyl-3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)propanoic acid	**BQ**	553.0, 555.1	12.36 (br. s, 1H), 10.84 (br. s, 1H), 10.58 (br. s, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.52 (d, *J* = 10.4 Hz, 2H), 6.54 (br. s, 1H), 4.06 (s, 3H), 3.20~3.26 (m, 2H), 1.66~1.72 (m, 1H), 0.12~0.74 (m, 5H)
145[b]	 3-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)-2-methylbutanoic acid	**BR**	541.0	10.67 (br. s., 1H), 7.91 - 7.82 (m, 2H), 7.82 - 7.75 (m, 2H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.47 (s, 1H), 6.16 (s, 1H), 4.06 (s, 3H), 3.80 (br. s., 1H), 2.55 (br. s., 1H), 0.94 (t, *J* = 5.9 Hz, 6H)
146[b]	 4-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)pentanoic acid	(±)-4-aminopentanoic acid	541.0	10.60 (br. s., 1H), 7.83 - 7.77 (m, 2H), 7.77 - 7.72 (m, 2H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.9 Hz, 1H), 7.46 (s, 1H), 5.92 (br. s., 1H), 4.05 (s, 3H), 2.55 (br. s., 1H), 2.11 (br. s., 2H), 1.52 (br. s., 2H), 0.95 (d, *J* = 6.5 Hz, 3H)

Example #	Structure	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^1H NMR (400MHz, DMSO-d_6) δ
147[c]	 (((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)carbamoyl)alanine	(±)-2-aminopropanoic acid	513.0	10.80 (s, 1H), 7.97 (d, *J* = 8.7 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.54 - 7.47 (m, 2H), 6.80 (br. s., 1H), 4.06 (s, 3H), 4.02 - 3.91 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H)

[a]Reaction was run at 140 °C for 2 hrs. [b]Reaction was run at 140 °C for 1 hr. [c]Reaction was run at 150 °C for 2 hrs.

Example 148: (±)-3-[[4-[(4-Chloro-5-methoxy-1-methyl-indole-2-carbonyl)amino]phenyl]-sulfonylcarbamoylamino]butanoic acid



Step 1 - *Tert*-butyl *N*-[4-[(4-chloro-5-methoxy-1-methyl-indole-2-carbonyl)amino]phenyl]-sulfonyl carbamate

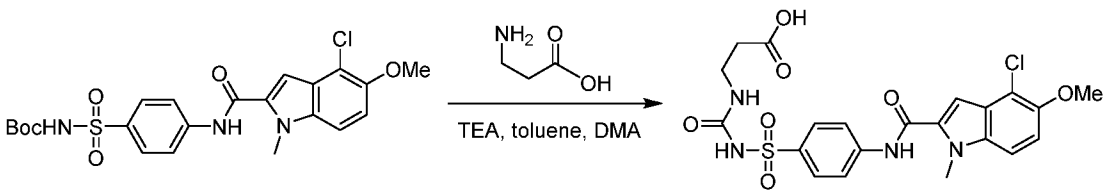
[00531] To a mixture of 4-chloro-5-methoxy-1-methyl-indole-2-carboxylic acid (140 mg, 0.584 mmol, Intermediate AW) and catalytic amount of *N,N*-dimethylformamide in dichloromethane (10 mL) was added oxalyl chloride (74.1 mg, 0.584 mmol) dropwise at 0 °C. The mixture was then warmed to 20 °C and stirred for 1 hr. On completion, the mixture was concentrated *in vacuo* to afford 4-chloro-5-methoxy-1-methyl-indole-2-carbonyl chloride (140 mg, crude) as yellow solid which was used for the next step without further purification.

[00532] To a solution of *tert*-butyl *N*-(4-aminophenyl)sulfonylcarbamate (147 mg, 0.542 mmol, synthesized via Intermediate AY, Steps 1-2) and triethylamine (164 mg, 1.63 mmol) in dichloromethane (5 mL) was added a solution of 4-chloro-5-methoxy-1-methyl-indole-2-carbonyl chloride (140 mg, 542 μmol in dichloromethane (5 mL) dropwise at 0 °C under a nitrogen atmosphere, then the mixture was stirred at 20 °C for 2 hrs. On completion, the mixture was concentrated *in vacuo* to afford a residue. The residue was purified with silica gel column (petroleum ether:ethyl acetate = 3:1) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 494.2, tR = 0.890.

Step 2 - (±)-3-[[4-[(4-Chloro-5-methoxy-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonyl-carbamoylamino]butanoic acid

[00533] To a solution of (±)-3-aminobutanoic acid (75.1 mg, 0.728 mmol) and triethylamine (442 mg, 4.37 mmol) in toluene (15 mL) and DMA (2 mL) was added *tert*-butyl *N*-[4-[(4-chloro-5-methoxy-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamate (90.0 mg, 0.182 mmol). The resulting mixture was heated to 150 °C and stirred for 3 hrs. The mixture was concentrated *in vacuo* to give a residue. The residue was purified with prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5μ; Mobile phase: 0.225% formic acid-acetonitrile) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 523.2, tR = 0.852. ^1H NMR (400MHz, DMSO-d_6) δ = 10.72 (s, 1H), 7.99 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 9.0 Hz, 1H), 7.39 (s, 1H), 7.29 (d, *J* = 9.0 Hz, 1H), 6.51 (br. s., 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.88 - 3.80 (m, 1H), 2.43 - 2.27 (m, 2H), 1.05 (d, *J* = 6.7 Hz, 3H).

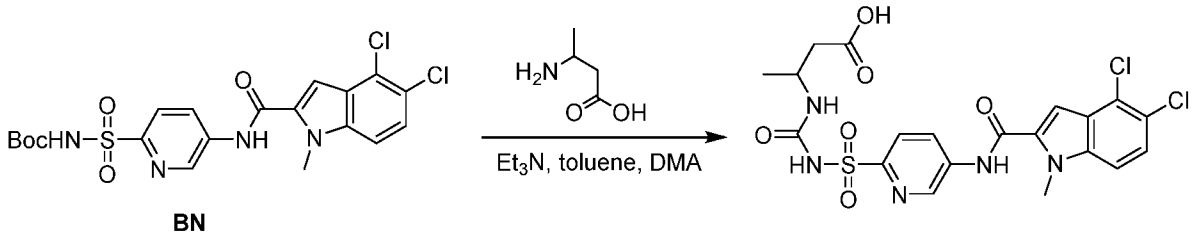
Example 149: 3-(3-((4-(4-chloro-5-methoxy-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)propanoic acid



[00534] To a solution of 3-aminopropanoic acid (72.1 mg, 0.809 mmol) and triethylamine (491 mg, 4.86 mmol) in toluene (15 mL) and dimethyl acetamide (2 mL) was added *tert*-butyl *N*-[4-[(4-chloro-5-methoxy-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamate (100 mg, 0.202 mmol, synthesized as shown above in Example 148). The resulting mixture was heated to

150 °C and stirred for 2 hrs. The mixture was concentrated *in vacuo* to give a residue. The residue was purified with prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5μ; Mobile phase: 0.225% formic acid-acetonitrile) to afford the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 509.2, tR = 0.825. ^1H NMR (400MHz, DMSO-d_6) δ = 10.72 (br. s., 1H), 7.98 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 7.9 Hz, 2H), 7.59 (d, *J* = 9.2 Hz, 1H), 7.39 (s, 1H), 7.30 (d, *J* = 9.2 Hz, 1H), 6.50 (br. s., 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.17 - 3.13 (m, 2H), 2.33 (s, 2H).

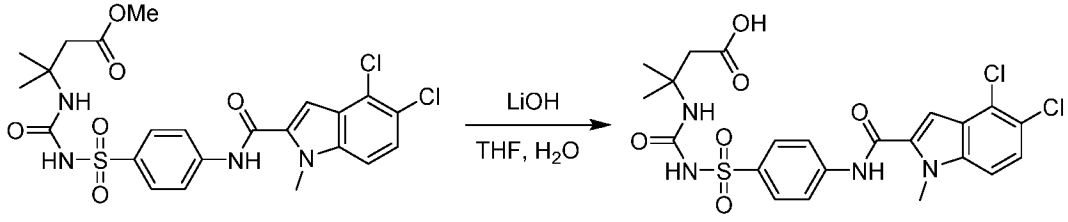
Example 150: 3-[[5-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]-2-pyridyl]sulfonyl-carbamoylamino]butanoic acid



