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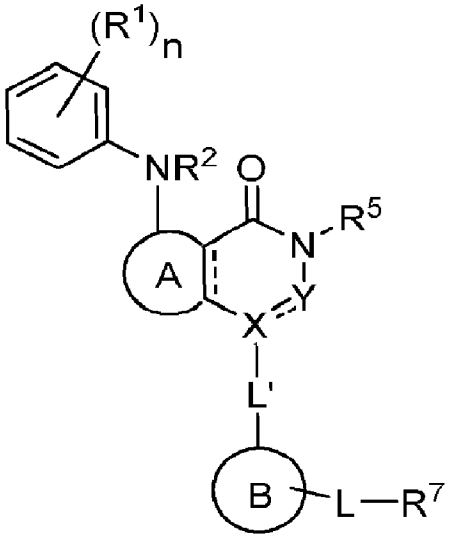
(54) **Titre : INHIBITEURS DE MEK ET LEURS UTILISATIONS**
(54) **Title: MEK INHIBITORS AND USES THEREOF**



(I')

(57) **Abrégé/Abstract:**
The present invention provides MEK inhibitors of formula (I'), compositions thereof, and methods of using the same.

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Abstract:

The present invention provides MEK inhibitors of formula (I'), compositions thereof, and methods of using the same.

MEK INHIBITORS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the priority of US provisional application number 63/175,837 filed April 16, 2021 and US provisional application number 63/262,093 filed October 5, 2021, each of which is hereby incorporated by reference in its entirety.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds and methods useful for inhibiting mitogen-activated protein kinase/extracellular signal-regulated kinase kinase (MEK). The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of proliferative disorders, such as cancers.

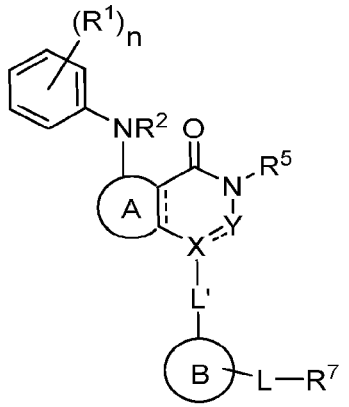
BACKGROUND

[0003] Activation of the p42/44 MAPK signaling pathway comprising mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) kinase (MEK)-ERK has been implicated in the pathogenesis and progression of various cancers. The MEK-ERK pathway is often activated by mutation of upstream factors, BRAF or Ras, or by the signals of constitutively activated cell-surface receptors. Inhibition of MEK can be a promising strategy for controlling the growth of tumors, for example, the tumors associated with MEK pathway signaling.

SUMMARY OF THE INVENTION

[0004] It has now been found that compounds of the present invention, and pharmaceutically acceptable compositions thereof, are effective as MEK inhibitors.

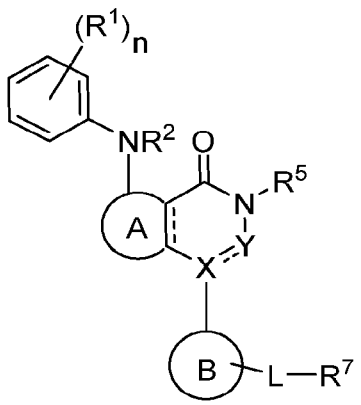
[0005] In one aspect, the instant invention provides a compound of formula **(I')**:



(I'),

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

[0006] In one aspect, the instant invention provides a compound of formula **(I)**:



(I),

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

[0007] Another aspect of the invention provides a method of treating a disorder mediated by MEK in a subject. The method comprises administering a therapeutically effective amount of a compound described herein to a subject in need thereof to treat the disorder mediated by MEK, as further described in the detailed description.

[0008] Another aspect of the invention provides a method of inhibiting MEK activity. The method comprises contacting MEK or a KSR-MEK complex or a RAF-MEK complex with an

effective amount of a compound described herein, as further described in the detailed description. In some embodiments, a method provided herein comprises contacting a MEK-KSR-RAF complex with an effective amount of a compound described herein, as further described in the detailed description.

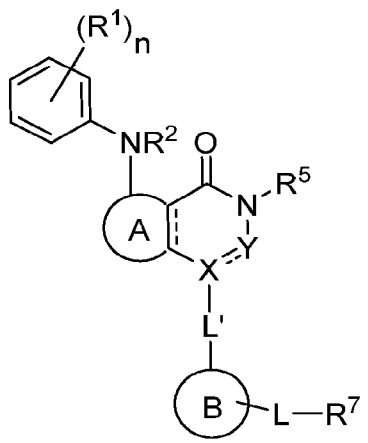
[0009] In some aspects, compounds of the present invention, and pharmaceutically acceptable compositions thereof, are useful for treating proliferative disorders, such as the cancers as described herein.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Certain Embodiments of the Invention:

[0010] Compounds of the present invention, and pharmaceutical compositions thereof, are useful as MEK inhibitors. Without wishing to be bound by any particular theory, it is believed that the compounds of the present invention may directly engage members of the RAF family of proteins at the MEK interface, and that RAF family members, specifically BRAF or CRAF, may remodel the prototypical allosteric pocket of the MEK inhibitor in the RAF-MEK complex. Without wishing to be bound by any particular theory, it is believed that the compounds of the present invention may bind the RAF-MEK complex and may disrupt the related RAF–MEK complex.

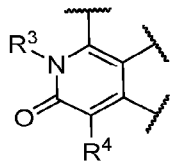
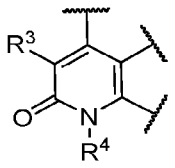
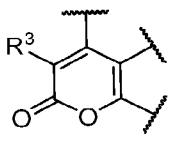
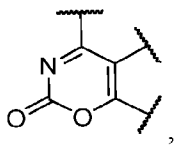
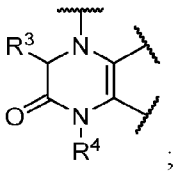
[0011] In one aspect, the present invention provides a compound of Formula (**I'**):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:

 ,  ,  ,  , and  ;

each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C, CH, or N;

Y is CR^6, C(O), or N;

L' is a covalent bond, -O-, $-C(R^9)_2-$, or $-NR^8-$;

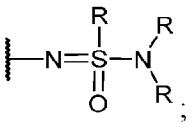
each of R^2, R^5, and R^8 is independently H or optionally substituted C_{1-6} aliphatic;

each of R^3, R^4, R^6, and R^9 is independently H, halogen, or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^+(R)_2-$, -CH(R)-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)-$, -C(=N-R)-, -C(=N-OR)-, -C(O)-, $-S(O)_2-$, $-(CH_2-CH_2-O)_{1-10}-$, -S(O)-, -N(R)-C(O)-, $-N(R)-S(O)_2-$, -C(O)-N(R)-, $-S(O)_2-N(R)-$, -P(O)(OR)-, or -Cy-;

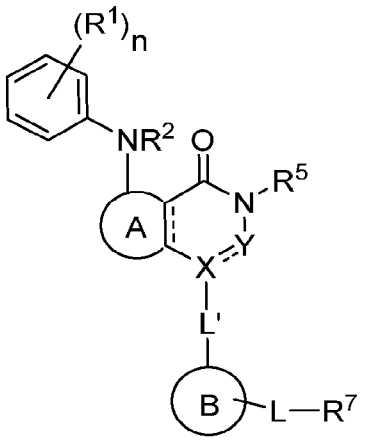
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

R^7 is R, -CN, $-S(O)_2-N(R)_2$, -NR-$S(O)_2$-R, $-P(O)(OR)-N(R)_2$, $-C(=N-R)-N(R)_2$, $-C(=N-OR)-N(R)_2$, -C(O)-R, -S(O)-R, $-N(R)_2$, -OR, -SR, or  ;

each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

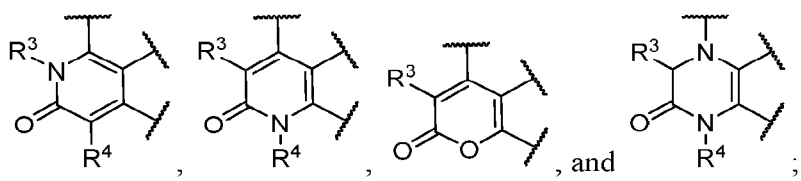
[0012] In one aspect, the present invention provides a compound of Formula (**I'**):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:

 ;

each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C, CH, or N;

Y is CR^6, C(O), or N;

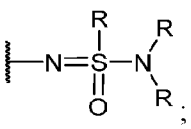
L' is a covalent bond, -O-, $-C(R^9)_2-$, or $-NR^8-$;

each of R^2, R^3, R^4, R^5, R^6, R^8, and R^9 is independently H or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^{+}(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-;

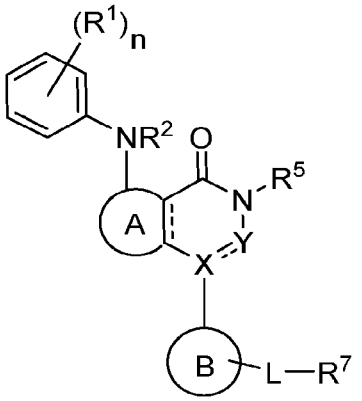
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

R^7 is R, -CN, -S(O)$_2$-N(R)$_2$, -NR-S(O)$_2$-R, -P(O)(OR)-N(R)$_2$, -C(=N-R)-N(R)$_2$, -C(=N-OR)-N(R)$_2$, -C(O)-R, -S(O)-R, -N(R)$_2$, -OR, -SR, or  ;

each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

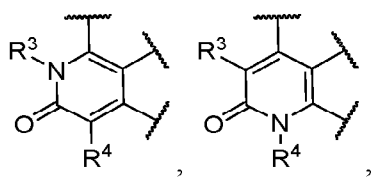
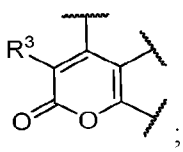
[0013] In one aspect, the present invention provides a compound of Formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:


, and  ;

each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C or N;

Y is CR^6, C(O), or N;

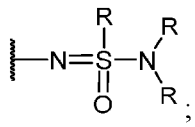
each of R^2, R^3, R^4, R^5, and R^6 is independently H or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-10 membered bicyclic aromatic ring, and a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^+(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)$-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, $-S(O)_2$-, -P(O)(OR)-, or -Cy-;

each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently

selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

R^7 is -CN, $-S(O)_2-N(R)_2$, $-NR-S(O)_2-R$, $-P(O)(OR)-N(R)_2$, $-C(=N-R)-N(R)_2$, $-C(=N-OR)-N(R)_2$, -C(O)-R, $-N(R)_2$, -OR, -SR, or  ;

each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

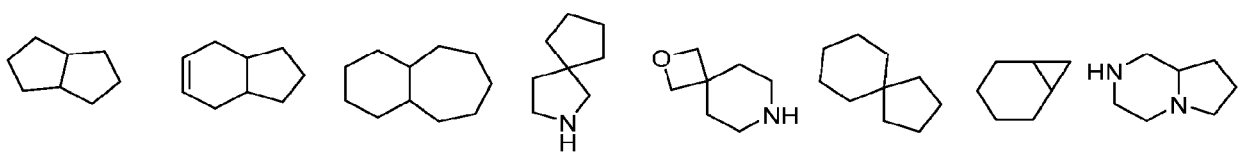
2. Compounds and Definitions:

[0014] 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.

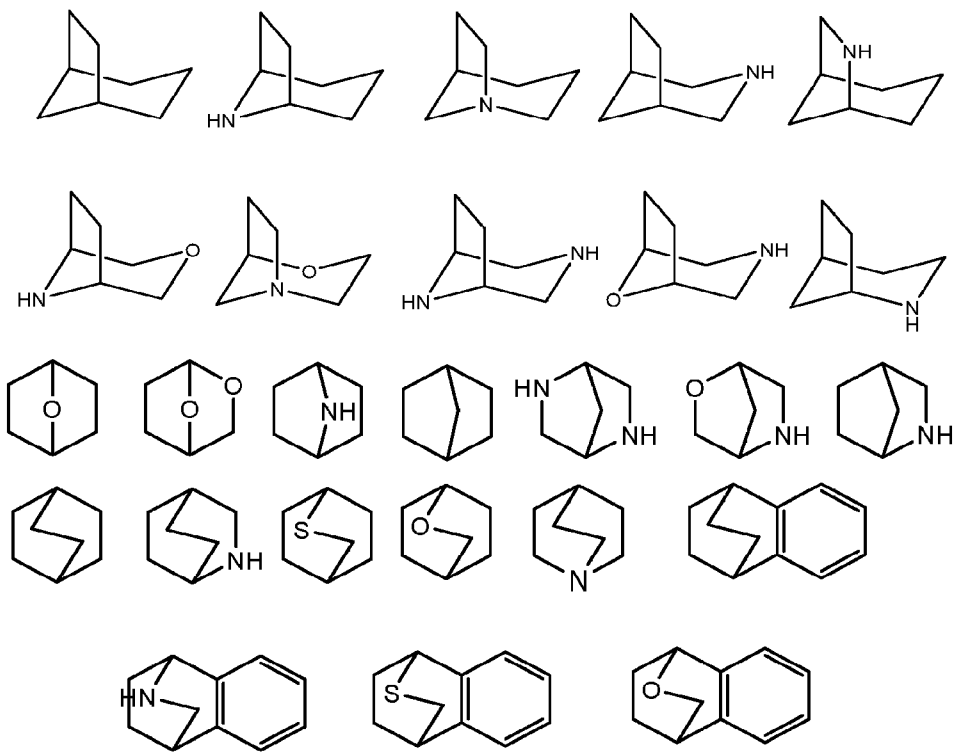
[0015] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (*i.e.*, unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon 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.

[0016] As used herein, the term "bicyclic ring" or "bicyclic ring system" refers to any bicyclic ring system, *i.e.*, carbocyclic or heterocyclic, saturated or having one or more units of unsaturation, having one or more atoms in common between the two rings of the ring system. Thus, the term includes any permissible ring fusion, such as *ortho*-fused or spirocyclic. As used herein, the term "heterobicyclic" is a subset of "bicyclic" that requires that one or more heteroatoms are present in one or both rings of the bicycle. Such heteroatoms may be present at ring junctions and are optionally substituted, and may be selected from nitrogen (including N-oxides), oxygen, sulfur (including oxidized forms such as sulfones and sulfonates), phosphorus (including oxidized forms such as phosphates), boron, etc. In some embodiments, a bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. 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 bicyclic rings include:



Exemplary bridged bicyclics include:



[0017] 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.

[0018] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

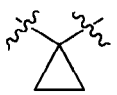
[0019] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0020] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0021] 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.

[0022] 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.

[0023] 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.

[0024] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0025] The term "halogen" means F, Cl, Br, or I.

[0026] 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.

[0027] 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.

[0028] 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).

[0029] 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.

[0030] 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.

[0031] 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.

[0032] Each optional substituent on a substitutable carbon is a monovalent substituent independently selected from halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, 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; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, SC(S)SR°; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; –SC(S)SR°, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; –

$C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-S(O)(NR^\circ)R^\circ$; $-S(O)_2N{=}C(NR^\circ_2)_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$.

[0033] 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, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$.

[0034] 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; 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.

[0035] When R^* is C_{1-6} aliphatic, R^* is optionally substituted with halogen, $-R^\bullet$, $-(haloR^\bullet)$, -OH, $-OR^\bullet$, $-O(haloR^\bullet)$, $-CN$, $-C(O)OH$, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, 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.

[0036] 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, $-R^\bullet$, -(haloR$^\bullet$), -OH, $-OR^\bullet$, -O(haloR$^\bullet$), –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.

[0037] 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.

[0038] 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, loweralkyl sulfonate and aryl sulfonate.

[0039] 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.

[0040] As used herein, the term "provided compound" refers to any MEK inhibitor genus, subgenus, and/or species set forth herein.

[0041] As used herein, the terms "inhibitor" or "MEK inhibitor" or "MEK antagonist" are defined as a compound that binds to and/or inhibits MEK with measurable affinity. In some embodiments, inhibition in the presence of a MEK inhibitor or a MEK antagonist is observed in a dose-dependent manner. In some embodiments, the measured signal (*e.g.*, signaling activity or biological activity) is at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least about 100% lower than the signal measured with a negative control under comparable conditions. The potency of an inhibitor is usually defined by its IC_{50} value (half maximal inhibitory concentration or concentration required to inhibit 50% of the agonist response). The lower the IC_{50} value the greater the potency of the antagonist and the lower the concentration that is required to inhibit the maximum biological response. 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.

[0042] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change or inhibition in MEK activity between a sample comprising a compound of the present invention, or composition thereof, and MEK, and an equivalent sample comprising MEK, in the absence of said compound, or composition thereof.

[0043] As used herein, the term "effective amount" refers to the amount of a compound sufficient to effect beneficial or desired results (*e.g.*, a therapeutic, ameliorative, inhibitory, or preventative result). An effective amount can be administered in one or more administrations, applications, or dosages and is not intended to be limited to a particular formulation or administration route.

[0044] As used herein, the term "treating" includes any effect, *e.g.*, lessening, reducing, modulating, ameliorating or eliminating, that results in the improvement of the condition, disease, disorder, and the like, or ameliorating a symptom thereof. In some embodiments, treatment can be administered after one or more symptoms have developed. In other embodiments, treatment can be administered in the absence of symptoms. For example,

treatment can 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 can also be continued after symptoms have resolved, for example, to prevent or delay their recurrence.

[0045] The phrases "disorder mediated by MEK" or "disease mediated by MEK" or "MEK-associated disease or disorder," as used herein, refer to diseases or disorders associated with, or mediated by, MEK or MEK activity. A non-limiting example of a MEK-associated disease or disorder is a MEK-associated cancer.

[0046] As used herein, the term "pharmaceutical composition" refers to the combination of an active agent with a carrier, inert or active, making the composition especially suitable for diagnostic or therapeutic use *in vivo* or *ex vivo*.

[0047] As used herein, the term "pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, such as a phosphate buffered saline solution, water, emulsions (*e.g.*, such as an oil/water or water/oil emulsions), and various types of wetting agents. The compositions also can include stabilizers and preservatives. For examples of carriers, stabilizers and adjuvants, *see e.g.*, Martin, Remington's Pharmaceutical Sciences, 15th Ed., Mack Publ. Co., Easton, PA [1975].

[0048] As used herein, a "non-ATP competitive" or "ATP non-competitive" MEK inhibitor refers to an inhibitor of MEK that does not bind in the ATP pocket of MEK, or does not displace ATP from the MEK active site, and can form direct contacts when co-bound to the MEK-ATP complex. Non-ATP competitive inhibition by a compound of the invention can be confirmed by art-recognized methods such as enzymology studies, competition assays, biophysical methods, including X-ray co-crystallography. An exemplary non-ATP competitive inhibitor of the invention inhibits recombinant MEK1 or MEK2 with an IC_{50} of from about 1 nM to about 50 μM. In some embodiments, an exemplary non-ATP competitive inhibitor of the invention inhibits recombinant MEK1 or MEK2 with an IC_{50} of about 1 nM to about 1000 nM, about 1 μM to about 50 μM, about 1 μM to about 25 μM, about 1 μM to about 10 μM, about 500 nM to about 5 μM, or about 10 nM to about 500 nM.

[0049] An "inhibitor pocket", as used herein, refers to a structure formed at the interface of the interaction between MEK and KSR or BRAF or CRAF with which an inhibitor of the invention is engaged.

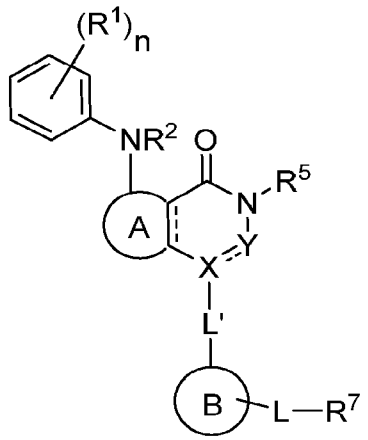
[0050] As used herein, a compound of the invention "allosterically binds an inhibitor pocket" when a compound binds outside the active site, including, for example, outside or adjacent to the ATP-binding site of a kinase.

[0051] As used herein, an "inhibitor-inhibitor pocket complex" describes a species in which an inhibitor of the invention allosterically binds an inhibitor pocket formed at an interaction interface between human MEK (MEK1 or MEK2) and human Kinase Suppressor of Ras (KSR1, KSR2, or the KSR homolog BRAF or CRAF) adjacent to ATP in a physiological complex between MEK and KSR.

[0052] As used herein, when a moiety on an inhibitor "engages" an amino acid residue of MEK and/or KSR and/or BRAF or CRAF in an inhibitor pocket, this interaction is detectable by X-ray crystallography, or similar structural methods, such as cryo-electron microscopy, NMR, or in silico docking, including fragment binding and computational simulations, which demonstrates that the interaction defining the engagement is a separation between the inhibitor moiety and the amino acid residue of not more than about 8 Å, including, for example, from about 2 Å to about 5 Å, or from about 5 Å to about 8 Å. The distances provided herein allow for the implicit inclusion of hydrogen atoms; however, hydrogen atoms were not included in the present crystallographic models, which is appropriate unless crystals diffract to very high resolutions (*i.e.*, better than 1.5 Angstroms). Literature surveys of drug-receptor atom pairs across all structures in the protein data bank have used 4-5 Angstrom distance cutoffs (PMID 29308120, 26517868, 19221587) to evaluate reasonable small molecule hydrophobic bonding interactions and have found that intermolecular carbon-carbon interactions similar to the trametinib-KSR contacts are among the most highly represented drug-receptor atom pairs within the protein data bank. With respect to the interactions between the inhibitors of the invention and the MEK-KSR and/or BRAF or CRAF complex, a 4 Angstrom contact is reasonable based on the nature of the trametinib-KSR interaction and precedence of known drug-receptor complexes. This contact is within the range of known contacts as defined by several independent groups (PMID 29308120, 26517868, 19221587).

3. Description of Exemplary Embodiments:

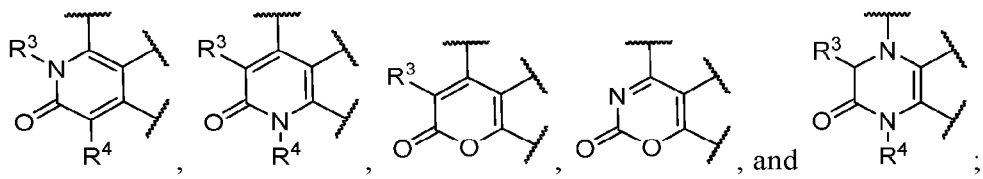
[0053] In one aspect, the present invention provides a compound of Formula (**I'**):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:



each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C, CH, or N;

Y is CR^6, C(O), or N;

L' is a covalent bond, -O-, $-C(R^9)_2-$, or $-NR^8-$;

each of R^2, R^5, and R^8 is independently H or optionally substituted C_{1-6} aliphatic;

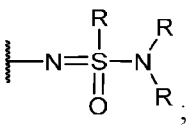
each of R^3, R^4, R^6, and R^9 is independently H, halogen, or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a

phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^{+}(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-;

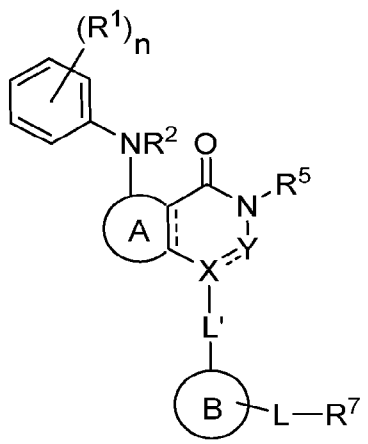
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

R^7 is R, -CN, -S(O)$_2$-N(R)$_2$, -NR-S(O)$_2$-R, -P(O)(OR)-N(R)$_2$, -C(=N-R)-N(R)$_2$, -C(=N-OR)-N(R)$_2$, -C(O)-R, -S(O)-R, -N(R)$_2$, -OR, -SR, or  ;

each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

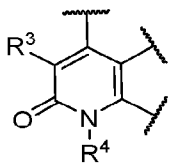
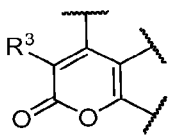
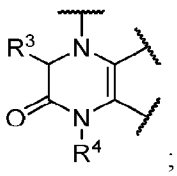
[0054] In one aspect, the present invention provides a compound of Formula (**I'**):



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:


, 
, 
, and 
;

each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C, CH, or N;

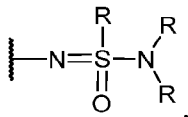
Y is CR^6, C(O), or N;

each of R^2, R^3, R^4, R^5, R^6, and R^8 is independently H or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^+(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)$-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, $-S(O)_2$-, $-(CH_2-CH_2-O)_{1-10}$-, -S(O)-, -N(R)-C(O)-, $-N(R)-S(O)_2$-, -C(O)-N(R)-, $-S(O)_2-N(R)$-, -P(O)(OR)-, or -Cy-;

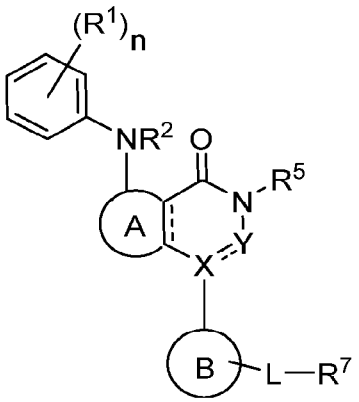
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

R^7 is R, -CN, $-S(O)_2-N(R)_2$, -NR-$S(O)_2$-R, -P(O)(OR)-$N(R)_2$, -C(=N-R)-$N(R)_2$, -C(=N-OR)-$N(R)_2$, -C(O)-R, -S(O)-R, $-N(R)_2$, -OR, -SR,  , or a fluorescent probe;

each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

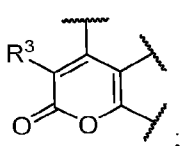
[0055] In one aspect, the present invention provides a compound of Formula (**I**):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:

 ,  , and  ;

each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C or N;

Y is CR^6, C(O), or N;

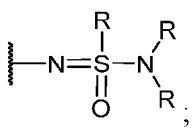
each of R^2, R^3, R^4, R^5, and R^6 is independently H or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-10

membered bicyclic aromatic ring, and a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

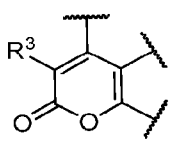
L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^{+}(R)_2-$, -CH(R)-, -CH(OR)-, -CH(SR)-, $-CH(N(R)_2)-$, -C(=N-R)-, -C(=N-OR)-, -C(O)-, $-S(O)_2-$, -P(O)(OR)-, or -Cy-;

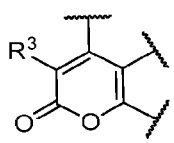
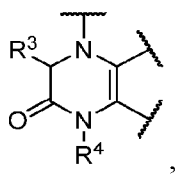
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

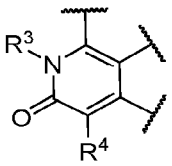
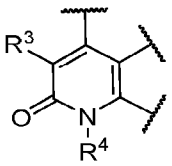
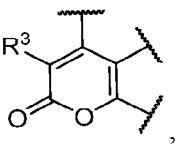
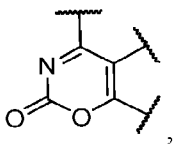
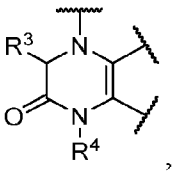
R^7 is -CN, $-S(O)_2-N(R)_2$, $-NR-S(O)_2-R$, $-P(O)(OR)-N(R)_2$, $-C(=N-R)-N(R)_2$, $-C(=N-OR)-N(R)_2$, -C(O)-R, $-N(R)_2$, -OR, -SR, or  ;

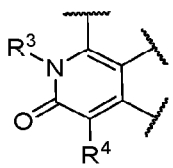
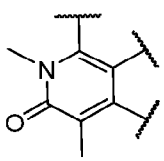
each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

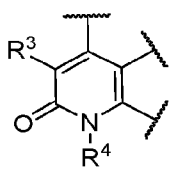
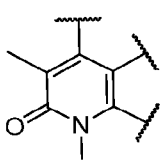
n is 0, 1, 2, 3, 4, or 5.

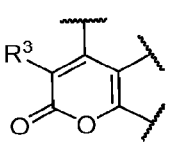
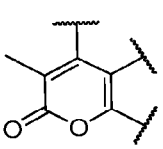
[0056] As defined generally above, Ring A is an optionally substituted 6-membered ring selected from:  ,  , and  , wherein each of R^3 and R^4 is independently as defined and described in embodiments herein.

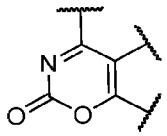
[0057] In some embodiments, Ring A is an optionally substituted 6-membered ring selected from:  ,  ,  , and  , wherein each of R^3 and R^4 is independently as defined and described in embodiments herein.

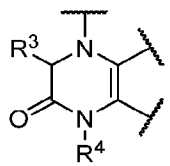
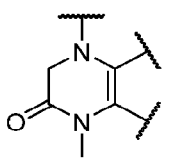
[0058] In some embodiments, Ring A is an optionally substituted 6-membered ring selected from:  ,  ,  ,  , and  , wherein each of R^3 and R^4 is independently as defined and described in embodiments herein.

[0059] In some embodiments, Ring A is  , wherein each of R^3 and R^4 is independently as defined and described in embodiments herein. In some embodiments, Ring A is  .

[0060] In some embodiments, Ring A is  , wherein each of R^3 and R^4 is independently as defined and described in embodiments herein. In some embodiments, Ring A is  .

[0061] In some embodiments, Ring A is  , wherein R^3 is as defined and described in embodiments herein. In some embodiments, Ring A is  .

[0062] In some embodiments, Ring A is  .

[0063] In some embodiments, Ring A is  , wherein each of R^3 and R^4 is as defined and described in embodiments herein. In some embodiments, Ring A is  .

[0064] In some embodiments, Ring A is selected from those depicted in Table **1**, below.

[0065] As defined generally above, each ==== independently represents a single bond or a double bond.

[0066] In some embodiments, ==== represents a single bond. In some embodiments, ==== represents a double bond.

[0067] In some embodiments, ==== is selected from those depicted in Table **1**, below.

[0068] As defined generally above, R^1 is H, halogen, -CN, or optionally substituted C_{1-6} aliphatic.

[0069] In some embodiments, R^1 is H.

[0070] In some embodiments, R^1 is halogen. In some embodiments, R^1 is F. In some embodiments, R^1 is Cl. In some embodiments, R^1 is Br. In some embodiments, R^1 is I.

[0071] In some embodiments, R^1 is -CN.

[0072] In some embodiments, R^1 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^1 is optionally substituted C_{1-6} alkyl. In some embodiments, R^1 is C_{1-6} aliphatic substituted 1-6 times by halogen. In some embodiments, R^1 is C_{1-6} alkyl substituted 1-6 times by halogen. In some embodiments, R^1 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^1 is cyclopropyl. In some embodiments, R^1 is -CH=CH. In some embodiments, R^1 is $-C\equiv CH$. In some embodiments, R^1 is $-C\equiv C-CH_3$. In some embodiments, R^1 is $-CH_2F$, $-CHF_2$, or $-CF_3$.

[0073] In some embodiments, R^1 is selected from those depicted in Table **1**, below.

[0074] As defined generally above, X is C or N.

[0075] In some embodiments, X is C. In some embodiments, X is CH. In some embodiments, X is N.

[0076] In some embodiments, X is selected from those depicted in Table **1**, below.

[0077] As defined generally above, Y is CR^6, C(O), or N.

[0078] In some embodiments, Y is CR^6, wherein R^6 is as defined and described in embodiments herein. In some embodiments, Y is C(O). In some embodiments, Y is N.

[0079] In some embodiments, Y is selected from those depicted in Table **1**, below.

[0080] As defined generally above, L' is a covalent bond, -O-, $-C(R^9)_2-$, or $-NR^8-$, wherein in R^8 is as defined and described in embodiments herein.

[0081] In some embodiments, L' is a covalent bond. In some embodiments, L' is -O-. In some embodiments, L' is $-C(R^9)_2-$. In some embodiments, L' is $-CH_2-$. In some embodiments, L' is $-NR^8-$. In some embodiments, L' is -NH-.

[0082] In some embodiments, L' is selected from those depicted in Table **1**, below.

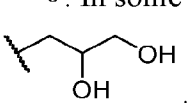
[0083] As defined generally above, each of R^2, R^3, R^4, R^5, and R^6 is independently H or optionally substituted C_{1-6} aliphatic.

[0084] In some embodiments, R^2 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^2 is H. In some embodiments, R^2 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^2 is optionally substituted C_{1-6} alkyl. In some embodiments, R^2 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^2 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^2 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^2 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^2 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^2 is cyclopropyl. In some embodiments, R^2 is $-CH=CH_2$. In some embodiments, R^2 is $-C\equiv CH$. In some embodiments, R^2 is $-C\equiv C-CH_3$. In some embodiments, R^2 is $-CH_2F$, $-CHF_2$, or $-CF_3$.

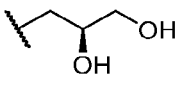
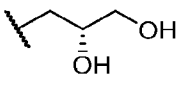
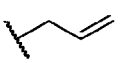
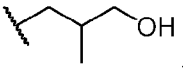
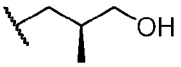
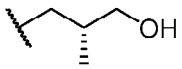
[0085] In some embodiments, R^3 is H, halogen, or optionally substituted C_{1-6} aliphatic. In some embodiments, R^3 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^3 is H. In some embodiments, R^3 is halogen. In some embodiments, R^3 is -F. In some embodiments, R^3 is -Cl. In some embodiments, R^3 is -I. In some embodiments, R^3 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^3 is optionally substituted C_{1-6} alkyl. In some embodiments, R^3 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^3 is C_{1-6}

alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^3 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^3 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^3 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^3 is cyclopropyl. In some embodiments, R^3 is -CH=CH_2. In some embodiments, R^3 is —C≡CH. In some embodiments, R^3 is —C≡C–CH_3. In some embodiments, R^3 is -CH_2F, -CHF_2, or -CF_3.

[0086] In some embodiments, R^4 is H, halogen, or optionally substituted C_{1-6} aliphatic. In some embodiments, R^4 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^4 is H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -F. In some embodiments, R^4 is -Cl. In some embodiments, R^4 is -I. In some embodiments, R^4 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^4 is optionally substituted C_{1-6} alkyl. In some embodiments, R^4 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^4 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^4 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^4 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^4 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^4 is cyclopropyl. In some embodiments, R^4 is -CH=CH_2. In some embodiments, R^4 is —C≡CH. In some embodiments, R^4 is —C≡C–CH_3. In some embodiments, R^4 is -CH_2F, -CHF_2, or -CF_3.

[0087] In some embodiments, R^5 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^5 is H. In some embodiments, R^5 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^5 is optionally substituted 3, 4, 5, or 6 membered saturated or unsaturated carbocyclyl. In some embodiments, R^5 is optionally substituted C_{1-6} alkyl. In some embodiments, R^5 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^5 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^5 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^5 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^5 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^5 is cyclopropyl. In some embodiments, R^5 is -CH=CH_2. In some embodiments, R^5 is —C≡CH. In some embodiments, R^5 is —C≡C–CH_3. In some embodiments, R^5 is -CH_2F, -CHF_2, or -CF_3. In some embodiments, R^5 is 

. In some

embodiments, R^5 is  ,  ,  ,  ,  , or  .

[0088] In some embodiments, R^6 is H, halogen, or optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is H. In some embodiments, R^6 is halogen. In some embodiments, R^6 is -F. In some embodiments, R^6 is -Cl. In some embodiments, R^6 is -I. In some embodiments, R^6 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^6 is optionally substituted C_{1-6} alkyl. In some embodiments, R^6 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^6 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^6 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^6 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^6 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^6 is cyclopropyl. In some embodiments, R^6 is $-CH{=}CH_2$. In some embodiments, R^6 is $-C{\equiv}CH$. In some embodiments, R^6 is $-C{\equiv}C-CH_3$. In some embodiments, R^6 is $-CH_2F$, $-CHF_2$, or $-CF_3$.

[0089] In some embodiments, R^8 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^8 is H. In some embodiments, R^8 is optionally substituted C_{1-6} aliphatic. In some embodiments, R^8 is optionally substituted C_{1-6} alkyl. In some embodiments, R^8 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^8 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^8 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^8 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^8 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^8 is cyclopropyl. In some embodiments, R^8 is $-CH{=}CH_2$. In some embodiments, R^8 is $-C{\equiv}CH$. In some embodiments, R^8 is $-C{\equiv}C-CH_3$. In some embodiments, R^8 is $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, R^8 is selected from those depicted in Table **1**, below.

[0090] In some embodiments, R^9 is H, halogen, or optionally substituted C_{1-6} aliphatic. In some embodiments, R^9 is H or optionally substituted C_{1-6} aliphatic. In some embodiments, R^9 is H. In some embodiments, R^9 is halogen. In some embodiments, R^9 is -F. In some embodiments, R^9 is -Cl. In some embodiments, R^9 is -I. In some embodiments, R^9 is optionally substituted C_{1-6}

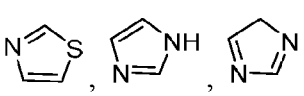
aliphatic. In some embodiments, R^9 is optionally substituted C_{1-6} alkyl. In some embodiments, R^9 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^9 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R^9 is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^9 is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R^9 is methyl, ethyl, propyl, or isopropyl. In some embodiments, R^9 is cyclopropyl. In some embodiments, R^9 is $-CH{=}CH_2$. In some embodiments, R^9 is $-C{\equiv}CH$. In some embodiments, R^9 is $-C{\equiv}C-CH_3$. In some embodiments, R^9 is $-CH_2F$, $-CHF_2$, or $-CF_3$. In some embodiments, R^9 is selected from those depicted in Table **1**, below.

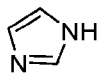
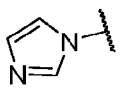
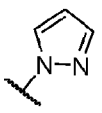
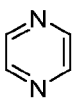
[0091] In some embodiments, each of R^2, R^3, R^4, R^5, and R^6 is independently selected from those depicted in Table **1**, below.

[0092] As defined generally above, Ring B is an optionally substituted ring selected from a phenyl ring, a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-10 membered bicyclic aromatic ring, and a 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S.

[0093] In some embodiments, Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S.

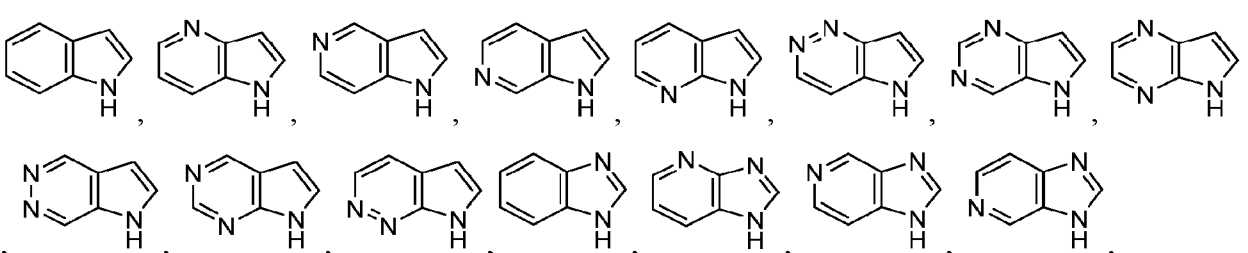
[0094] In some embodiments, Ring B is an optionally substituted phenyl ring.

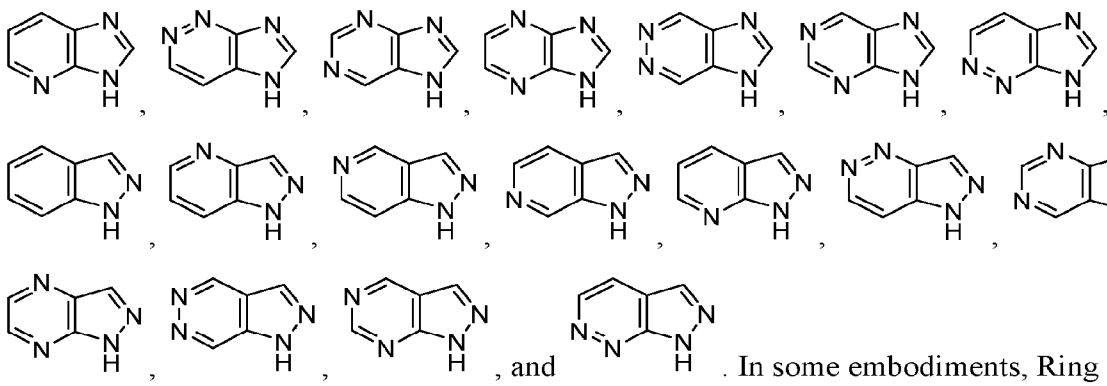
[0095] In some embodiments, Ring B is an optionally substituted 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 5 membered heteroaromatic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 5 membered heteroaromatic ring selected from  ,

and  . In some embodiments, Ring B is selected from  ,  ,  , and  , which is substituted by a methyl group. In some embodiments, Ring B is an optionally substituted 5 membered heteroaromatic ring selected from  and  . In some embodiments, Ring B is an optionally substituted 6 membered heteroaromatic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 6 membered heteroaromatic ring selected from  ,  ,  , and  .

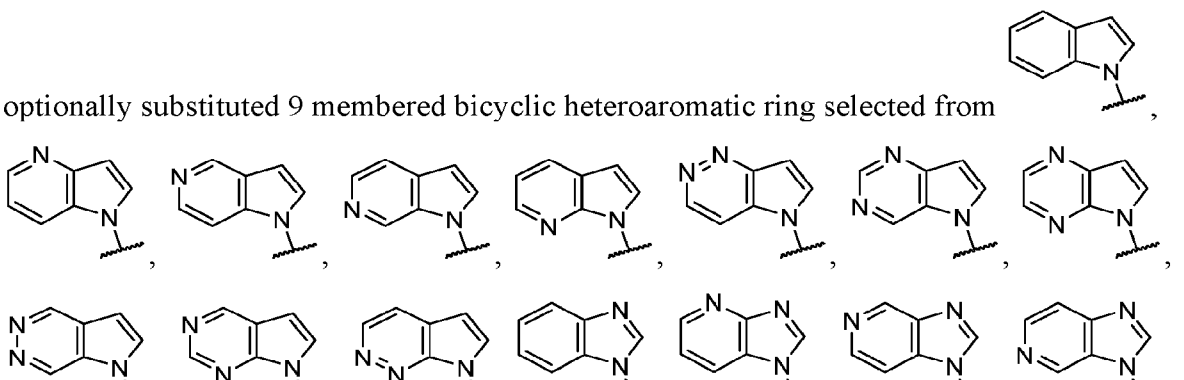
[0096] In some embodiments, Ring B is an optionally substituted 8, 9, or 10 membered bicyclic aromatic ring. In some embodiments, Ring B is an optionally substituted 11 membered bicyclic aromatic ring.

[0097] In some embodiments, Ring B is an optionally substituted 8, 9, or 10 membered bicyclic heteroaromatic ring having 1, 2, 3, 4, or 5 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 11 membered bicyclic heteroaromatic ring having 1, 2, 3, 4, or 5 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 9 membered bicyclic heteroaromatic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 11 membered bicyclic heteroaromatic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is an optionally substituted 9 membered bicyclic heteroaromatic ring selected from

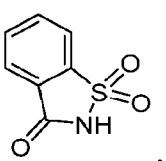


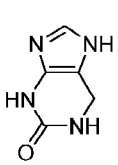
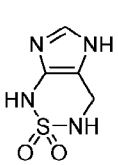
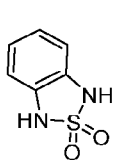
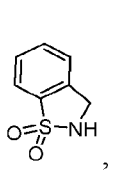
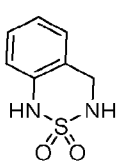
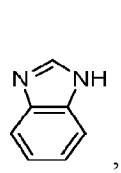
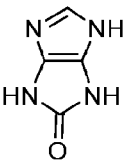
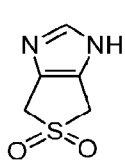
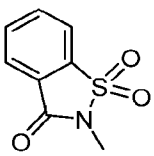
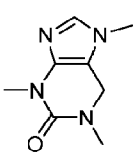
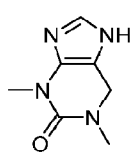
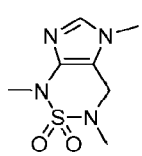
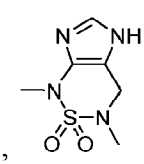
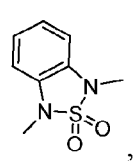
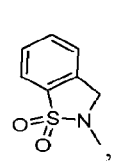
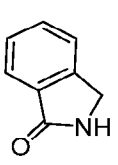
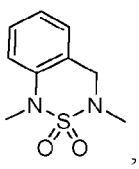
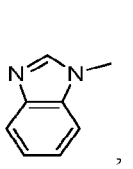
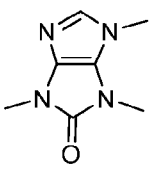
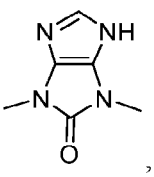
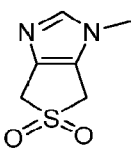
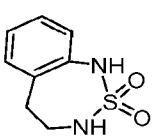
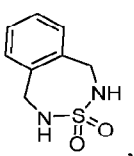
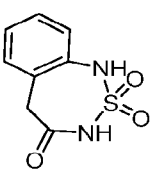
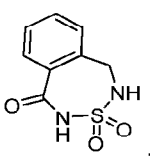


optionally substituted 9 membered bicyclic heteroaromatic ring selected from



optionally substituted 9 membered bicyclic heteroaromatic ring selected from

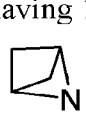


 ,  ,  ,  ,  ,  ,  , and  . In some embodiments, Ring B is an optionally substituted 9 membered bicyclic heteroaromatic ring selected from  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, Ring B is an optionally substituted 11 membered bicyclic heteroaromatic ring selected from  ,  ,  , and  .

[0098] In some embodiments, Ring B is an optionally substituted 3, 4, 5, 6, 7, or 8 membered monocyclic carbocyclic ring. In some embodiments, Ring B is .

[0099] In some embodiments, Ring B is an optionally substituted 3, 4, 5, 6, 7, or 8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is  .

[00100] In some embodiments, Ring B is an optionally substituted 5, 6, 7, 8, 9, 10, or 11 membered bicyclic carbocyclic ring. In some embodiments, Ring B is  .

[00101] In some embodiments, Ring B is an optionally substituted 5, 6, 7, 8, 9, 10, or 11 membered bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S. In some embodiments, Ring B is  .

[00102] In some embodiments, Ring B is substituted 1-2 times by halogen. In some embodiments, Ring B is substituted 1-2 times by R, wherein each R is independently as defined and described in embodiments herein. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is C_{1-6} aliphatic substituted 1-6 times by halogen. In some embodiments, R is C_{1-6} alkyl substituted 1-6 times by halogen. In some embodiments, R is methyl, ethyl, propyl, or isopropyl. In some embodiments, R is cyclopropyl. In some embodiments, R is -CH=CH_2. In some embodiments, R is —C≡CH. In some embodiments, R is —C≡C−CH_3. In some embodiments, R is -CH_2F, -CHF_2, or -CF_3.

[00103] In some embodiments, Ring B is selected from those depicted in Table **1**, below.

[00104] As defined generally above, L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, -$N^+(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -$S(O)_2$-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein.

[00105] In some embodiments, L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, -$N^+(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -$S(O)_2$-, -(CH_2-CH_2-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-$S(O)_2$-, -C(O)-N(R)-, -$S(O)_2$-N(R)-, -P(O)(OR)-, or -Cy-.