BN

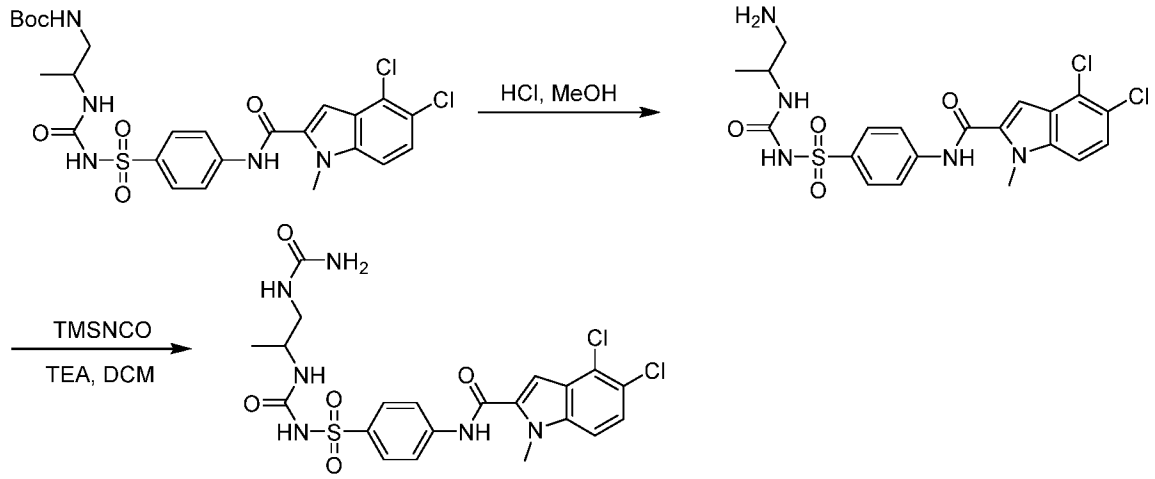
[00535] To a mixture of *tert*-butyl *N*-[[5-[(4,5-dichloro-1-methyl-indole-2-carbonyl)-amino]-2-pyridyl]-sulfonyl]-carbamate (100 mg, 0.200 mmol, Intermediate BN) and 3-aminobutanoic acid (103 mg, 1.00 mmol) in toluene (4 mL) and *N,N*-dimethylacetamide (2 mL) was added triethylamine (101 mg, 1.00 mmol) in one portion at 25 °C under a nitrogen. The mixture was heated to 120 °C and stirred for 2 hours. On completion, the reaction was concentrated *in vacuo*. The residue was purified by prep-HPLC (condition: 0.1% TFA-MeCN; Phenomenex Synergi C18 100*21.2 mm*4 μm) to give the title compound. LCMS (ES^+): 528.0 m/z $(M+H)^+$, tR = 1.010 min. ^1H NMR (400 MHz, DMSO-d_6) δ = 12.25 (br s, 1H), 11.00 (s, 1H), 10.77 (br s, 1H), 9.08 (d, *J* = 2.0 Hz, 1H), 8.48 - 8.45 (m, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.53 (d, *J* = 9.6 Hz, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 4.06 (s, 3H), 3.83-3.80 (m, 1H), 2.36 - 2.32 (m, 2H), 1.05-1.04 (m, 3H).

Example 151: 3-[[4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]phenyl] sulfonyl-carbamoylamino]-3-methyl-butanoic acid



[00536] To a mixture of methyl 3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]-phenyl]sulfonylcarbamoylamino]-3-methyl-butanoate (80.0 mg, 0.144 mmol, synthesized via Method 15 with intermediate AY and methyl 3-amino-3-methyl-butanoate) in tetrahydrofuran (2 mL) and water (1 mL) was added lithium hydroxide (24.1 mg, 0.576 mmol). Then the mixture was stirred at 25 °C for 12 hours. On completion, the mixture was quenched with 1.0 M hydrochloric acid to pH = 6.0. The residue was purified by prep-HPLC (Condition: 0.225% FA-MeCN; Column: Phenomenex Synergi C18 150*25*10 μm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 541.2, tR = 0.931. ^1H NMR (400MHz, DMSO-d_6) δ = 10.81 (br. s., 1H), 8.03 - 7.93 (m, 2H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.73 - 7.62 (m, 1H), 7.50 (s, 2H), 6.43 (br. s., 1H), 4.06 (s, 3H), 2.50 - 2.45 (m, 2H), 1.25 (s, 6H).

Example 152: (±)-4,5-Dichloro-1-methyl-*N*-[4-[(1-methyl-2-ureido-ethyl)carbamoyl-sulfamoyl]phenyl]indole-2-carboxamide



Step 1 - (±)-*N*-[4-[(2-amino-1-methyl-ethyl)carbamoylsulfamoyl]phenyl]-4,5-dichloro-1-methyl-indole-2-carboxamide

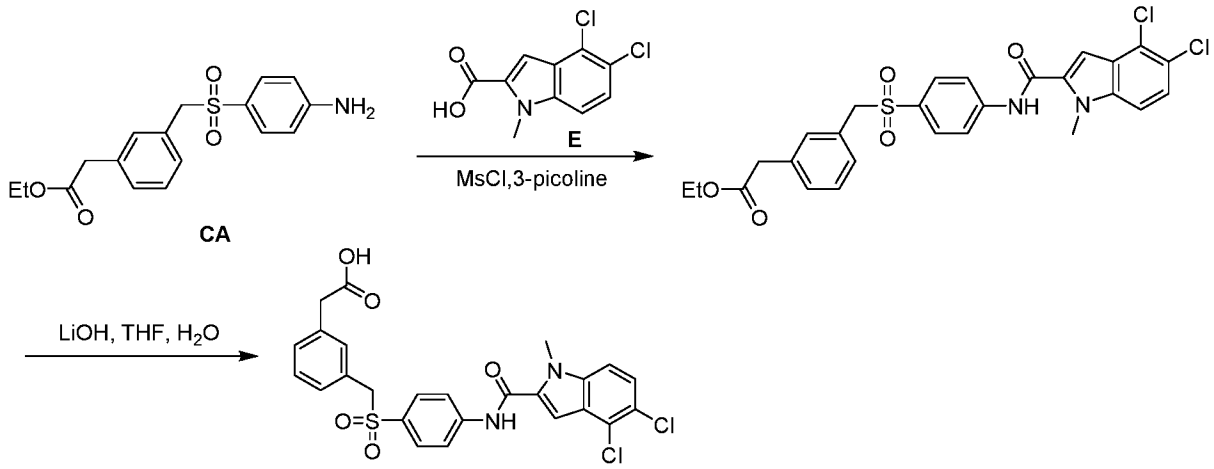
[00537] A mixture of (±)-*tert*-butyl (2-(3-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)ureido)propyl)carbamate (200 mg, 0.334 mmol, synthesized via Method 15 with intermediate AY and *tert*-butyl *N*-(2-aminopropyl)carbamate, CAS# 255735-88-7) in hydrochloride/methanol (10 mL) was stirred at 25 °C for 1 hr. On completion, the mixture was concentrated *in vacuo* to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 498.2, tR = 1.017.

Step 2 - (±)-4,5-Dichloro-1-methyl-*N*-[4-[(1-methyl-2-ureido-ethyl)carbamoylsulfamoyl]phenyl] indole-2-carboxamide

[00538] A solution of (±)-*N*-[4-[(2-amino-1-methyl-ethyl)carbamoylsulfamoyl]phenyl]-4,5-dichloro-1-methyl-indole-2-carboxamide (100 mg, 0.175 mmol) and triethylamine (88.5 mg, 0.875 mmol) in dichloromethane (2 mL) was stirred at 25 °C for 0.5 hr under a nitrogen atmosphere. To this mixture was added isocyanatotrimethylsilane (TMSNCO) (30.2 mg, 262 mmol), and the mixture was stirred at 25 °C for a further 0.5 hr under a nitrogen atmosphere. On completion, the mixture was concentrated *in vacuo* to give a residue. The residue was purified with prep-HPLC (Instrument: GX-D; Column: Boston Green ODS 150*30 5 μ; Mobile phase: 0.225% formic acid- acetonitrile) to give the title compound. LCMS: (ES$^+$) m/z $(M+H)^+$ = 541.1, tR = 0.782. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.82 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.55 - 7.47 (m, 2H), 6.40 (d, *J* = 6.8 Hz, 1H), 6.04 (t, *J* = 5.6 Hz, 1H), 5.51 (br. s., 2H), 4.06 (s, 3H), 3.52 (td, *J* = 6.6, 13.2 Hz, 1H), 2.96 (t, *J* = 5.8 Hz, 2H), 0.94 (d, *J* = 6.5 Hz, 3H).

Examples 153-157 (Method 16)

2-[3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]-phenyl]sulfonylmethyl]phenyl] acetic acid (Example 153)



Step 1 - Ethyl 2-[3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylmethyl] phenyl]acetate

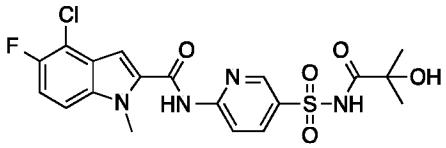
[00539] To a solution of ethyl 2-[3-[(4-aminophenyl)sulfonylmethyl]phenyl]acetate (100 mg, 0.299 mmol) in acetonitrile (10 mL) was added 3-picoline (83 mg, 0.899 mmol) and

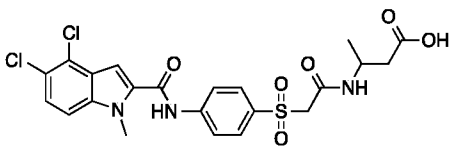
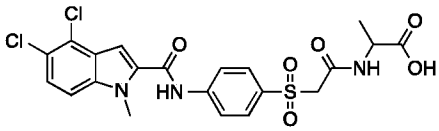
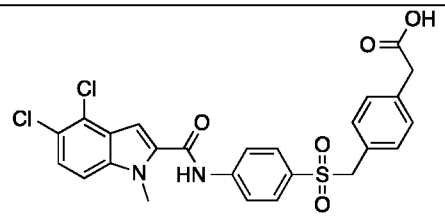
methanesulfonyl chloride (103 mg, 0.899 mmol) in one portion at 0 °C, and the reaction was stirred at 30 °C for 12 hours. On completion, the reaction was concentrated *in vacuo*, the residue was purified by column chromatography (petroleum ether:ethyl acetate = 100:1 to 1:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 559.0, tR = 1.248.