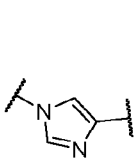
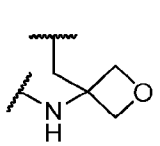
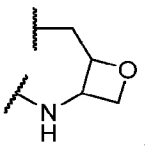
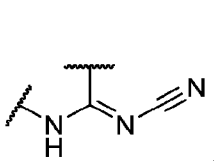
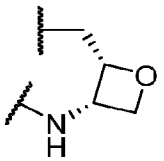
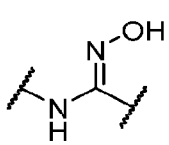
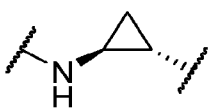
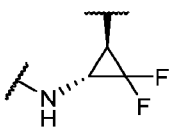
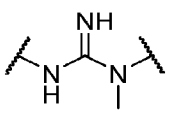
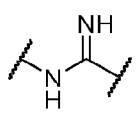
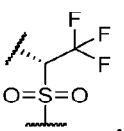
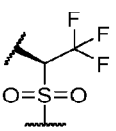
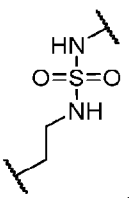
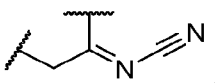
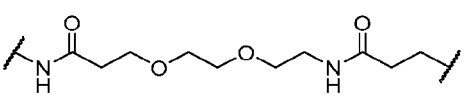
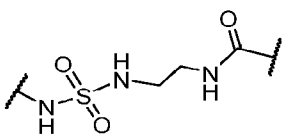
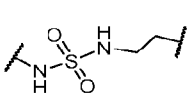
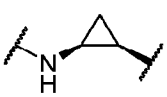
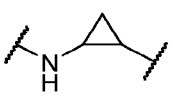
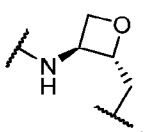
[00106] In some embodiments, L is a covalent bond.

[00107] In some embodiments, L is a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, -$N^+(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH($N(R)_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -$S(O)_2$-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. In some embodiments, L is a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -N(R)-, -CH(R)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -$S(O)_2$-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. In some embodiments, R is hydrogen. In some embodiments, R is methyl. In some embodiments, R is -CN. In some embodiments, L is a C_{1-10} bivalent straight or branched

hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, -N^+(R)$_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. In some embodiments, L is a C$_{1-10}$ bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -N(R)-, -CH(R)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. The moiety -(CH$_2$-CH$_2$-O)$_{1-10}$- can be -CH$_2$-CH$_2$-O-, -(CH$_2$-CH$_2$-O)$_2$-, -(CH$_2$-CH$_2$-O)$_3$-, -(CH$_2$-CH$_2$-O)$_4$-, -(CH$_2$-CH$_2$-O)$_5$-, -(CH$_2$-CH$_2$-O)$_6$-, -(CH$_2$-CH$_2$-O)$_7$-, -(CH$_2$-CH$_2$-O)$_8$-, -(CH$_2$-CH$_2$-O)$_9$-, or -(CH$_2$-CH$_2$-O)$_{10}$-.

[00108] 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 and optionally replaced with -O-, -S-, -N(R)-, -N^+(R)$_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. 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 and optionally replaced with -O-, -N(R)-, -CH(R)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. In some embodiments, R is hydrogen. In some embodiments, R is methyl. In some embodiments, R is -CN. 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 and optionally replaced with -O-, -S-, -N(R)-, -N^+(R)$_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein. 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 and optionally replaced with -O-, -N(R)-, -CH(R)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-,-(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-

N(R)-, -P(O)(OR)-, or -Cy-, wherein each of R and -Cy- is independently as defined and described in embodiments herein.

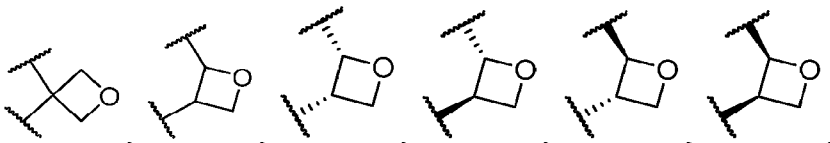
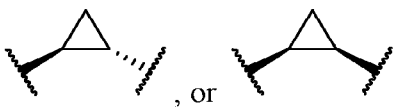
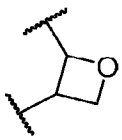
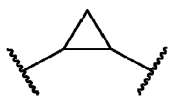
[00109] In some embodiments, L is selected from -CH_2-, -NH-, -$S(O)_2$-, -NH-$S(O)_2$-, -CH_2-$S(O)_2$-, -CH_2-P(O)(OH)-, -$CH(CF_3)$-, -$CH(CF_3)$-$S(O)_2$-, -NH-C(O)-NH-, -NH-C(O)-, -O-, -O-$S(O)_2$-,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  . In some embodiments, L is selected from -NH-S(O)-, -$N(CH_3)$-,  ,  ,  ,  ,  , and  .

[00110] In some embodiments, L is selected from those depicted in Table **1**, below.

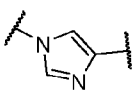
[00111] As defined generally above, each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S.

[00112] In some embodiments, -Cy- is an optionally substituted 3, 4, 5, 6, or 7 membered carbocyclic ring.

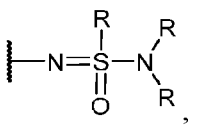
[00113] In some embodiments, -Cy- is an optionally substituted 3, 4, 5, 6, or 7 membered heterocyclic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some

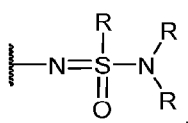
embodiments, -Cy- is  ,  , or . In some embodiments, -Cy- is  or  .

[00114] In some embodiments, -Cy- is an optionally substituted phenyl ring.

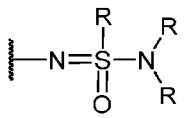
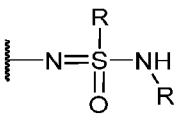
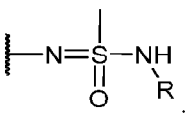
[00115] In some embodiments, -Cy- is an optionally substituted 5 or 6 membered heteroaromatic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S. In some embodiments, -Cy- is  .

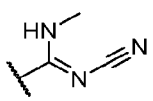
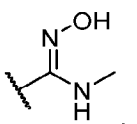
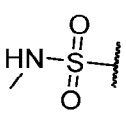
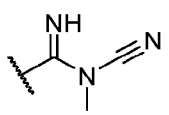
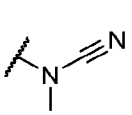
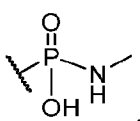
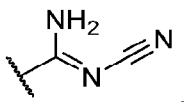
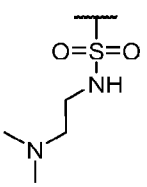
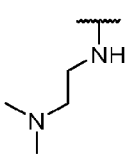
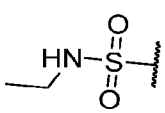
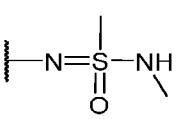
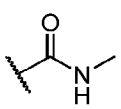
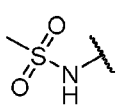
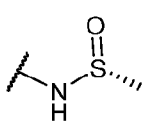
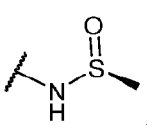
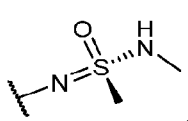
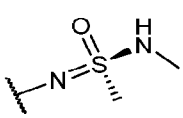
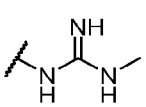
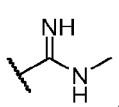
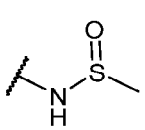
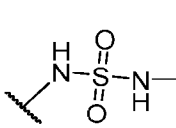
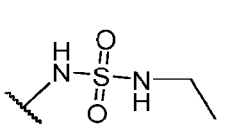
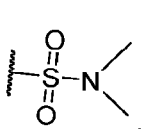
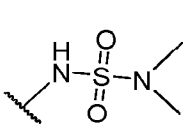
[00116] In some embodiments, -Cy- is selected from those depicted in Table **1**, below.

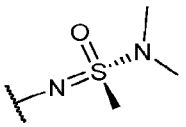
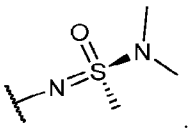
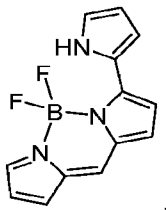
[00117] As defined generally above, R^7 is -CN, $-S(O)_2-N(R)_2$, $-NR-S(O)_2-R$, $-P(O)(OR)-N(R)_2$, $-C(=N-R)-N(R)_2$, $-C(=N-OR)-N(R)_2$, -C(O)-R, $-N(R)_2$, -OR, -SR, or  , wherein each R is independently as defined and described in embodiments herein.

[00118] In some embodiments, R^7 is R, -CN, $-S(O)_2-N(R)_2$, $-NR-S(O)_2-R$, $-P(O)(OR)-N(R)_2$, $-C(=N-R)-N(R)_2$, $-C(=N-OR)-N(R)_2$, -C(O)-R, -S(O)-R, $-N(R)_2$, -OR, -SR, or  .

[00119] In some embodiments, R^7 is R as defined and described in embodiments herein. In some embodiments, R^7 is -CN. In some embodiments, R^7 is $-S(O)_2-N(R)_2$. In some embodiments, R^7 is $-S(O)_2-NHR$. In some embodiments, R^7 is $-NR-S(O)_2-R$. In some embodiments, R^7 is $-NH-S(O)_2-R$. In some embodiments, R^7 is $-P(O)(OR)-N(R)_2$. In some embodiments, R^7 is $-P(O)(OH)-N(R)_2$. In some embodiments, R^7 is $-P(O)(OR)-NHR$. In some embodiments, R^7 is $-P(O)(OH)-NHR$. In some embodiments, R^7 is $-C(=N-R)-N(R)_2$. In some embodiments, R^7 is $-C(=N-R)-NHR$. In some embodiments, R^7 is $-C(=N-H)-N(R)_2$. In some embodiments, R^7 is $-C(=N-CN)-N(R)_2$. In some embodiments, R^7 is $-C(=N-H)-NHR$. In some embodiments, R^7 is $-C(=N-CN)-NHR$. In some embodiments, R^7 is $-C(=N-OR)-N(R)_2$. In some

embodiments, R^7 is -C(=N-OR)-NHR. In some embodiments, R^7 is -C(=N-OH)-NHR. In some embodiments, R^7 is -C(O)-R. In some embodiments, R^7 is -S(O)-R. In some embodiments, R^7 is $-N(R)_2$. In some embodiments, R^7 is -NHR. In some embodiments, R^7 is -OR. In some embodiments, R^7 is -SR. In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R is hydrogen. In some embodiments, R is methyl. In some embodiments, R is -CN.

[00120] In some embodiments, R^7 is selected from -CN, $-NH_2$, -OH, $-NHCH_3$,  ,  ,  ,  ,  ,  , $-C(O)-CH_3$,  ,  ,  ,  ,  ,  , and  . In some embodiments, R^7 is $-S(O)-CH_3$, $-O-C(CH_3)_3$,  ,  ,  , or  . In some embodiments, R^7 is  or  . In some embodiments, R^7 is  ,  ,  ,  , or  . In some

embodiments, R^7 is  or  . In some embodiments, R^7 is a fluorescent probe, including, for example,  .

[00121] In some embodiments, R^7 is selected from those depicted in Table **1**, below.

[00122] As defined generally above, each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic.

[00123] In some embodiments, R is H. In some embodiments, R is -CN.

[00124] In some embodiments, R is optionally substituted C_{1-6} aliphatic. In some embodiments, R is optionally substituted C_{1-6} alkyl. In some embodiments, R is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by halogen. In some embodiments, R is C_{1-6} aliphatic substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R is C_{1-6} alkyl substituted 1, 2, 3, 4, 5, or 6 times by -OH. In some embodiments, R is methyl, ethyl, propyl, or isopropyl. In some embodiments, R is cyclopropyl. In some embodiments, R is $-CH{=}CH_2$. In some embodiments, R is $-C{\equiv}CH$. In some embodiments, R is $-C{\equiv}C-CH_3$. In some embodiments, R is $-CH_2F$, $-CHF_2$, or $-CF_3$.

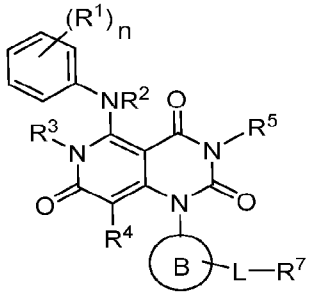
[00125] In some embodiments, R is selected from those depicted in Table **1**, below.

[00126] As defined generally above, n is 0, 1, 2, 3, 4, or 5.

[00127] 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. In some embodiments, n is 5.

[00128] In some embodiments, R is selected from those depicted in Table **1**, below.

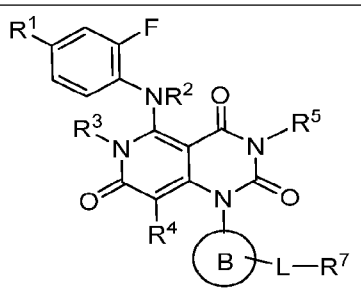
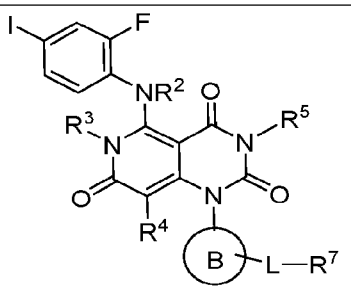
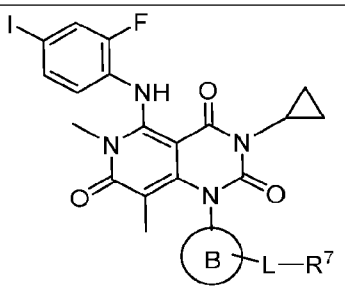
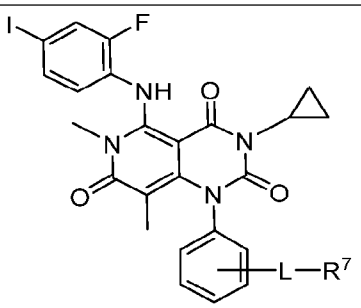
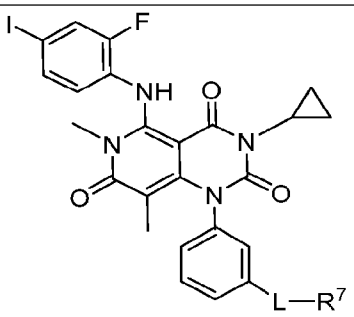
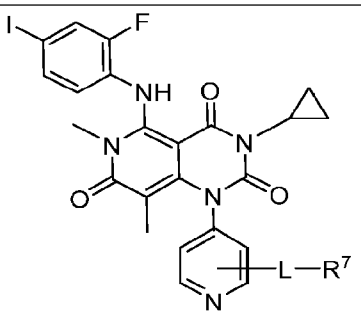
[00129] In some embodiments, the present invention provides a compound of Formula (**II**):

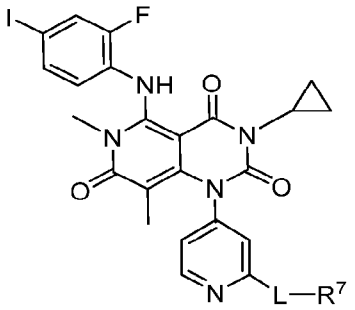
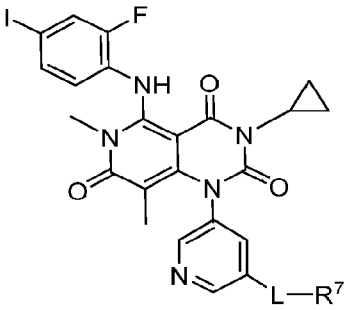
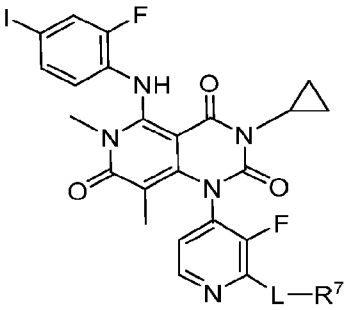
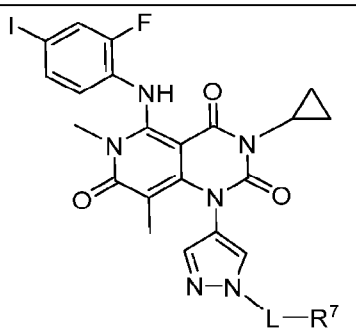
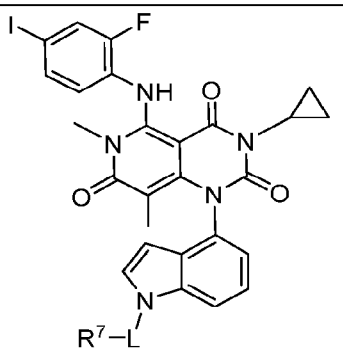
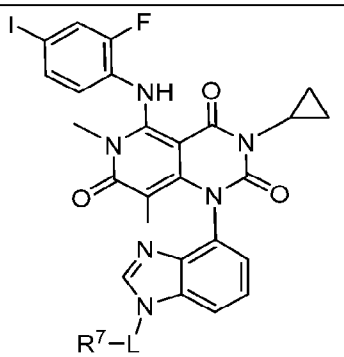
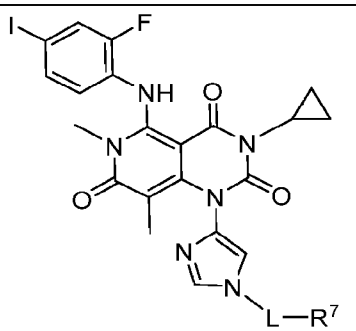
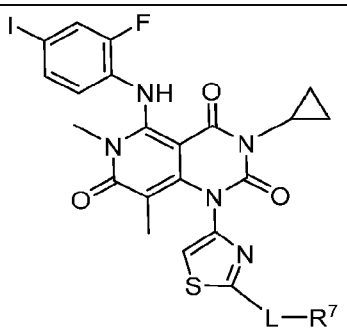
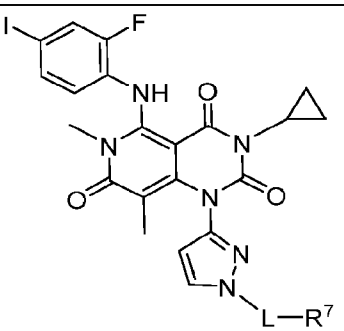


(II)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

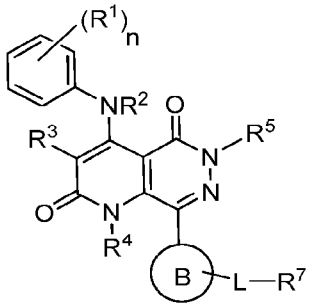
[00130] In some embodiments, the present invention provides a compound selected from Formulae **(II-a)** to **(II-o)**:

 **(II-a)**	 **(II-b)**	 **(II-c)**
 **(II-d)**	 **(II-e)**	 **(II-f)**

 **(II-g)**	 **(II-h)**	 **(II-i)**
 **(II-j)**	 **(II-k)**	 **(II-l)**
 **(II-m)**	 **(II-n)**	 **(II-o)**

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

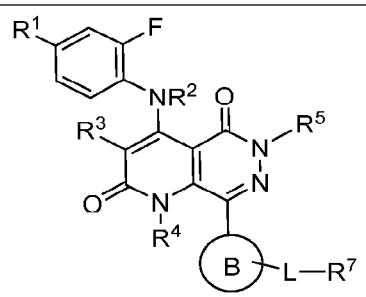
[00131] In some embodiments, the present invention provides a compound of Formula **(III)**:



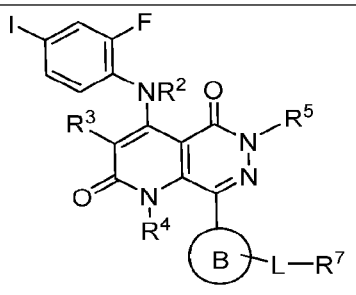
(III)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

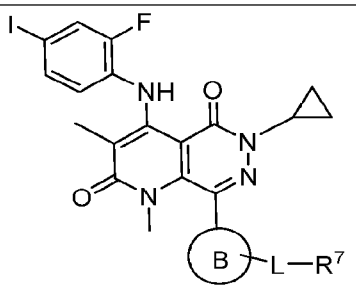
[00132] In some embodiments, the present invention provides a compound selected from Formulae **(III-a)** to **(III-e)**:



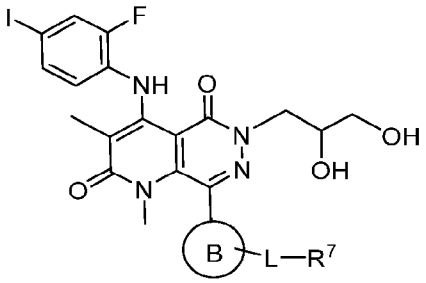
(III-a)



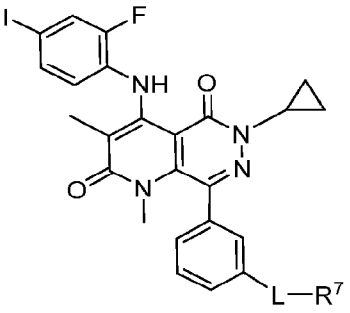
(III-b)



(III-c)



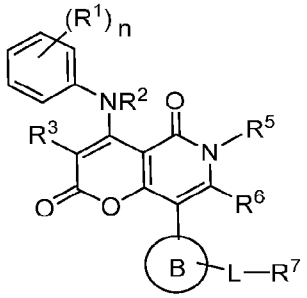
(III-d)



(III-e)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

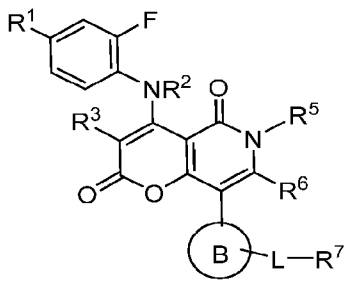
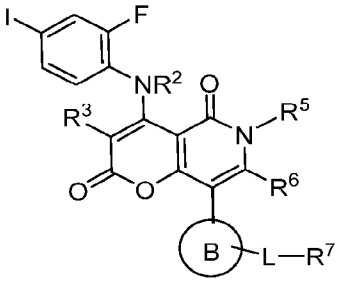
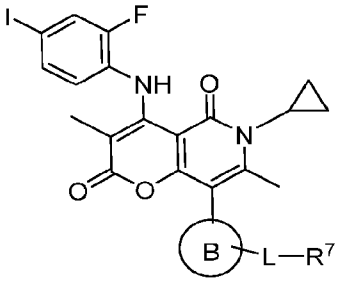
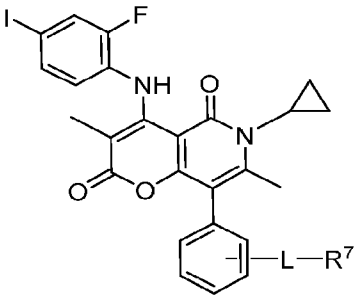
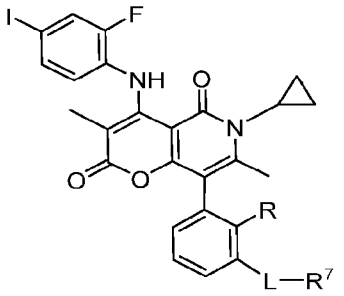
[00133] In some embodiments, the present invention provides a compound of Formula **(IV)**:



(IV)