Step 2 - 2-[3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylmethyl]-phenyl] acetic acid

[00540] To a solution of ethyl 2-[3-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylmethyl] phenyl]acetate (60.0 mg, 0.109 mmol) in a mixture of tetrahydrofuran (10 mL) and water (10 mL) was added lithium hydroxide (7.90 mg, 0.329 mmol) in one portion at 30 °C, and the reaction was stirred at 30 °C for 2 hours. On completion, the reaction was concentrated *in vacuo*. The residue was adjusted to pH = 2 with 1 M hydrochloric acid (5 mL), then extracted with ethyl acetate (3 x 20 mL). The organic phase was concentrated *in vacuo*, and the residue was purified by prep-HPLC (condition: water (0.225% FA-MeCN, column: Phenomenex Synergi C18 150*25*10 µm) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 529.0, tR = 1.469. ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.85 (s, 1H), 7.99 (d, *J* = 8.7 Hz, 2H), 7.75 - 7.66 (m, 3H), 7.56 - 7.49 (m, 2H), 7.22 (dd, *J* = 4.6 Hz, 2H), 7.11 (s, 1H), 7.00 (br. s., 1H), 4.61 (s, 2H), 4.05 (s, 3H), 3.46 (s, 2H).

Method 16 Table: Additional compounds synthesized using Method 16 from the appropriate acids and amines

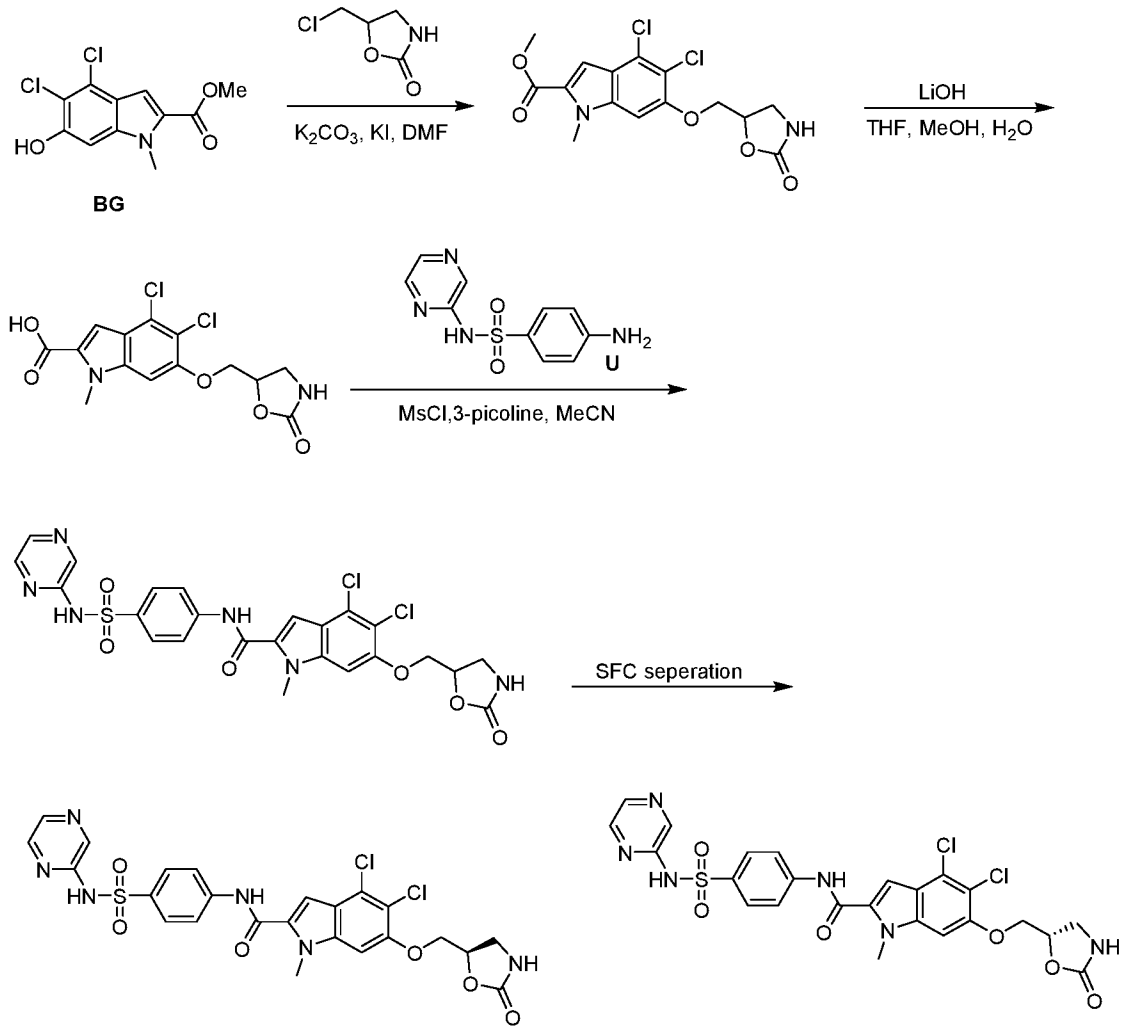
Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z $(M+H)^+$	^{1}H NMR (400MHz, DMSO-d_6) δ
154[a]	 4-chloro-5-fluoro-*N*-(5-(*N*-(2-hydroxy-2-methylpropanoyl)sulfamoyl)pyridin-2-yl)-1-methyl-1*H*-indole-2-carboxamide	**F**	**AJ**	469.0	11.35 (br. s., 1H), 8.77 (br. s., 1H), 8.32 - 8.17 (m, 2H), 8.14 (s, 1H), 7.71 (s, 1H), 7.67 (dd, *J* = 3.8, 9.3 Hz, 1H), 7.40 (t, *J* = 9.5 Hz, 1H), 4.06 (s, 3H), 1.16 (s, 6H)

Example #	Structure	Inter-mediate Acid	Inter-mediate Amine	LCMS (ES^+) m/z (M+H)+	^{1}H NMR (400MHz, DMSO-d_6) δ
155	 3-(2-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)acetamido)butanoic acid	**E**	**BT**	526.0	12.25 (br. s., 1 H), 10.86 (s, 1 H), 8.17 (d, *J* = 7.8 Hz, 1 H), 8.04 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.5 Hz, 2 H), 7.69 (d, *J* = 8.8 Hz, 1 H), 7.52 (d, *J* = 4.0 Hz, 2 H), 4.18 (d, *J* = 1.8 Hz, 2 H), 4.06 (s, 3 H), 3.91 - 3.98 (m, 1 H), 2.35 - 2.40 (m, 1 H), 2.21 (dd, *J* = 15.8, 1 H), 1.02 (d, *J* = 6.53 Hz, 3 H)
156	 (2-((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)acetyl)alanine	**E**	**BX**	512.0	10.9 (s, 1H), 8.50 (d, *J* =7.3 Hz, 1H), 8.03 (d, *J* = 8. 8 Hz, 2H), 7.86 (d, *J* = 8. 8 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.52 - 7.50 (m, 2H), 4.34 - 4.25 (m, 2H), 4.15 - 4.09 (m, 1H), 4.05 (s, 3H), 1.22 (d, *J* = 7.3 Hz, 3H)
157	 2-(4-(((4-(4,5-dichloro-1-methyl-1*H*-indole-2-carboxamido)phenyl)sulfonyl)methyl)phenyl)acetic acid	**E**	**BZ**	529.0	10.85 (s, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.77 - 7.66 (m, 3H), 7.54 - 7.48 (m, 2H), 7.23 - 7.17 (m, 2H), 7.12 (d, *J* = 7.9 Hz, 2H), 4.63 (s, 2H), 4.06 (s, 3H), 3.53 (s, 2H)

[a]Hydrolysis performed at 40 °C for 15 min.

Examples 159, 160, and 161: (±)-4,5-Dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl) phenyl]indole-2-carboxamide, (*S*)-4,5-Dichloro-1-methyl-6-

[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl) phenyl]indole-2-carboxamide, and (*R*)-4,5-Dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl) phenyl]indole-2-carboxamide



Step 1 - (±)-Methyl 4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]indole-2-carboxylate

[00541] To a solution of methyl 4,5-dichloro-6-hydroxy-1-methyl-1*H*-indole-2-carboxylate (600 mg, 2.19 mmol, Intermediate BG) and (±)-5-(chloromethyl)oxazolidin-2-one (356.06 mg, 2.63 mmol, CAS# 22625-57-6) in DMF (15 mL) was added potassium carbonate (605 mg, 4.38 mmol) and potassium iodide (18.17 mg, 0.109 mmol). The mixture was stirred at 100 °C for 12 hours. On completion, the reaction mixture was quenched by addition of water (100 mL) at 0 °C, and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed

with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (petroleum ether:ethyl acetate = 3:1 to 0:1) to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.96 (s, 1 H), 7.67 (s, 1 H), 7.42 (s, 1 H), 7.17 (s, 1 H), 5.02 (m, 1 H), 4.40 - 4.30 (m, 2 H), 4.03 (s, 3 H), 3.86 (s, 3 H), 3.70 (t, *J* = 8.95 Hz, 1 H), 3.51 (d, *J* = 8.29 Hz, 1 H).