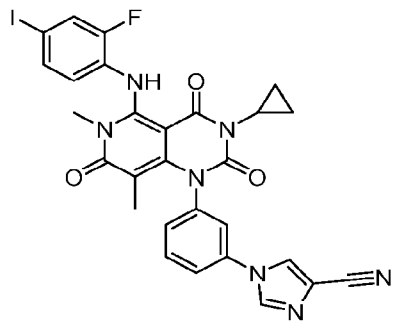
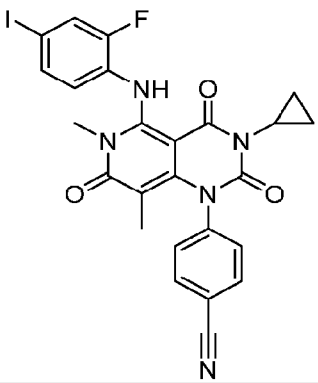
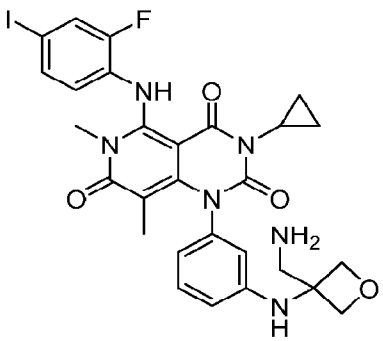
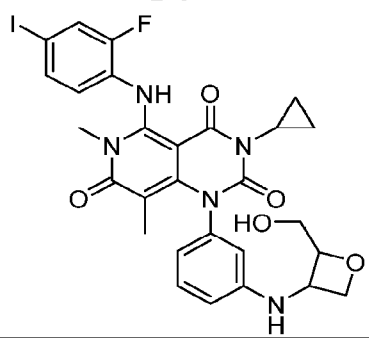
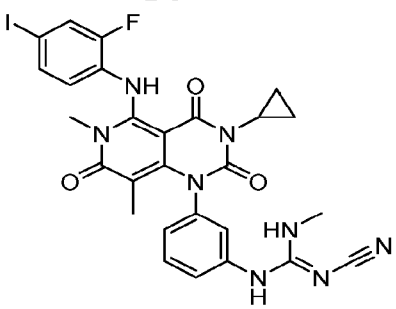
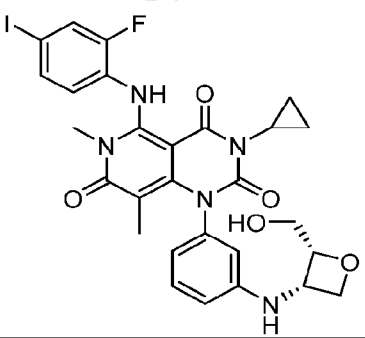
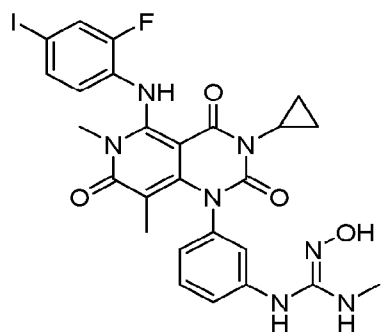
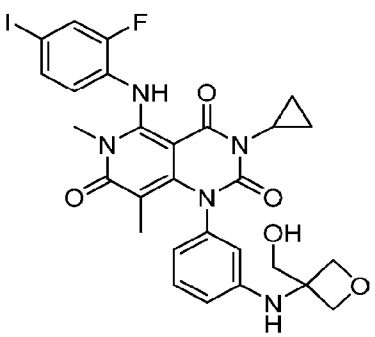
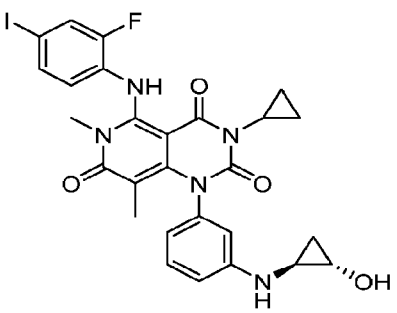
or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

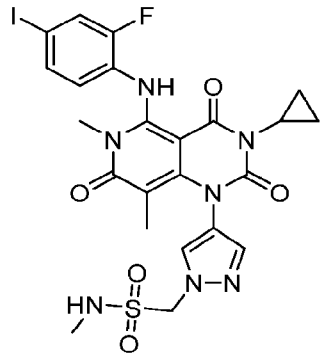
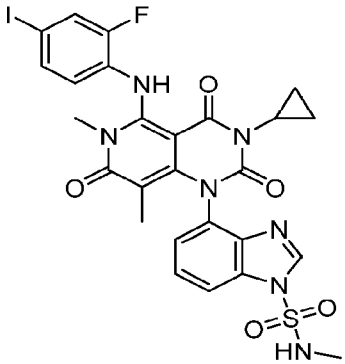
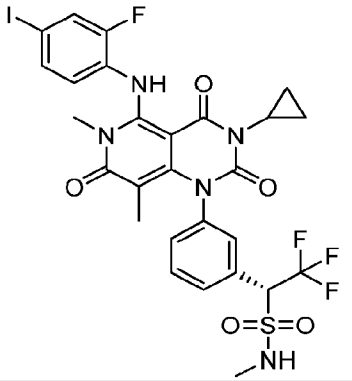
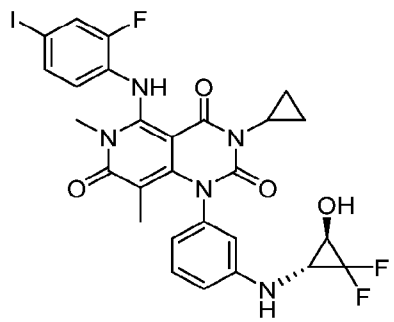
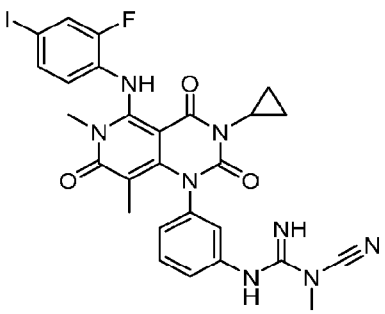
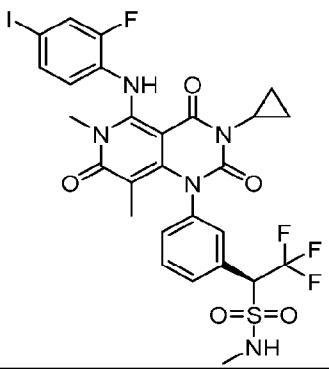
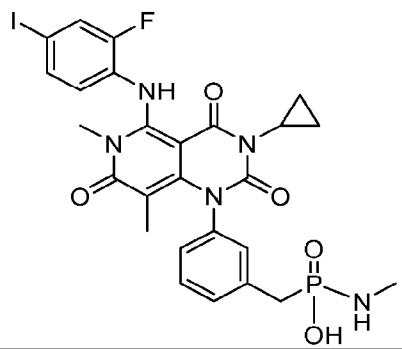
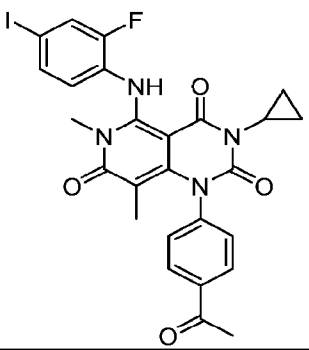
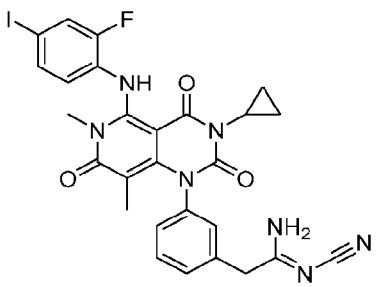
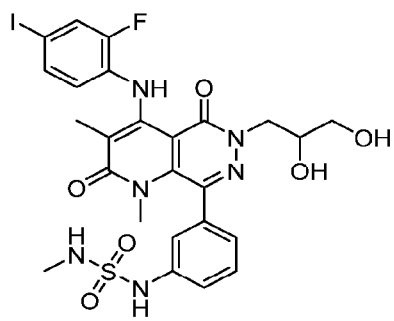
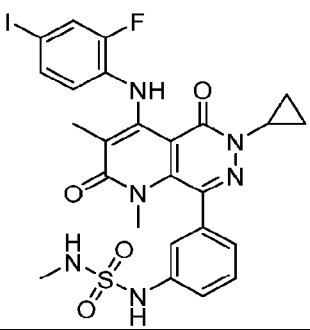
[00134] In some embodiments, the present invention provides a compound selected from Formulae (**IV-a**) to (**IV-e**):

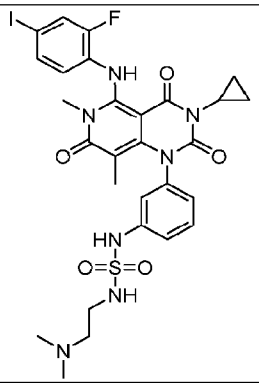
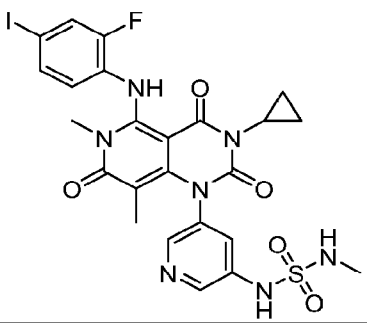
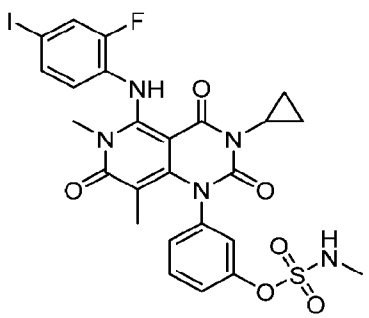
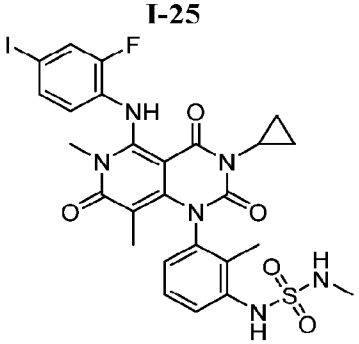
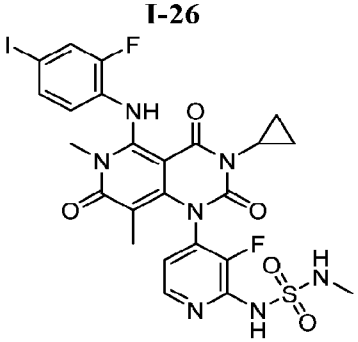
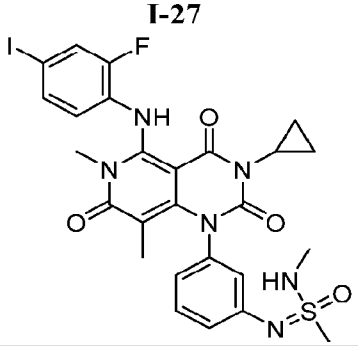
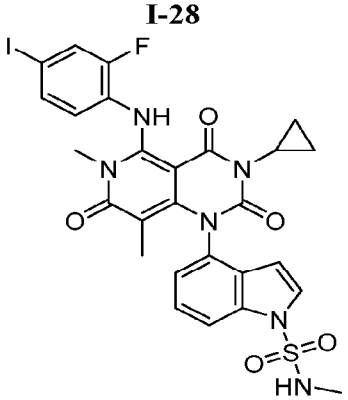
 **(IV-a)**	 **(IV-b)**	 **(IV-c)**
 **(IV-d)**	 **(IV-e)**	

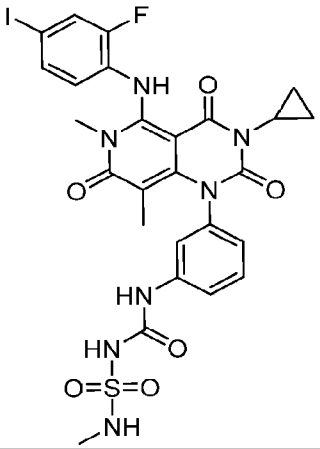
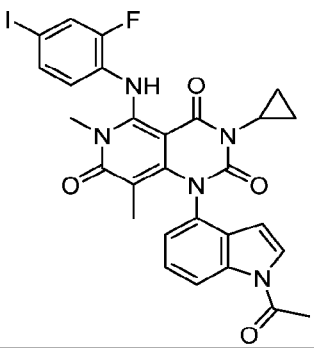
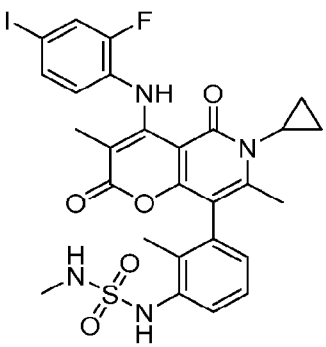
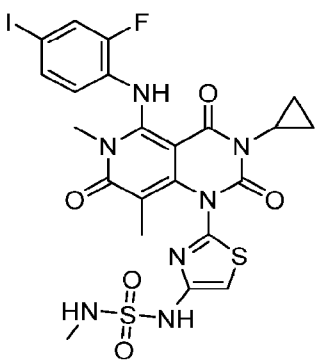
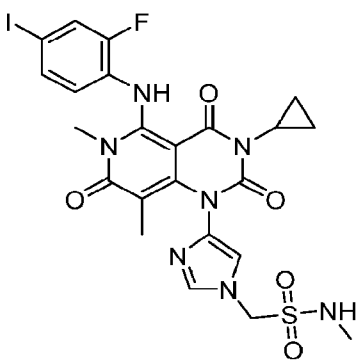
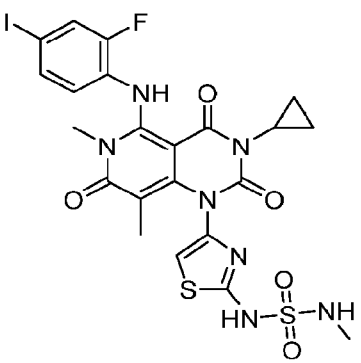
or a pharmaceutically acceptable salt thereof, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

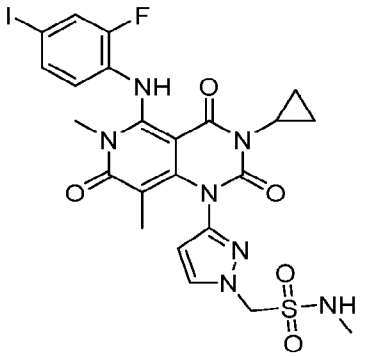
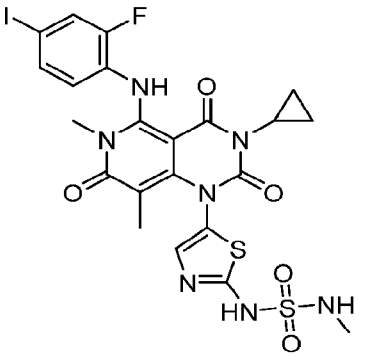
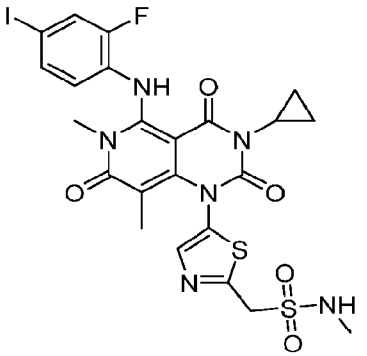
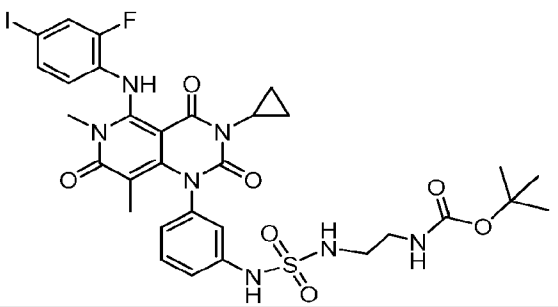
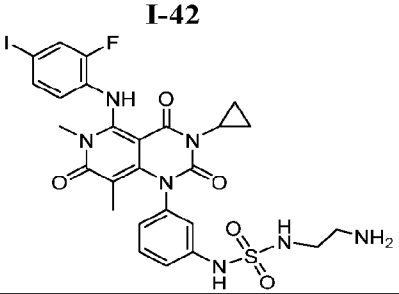
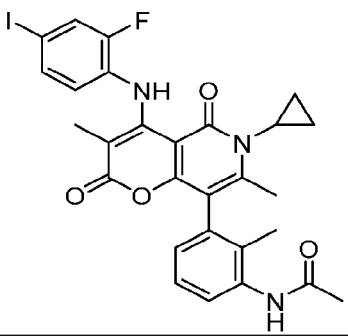
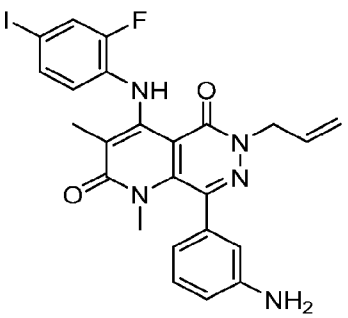
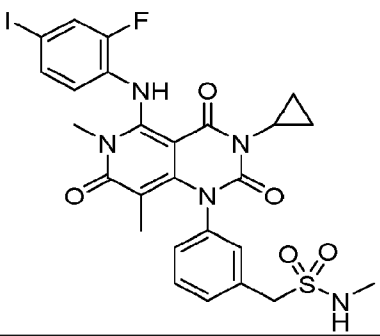
Table 1: Exemplary Compounds.

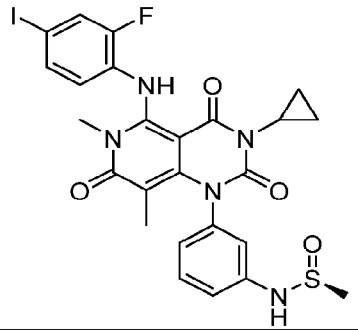
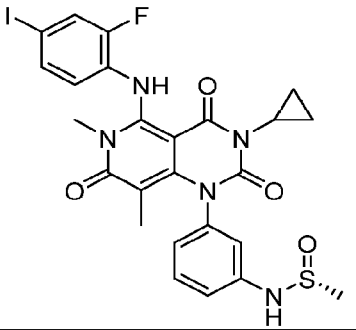
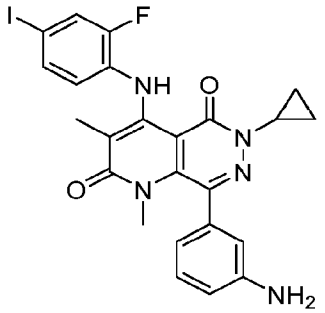
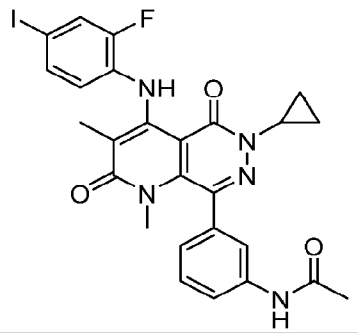
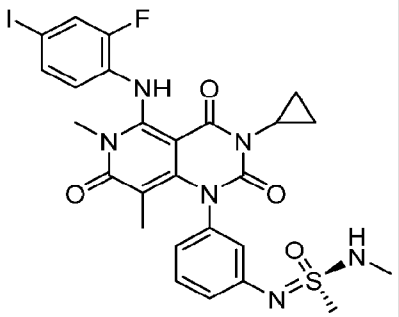
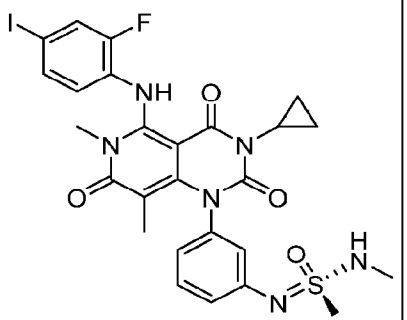
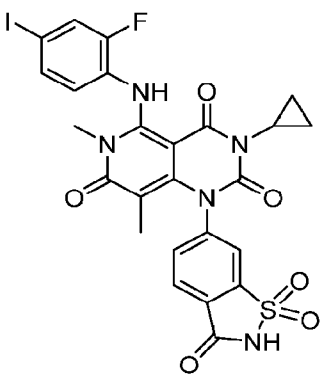
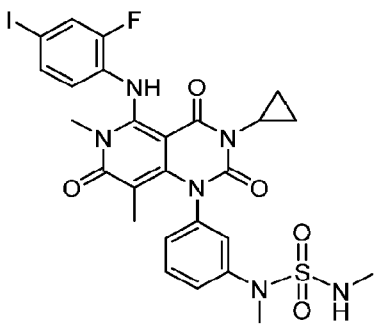
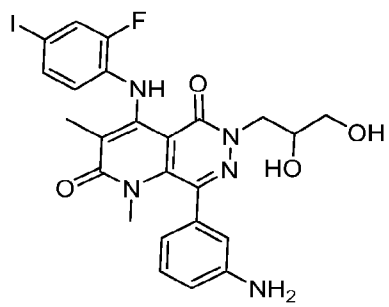
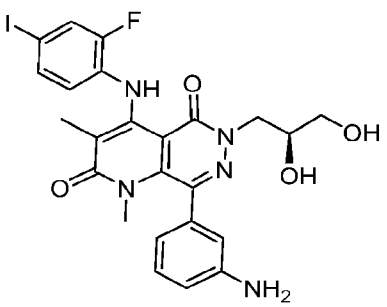
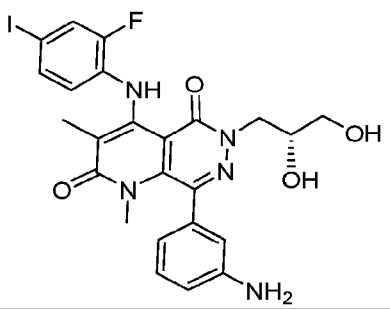
I-1 	**I-2** 	**I-3** 
I-4 	**I-5** 	**I-6** 
I-7 	**I-8** 	**I-9** 
I-10	**I-11**	**I-12**

		
I-13 	**I-14** 	**I-15** 
I-16 	**I-17** 	**I-18** 
I-19 	**I-20** 	**I-21**

		
I-22 		**I-24** 
I-25 	**I-26** 	**I-27** 
I-28 	**I-29**	

		
I-31 		**I-33** 
I-34 	**I-35** 	**I-36** 
I-37	**I-38**	**I-39**

		
	I-41 	
I-42 		
I-44 	**I-45** 	**I-46** 
I-47	**I-48**	**I-49**

		
I-50	**I-51**	**I-52**
		
	I-54	**I-55**
		
I-56	**I-57**	**I-58**
		
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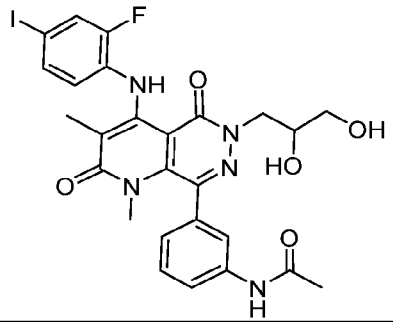
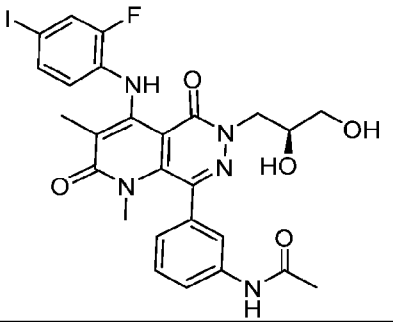
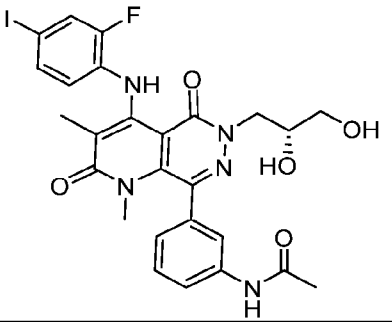
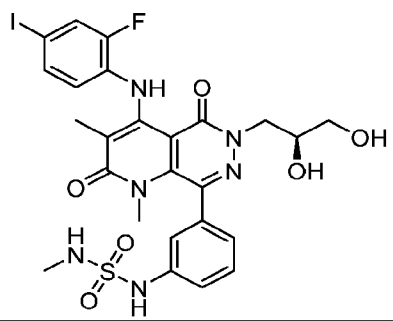
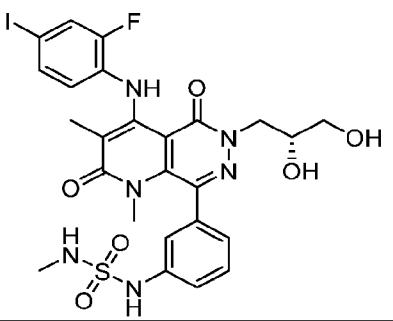
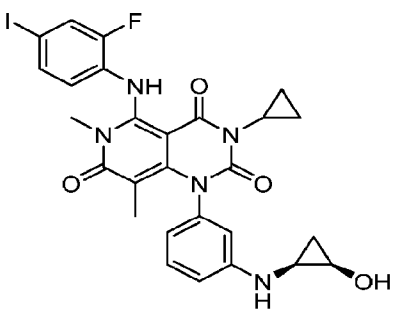
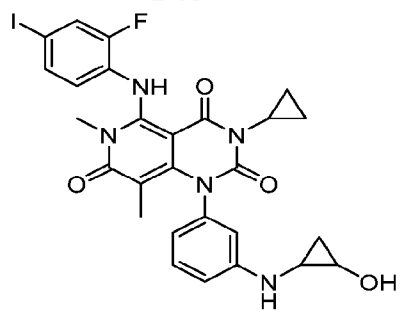
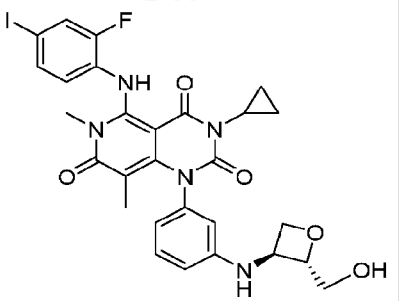
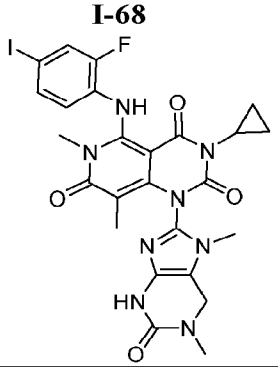
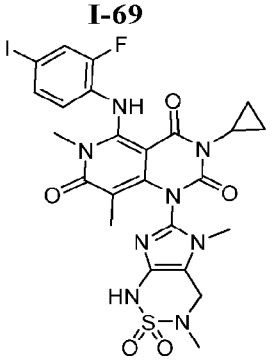
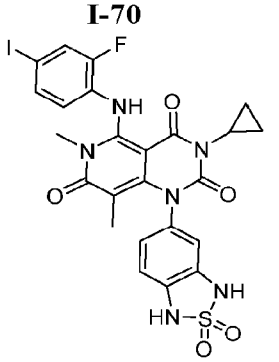
		