Step 2 - (±)-4,5-Dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]indole-2-carboxylic acid

[00542] To a solution of (±)-methyl 4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]indole-2-carboxylate (550 mg, 1.47 mmol) in tetrahydrofuran (10 mL), methanol (6 mL) and water (2 mL) was added lithium hydroxide (308 mg, 7.35 mmol). The mixture was stirred at 25 °C for 2 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was diluted with water (10 mL) and adjusted to pH = 2-3 with hydrochloric acid (1 M) then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a residue. The residue was purified by prep-HPLC (column: Phenomenex Synergi Max-RP 250*80 10 μ, condition: 0.225% FA-MeCN) and lyophilized *in vacuo* to give the title compound. ^{1}H NMR (300 MHz, DMSO-d_6) δ = 7.66 (s, 1 H), 7.40 (s, 1 H), 7.13 (s, 1 H), 5.00 (d, *J* = 2.64 Hz, 1 H), 4.44 - 4.26 (m, 2 H), 4.03 (s, 3 H), 3.67 (t, *J* = 8.95 Hz, 1 H), 3.43 (d, *J* = 8.29 Hz, 1 H).

Step 3 - (±)-4,5-Dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl) phenyl]indole-2-carboxamide

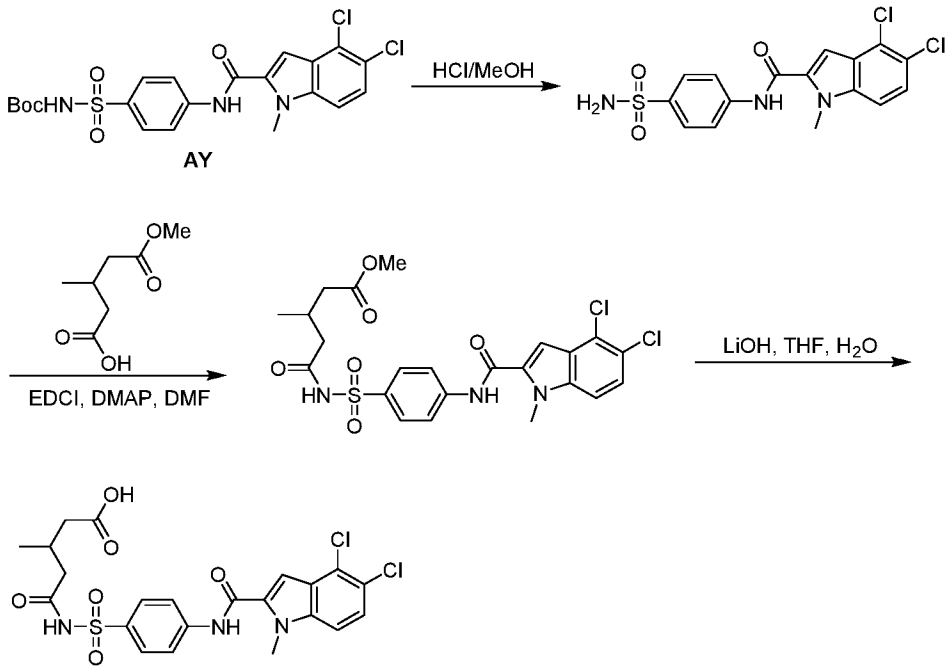
[00543] To a solution of (±)-4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]indole-2-carboxylic acid (120 mg, 0.334 mmol) and 4-amino-*N*-(pyrazin-2-yl)benzenesulfonamide (83 mg, 0.334 mmol) in acetonitrile (5 mL) was added 3-picoline (108 mg, 1.17 mmol) and methanesulfonyl chloride (68.8 mg, 0.601 mmol) at 0 °C. The mixture was stirred at 25 °C for 12 hours. On completion, the reaction mixture was quenched by addition of hydrochloric acid (1 M) (5 mL) at 0 °C, and then extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give a residue. The residue was purified by column chromatography (0.225% FA-MeCN and lyophilized *in vacuo* to give the title compound. LCMS: (ES+) m/z

$(M+H)^+$ = 591.0, tR = 2.653, ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.28 (br. s., 1 H), 8.19 - 8.08 (m, 2 H), 8.01 - 7.84 (m, 4 H), 7.66 (s, 1 H), 7.43 (s, 2 H), 5.05 - 4.98 (m, 1 H), 4.42 - 4.30 (m, 2 H), 4.02 (s, 3 H), 3.68 (t, *J* = 9.03 Hz, 1 H), 3.45 - 3.42 (m, 1 H).

[00544] Step 4 - (*S*)-4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]indole-2-carboxamide and (*R*)-4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]indole-2-carboxamide

[00545] (±)-4,5-Dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl)-phenyl]indole-2-carboxamide (60.0 mg) was purified by chiral SFC (instrument: SFC-A; column: AS(250mm*30 mm, 10 μm); condition: Base-EtOH) to afford (*S*)-4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]indole-2-carboxamide and (*R*)-4,5-dichloro-1-methyl-6-[(2-oxooxazolidin-5-yl)methoxy]-*N*-[4-(pyrazin-2-ylsulfamoyl)phenyl]indole-2-carboxamide. Peak 1: SFC tR = 3.116, LCMS: (ES+) m/z $(M+H)^+$ = 591.0, tR = 2.653, ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.20 (br. s., 1H), 8.07 (br. s., 1H), 7.99 (br. s., 1H), 7.85 (br. s., 4H), 7.65 (br. s., 1H), 7.41 (s, 2H), 5.02 (br. s., 1H), 4.42 - 4.30 (m, 2H), 4.02 (s, 3H), 3.70 - 3.66 (m, 1H). Peak 2: SFC tR = 3.339, LCMS: (ES+) m/z $(M+H)^+$ = 591.1, tR = 2.938, ^{1}H NMR (400MHz, DMSO-d_6) δ = 8.21 (br. s., 1H), 8.07 (br. s., 1H), 7.96 (br. s., 1H), 7.94 - 7.80 (m, 4H), 7.65 (s, 1H), 7.42 (s, 2H), 5.06 – 4.97 (m, 1H), 4.42 - 4.30 (m, 2H), 4.02 (s, 3H), 3.68 (t, *J* = 8.91 Hz, 1H), 3.45 (br. s., 1H).

Example 162: 3 (±)-5-[[4-[(4, 5-Dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]-sulfonylamino]-3-methyl -5-oxo-pentanoic acid



Step 1 - 4,5-Dichloro-1-methyl-*N*-(4-sulfamoylphenyl)indole-2-carboxamide

[00546] *Tert*-butyl *N*-[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylcarbamate (400 mg, 0.802 mmol) was dissolved in hydrochloric acid/methanol solution (2 M, 20 mL). The reaction mixture was stirred at 18 °C for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give the title compound (300 mg, 80% yield) as a white solid. ^{1}H NMR (400MHz, DMSO-d$_6$) δ = 10.76 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.53 - 7.48 (m, 2H), 7.31 (s, 2H), 4.06 (s, 3H).

Step 2 - (±)-Methyl 5-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonyl-amino]- 3-methyl-5-oxo-pentanoate

[00547] A mixture of 4,5-dichloro-1-methyl-*N*-(4-sulfamoylphenyl)indole-2-carboxamide (250 mg, 0.627 mmol), (±)-5-methoxy-3-methyl-5-oxo-pentanoic acid (150 mg, 0.941 mmol), EDCI (361 mg, 1.88 mmol), dimethylaminopyridine (306 mg, 2.51 mmol) in *N,N*-dimethylformamide (5 mL) was stirred at 18 °C for 16 hrs under nitrogen atmosphere. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was

purified by column chromatography (dichloromethane:methanol = 20:1) to give the title compound. LCMS: (ES^+) m/z $(M+H)^+$ = 539.9, tR = 1.408.

Step 3 (±)-5-[[4-[(4,5-Dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]sulfonylamino]-3-methyl-5-oxo-pentanoic acid

[00548] To a solution of (±)-methyl 5-[[4-[(4,5-dichloro-1-methyl-indole-2-carbonyl)amino]phenyl]-sulfonylamino]-3-methyl-5-oxo-pentanoate (150 mg, 0.277 mmol) in a mixture of tetrahydrofuran (15 mL) and water (5 mL) was added lithium hydroxide (19.9 mg, 0.832 mmol). The reaction mixture was stirred at 20 ℃ for 16 hrs. On completion, the reaction mixture was concentrated *in vacuo* to give a residue. The residue was acidified with 2 M hydrochloric acid and filtered to get the crude product. The crude product was purified by prep-HPLC (0.1% TFA-MeCN, Welch Ultimate AQ-C18 150*30 mm; Particle size: 5 μm) to give the title compound (82.6 mg, 54% yield) as a white solid. LCMS: (ES^+) m/z $(M+H)^+$ = 526.0, tR = 1.035 ^{1}H NMR (400MHz, DMSO-d_6) δ = 10.83 (s, 1H), 8.04 - 7.96 (m, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.9 Hz, 1H), 7.53 - 7.48 (m, 2H), 4.05 (s, 3H), 2.27 - 2.07 (m, 4H), 2.05 - 1.96 (m, 1H), 0.79 (d, J = 5.9 Hz, 3H).

Example 163: Full length (FL) 3-Phosphoglycerate Dehydrogenase (PHGDH) Diaphorase coupled assay (500 μM NAD)

[00549] PHGDH activity was determined by detecting the NADH produced during the reaction. Diaphorase was used to catalyze the oxidation of NADH with the concomitant reduction of resazurin to the fluorescent product resorufin. Resorufin fluorescence quantitatively reflected the production of NADH by the PHGDH reaction. To drive the forward reaction, two enzymes in the serine synthesis pathway subsequent to PHGDH, Phosphoserine aminotransferase (PSAT1) and phosphoserine phosphatase (PSPH) were also added to the reaction.