I-62 	**I-63** 	**I-64** 
I-65 	**I-66** 	
I-68 	**I-69** 	**I-70** 
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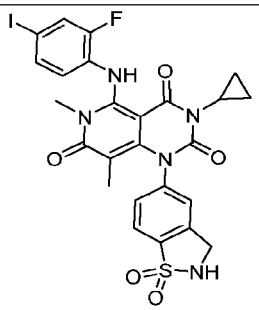
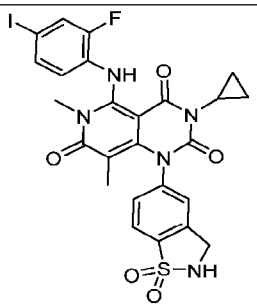
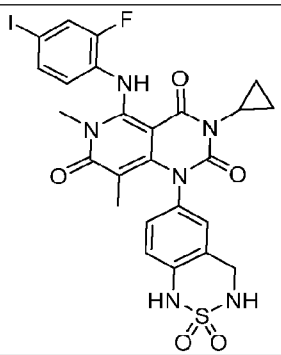
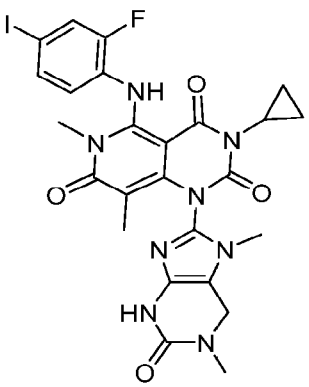
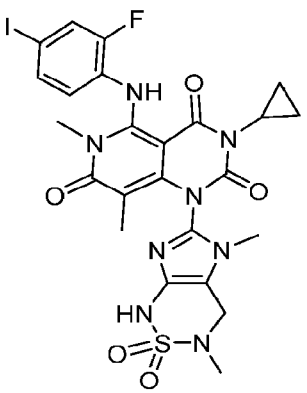
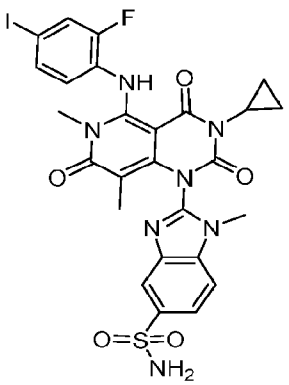
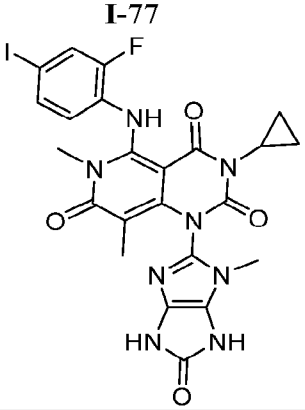
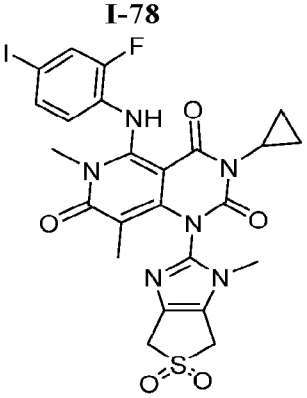
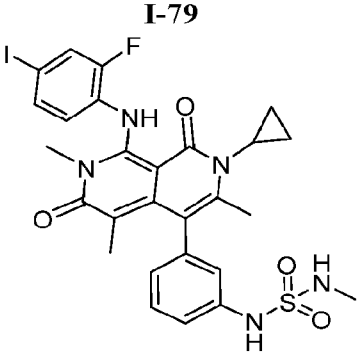
		
I-74 	**I-75** 	**I-76** 
I-77 	**I-78** 	**I-79** 
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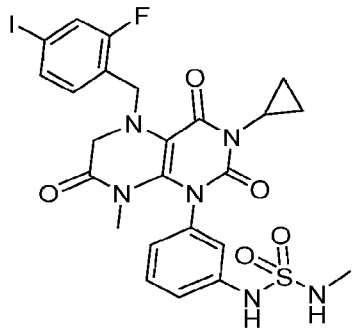
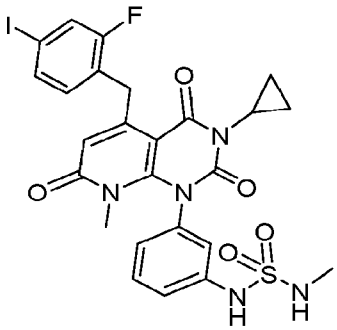
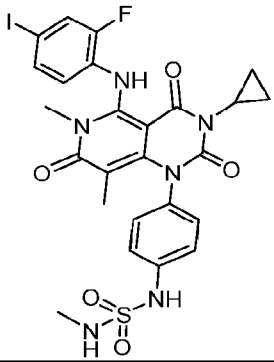
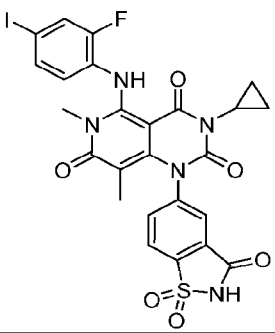
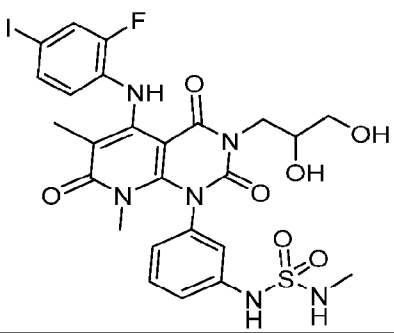
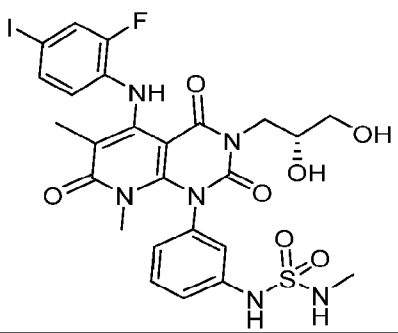
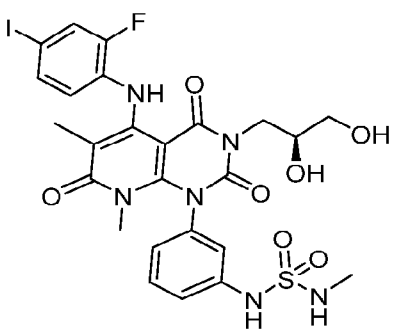
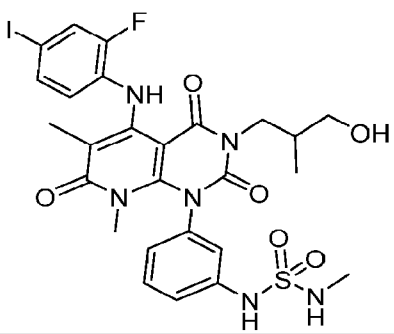
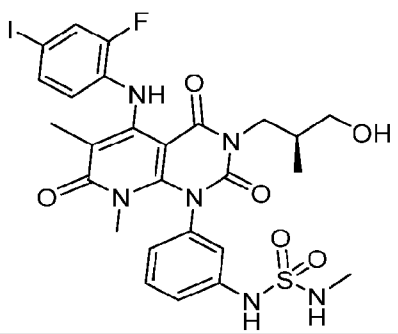
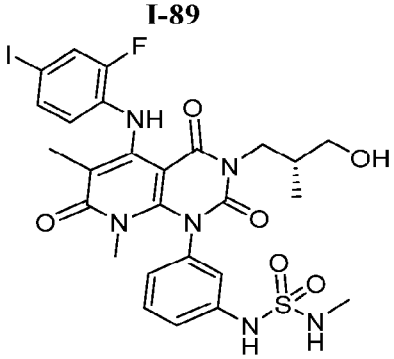
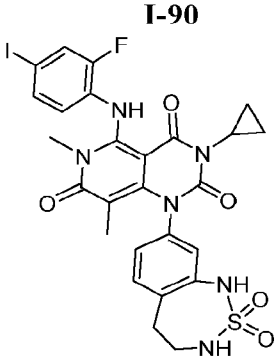
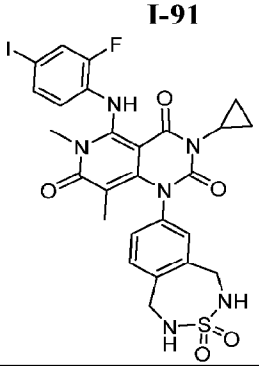
		
I-83 	**I-84** 	**I-85** 
I-86 	**I-87** 	**I-88** 
I-89 	**I-90** 	**I-91** 
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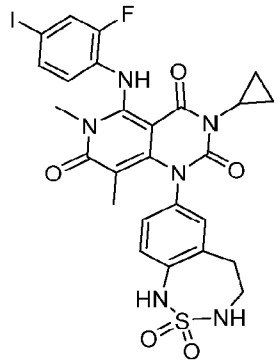	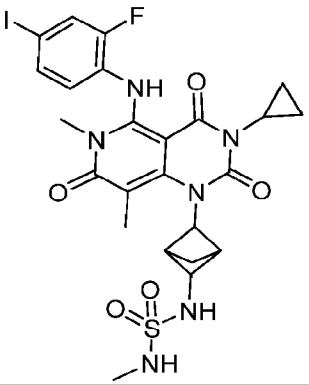	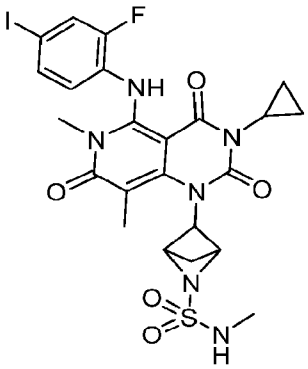
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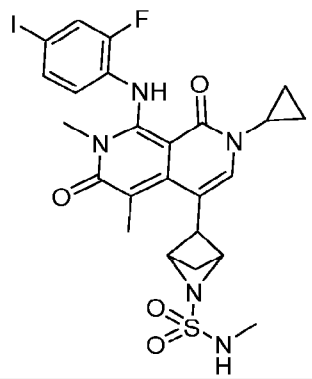	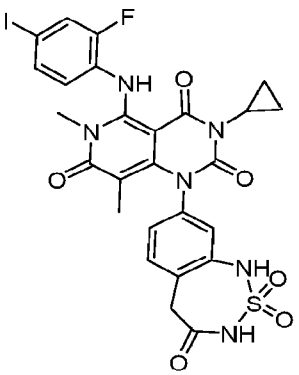	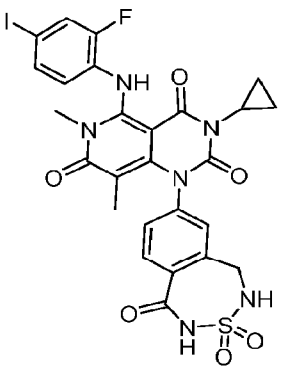
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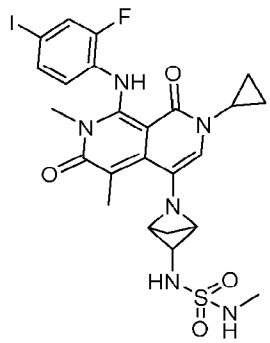	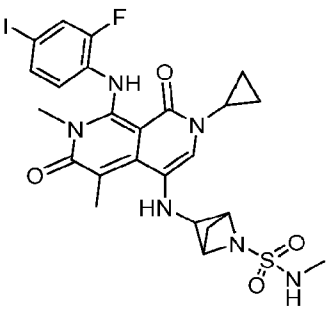	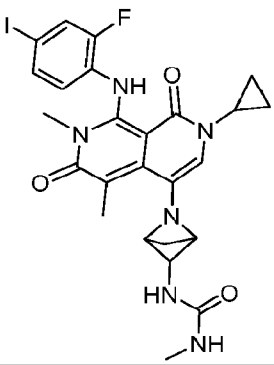
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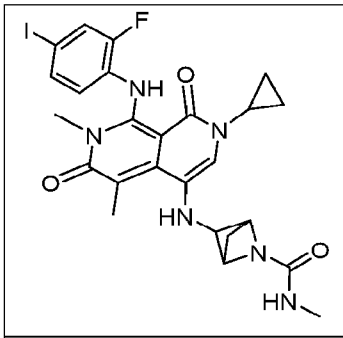	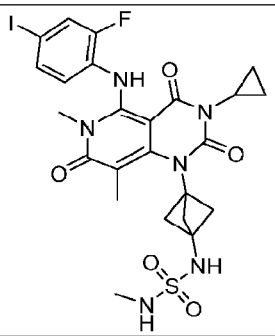	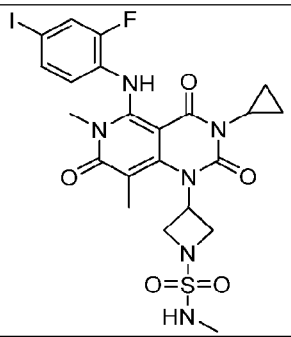
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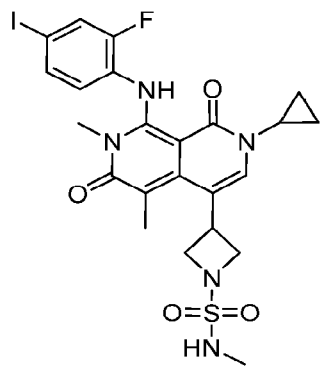	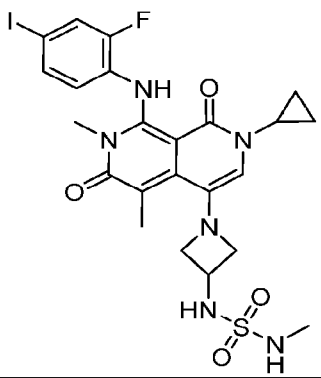	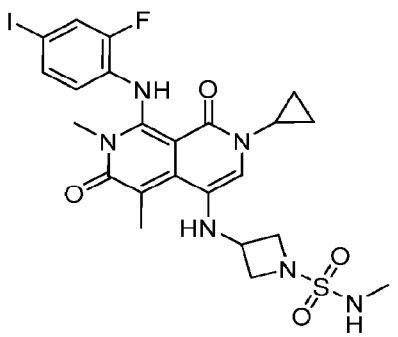
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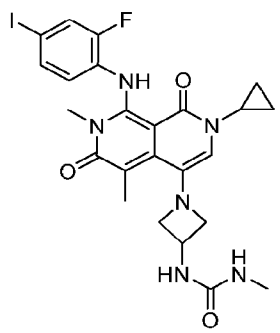	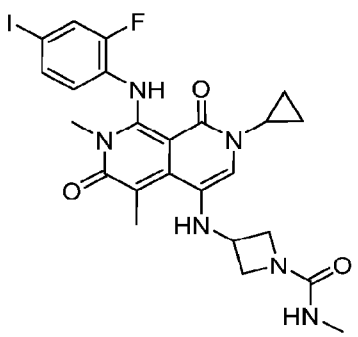	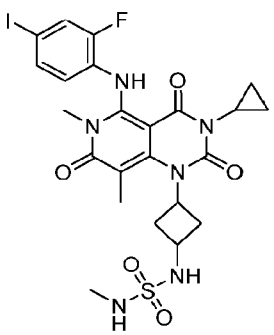
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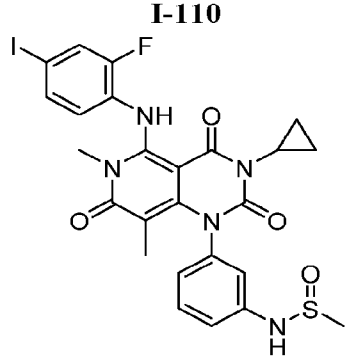	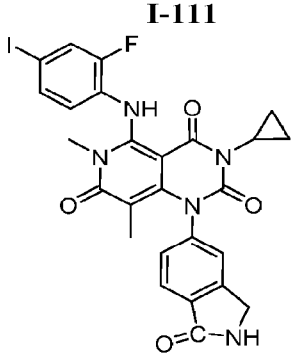	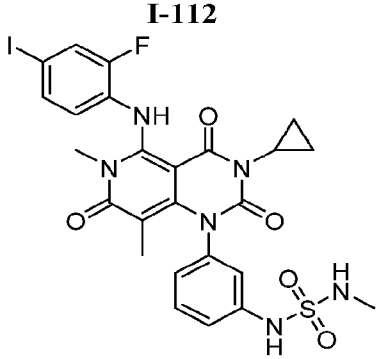
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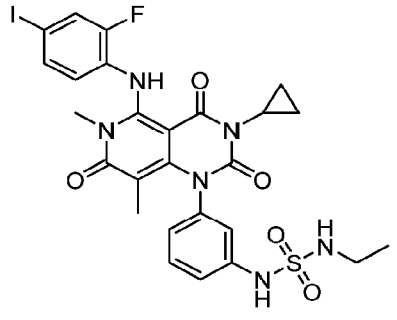	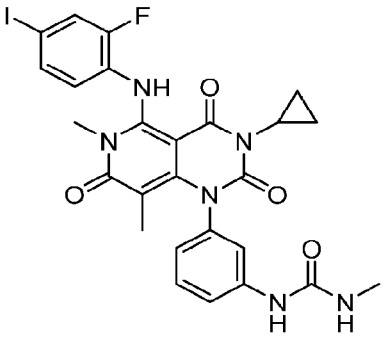	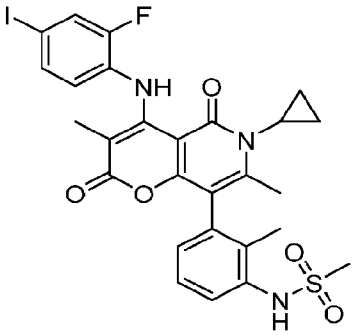
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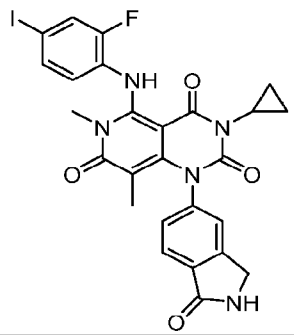	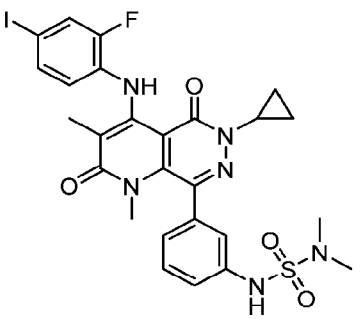	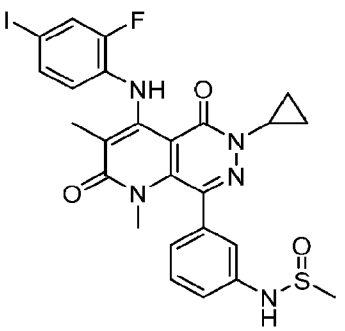
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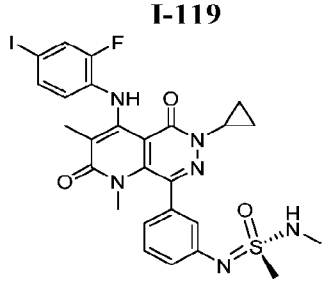	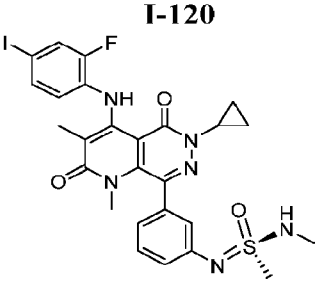	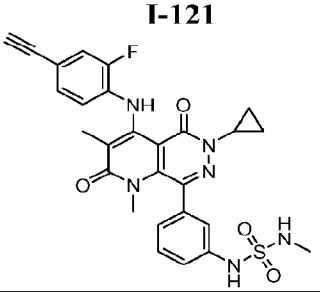
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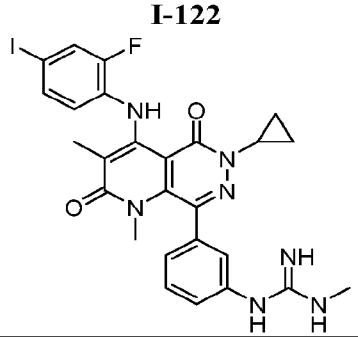	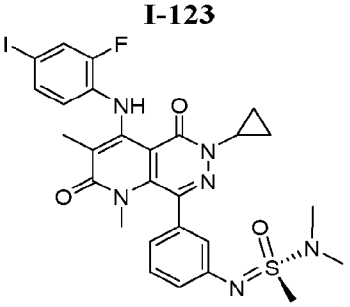	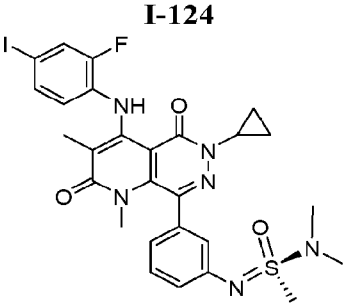
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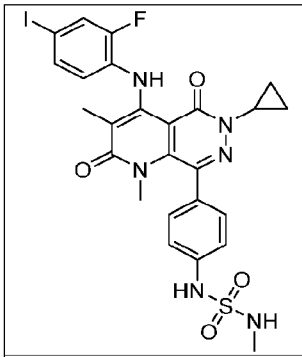
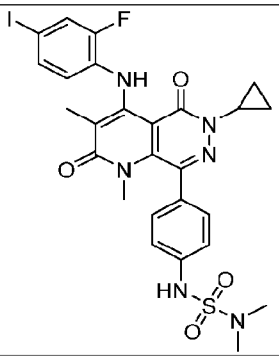
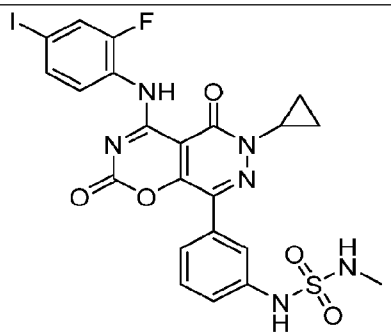
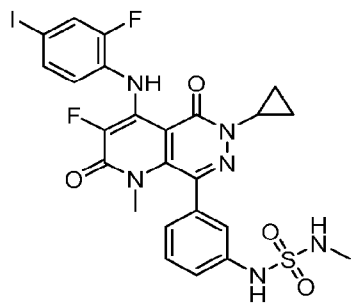
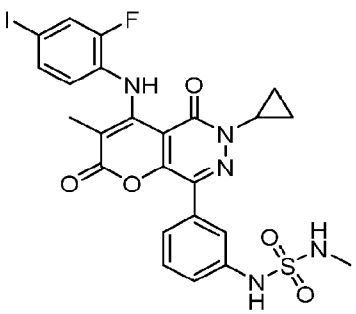
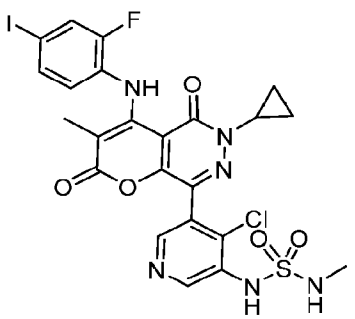
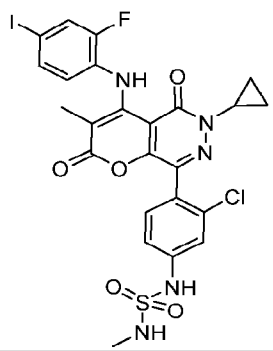
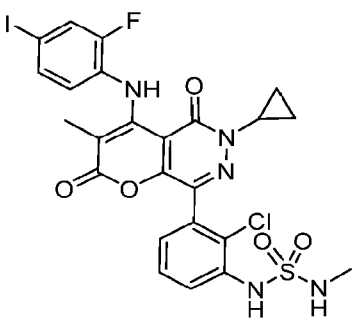
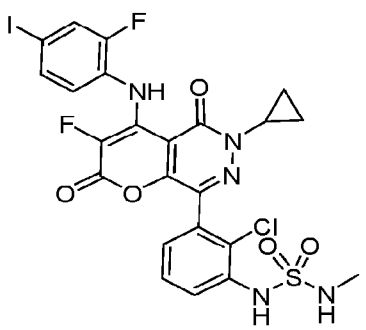
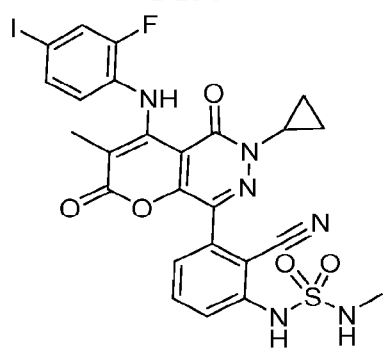
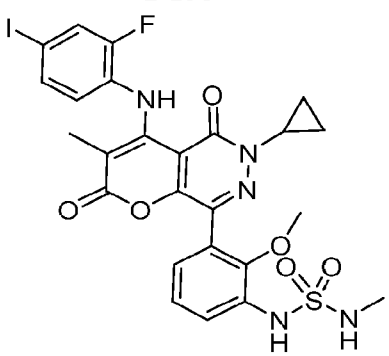
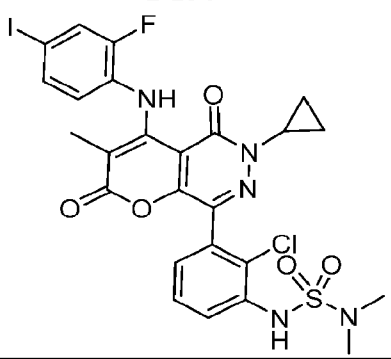
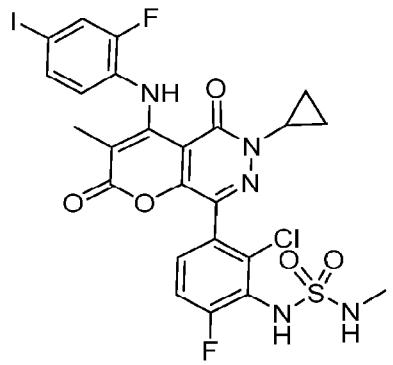
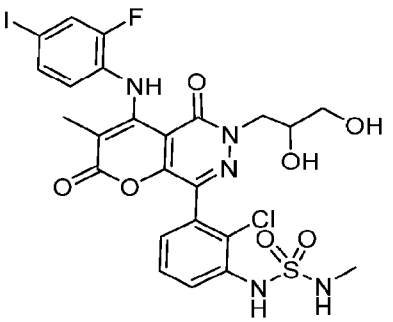
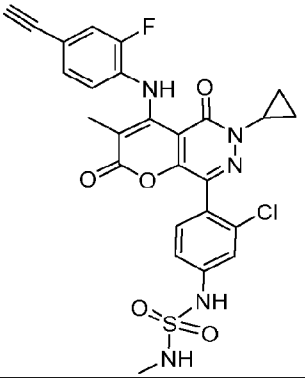
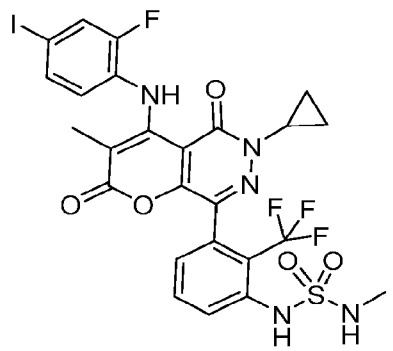
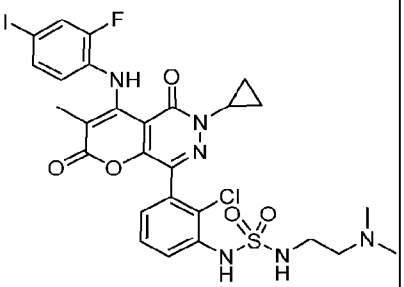
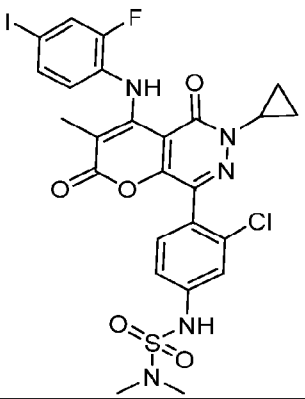
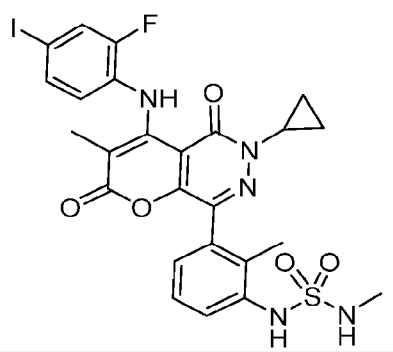
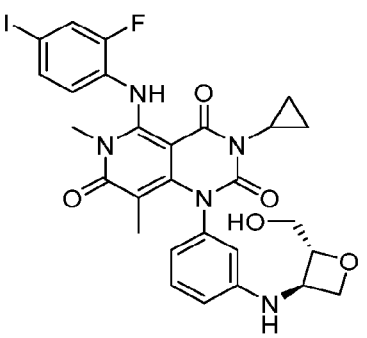
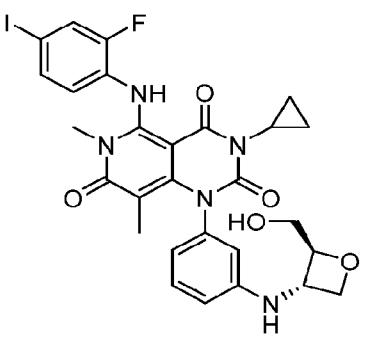
		