[00550] Briefly, serial dilution of compounds were incubated in a volume of 20 μL in 384 well plates with the assay mixture containing 5 nM PHGDH, 500 nM PSAT1, 500 nM PSPH, 500 μM NAD^+, 80 μM 3-phosphoglycerate, 1 mM glutamate, 57 μM Resazurin and 0.2 mg/mL Diaphorase in assay buffer containing 50 mM Trisethanoloamine (TEA) pH 8.0, 10 mM $MgCl_2$, 0.01% Tween-20 and 0.05% Bovine Serum Albumin (BSA). The plate was then incubated at 30 °C for 60 minutes and resorufin fluorescence was measured at emission wavelength 598 nm

following excitation at 525 nm. The positive control consisted of the complete reaction mixture with 4% DMSO and was set to 0% inhibition. The negative control consisted of the reaction mix lacking PHGDH with 4% DMSO and was set to 100% inhibition. Percent inhibition with the compounds was then calculated by normalizing the fluorescence observed at a given compound concentration to the positive and negative controls. IC_{50} was calculated by plotting the % inhibition versus concentration and using hyperbolic fit to determine compound concentration corresponding to 50% inhibition.

Example 164: Full length (FL) 3-Phosphoglycerate Dehydrogenase (PHGDH) Diaphorase coupled assay (20 μM NAD)

[00551] Serial dilution of compounds were incubated in a volume of 20 μL in 384 well plates with the assay mixture containing 10 nM PHGDH, 500 nM PSAT1, 500 nM PSPH, 20 μM NAD^+, 80 μM 3-phosphoglycerate, 1 mM glutamate, 57 μM Resazurin and 0.2 mg/mL Diaphorase in assay buffer containing 50 mM Trisethanoloamine (TEA) pH 8.0, 10 mM $MgCl_2$, 0.01% Tween-20 and 0.05% Bovine Serum Albumin (BSA). The plate was then incubated at 30 °C for 60 minutes and resorufin fluorescence was measured at emission wavelength 598 nm following excitation at 525 nm. The positive control consisted of the complete reaction mixture with 4% DMSO and was set to 0% inhibition. The negative control consisted of the reaction mix lacking PHGDH with 4% DMSO and was set to 100% inhibition. Percent inhibition with the compounds was then calculated by normalizing the fluorescence observed at a given compound concentration to the positive and negative controls. IC_{50} was calculated by plotting the % inhibition versus concentration and using hyperbolic fit to determine compound concentration corresponding to 50% inhibition.

Results of Assays

[00552] **Table 2** shows the activity of selected compounds of this invention in the PHGDH activity inhibition assays. The compound numbers correspond to the compound numbers in **Table 1**. Compounds having an activity designated as "A" provided an IC_{50} of 0.001 to <0.5 μM; compounds having an activity designated as "B" provided an IC_{50} of 0.5 to <1 μM; compounds having an activity designated as "C" provided an IC_{50} of 1 to <5 μM; and compounds having an activity designated as "D" provided an IC_{50} of 5 μM or greater.

Table 2

Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-1	123	C	-
I-2	153	C	-
I-3	157	D	-
I-4	124	C	-
I-5	156	-	C
I-6	68	-	D
I-7 or I-8	161 (peak 2)	-	C
I-8 or I-7	160 (peak 1)	-	A
I-9	152	-	B
I-10	143	-	A
I-11	141	B	-
I-12	150	-	A
I-13	125	-	A
I-14	70	-	B
I-15	140	-	A
I-16	122	-	A
I-17	155	-	B
I-18	151	-	A
I-19	107	-	B
I-20	106	-	A
I-21	105	-	A
I-22	145	-	A
I-23	139	-	A
I-24	146	-	A
I-25	142	-	A
I-26	108	-	C

Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-27	147	-	A
I-28	149	-	A
I-29	162	-	A
I-30	136	-	A
I-31	135	-	A
I-32	134	-	A
I-33	148	-	A
I-34	144	-	A
I-35	133	-	A
I-36	132	-	A
I-37 or I-38	138 (peak 2)	-	A
I-38 or I-37	137 (peak 1)	-	A
I-39	159	-	A
I-40	121	-	C
I-41	69	-	C
I-42	130	-	A
I-43	131	-	A
I-44	129	-	A
I-45	128	-	A
I-46	127	-	A
I-47	126	-	A
I-48	95	-	C
I-49	101	-	A
I-50	100	-	C
I-51	120	-	C
I-52	67	-	A
I-53	119	-	A

Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-54	97	-	D
I-55	104	-	A
I-56	66	-	A
I-57	109	-	A
I-58	65	-	A
I-59	102	-	B
I-60	96	-	B
I-61	118	-	B
I-62	94	-	C
I-63	154	-	C
I-64	64	-	C
I-65	103	-	A
I-66	117	-	A
I-67	116	-	A
I-68	93	-	D
I-69	114	-	A
I-70	113	-	A
I-71	112	-	A
I-72	111	-	A
I-73	62	-	A
I-74	61	-	B
I-75	110	-	A
I-76	60	-	A
I-77	99	-	A
I-78	59	-	A
I-79	58	-	A
I-80	76	-	D

Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-81	75	-	C
I-82	98	-	C
I-83	74	-	B
I-84	72	-	C
I-85	90	-	B
I-86	88	-	A
I-87	84	-	B
I-88	82	-	A
I-89	80	-	A
I-90	77	-	A
I-91	89	-	C
I-92	79	-	B
I-93	56	-	B
I-94	23	-	A
I-95	28	-	A
I-96	22	-	A
I-97	54	-	B
I-98	27	-	A
I-99	73	-	A
I-100	50	-	C
I-101	87	-	B
I-102	83	-	C
I-103	81	-	B
I-104	78	-	B
I-105	41	-	C
I-106	35	-	A
I-107	57	-	B

Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-108	40	-	B
I-109	34	-	A
I-110	30	-	A
I-111	24	-	A
I-112	33	-	A
I-113	29	-	A
I-114	55	-	A
I-115	46	-	A
I-116	38	-	B
I-117	32	-	A
I-118	45	-	A
I-119	37	-	B
I-120	31	-	A
I-121	44	-	A
I-122	36	-	A
I-123	20	-	A
I-124	26	-	A
I-125	21	-	A
I-126	92	-	C
I-127	49	-	B
I-128	91	-	B
I-129	25	-	B
I-130	48	-	B
I-131	47	-	A
I-132	39	-	B
I-133	53	-	C
I-134	7	-	B

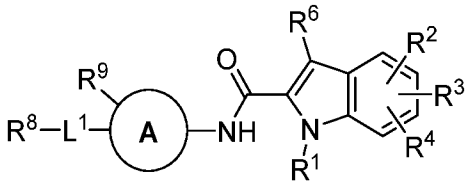
Compound #	Example #	Diaphorase 500 μM NAD IC_{50} (μM)	Diaphorase 20 μM NAD IC_{50} (μM)
I-135	6	-	D
I-136	5	-	D
I-137	12	-	B
I-138	13	-	C
I-139	1	-	C
I-140	3	-	D
I-141	11	-	C
I-142	10	-	C
I-143	4	-	D
I-144	2	-	A
I-145	9	-	C
I-146	15	-	C
I-147	14	-	C
I-148	16	-	C
I-149	18	-	A
I-150	8	-	A
I-151	71	-	A
I-152	19	-	D
I-153	17	-	A
I-154	115	-	B

[00553] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen or C_{1-4} alkyl;

each of R^2 and R^3 is independently halogen, -OR, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R'; or R^2 and R^3 are optionally taken together with the carbon atoms to which they are attached and any intervening atoms to form a 5-8 membered partially unsaturated ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, phenyl, an 8-10 membered bicyclic aromatic carbocyclic ring, a 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each L is independently a C_{1-6} bivalent straight or branched hydrocarbon chain wherein 1-4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -C(O)N(R)-, -(R)NC(O)-, -N(R)-, -N(R)C(O)N(R)-, -S-, -SO-, or $-SO_2-$;

each R' is independently hydrogen, C_{1-6} aliphatic, or an optionally substituted 4-8 membered saturated or partially unsaturated monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^4 is hydrogen, halogen, $-OR^5$, -CN, C_{1-6} aliphatic optionally substituted with 1, 2, or 3 halogens, or -L-R';

R^5 is hydrogen, $-(CH_2)_n$-phenyl, or C_{1-6} alkyl optionally substituted with 1, 2, or 3 halogens;

n is 0, 1, 2, 3, or 4;

R^6 is hydrogen or C_{1-4} alkyl;

Ring A is phenyl or pyridyl;

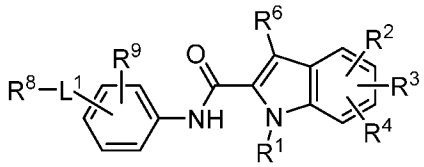
L^1 is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1-5 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2$-, $-SO_2N(R)$-, $-(R)NSO_2$-, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; or L^1 and R^8 are optionally taken together with any intervening atoms to form a 5-6 membered optionally substituted partially unsaturated heterocyclic ring that is fused with Ring A having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each -Cy- is independently a bivalent 6-membered arylene ring containing 0-2 nitrogen atoms , or a bivalent 5-membered heteroarylene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a bivalent partially unsaturated 8-10 membered bicyclic heterocyclene ring with 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein -Cy- is optionally substituted with 1 or 2 substituents independently selected from C_{1-4} alkyl or -OR;

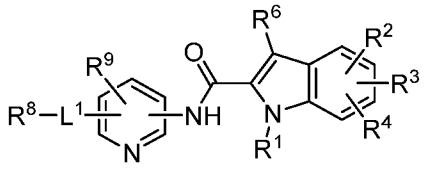
R^8 is hydrogen, $-CO_2R$, or a C_{1-6} optionally substituted aliphatic group; and

R^9 is hydrogen, halogen, C_{1-4} alkyl, optionally substituted phenyl, or C_{1-4} alkyl substituted with an optionally substituted phenyl.

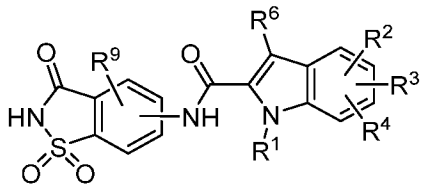
2. The compound according to claim 1, wherein the compound is represented by formulae **II-a**, **II-b**, or **II-c**:



II-a



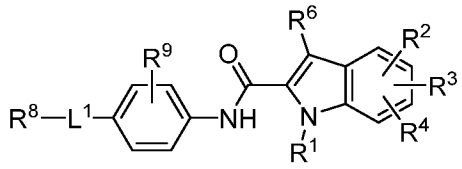
II-b



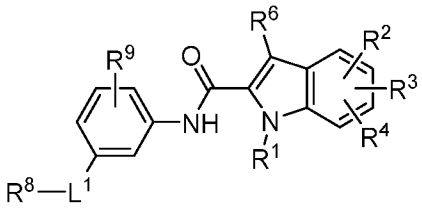
II-c

or a pharmaceutically acceptable salt thereof.

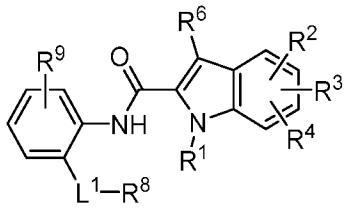
3. The compound according to claim 1, wherein the compound is represented by formulae **III-a**, **III-b**, **III-c**, or **III-d**:



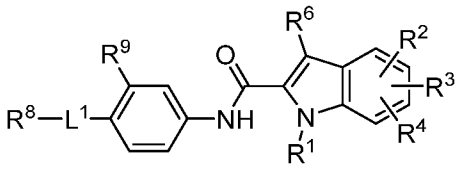
III-a



III-b



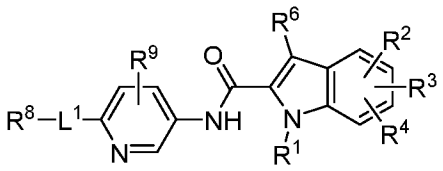
III-c



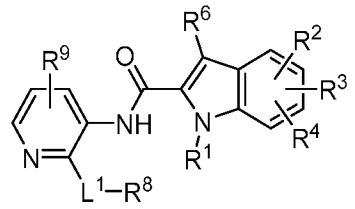
III-d

or a pharmaceutically acceptable salt thereof.

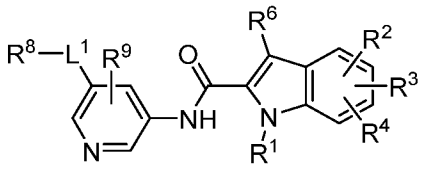
4. The compound according to claim 1, wherein the compound is represented by formulae **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



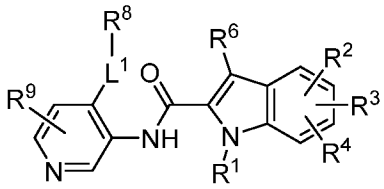
IV-a



IV-b



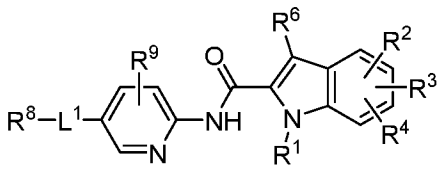
IV-c



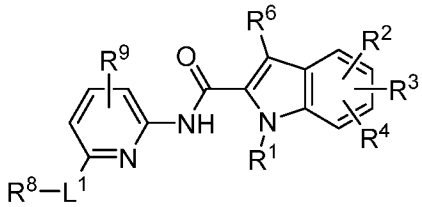
IV-d

or a pharmaceutically acceptable salt thereof.

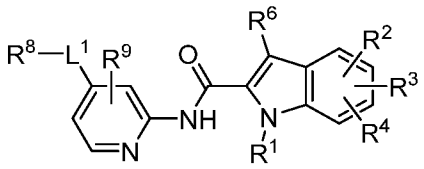
5. The compound according to claim 1, wherein the compound is represented by formulae **V-a**, **V-b**, **V-c**, or **V-d**:



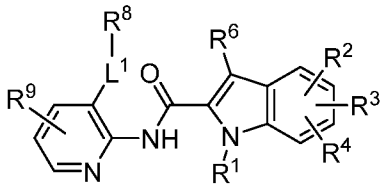
V-a



V-b



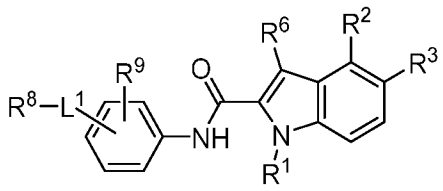
V-c



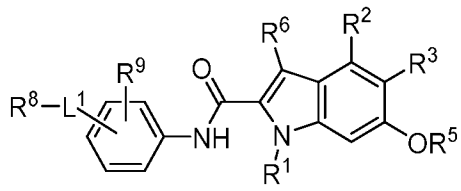
V-d

or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1, wherein the compound is represented by formulae **VI-a** or **VI-b**:



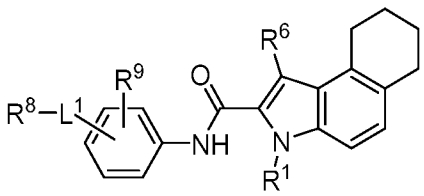
VI-a



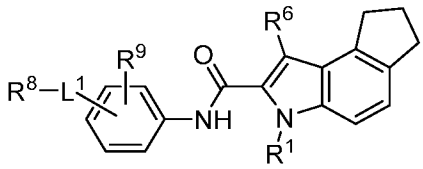
VI-b

or a pharmaceutically acceptable salt thereof.

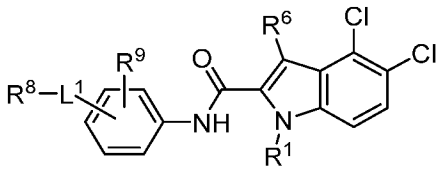
7. The compound according to claim 1, wherein the compound is represented by formulae **VI-c**, **VI-d**, or **VI-e**:



VI-c



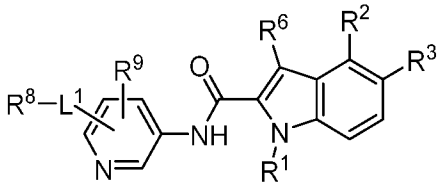
VI-d



VI-e

or a pharmaceutically acceptable salt thereof.

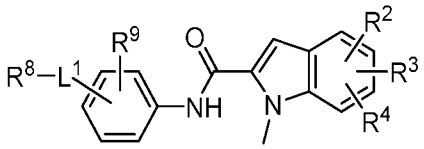
8. The compound according to claim 1, wherein the compound is represented by formula **VII**:



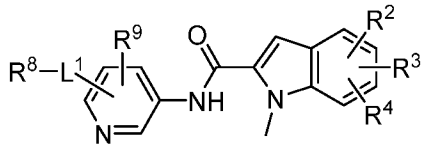
VII

or a pharmaceutically acceptable salt thereof.

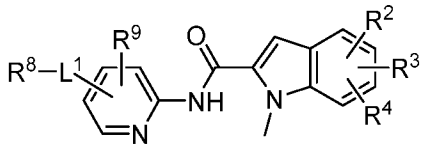
9. The compound according to claim 1, wherein the compound is represented by formulae **VIII-a**, **VIII-b**, or **VIII-c**:



VIII-a



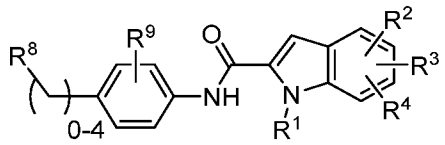
VIII-b



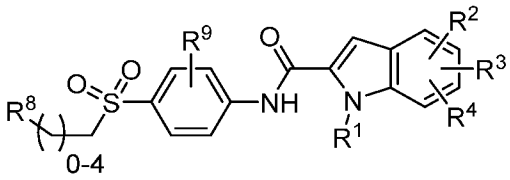
VIII-c

or a pharmaceutically acceptable salt thereof.