I-128 	**I-129** 	**I-130** 
I-131 	**I-132** 	**I-133** 
I-134 	**I-135** 	**I-136** 

I-137 	**I-138** 	**I-139** 
I-140 	**I-141** 	**I-142** 
I-143 	**I-144** 	**I-145** 
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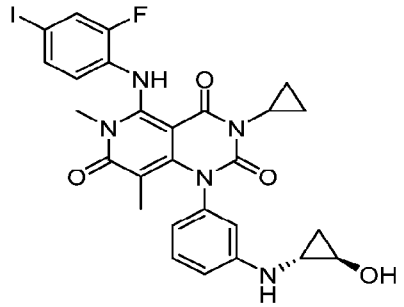
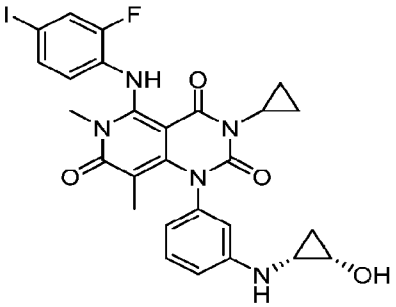
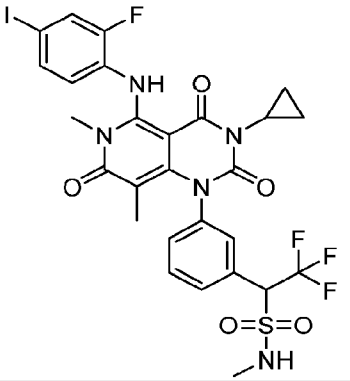
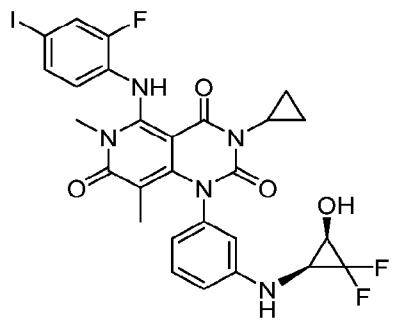
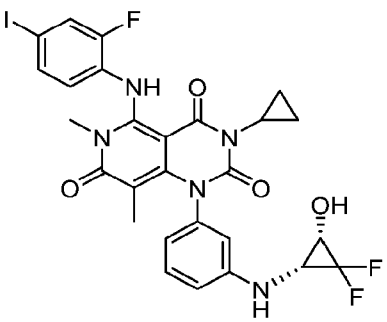
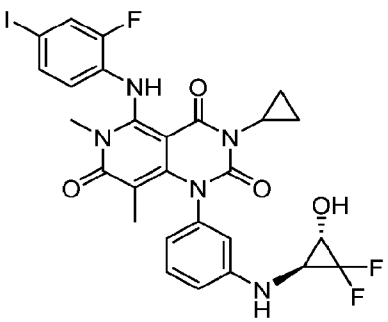
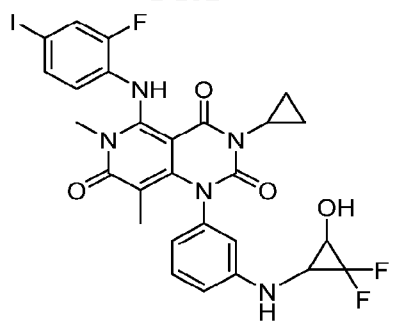
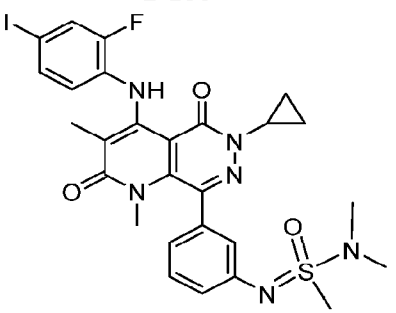
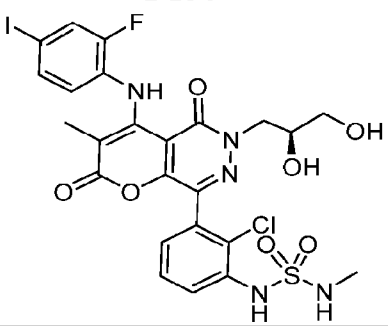
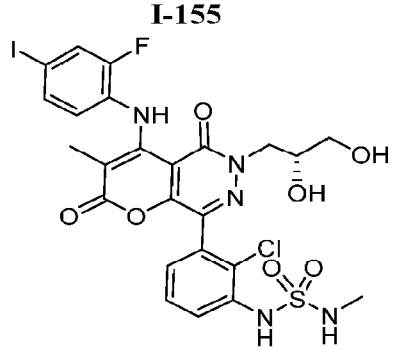
		
I-149 	**I-150** 	**I-151** 
I-152 	**I-153** 	**I-154** 
I-155 		

[00135] In some embodiments, the present invention provides a compound set forth in **Table 1** above, or a pharmaceutically acceptable salt thereof.

[00136] In some embodiments, the present invention provides a compound selected from the starting materials, intermediates, and products as described in the Examples herein, or a salt thereof.

4. General Methods of Providing the Present Compounds:

[00137] 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.

[00138] 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.

[00139] 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.

[00140] 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, and Philip Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994, the entireties 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-benzylbenzoate, 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.

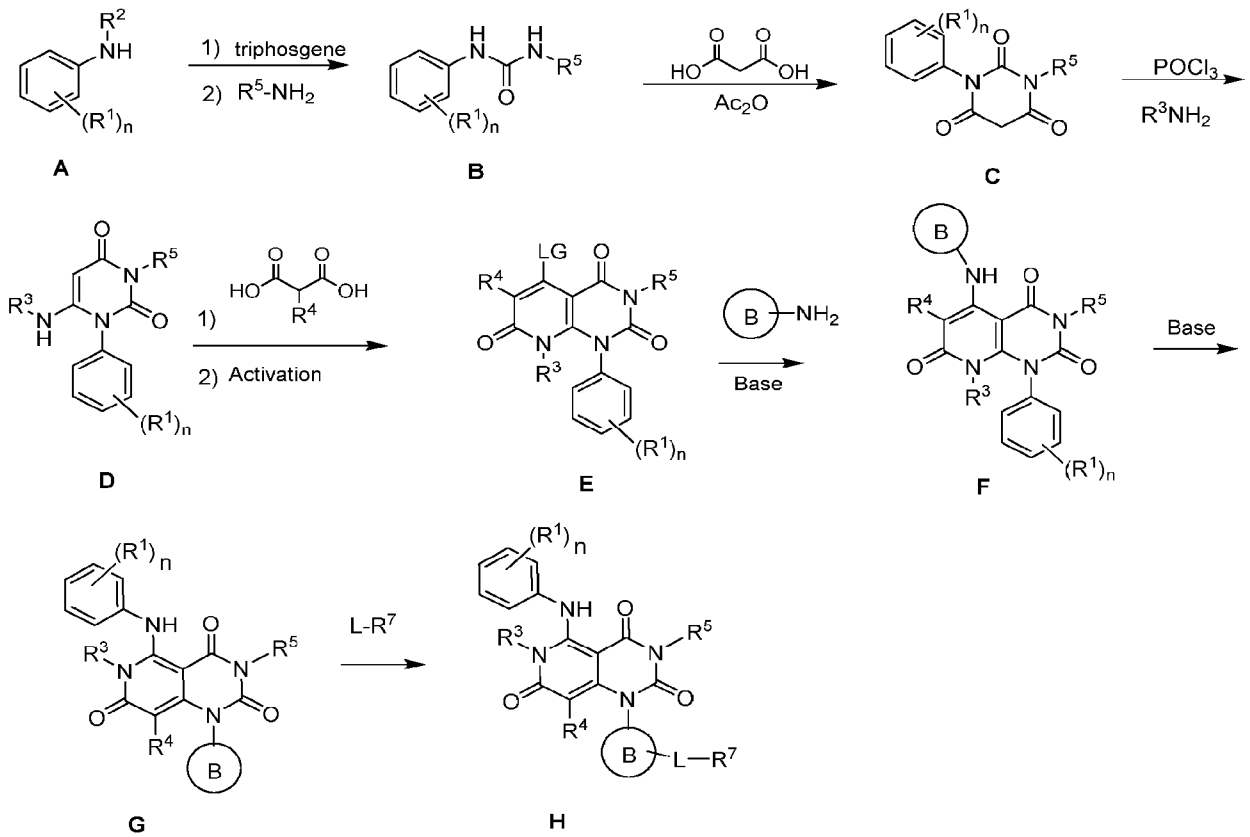
[00141] Amino protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, and Philip Kocienski, in "Protecting Groups", Georg Thieme Verlag Stuttgart, New York, 1994, the entireties 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.

[00142] 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

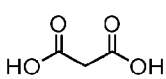
interconversions may require one or more of the aforementioned techniques, and certain methods for synthesizing compounds of the invention are described below.

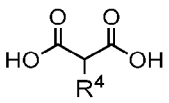
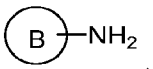
[00143] In one aspect, certain compounds of the present invention of Formula **I**, or salts thereof, are generally prepared according to **Scheme 1** set forth below:

Scheme 1.



[00144] In **Scheme 1** above, LG is a leaving group, and each of the variables, for example, R^1, R^2, R^3, R^4, R^5, R^7, L, n, and Ring B, is as defined above and described in embodiments herein, both singly and in combination.

[00145] As shown generally in **Scheme 1**, the starting material compound **A** is converted to compound **B**, for example by reacting with triphosgene and R^5-NH_2. Compound **B** is then converted to compound **C**, for example by a condensation with  and acetic anhydride to form a ring. Compound **C** is reduced to Compound **D**, for example by reacting with $POCl_3$ and

R^3NH_2. Compound **D** can be converted to Compound **E**, for example, by a reaction with  , followed by activating the resulting alcohol to form a leaving group, for example by reacting the resulting alcohol with TsCl and a base. Compound **E** is then converted to Compound **F**, for example, by a coupling reaction with  . Compound **F** can undergo a rearrangement to provide compound **G**, for example, in a basic condition. Compound **G** is then converted to Compound **H**, for example, by reacting with L-R^7.

[00146] In some embodiment, the present invention provides a synthesis method as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **B** from Compound **A**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **C** from Compound **B**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **D** from Compound **C**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing Compound **E** from Compound **D**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **F** from Compound **E**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **G** from Compound **F**, as depicted in **Scheme 1**, above. In some embodiment, the present invention provides a method of preparing compound **H** from Compound **G**, as depicted in **Scheme 1**, above.

[00147] In some embodiment, the present invention provides a compound selected from Compound **A**, Compound **B**, Compound **C**, Compound **D**, Compound **E**, Compound **F**, Compound **G**, and Compound **H**, wherein each variable is as defined above and described in embodiments herein, both singly and in combination.

5. Uses, Formulation and Administration:

Pharmaceutically acceptable compositions

[00148] According to another embodiment, the invention provides a pharmaceutical 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 MEK, or a variant or 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 MEK, or a variant or 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.

[00149] As used herein, the terms "subject" and "patient" are used interchangeably and refer to organisms to be treated by the methods of the present invention. Such organisms preferably include, but are not limited to, mammals (*e.g.*, murines, simians, equines, bovines, porcines, canines, felines, and the like), and, most preferably, humans.

[00150] 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.

[00151] 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 active metabolite or residue thereof.

[00152] As used herein, the term "active metabolite or residue thereof" means that a metabolite or residue thereof also inhibits MEK, or a variant or mutant thereof.

[00153] Compositions of the present invention can 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 can be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation can 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 can 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.

[00154] For this purpose, any bland fixed oil can 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 can 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.

[00155] Pharmaceutically acceptable compositions of this invention can 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 can also be added.

[00156] Alternatively, pharmaceutically acceptable compositions of this invention can 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.

[00157] Pharmaceutically acceptable compositions of this invention can 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.

[00158] 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 can also be used.

[00159] For topical applications, provided pharmaceutically acceptable compositions can 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.

[00160] 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 can be formulated in an ointment such as petrolatum.

[00161] Pharmaceutically acceptable compositions of this invention can 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.

[00162] 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.

[00163] The amount of compounds of the present invention that can 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.

[00164] It should also be understood that a specific dosage and treatment regimen for any particular patient depends 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 also depends upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00165] In some embodiments, the present invention provides a method of using a compound as described herein for treating a disease or disorder associated with MEK. In some embodiments, a disease or disorder associated with MEK is a proliferative disorder. In some embodiments, a disease or disorder associated with MEK is a cancer. In some embodiments, a disease or disorder associated with MEK is a cancer as described herein.

[00166] In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, of a disease or disorder characterized by or associated with increased MEK expression and/or increased MEK activity, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present

invention, or pharmaceutically acceptable composition thereof. In some aspects and embodiments, provided herein are methods of treating, reducing the severity of, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof of a disease or disorder in which inhibition or antagonizing of MEK activity is beneficial, comprising the step of administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00167] In some embodiments, a compound as described herein is an "ATP non-competitive MEK inhibitor" that stabilizes or "glues" the complex formed between MEK and KSR, and/or BRAF/CRAF. In some embodiments, a compound as described herein allosterically binds an "inhibitor pocket" formed at an interaction interface between human MEK (MEK1 or MEK2) and human Kinase Suppressor of Ras (KSR1 or KSR2 or the KSR homolog BRAF or CRAF) adjacent to ATP in a physiological complex between MEK and KSR (or BRAF or CRAF), forming an inhibitor-inhibitor pocket complex. In some embodiments, a compound as described herein is an ATP non-competitive kinase inhibitor. In some embodiments, a compound as described herein has a structure such that when bound to the inhibitor-inhibitor pocket complex, the complex comprises the structural elements: (a) at least one moiety of the inhibitor engaging A825 of hKSR1, or P878 of hKSR2, or R662 of BRAF, or R554 of CRAF (b) at least one moiety engaging R234 of hMEK1 or R238 of hMEK2, wherein R234 is within about 5 Å to about 8 Å from any atoms of hKSR1 or hKSR2 or BRAF or CRAF. The structures of complexes described herein, including for example, the MEK and KSR (or BRAF or CRAF) complex, and the inhibitor-inhibitor pocket complex, can be found in WO 2021142345, the content of which is incorporated herein by reference in its entirety. Reference Uniprot sequences for human MEK1, human MEK2, human KSR1, human KSR2, human BRAF, and human CRAF are Uniprot ID Q02750, Uniprot ID P36507, Uniprot ID Q8IVT5, Uniprot ID Q6VAB6, Uniprot ID P15056, and Uniprot ID P04049, respectively.

[00168] In some embodiments, a compound as described herein does not engage one or more of I216 in hMEK1 or I220 of hMEK2 and A825 in KSR1 or P878 in KSR2. In some embodiments, a compound as described herein comprises a structural element according to (a) as described in the above paragraph, which is an H-bond acceptor, *inter alia*, an oxygen or nitrogen atom, or a fluorine atom attached to an aromatic ring, or an H bond donor. In some

embodiments, a compound as described herein comprises a structural element according to (a) as described in the above paragraph, which is a moiety of a linker engaging the backbone of A825 of hKSR1, or P878 of hKSR2, or R662 of hBRAF, or R554 of CRAF, directly or through a water-mediated contact.

[00169] In some embodiments, a compound as described herein comprising one or more of the following:

(c) at least one moiety engaging M230 of hMEK1 or M234 of hMEK2, wherein M230 or M234 are within about 5 Å to about 8 Å from terminal atom (CB) of A825 of KSR1 or (CG) of P878 of hKSR2 or (CG) N661 of hBRAF or N553 of CRAF;

(d) at least one moiety is a H-bond acceptor or donor engaging the backbone carbonyl of N823 of hKSR1, or T876 of hKSR2 through a water-mediated contact or backbone amino group of R662 of hBRAF or R554 of hCRAF directly;

(e) at least one moiety engaging Q824 of hKSR1 or Q877 of hKSR2 or Q664 of hBRAF or Q556 of hCRAF;

(f) at least one moiety engaging a side chain atom of A826 of hKSR1 or A879 of hKSR2 or R662 of BRAF or R554 of CRAF;

(g) at least one moiety is a heteroaryl group engaging M143 of hMEK1 or M147 of hMEK2;

(h) at least one moiety is a heteroaryl group engaging F209 of hMEK1 or F213 of hMEK2;

(i) at least one moiety (*inter alia*, a H-bond acceptor) is engaging the backbone amino group of S212 of hMEK1 or S216 of hMEK2;

(j) at least one moiety engaging L215 of of hMEK1 or L219 of hMEK2;

(k) at least one moiety engaging I216 of hMEK1 or I220 of hMEK2; and

(l) at least one moiety engaging M219 of hMEK1 or M223 of hMEK2 where hMEK1 residues 215-219 adopt a helical conformation.

[00170] In some embodiments, a moiety corresponding to (c) as described above is selected from substituted or unsubstituted alkyl or cycloalkyl.

[00171] In some embodiments, a backbone CO residue of a compound as described herein engages with T876 of hKSR2 or N823 of hKSR1.

[00172] In some embodiments, a compound as described herein engages with a binding pocket, which is lined by the hMEK1 residues R234 and M230, or hMEK2 residues R238 and M234, and P877 of KSR2 or A825 of KSR1 or R662 of BRAF or R554 of CRAF.

[00173] In some embodiments, a compound as described herein engages a binding pocket via multiple hydrogen bond contacts, including through a water mediated H-bond to Arg189 and Arg234 in hMEK1 or ARG193 and A238 of hMEK2, as well as a direct H-bond to the backbone of the pre-helix αG loop -NH- of Arg662 of BRAF or ARG 554 of CRAF.

[00174] In some embodiments, a compound as described herein engage A825 of hKSR1 or P878 of hKSR2 or R662 of BRAF or R554 of CRAF. In some embodiments, a compound as described herein has a distance of less than or equal to about 5 Å to about 8 Å from at least one moiety selected from A825 of hKSR1, P878 of hKSR2, and R662 of BRAF and R554 of CRAF.

[00175] Accordingly, in some aspects and 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, comprising administering to a patient in need thereof, a MEK inhibitor compound as described herein, or a pharmaceutical salt or composition thereof. In some embodiments, the cellular proliferative disorder is cancer. In some embodiments, the cancer is characterized by increased MEK expression and/or increased MEK activity, *i.e.*, "increased activated MEK."

[00176] As used herein, the terms "increased," "elevated," or "enhanced," are used interchangeably and encompass any measurable increase in a biological function and/or biological activity and/or a concentration. For example, an increase can be by at least about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to a control or baseline amount of a function, or activity, or concentration.

[00177] As used herein, the terms "increased expression" and/or "increased activity" of a substance, such as MEK, in a sample or cancer or patient, refers to an increase in the amount of the substance, such as MEK, of about 5%, about 10%, about 15%, about 20%, about 25%, about

30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, about 100%, about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 6-fold, about 7-fold, about 8-fold, about 9-fold, about 10-fold, about 20-fold, about 25-fold, about 50-fold, about 100-fold, or higher, relative to the amount of the substance, such as MEK, in a control sample or control samples, such as an individual or group of individuals who are not suffering from the disease or disorder (*e.g.*, cancer) or an internal control, as determined by techniques known in the art. A subject can also be determined to have an "increased expression" or "increased activity" of MEK if the expression and/or activity of MEK is increased by one standard deviation, two standard deviations, three standard deviations, four standard deviations, five standard deviations, or more, relative to the mean (average) or median amount of MEK in a control group of samples or a baseline group of samples or a retrospective analysis of patient samples. As practiced in the art, such control or baseline expression levels can be previously determined, or measured prior to the measurement in the sample or cancer or subject, or can be obtained from a database of such control samples.

Cancer

[00178] In some embodiments, the present invention provides a method for treating or preventing or reducing the risk of a cancer in patient comprising administering to the patient a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition thereof.

[00179] A "cancer," as used herein, refers a broad group of various diseases characterized by the uncontrolled growth of abnormal cells in the body. Unregulated cell division and growth divide and grow results in the formation of malignant tumors that invade neighboring tissues and can also metastasize to distant parts of the body through the lymphatic system or bloodstream.

[00180] The cancer or proliferative disorder or tumor to be treated using the compounds and methods and uses described herein include, but are not limited to, a hematological cancer, a lymphoma, a myeloma, a leukemia, a neurological cancer, skin cancer, breast cancer, a prostate cancer, a colorectal cancer, a lung cancer, a head and neck cancer, a gastrointestinal cancer, a liver cancer, a pancreatic cancer, a genitourinary cancer, a bone cancer, renal cancer, and

a vascular cancer. In some embodiments, the lung cancer is selected from the group consisting of non-small cell lung cancer, small cell lung cancer, and lung carcinoid tumor.

[00181] In some embodiments, the cancer is a K-Ras mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12 mutant cancer. In some embodiments, the K-Ras mutant G12 cancer is a K-Ras G12D mutant cancer, K-Ras G12V mutant cancer, K-Ras G12C mutant cancer, K-Ras G12R mutant cancer, or K-Ras G12S mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12D mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12V mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12C mutant cancer. In some embodiments, the cancer is a mutant B-Raf cancer, such as a B-Raf V600E mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G13 mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G13D mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12R mutant cancer. In some embodiments, the K-Ras mutant cancer is a K-Ras G12S mutant cancer.

[00182] In some embodiments of the methods and uses described herein, the cancer is lung cancer, thyroid cancer, ovarian cancer, colorectal cancer, prostate cancer, cancer of the pancreas, cancer of the esophagus, liver cancer, breast cancer, skin cancer, or mesothelioma. In some embodiments, the cancer is mesothelioma, such as malignant mesothelioma. In some embodiments, a cancer includes, 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, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, and retinoblastoma).

[00183] In some embodiments, a cancer is glioma, astrocytoma, glioblastoma multiforme (GBM, also known as glioblastoma), medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, schwannoma, neurofibrosarcoma, meningioma, melanoma, neuroblastoma, or retinoblastoma.

[00184] In some embodiments, a cancer is acoustic neuroma, astrocytoma (*e.g.* Grade I – Pilocytic Astrocytoma, Grade II – Low-grade Astrocytoma, Grade III – Anaplastic Astrocytoma, or Grade IV – Glioblastoma (GBM)), chordoma, CNS lymphoma, craniopharyngioma, brain stem glioma, ependymoma, mixed glioma, optic nerve glioma, subependymoma, medulloblastoma, meningioma, metastatic brain tumor, oligodendroglioma, pituitary tumors, primitive neuroectodermal (PNET) tumor, or schwannoma. In some embodiments, the cancer is a type found more commonly in children than adults, such as brain stem glioma, craniopharyngioma, ependymoma, juvenile pilocytic astrocytoma (JPA), medulloblastoma, optic nerve glioma, pineal tumor, primitive neuroectodermal tumors (PNET), or rhabdoid tumor. In some embodiments, the patient is an adult human. In some embodiments, the patient is a child or pediatric patient.

[00185] Cancer 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-Hodgkins'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.

[00186] In some embodiments, a cancer is a solid tumor, such as a sarcoma, carcinoma, or lymphoma. Solid tumors generally comprise an abnormal mass of tissue that typically does not include cysts or liquid areas. In some embodiments, the cancer is selected from renal cell carcinoma, or kidney cancer; hepatocellular carcinoma (HCC) or hepatoblastoma, or liver cancer; melanoma; breast cancer; colorectal carcinoma, or colorectal cancer; colon cancer; rectal cancer; anal cancer; lung cancer, such as non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC); ovarian cancer, ovarian epithelial cancer, ovarian carcinoma, or fallopian tube cancer; papillary serous cystadenocarcinoma or uterine papillary serous carcinoma (UPSC); prostate cancer; testicular cancer; gallbladder cancer; hepatocholangiocarcinoma; soft tissue and bone synovial sarcoma; rhabdomyosarcoma; osteosarcoma; chondrosarcoma; Ewing sarcoma; anaplastic thyroid cancer; adrenocortical carcinoma; pancreatic cancer; pancreatic ductal carcinoma or pancreatic adenocarcinoma; gastrointestinal/stomach (GIST) cancer; lymphoma; squamous cell carcinoma of the head and neck (SCCHN); salivary gland cancer; glioma, or brain cancer; neurofibromatosis-1 associated malignant peripheral nerve sheath tumors (MPNST); Waldenstrom's macroglobulinemia; or medulloblastoma.

[00187] In some embodiments, a cancer is hepatocellular carcinoma (HCC). In some embodiments, the cancer is hepatoblastoma. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is rectal cancer. In some embodiments, the cancer is ovarian cancer, or ovarian carcinoma. In some embodiments, the cancer is ovarian epithelial cancer. In some embodiments, the cancer is fallopian tube cancer. In some embodiments, the cancer is papillary serous cystadenocarcinoma. In some embodiments, the cancer is uterine papillary serous carcinoma (UPSC). In some embodiments, the cancer is hepatocholangiocarcinoma. In some embodiments, the cancer is soft tissue and bone synovial sarcoma. In some embodiments, the cancer is rhabdomyosarcoma. In some embodiments, the cancer is osteosarcoma. In some embodiments, the cancer is anaplastic thyroid cancer. In some embodiments, the cancer is adrenocortical carcinoma. In some embodiments, the cancer is pancreatic cancer, or pancreatic

ductal carcinoma. In some embodiments, the cancer is pancreatic adenocarcinoma. In some embodiments, the cancer is glioma. In some embodiments, the cancer is malignant peripheral nerve sheath tumors (MPNST). In some embodiments, the cancer is neurofibromatosis-1 associated MPNST. In some embodiments, the cancer is Waldenstrom's macroglobulinemia. In some embodiments, the cancer is medulloblastoma.

[00188] In some embodiments, a cancer is a viral-associated cancer, including human immunodeficiency virus (HIV) associated solid tumors, human papilloma virus (HPV)-16 positive incurable solid tumors, and adult T-cell leukemia, which is caused by human T-cell leukemia virus type I (HTLV-I) and is a highly aggressive form of CD4+ T-cell leukemia characterized by clonal integration of HTLV-I in leukemic cells (See https://clinicaltrials.gov/ct2/show/study/NCT02631746); as well as virus-associated tumors in gastric cancer, nasopharyngeal carcinoma, cervical cancer, vaginal cancer, vulvar cancer, squamous cell carcinoma of the head and neck, and Merkel cell carcinoma. (See https://clinicaltrials.gov/ct2/show/study/NCT02488759; see also https://clinicaltrials.gov/ct2/show/study/NCT0240886; https://clinicaltrials.gov/ct2/show/NCT02426892)

[00189] In some embodiments, the methods or uses described herein inhibit or reduce or arrest or ameliorate the growth or spread of a cancer or tumor. In some embodiments, the tumor is treated by arresting, reducing, or inhibiting further growth of the cancer or tumor. In some embodiments, the methods or uses described herein increase or potentiate or activate one or more immune responses to inhibit or reduce or arrest or ameliorate the growth or spread of a cancer or tumor. In some embodiments, the cancer or tumor is treated by reducing the size (*e.g.*, volume or mass) of the cancer or tumor by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% relative to the size of the cancer or tumor prior to treatment. In some embodiments, cancers or tumors are treated by reducing the quantity of the cancers or tumors in the patient by at least 5%, at least 10%, at least 25%, at least 50%, at least 75%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, or at least 99% relative to the quantity of cancers or tumors prior to treatment.

[00190] In some embodiments, a patient treated using the methods or uses described herein exhibits progression-free survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least

about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about one year, at least about eighteen months, at least about two years, at least about three years, at least about four years, or at least about five years after the treatment is initiated. In some embodiments, a patient treated using the methods or uses described herein exhibits an overall survival of at least about one month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about one year, at least about 14 months, at least about 16 months, at least about 18 months, at least about 20 months, at least about 22 months, at least about two years, at least about three years, at least about four years, or at least about five years after the treatment is initiated.

[00191] In some embodiments, a patient treated using the methods or uses described herein exhibits an objective response rate (ORR) of at least about 15%, at least about 20%, at least about 25%, at least about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%.

[00192] 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 inhibiting MEK and treating or lessening the severity of a disease, for example, as those described herein. 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 disease or condition, 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.

[00193] 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), bucally, as an oral or nasal spray, or the like, depending on the severity of the disease or disorder 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.

[00194] 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.

[00195] 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.

[00196] 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.

[00197] 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 microencapsule 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.

[00198] 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.

[00199] 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.

[00200] 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.

[00201] 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.

[00202] 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.

Co-Administration with One or More Other Therapeutic Agent(s)

[00203] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents that are normally administered to treat that condition, can 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."

[00204] In some embodiments, the present invention provides a method of treating a disclosed disease or condition comprising administering to a patient in need thereof an effective amount of a compound disclosed herein or a pharmaceutically acceptable salt thereof and co-administering simultaneously or sequentially an effective amount of one or more additional therapeutic agents, such as those described herein. In some embodiments, the method includes co-administering one additional therapeutic agent. In some embodiments, the method includes co-administering two additional therapeutic agents. In some embodiments, the combination of the disclosed compound and the additional therapeutic agent or agents acts synergistically.

[00205] 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.

[00206] One or more other therapeutic agent(s) can be administered separately from a compound or composition of the invention, as part of a multiple dosage regimen. Alternatively, one or more other therapeutic agent(s) may be part of a single dosage form, mixed together with a

compound of this invention in a single composition. If administered as a multiple dosage regime, one or more other therapeutic agent(s) and a compound or composition of the invention can be administered simultaneously, sequentially or within a period of time from one another, for example within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours from one another. In some embodiments, one or more other therapeutic agent(s) and a compound or composition of the invention are administered as a multiple dosage regimen within greater than 24 hours apart.

[00207] 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 can be administered with one or more other therapeutic agent(s) 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, one or more other therapeutic agent(s), and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00208] The amount of a compound of the invention and one or more other therapeutic agent(s) (in those compositions which comprise an additional therapeutic agent as described above) that can be combined with the carrier materials to produce a single dosage form varies depending upon the host treated and the particular mode of administration. Preferably, a composition of the invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of a compound of the invention can be administered.

[00209] In those compositions which comprise one or more other therapeutic agent(s), the one or more other therapeutic agent(s) and a compound of the invention can act synergistically. Therefore, the amount of the one or more other therapeutic agent(s) in such compositions may be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 - 1,000 g/kg body weight/day of the one or more other therapeutic agent(s) can be administered.

[00210] The amount of one or more other therapeutic agent(s) present in the compositions of this invention may 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 one or more other therapeutic agent(s) in the presently disclosed compositions ranges from about

50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent. In some embodiments, one or more other therapeutic agent(s) is administered at a dosage of about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95% of the amount normally administered for that agent. As used herein, the phrase "normally administered" means the amount an FDA approved therapeutic agent is approved for dosing per the FDA label insert.

[00211] The compounds of this invention, or pharmaceutical compositions thereof, can 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.

Exemplary Other Therapeutic Agents

[00212] In some embodiments, the one or more other therapeutic agent is a TEAD inhibitor. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2020/243415, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in WO 2020/243423, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the TEAD inhibitor is selected from those described in US Patent No. 11,247,082, the contents of which are herein incorporated by reference in their entirety.

[00213] TEAD inhibitors can be produced by organic synthesis methods known to one of ordinary skill in the art. Additionally, certain TEAD inhibitors can be prepared as described in Pobbati *et al.*, "Targeting the Central Pocket in Human Transcription Factor TEAD as a Potential Cancer Therapeutic Strategy," Structure 2015, 23, 2076-2086; Gibault et al., "Targeting Transcriptional Enhanced Associate Domains (TEADs)," J. Med. Chem. 2018, 61, 5057-5072; Bum-Erdene et al., "Small-Molecule Covalent Modification of Conserved Cysteine Leads to Allosteric Inhibition of the TEADoYap Protein-Protein Interaction," Cell Chemical Biology 2019, 26, 1-12; Holden et al., "Small Molecule Dysregulation of TEAD Lipidation Induces a

Dominant-Negative Inhibition of HippoPathway Signaling," Cell Reports 2020, 31, 107809; WO 2017/053706, WO 2017/111076, WO 2018/204532, WO 2018/235926, US 20190010136, WO 2019/040380, WO 2019/113236, WO 2019/222431, WO 2019/232216, WO 2020/051099, WO 2020/081572, WO 2020/097389, WO 2020/190774, WO 2020/214734, PCT/US2020/35098, and PCT/US2020/35111, the contents of each of which are herein incorporated by reference in its entirety.

[00214] In some embodiments, the one or more other therapeutic agent is an ERK5 inhibitor. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051567, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051565, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051569, the contents of which are herein incorporated by reference in their entirety. In certain embodiments, the ERK5 inhibitor is selected from those described in WO 2022/051568, the contents of which are herein incorporated by reference in their entirety.

[00215] In some embodiments, one or more other therapeutic agent is a Poly ADP ribose polymerase (PARP) inhibitor. In some embodiments, a PARP inhibitor is selected from olaparib (LYNPARZA®, AstraZeneca); rucaparib (RUBRACA®, Clovis Oncology); niraparib (ZEJULA®, Tesaro); talazoparib (MDV3800/BMN 673/LT00673, Medivation/Pfizer/Biomarin); veliparib (ABT-888, AbbVie); and BGB-290 (BeiGene, Inc.).

[00216] In some embodiments, one or more other therapeutic agent is a histone deacetylase (HDAC) inhibitor. In some embodiments, an HDAC inhibitor is selected from vorinostat (ZOLINZA®, Merck); romidepsin (ISTODAX®, Celgene); panobinostat (FARYDAK®, Novartis); belinostat (BELEODAQ®, Spectrum Pharmaceuticals); entinostat (SNDX-275, Syndax Pharmaceuticals) (NCT00866333); and chidamide (EPIDAZA®, HBI-8000, Chipscreen Biosciences, China).

[00217] In some embodiments, one or more other therapeutic agent is a CDK inhibitor, such as a CDK4/CDK6 inhibitor. In some embodiments, a CDK 4/6 inhibitor is selected from palbociclib (IBRANCE®, Pfizer); ribociclib (KISQALI®, Novartis); abemaciclib (Ly2835219, Eli Lilly); and trilaciclib (G1T28, G1 Therapeutics).

[00218] In some embodiments, one or more other therapeutic agent is a phosphatidylinositol 3 kinase (PI3K) inhibitor. In some embodiments, a PI3K inhibitor is selected from idelalisib (ZYDELIG®, Gilead), alpelisib (BYL719, Novartis), taselisib (GDC-0032, Genentech/Roche); pictilisib (GDC-0941, Genentech/Roche); copanlisib (BAY806946, Bayer); duvelisib (formerly IPI-145, Infinity Pharmaceuticals); PQR309 (Piqur Therapeutics, Switzerland); and TGR1202 (formerly RP5230, TG Therapeutics).

[00219] In some embodiments, one or more other therapeutic agent is a platinum-based therapeutic, also referred to as platins. Platins cause cross-linking of DNA, such that they inhibit DNA repair and/or DNA synthesis, mostly in rapidly reproducing cells, such as cancer cells.

[00220] In some embodiments, a platinum-based therapeutic is selected from cisplatin (PLATINOL®, Bristol-Myers Squibb); carboplatin (PARAPLATIN®, Bristol-Myers Squibb; also, Teva; Pfizer); oxaliplatin (ELOXITIN® Sanofi-Aventis); nedaplatin (AQUPLA®, Shionogi), picoplatin (Poniard Pharmaceuticals); and satraplatin (JM-216, Agennix).

[00221] In some embodiments, one or more other therapeutic agent is a taxane compound, which causes disruption of microtubules, which are essential for cell division. In some embodiments, a taxane compound is selected from paclitaxel (TAXOL®, Bristol-Myers Squibb), docetaxel (TAXOTERE®, Sanofi-Aventis; DOCEFREZ®, Sun Pharmaceutical), albumin-bound paclitaxel (ABRAXANE®; Abraxis/Celgene), cabazitaxel (JEVTANA®, Sanofi-Aventis), and SID530 (SK Chemicals, Co.) (NCT00931008).

[00222] In some embodiments, one or more other therapeutic agent is a nucleoside inhibitor, or a therapeutic agent that interferes with normal DNA synthesis, protein synthesis, cell replication, or will otherwise inhibit rapidly proliferating cells.

[00223] In some embodiments, a nucleoside inhibitor is selected from trabectedin (guanidine alkylating agent, YONDELIS®, Janssen Oncology), mechlorethamine (alkylating agent, VALCHLOR®, Aktelion Pharmaceuticals); vincristine (ONCOVIN®, Eli Lilly; VINCASAR®, Teva Pharmaceuticals; MARQIBO®, Talon Therapeutics); temozolomide (prodrug to alkylating agent 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) TEMODAR®, Merck); cytarabine injection (ara-C, antimetabolic cytidine analog, Pfizer); lomustine (alkylating agent, CEENU®, Bristol-Myers Squibb; GLEOSTINE®, NextSource Biotechnology); azacitidine (pyrimidine nucleoside analog of cytidine, VIDAZA®, Celgene); omacetaxine mepesuccinate

(cephalotaxine ester) (protein synthesis inhibitor, SYNRIBO®; Teva Pharmaceuticals); asparaginase *Erwinia chrysanthemi* (enzyme for depletion of asparagine, ELSPAR®, Lundbeck; ERWINAZE®, EUSA Pharma); eribulin mesylate (microtubule inhibitor, tubulin-based antimitotic, HALAVEN®, Eisai); cabazitaxel (microtubule inhibitor, tubulin-based antimitotic, JEVTANA®, Sanofi-Aventis); capacetrine (thymidylate synthase inhibitor, XELODA®, Genentech); bendamustine (bifunctional mechlorethamine derivative, believed to form interstrand DNA cross-links, TREANDA®, Cephalon/Teva); ixabepilone (semi-synthetic analog of epothilone B, microtubule inhibitor, tubulin-based antimitotic, IXEMPRA®, Bristol-Myers Squibb); nelarabine (prodrug of deoxyguanosine analog, nucleoside metabolic inhibitor, ARRANON®, Novartis); clorafabine (prodrug of ribonucleotide reductase inhibitor, competitive inhibitor of deoxycytidine, CLOLAR®, Sanofi-Aventis); and trifluridine and tipiracil (thymidine-based nucleoside analog and thymidine phosphorylase inhibitor, LONSURF®, Taiho Oncology).

[00224] In some embodiments, one or more other therapeutic agent is a kinase inhibitor or VEGF-R antagonist. Approved VEGF inhibitors and kinase inhibitors useful in the present invention include: bevacizumab (AVASTIN®, Genentech/Roche) an anti-VEGF monoclonal antibody; ramucirumab (CYRAMZA®, Eli Lilly), an anti-VEGFR-2 antibody and ziv-aflibercept, also known as VEGF Trap (ZALTRAP®; Regeneron/Sanofi). VEGFR inhibitors, such as regorafenib (STIVARGA®, Bayer); vandetanib (CAPRELSA®, AstraZeneca); axitinib (INLYTA®, Pfizer); and lenvatinib (LENVIMA®, Eisai); Raf inhibitors, such as sorafenib (NEXAVAR®, Bayer AG and Onyx); dabrafenib (TAFINLAR®, Novartis); and vemurafenib (ZELBORAF®, Genentech/Roche); MEK inhibitors, such as cobimetanib (COTELLIC®, Exelexis/Genentech/Roche); trametinib (MEKINIST®, Novartis); Bcr-Abl tyrosine kinase inhibitors, such as imatinib (GLEEVEC®, Novartis); nilotinib (TASIGNA®, Novartis); dasatinib (SPRYCEL®, BristolMyersSquibb); bosutinib (BOSULIF®, Pfizer); and ponatinib (INCLUSIG®, Ariad Pharmaceuticals); Her2 and EGFR inhibitors, such as gefitinib (IRESSA®, AstraZeneca); erlotinib (TARCEEVA®, Genentech/Roche/Astellas); lapatinib (TYKERB®, Novartis); afatinib (GILOTRIF®, Boehringer Ingelheim); osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca); and brigatinib (ALUNBRIG®, Ariad Pharmaceuticals); c-Met and VEGFR2 inhibitors, such as cabozanitib (COMETRIQ®, Exelexis); and multikinase inhibitors, such as sunitinib (SUTENT®, Pfizer); pazopanib (VOTRIENT®, Novartis); ALK inhibitors, such

as crizotinib (XALKORI®, Pfizer); ceritinib (ZYKADIA®, Novartis); and alectinib (ALECENZa®, Genentech/Roche); Bruton's tyrosine kinase inhibitors, such as ibrutinib (IMBRUVICA®, Pharmacyclics/Janssen); and Flt3 receptor inhibitors, such as midostaurin (RYDAPT®, Novartis).