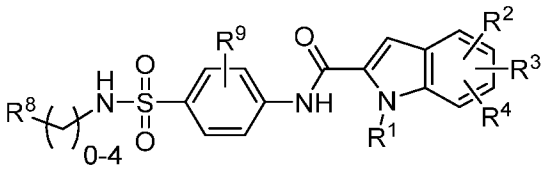
10. The compound according to claim 1, wherein the compound is represented by formulae **IX-a**, **IX-b**, **IX-c**, **IX-d**, **IX-e**, **IX-f**, **IX-g**, **IX-h**, **IX-i**, **IX-j**, **IX-k**, **IX-l**, **IX-m**, **IX-n**, **IX-o**, **IX-p**, or **IX-q:**



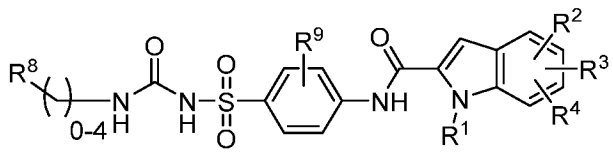
IX-a



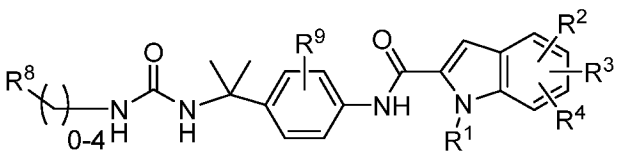
IX-b



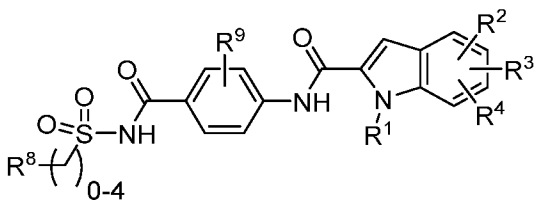
IX-c



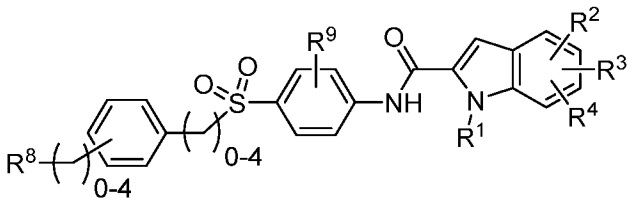
IX-d



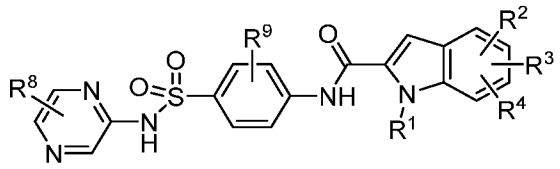
IX-e



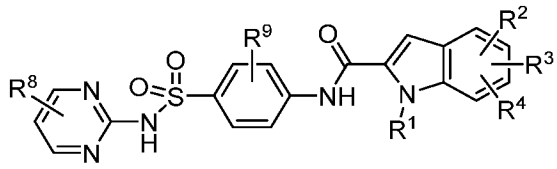
IX-f



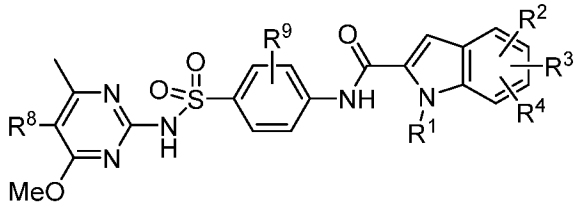
IX-g



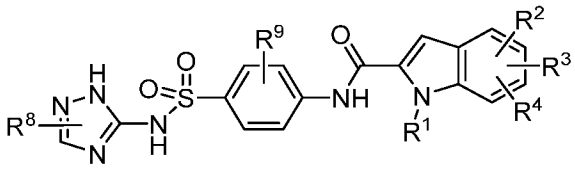
IX-h



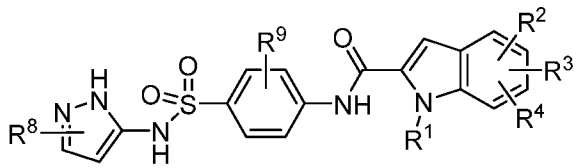
IX-i



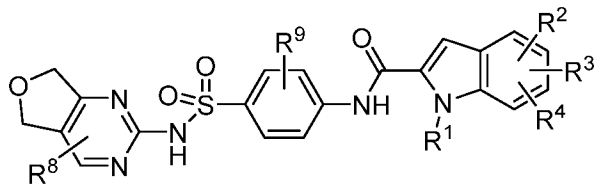
IX-j



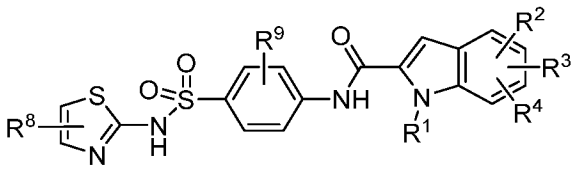
IX-k



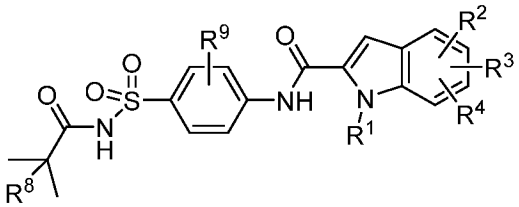
IX-l



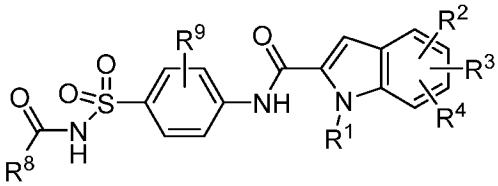
IX-m



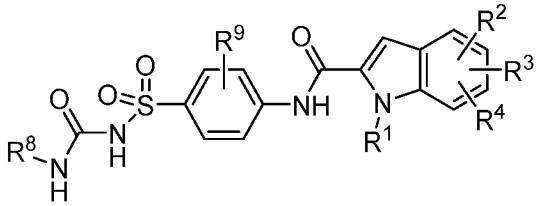
IX-n



IX-o



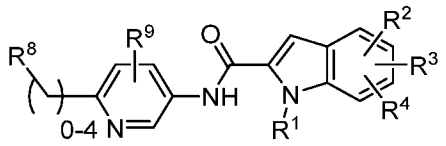
IX-p



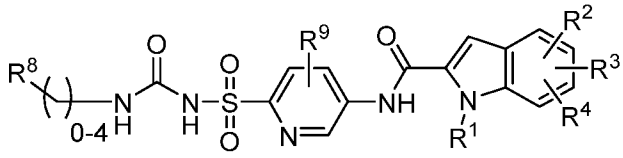
IX-q

or a pharmaceutically acceptable salt thereof.

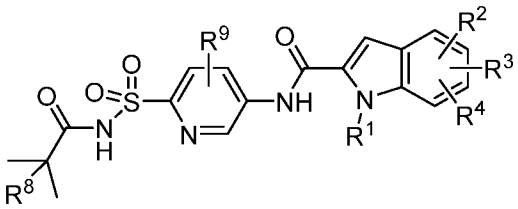
11. The compound according to claim 1, wherein the compound is represented by formulae **X-a**, **X-b**, **X-c**, **X-d**, **X-e**, **X-f**, or **X-g**:



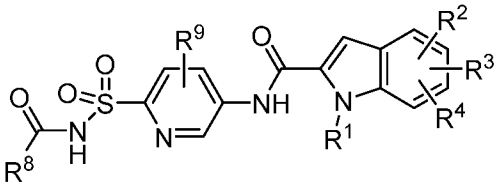
X-a



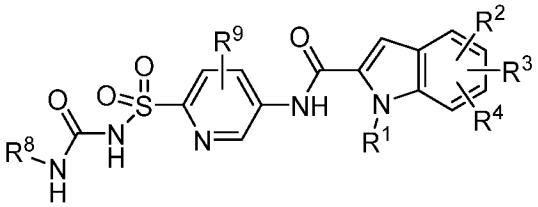
X-b



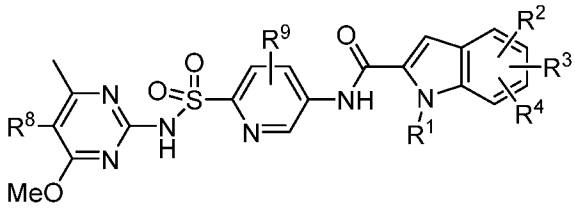
X-c



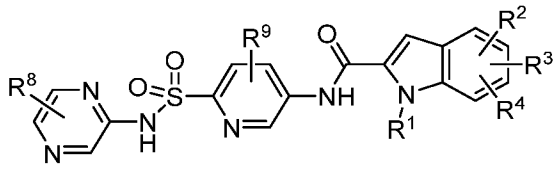
X-d



X-e



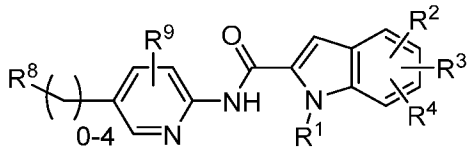
X-f



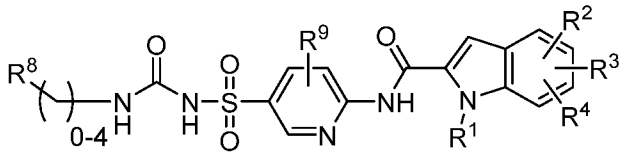
X-g

or a pharmaceutically acceptable salt thereof.

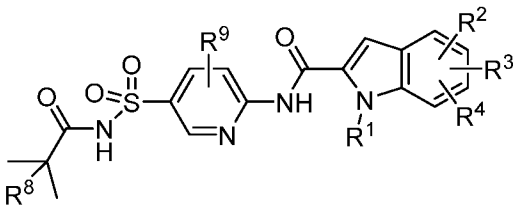
12. The compound according to claim 1, wherein the compound is represented by formulae **XI-a**, **XI-b**, **XI-c**, **XI-d**, **XI-e**, **XI-f**, or **XI-g**:



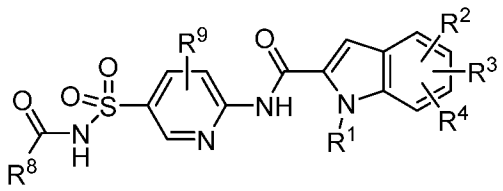
XI-a



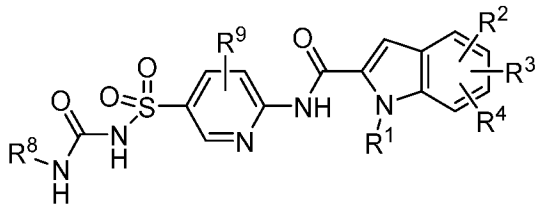
XI-b



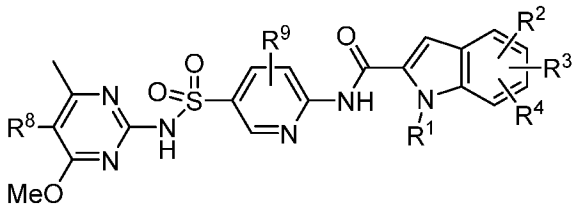
XI-c



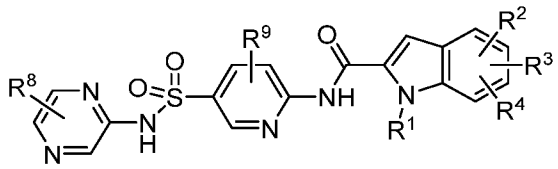
XI-d



XI-e



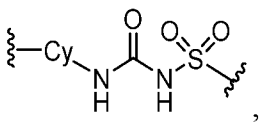
XI-f

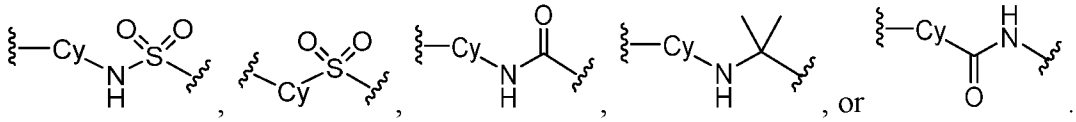


XI-g

or a pharmaceutically acceptable salt thereof.

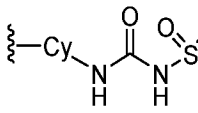
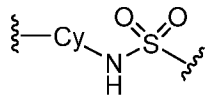
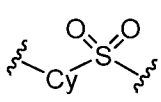
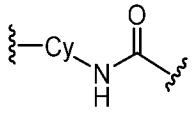
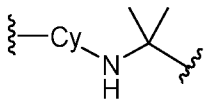
13. The compound according to any one of claims 1-9, wherein L^1 is a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, 3, or 4 methylene units of the chain are independently and optionally replaced with -O-, -C(O)-, -C(O)O-, -OC(O)-, -N(R)-, -C(O)N(R)-, -(R)NC(O)-, -OC(O)N(R)-, -(R)NC(O)O-, -N(R)C(O)N(R)-, -S-, -SO-, $-SO_2-$, $-SO_2N(R)-$, $-(R)NSO_2-$, -C(S)-, -C(S)O-, -OC(S)-, -C(S)N(R)-, -(R)NC(S)-, -(R)NC(S)N(R)-, or -Cy-; wherein each R is independently hydrogen, $-CH_2$-phenyl, phenyl, $-CH_3$, $-CH_2CH_3$, cyclopentyl, cyclohexyl, $-CH_2F$, $-CHF_2$, $-CF_3$, $-CH_2CHF_2$, or $-CH_2CF_3$.

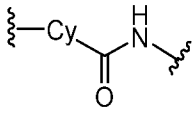
14. The compound according to any one of claims 1-9, wherein L^1 is  ,

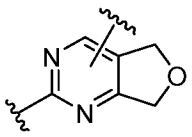
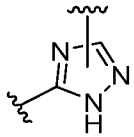
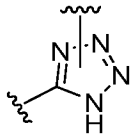
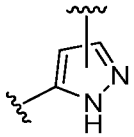
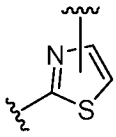


.

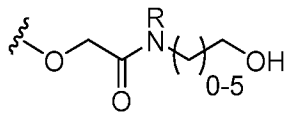
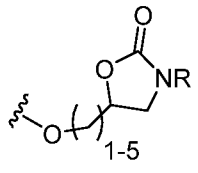
15. The compound according to any one of claims 1-9, 13, or 14, wherein L^1 is






, or


and each -Cy- is independently phenylene, pyridinylene, pyrimidinylene, pyrazinylene,





, or

.

16. The compound according to any one of claims 1-6 or 8-15, wherein R^2 and R^3 are each independently selected from halogen, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2Ph$, -OMe, -CN, $-CH_3$,


, or

.

17. The compound according to any one of claims 1-16, wherein R^4 is hydrogen.

18. The compound according to any one of claims 1-17, wherein R^2 and R^3 are each independently selected from F, Cl, $-CF_3$, $-OCF_3$, $-OCHF_2$, $-OCH_2Ph$, -OMe, -CN, or $-CH_3$.

19. The compound according to any one of claims 1-8 or 10-18, wherein R^1 is C_{1-4} alkyl.

20. The compound according to claim 1, wherein the compound is selected from those depicted in Table 1, or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound according to any one of claims 1-20 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

22. A method for treating a PHGDH-mediated disorder in a patient in need thereof, comprising administering to said patient the compound of any one of claims 1-20 or a pharmaceutical composition thereof.

23. A method for treating cancer in a patient in need thereof, comprising administering to said patient the compound of any one of claims 1-20.

24. The method of claim 23, wherein the cancer is melanoma or breast cancer.

25. A method for treating a tumor in a patient in need thereof, comprising administering to said patient the compound of any one of claims 1-20.

26. The method of claim 25, wherein the tumor comprises a melanoma, breast, or lung cancer.

27. The method of claim 25, wherein the tumor comprises a small cell lung cancer (SCLC) or a non-small cell lung cancer (NSCLC).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/021438

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/395; A61K 31/397; A61K 31/497; C07D 237/20; C07D 403/02; C07D 403/12 (2017.01)
CPC - A61K 31/395; A61K 31/397; A61K 31/497; C07D 237/20; C07D 403/02; C07D 403/12 (2017.05)

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)
See Search History document

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)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2011/0207767 A1 (BEUSKER et al) 25 August 2011 (25.08.2011) entire document	1-3, 6, 10-12
A	WO 2015/150097 A1 (IOMET PHARMA LTD) 08 October 2015 (08.10.2015) entire document	1-3, 6, 10-12
A	PUBCHEM, Substance Record for SID 113608133. Create Date: 2011-03 17. [retrieved on 11 April 2017]. Retrieved from the Internet: <https://pubchem.ncbi.nlm.nih.gov/substance/113608133>. entire document	1-3, 6, 10-12

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 June 2017	03 JUL 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, VA 22313-1450 Facsimile No. 571-273-8300	Authorized officer Blaine R. Copenheaver PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/021438

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 15-19, 21-27
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

Claims 1-3, 6, and 10-12 have been analyzed subject to the restriction that the claims read on a compound of formula I: or a pharmaceutically acceptable salt thereof, wherein: R1 is hydrogen; each of R2 and R3 is independently halogen, wherein the halogen is F, wherein R2 and R3 are attached to the indole ring as shown in the compound represented of formula VI-a of the instant invention; R4 is hydrogen; R6 is hydrogen; Ring A is phenyl; L1 is a covalent bond; R8 is hydrogen; and R9 is hydrogen.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 6, 10-12

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2017/021438

Continued from Box No. III Observations where unity of invention is lacking

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-14 and 20 are drawn to compounds of formula I or a pharmaceutically acceptable salt thereof.

The first invention of Group I+ is restricted to a compound of formula I: or a pharmaceutically acceptable salt thereof, wherein: R1 is hydrogen; each of R2 and R3 is independently halogen, wherein the halogen is F, wherein R2 and R3 are attached to the indole ring as shown in the compound represented of formula VI-a of the instant invention; R4 is hydrogen; R6 is hydrogen; Ring A is phenyl; L1 is a covalent bond; R8 is hydrogen; and R9 is hydrogen. It is believed that claims 1-3, 6, and 10-12 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. Each additional elected formula(e) requires the selection of a single definition for each compound variable. An exemplary election would be to a compound of formula I: or a pharmaceutically acceptable salt thereof, wherein: R1 is C1 alkyl; each of R2 and R3 is -CN, wherein R2 and R3 are attached to the indole ring as shown in the compound represented of formula VI-a of the instant invention; R4 is hydrogen; R6 is hydrogen; Ring A is phenyl; L1 is a covalent bond; R8 is hydrogen; and R9 is hydrogen. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The Groups I+ formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, R3, R4, R6, R8, R9, L1, and Ring A.

The Groups I+ share the technical features of a compound of formula I or a pharmaceutically acceptable salt thereof. However, these shared technical features do not represent a contribution over the prior art.

Specifically, Substance Record for SID 113608133 to PubChem teaches a compound of formula I: wherein R1 is hydrogen; each of R2 and R3 is independently –OR; each R is independently C1 aliphatic; R4 is –OR5; R5 is C1 alkyl; R6 is hydrogen; Ring A is phenyl; L1 is a covalent bond; R8 is hydrogen; and R9 is halogen (Pg. 3;...see shown structure...).

The inventions listed in Groups I+ therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.