[00225] Other kinase inhibitors and VEGF-R antagonists that are in development and may be used in the present invention include tivozanib (Aveo Pharmaecuticals); vatalanib (Bayer/Novartis); lucitanib (Clovis Oncology); dovitinib (TKI258, Novartis); Chiauanib (Chipscreen Biosciences); CEP-11981 (Cephalon); linifanib (Abbott Laboratories); neratinib (HKI-272, Puma Biotechnology); radotinib (SUPECT®, IY5511, Il-Yang Pharmaceuticals, S. Korea); ruxolitinib (JAKAFI®, Incyte Corporation); PTC299 (PTC Therapeutics); CP-547,632 (Pfizer); foretinib (Exelexis, GlaxoSmithKline); quizartinib (Daiichi Sankyo) and motesanib (Amgen/Takeda).

[00226] In some embodiments, one or more other therapeutic agent is an mTOR inhibitor, which inhibits cell proliferation, angiogenesis and glucose uptake. In some embodiments, an mTOR inhibitor is everolimus (AFINITOR®, Novartis); temsirolimus (TORISEL®, Pfizer); and sirolimus (RAPAMUNE®, Pfizer).

[00227] In some embodiments, one or more other therapeutic agent is a proteasome inhibitor. Approved proteasome inhibitors useful in the present invention include bortezomib (VELCADE®, Takeda); carfilzomib (KYPROLIS®, Amgen); and ixazomib (NINLARO®, Takeda).

[00228] In some embodiments, one or more other therapeutic agent is a growth factor antagonist, such as an antagonist of platelet-derived growth factor (PDGF), or epidermal growth factor (EGF) or its receptor (EGFR). Approved PDGF antagonists which may be used in the present invention include olaratumab (LARTRUVO®; Eli Lilly). Approved EGFR antagonists which may be used in the present invention include cetuximab (ERBITUX®, Eli Lilly); necitumumab (PORTRAZZA®, Eli Lilly), panitumumab (VECTIBIX®, Amgen); and osimertinib (targeting activated EGFR, TAGRISSO®, AstraZeneca).

[00229] In some embodiments, one or more other therapeutic agent is an aromatase inhibitor. In some embodiments, an aromatase inhibitor is selected from exemestane (AROMASIN®, Pfizer); anastazole (ARIMIDEX®, AstraZeneca) and letrozole (FEMARA®, Novartis).

[00230] In some embodiments, one or more other therapeutic agent is an antagonist of the hedgehog pathway. Approved hedgehog pathway inhibitors which may be used in the present invention include sonidegib (ODOMZO®, Sun Pharmaceuticals); and vismodegib (ERIVEDGE®, Genentech), both for treatment of basal cell carcinoma.

[00231] In some embodiments, one or more other therapeutic agent is a folic acid inhibitor. Approved folic acid inhibitors useful in the present invention include pemetrexed (ALIMTA®, Eli Lilly).

[00232] In some embodiments, one or more other therapeutic agent is a CC chemokine receptor 4 (CCR4) inhibitor. CCR4 inhibitors being studied that may be useful in the present invention include mogamulizumab (POTELIGEO®, Kyowa Hakko Kirin, Japan).

[00233] In some embodiments, one or more other therapeutic agent is an isocitrate dehydrogenase (IDH) inhibitor. IDH inhibitors being studied which may be used in the present invention include AG120 (Celgene; NCT02677922); AG221 (Celgene, NCT02677922; NCT02577406); BAY1436032 (Bayer, NCT02746081); IDH305 (Novartis, NCT02987010).

[00234] In some embodiments, one or more other therapeutic agent is an arginase inhibitor. Arginase inhibitors being studied which may be used in the present invention include AEB1102 (pegylated recombinant arginase, Aeglea Biotherapeutics), which is being studied in Phase 1 clinical trials for acute myeloid leukemia and myelodysplastic syndrome (NCT02732184) and solid tumors (NCT02561234); and CB-1158 (Calithera Biosciences).

[00235] In some embodiments, one or more other therapeutic agent is a glutaminase inhibitor. Glutaminase inhibitors being studied which may be used in the present invention include CB-839 (Calithera Biosciences).

[00236] In some embodiments, one or more other therapeutic agent is an antibody that binds to tumor antigens, that is, proteins expressed on the cell surface of tumor cells. Approved antibodies that bind to tumor antigens which may be used in the present invention include rituximab (RITUXAN®, Genentech/BiogenIdec); ofatumumab (anti-CD20, ARZERRA®, GlaxoSmithKline); obinutuzumab (anti-CD20, GAZYVA®, Genentech), ibritumomab (anti-CD20 and Yttrium-90, ZEVALIN®, Spectrum Pharmaceuticals); daratumumab (anti-CD38, DARZALEX®, Janssen Biotech), dinutuximab (anti-glycolipid GD2, UNITUXIN®, United Therapeutics); trastuzumab (anti-HER2, HERCEPTIN®, Genentech); ado-trastuzumab emtansine

(anti-HER2, fused to emtansine, KADCYLA®, Genentech); and pertuzumab (anti-HER2, PERJETA®, Genentech); and brentuximab vedotin (anti-CD30-drug conjugate, ADCETRIS®, Seattle Genetics).

[00237] In some embodiments, one or more other therapeutic agent is a topoisomerase inhibitor. Approved topoisomerase inhibitors useful in the present invention include irinotecan (ONIVYDE®, Merrimack Pharmaceuticals); topotecan (HYCAMTIN®, GlaxoSmithKline). Topoisomerase inhibitors being studied which may be used in the present invention include pixantrone (PIXUVRI®, CTI Biopharma).

[00238] In some embodiments, one or more other therapeutic agent is an inhibitor of anti-apoptotic proteins, such as BCL-2. Approved anti-apoptotics which may be used in the present invention include venetoclax (VENCLEXTA®, AbbVie/Genentech); and blinatumomab (BLINCYTO®, Amgen). Other therapeutic agents targeting apoptotic proteins which have undergone clinical testing and may be used in the present invention include navitoclax (ABT-263, Abbott), a BCL-2 inhibitor (NCT02079740).

[00239] In some embodiments, one or more other therapeutic agent is an androgen receptor inhibitor. Approved androgen receptor inhibitors useful in the present invention include enzalutamide (XTANDI®, Astellas/Medivation); approved inhibitors of androgen synthesis include abiraterone (ZYTIGA®, Centocor/Ortho); approved antagonist of gonadotropin-releasing hormone (GnRH) receptor (degaralix, FIRMAGON®, Ferring Pharmaceuticals).

[00240] In some embodiments, one or more other therapeutic agent is a selective estrogen receptor modulator (SERM), which interferes with the synthesis or activity of estrogens. Approved SERMs useful in the present invention include raloxifene (EVISTA®, Eli Lilly).

[00241] In some embodiments, one or more other therapeutic agent is an inhibitor of bone resorption. An approved therapeutic which inhibits bone resorption is Denosumab (XGEVA®, Amgen), an antibody that binds to RANKL, prevents binding to its receptor RANK, found on the surface of osteoclasts, their precursors, and osteoclast-like giant cells, which mediates bone pathology in solid tumors with osseous metastases. Other approved therapeutics that inhibit bone resorption include bisphosphonates, such as zoledronic acid (ZOMETA®, Novartis).

[00242] In some embodiments, one or more other therapeutic agent is an inhibitor of interaction between the two primary p53 suppressor proteins, MDMX and MDM2. Inhibitors of p53

suppression proteins being studied which may be used in the present invention include ALRN-6924 (Aileron), a stapled peptide that equipotently binds to and disrupts the interaction of MDMX and MDM2 with p53. ALRN-6924 is currently being evaluated in clinical trials for the treatment of AML, advanced myelodysplastic syndrome (MDS) and peripheral T-cell lymphoma (PTCL) (NCT02909972; NCT02264613).

[00243] In some embodiments, one or more other therapeutic agent is an inhibitor of transforming growth factor-beta (TGF-beta or TGF-β). Inhibitors of TGF-beta proteins being studied which may be used in the present invention include NIS793 (Novartis), an anti-TGF-beta antibody being tested in the clinic for treatment of various cancers, including breast, lung, hepatocellular, colorectal, pancreatic, prostate and renal cancer (NCT 02947165). In some embodiments, the inhibitor of TGF-beta proteins is fresolimumab (GC1008; Sanofi-Genzyme), which is being studied for melanoma (NCT00923169); renal cell carcinoma (NCT00356460); and non-small cell lung cancer (NCT02581787). Additionally, in some embodiments, the additional therapeutic agent is a TGF-beta trap, such as described in Connolly et al. (2012) Int'l J. Biological Sciences 8:964-978. One therapeutic compound currently in clinical trials for treatment of solid tumors is M7824 (Merck KgaA - formerly MSB0011459X), which is a bispecific, anti-PD-L1/TGF-β trap compound (NCT02699515); and (NCT02517398). M7824 is comprised of a fully human IgG1 antibody against PD-L1 fused to the extracellular domain of human TGF-beta receptor II, which functions as a TGF-β "trap."

[00244] In some embodiments, one or more other therapeutic agent is selected from glembatumumab vedotin-monomethyl auristatin E (MMAE) (Celldex), an anti-glycoprotein NMB (gpNMB) antibody (CR011) linked to the cytotoxic MMAE. gpNMB is a protein overexpressed by multiple tumor types associated with cancer cells' ability to metastasize.

[00245] In some embodiments, one or more other therapeutic agents is an antiproliferative compound. 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, AZd$_6$244 from AstraZeneca, PD181461 from Pfizer and leucovorin.

[00246] 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.

[00247] 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™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.

[00248] 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™.

[00249] The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian 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™.

[00250] 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™.

[00251] The term "microtubule active agent" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin 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; cochicine 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™.

[00252] 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™.

[00253] 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).

[00254] 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™.

[00255] 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™.

[00256] 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 AxI 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; llmofosine; RO 318220 and RO 320432; GO 6976; lsis 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).

[00257] 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.

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] 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.

[00266] 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.

[00267] 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.

[00268] 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.

[00269] 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 (

[00270] 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.

[00271] 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.

[00272] 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.

[00273] 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.

[00274] 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.

[00275] 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.

[00276] 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.

[00277] 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.

[00278] 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.

[00279] 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.

[00280] 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.

[00281] 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.

[00282] 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).

[00283] 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.

[00284] 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; Zd_6474; 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™).

[00285] 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.

[00286] 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.

[00287] Implants containing corticosteroids refers to compounds, such as fluocinolone and dexamethasone.

[00288] 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.

[00289] 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).

Exemplary Immuno-Oncology agents

[00290] In some embodiments, one or more other therapeutic agent is an immuno-oncology agent. As used herein, the term “an immuno-oncology agent” refers to an agent which is effective

to enhance, stimulate, and/or up-regulate immune responses in a subject. In some embodiments, the administration of an immuno-oncology agent with a compound of the invention has a synergic effect in treating a cancer.

[00291] An immuno-oncology agent can be, for example, a small molecule drug, an antibody, or a biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In some embodiments, an antibody is a monoclonal antibody. In some embodiments, a monoclonal antibody is humanized or human.

[00292] In some embodiments, an immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses.

[00293] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α1β2, FAS, FASL, RELT, DR6, TROY, NGFR.

[00294] In some embodiments, an immuno-oncology agent is a cytokine that inhibits T cell activation (*e.g.*, IL-6, IL-10, TGF-β, VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[00295] In some embodiments, a combination of a compound of the invention and an immuno-oncology agent can stimulate T cell responses. In some embodiments, an immuno-oncology agent is: (i) an antagonist of a protein that inhibits T cell activation (*e.g.*, immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-

4; or (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[00296] In some embodiments, an immuno-oncology agent is an antagonist of inhibitory receptors on NK cells or an agonist of activating receptors on NK cells. In some embodiments, an immuno-oncology agent is an antagonist of KIR, such as lirilumab.

[00297] In some embodiments, an immuno-oncology agent is an agent that inhibits or depletes macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

[00298] In some embodiments, an immuno-oncology agent is selected from agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (*e.g.*, block inhibitory receptor engagement (*e.g.*, PD-L1/PD-1 interactions), deplete or inhibit Tregs (*e.g.*, using an anti-CD25 monoclonal antibody (*e.g.*, daclizumab) or by *ex vivo* anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell energy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[00299] In some embodiments, an immuno-oncology agent is a CTLA-4 antagonist. In some embodiments, a CTLA-4 antagonist is an antagonistic CTLA-4 antibody. In some embodiments, an antagonistic CTLA-4 antibody is YERVOY (ipilimumab) or tremelimumab.

[00300] In some embodiments, an immuno-oncology agent is a PD-1 antagonist. In some embodiments, a PD-1 antagonist is administered by infusion. In some embodiments, an immuno-oncology agent is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity. In some embodiments, a PD-1 antagonist is an antagonistic PD-1 antibody. In some embodiments, an antagonistic PD-1 antibody is OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). In some embodiments, an immuno-oncology agent may be pidilizumab (CT-

011). In some embodiments, an immuno-oncology agent is a recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224.

[00301] In some embodiments, an immuno-oncology agent is a PD-L1 antagonist. In some embodiments, a PD-L1 antagonist is an antagonistic PD-L1 antibody. In some embodiments, a PD-L1 antibody is MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

[00302] In some embodiments, an immuno-oncology agent is a LAG-3 antagonist. In some embodiments, a LAG-3 antagonist is an antagonistic LAG-3 antibody. In some embodiments, a LAG3 antibody is BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO009/44273).

[00303] In some embodiments, an immuno-oncology agent is a CD137 (4-1BB) agonist. In some embodiments, a CD137 (4-1BB) agonist is an agonistic CD137 antibody. In some embodiments, a CD137 antibody is urelumab or PF-05082566 (WO12/32433).

[00304] In some embodiments, an immuno-oncology agent is a GITR agonist. In some embodiments, a GITR agonist is an agonistic GITR antibody. In some embodiments, a GITR antibody is BMS-986153, BMS-986156, TRX-518 (WO006/105021, WO009/009116), or MK-4166 (WO11/028683).

[00305] In some embodiments, an immuno-oncology agent is an indoleamine (2,3)-dioxygenase (IDO) antagonist. In some embodiments, an IDO antagonist is selected from epacadostat (INCB024360, Incyte); indoximod (NLG-8189, NewLink Genetics Corporation); capmanitib (INC280, Novartis); GDC-0919 (Genentech/Roche); PF-06840003 (Pfizer); BMS:F001287 (Bristol-Myers Squibb); Phy906/KD108 (Phytoceutica); an enzyme that breaks down kynurenine (Kynase, Ikena Oncology, formerly known as Kyn Therapeutics); and NLG-919 (WO09/73620, WO009/1156652, WO11/56652, WO12/142237).

[00306] In some embodiments, an immuno-oncology agent is an OX40 agonist. In some embodiments, an OX40 agonist is an agonistic OX40 antibody. In some embodiments, an OX40 antibody is MEDI-6383 or MEDI-6469.

[00307] In some embodiments, an immuno-oncology agent is an OX40L antagonist. In some embodiments, an OX40L antagonist is an antagonistic OX40 antibody. In some embodiments, an OX40L antagonist is RG-7888 (WO06/029879).

[00308] In some embodiments, an immuno-oncology agent is a CD40 agonist. In some embodiments, a CD40 agonist is an agonistic CD40 antibody. In some embodiments, an immuno-oncology agent is a CD40 antagonist. In some embodiments, a CD40 antagonist is an antagonistic CD40 antibody. In some embodiments, a CD40 antibody is lucatumumab or dacetuzumab.

[00309] In some embodiments, an immuno-oncology agent is a CD27 agonist. In some embodiments, a CD27 agonist is an agonistic CD27 antibody. In some embodiments, a CD27 antibody is varlilumab.

[00310] In some embodiments, an immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[00311] In some embodiments, an immuno-oncology agent is abagovomab, adecatumumab, afutuzumab, alemtuzumab, anatumomab mafenatox, apolizumab, atezolimab, avelumab, blinatumomab, BMS-936559, catumaxomab, durvalumab, epacadostat, epratuzumab, indoximod, inotuzumab ozogamicin, intelumumab, ipilimumab, isatuximab, lambrolizumab, MED14736, MPDL3280A, nivolumab, obinutuzumab, ocaratuzumab, ofatumumab, olatatumab, pembrolizumab, pidilizumab, rituximab, ticilimumab, samalizumab, or tremelimumab.

[00312] In some embodiments, an immuno-oncology agent is an immunostimulatory agent. For example, antibodies blocking the PD-1 and PD-L1 inhibitory axis can unleash activated tumor-reactive T cells and have been shown in clinical trials to induce durable anti-tumor responses in increasing numbers of tumor histologies, including some tumor types that conventionally have not been considered immunotherapy sensitive. See, *e.g.*, Okazaki, T. *et al.* (2013) Nat. Immunol. 14, 1212–1218; Zou *et al.* (2016) Sci. Transl. Med. 8. The anti-PD-1 antibody nivolumab (OPDIVO®, Bristol-Myers Squibb, also known as ONO-4538, MDX1106 and BMS-936558), has shown potential to improve the overall survival in patients with RCC who had experienced disease progression during or after prior anti-angiogenic therapy.

[00313] In some embodiments, the immunomodulatory therapeutic specifically induces apoptosis of tumor cells. Approved immunomodulatory therapeutics which may be used in the present invention include pomalidomide (POMALYST®, Celgene); lenalidomide (REVLIMID®, Celgene); ingenol mebutate (PICATO®, LEO Pharma).

[00314] In some embodiments, an immuno-oncology agent is a cancer vaccine. In some embodiments, the cancer vaccine is selected from sipuleucel-T (PROVENGE®,

Dendreon/Valeant Pharmaceuticals), which has been approved for treatment of asymptomatic, or minimally symptomatic metastatic castrate-resistant (hormone-refractory) prostate cancer; and talimogene laherparepvec (IMLYGIC®, BioVex/Amgen, previously known as T-VEC), a genetically modified oncolytic viral therapy approved for treatment of unresectable cutaneous, subcutaneous and nodal lesions in melanoma. In some embodiments, an immuno-oncology agent is selected from an oncolytic viral therapy such as pexastimogene devacirepvec (PexaVec/JX-594, SillaJen/formerly Jennerex Biotherapeutics), a thymidine kinase- (TK-) deficient vaccinia virus engineered to express GM-CSF, for hepatocellular carcinoma (NCT02562755) and melanoma (NCT00429312); pelareorep (REOLYSIN®, Oncolytics Biotech), a variant of respiratory enteric orphan virus (reovirus) which does not replicate in cells that are not RAS-activated, in numerous cancers, including colorectal cancer (NCT01622543); prostate cancer (NCT01619813); head and neck squamous cell cancer (NCT01166542); pancreatic adenocarcinoma (NCT00998322); and non-small cell lung cancer (NSCLC) (NCT 00861627); enadenotucirev (NG-348, PsiOxus, formerly known as ColoAd1), an adenovirus engineered to express a full length CD80 and an antibody fragment specific for the T-cell receptor CD3 protein, in ovarian cancer (NCT02028117); metastatic or advanced epithelial tumors such as in colorectal cancer, bladder cancer, head and neck squamous cell carcinoma and salivary gland cancer (NCT02636036); ONCOS-102 (Targovax/formerly Oncos), an adenovirus engineered to express GM-CSF, in melanoma (NCT03003676); and peritoneal disease, colorectal cancer or ovarian cancer (NCT02963831); GL-ONC1 (GLV-1h68/GLV-1h153, Genelux GmbH), vaccinia viruses engineered to express beta-galactosidase (beta-gal)/beta-glucoronidase or beta-gal/human sodium iodide symporter (hNIS), respectively, were studied in peritoneal carcinomatosis (NCT01443260); fallopian tube cancer, ovarian cancer (NCT 02759588); or CG0070 (Cold Genesys), an adenovirus engineered to express GM-CSF, in bladder cancer (NCT02365818).

[00315] In some embodiments, an immuno-oncology agent is selected from JX-929 (SillaJen/formerly Jennerex Biotherapeutics), a TK- and vaccinia growth factor-deficient vaccinia virus engineered to express cytosine deaminase, which is able to convert the prodrug 5-fluorocytosine to the cytotoxic drug 5-fluorouracil; TG01 and TG02 (Targovax/formerly Oncos), peptide-based immunotherapy agents targeted for difficult-to-treat RAS mutations; and TILT-123 (TILT Biotherapeutics), an engineered adenovirus designated: Ad5/3-E2F-delta24-hTNFα-IRES-

hIL20; and VSV-GP (ViraTherapeutics) a vesicular stomatitis virus (VSV) engineered to express the glycoprotein (GP) of lymphocytic choriomeningitis virus (LCMV), which can be further engineered to express antigens designed to raise an antigen-specific $CD8^+$ T cell response.

[00316] In some embodiments, an immuno-oncology agent is a T-cell engineered to express a chimeric antigen receptor, or CAR. The T-cells engineered to express such chimeric antigen receptor are referred to as a CAR-T cells.

[00317] CARs have been constructed that consist of binding domains, which may be derived from natural ligands, single chain variable fragments (scFv) derived from monoclonal antibodies specific for cell-surface antigens, fused to endodomains that are the functional end of the T-cell receptor (TCR), such as the CD3-zeta signaling domain from TCRs, which is capable of generating an activation signal in T lymphocytes. Upon antigen binding, such CARs link to endogenous signaling pathways in the effector cell and generate activating signals similar to those initiated by the TCR complex.

[00318] For example, in some embodiments the CAR-T cell is one of those described in U.S. Patent 8,906,682 (June *et al.*; hereby incorporated by reference in its entirety), which discloses CAR-T cells engineered to comprise an extracellular domain having an antigen binding domain (such as a domain that binds to CD19), fused to an intracellular signaling domain of the T cell antigen receptor complex zeta chain (such as CD3 zeta). When expressed in the T cell, the CAR is able to redirect antigen recognition based on the antigen binding specificity. In the case of CD19, the antigen is expressed on malignant B cells. Over 200 clinical trials are currently in progress employing CAR-T in a wide range of indications. [https://clinicaltrials.gov/ct2/results?term=chimeric+antigen+receptors&pg=1].

[00319] In some embodiments, an immunostimulatory agent is an activator of retinoic acid receptor-related orphan receptor γ (RORγt). RORγt is a transcription factor with key roles in the differentiation and maintenance of Type 17 effector subsets of CD4+ (Th17) and CD8+ (Tc17) T cells, as well as the differentiation of IL-17 expressing innate immune cell subpopulations such as NK cells. In some embodiments, an activator of RORγt is LYC-55716 (Lycera), which is currently being evaluated in clinical trials for the treatment of solid tumors (NCT02929862).

[00320] In some embodiments, an immunostimulatory agent is an agonist or activator of a toll-like receptor (TLR). Suitable activators of TLRs include an agonist or activator of TLR9 such as

SD-101 (Dynavax). SD-101 is an immunostimulatory CpG which is being studied for B-cell, follicular and other lymphomas (NCT02254772). Agonists or activators of TLR8 which may be used in the present invention include motolimod (VTX-2337, VentiRx Pharmaceuticals) which is being studied for squamous cell cancer of the head and neck (NCT02124850) and ovarian cancer (NCT02431559).

[00321] Other immuno-oncology agents that can be used in the present invention include urelumab (BMS-663513, Bristol-Myers Squibb), an anti-CD137 monoclonal antibody; varlilumab (CDX-1127, Celldex Therapeutics), an anti-CD27 monoclonal antibody; BMS-986178 (Bristol-Myers Squibb), an anti-OX40 monoclonal antibody; lirilumab (IPH2102/BMS-986015, Innate Pharma, Bristol-Myers Squibb), an anti-KIR monoclonal antibody; monalizumab (IPH2201, Innate Pharma, AstraZeneca) an anti-NKG2A monoclonal antibody; andecaliximab (GS-5745, Gilead Sciences), an anti-MMP9 antibody; MK-4166 (Merck & Co.), an anti-GITR monoclonal antibody.

[00322] In some embodiments, an immunostimulatory agent is selected from elotuzumab, mifamurtide, an agonist or activator of a toll-like receptor, and an activator of RORγt.

[00323] In some embodiments, an immunostimulatory therapeutic is recombinant human interleukin 15 (rhIL-15). rhIL-15 has been tested in the clinic as a therapy for melanoma and renal cell carcinoma (NCT01021059 and NCT01369888) and leukemias (NCT02689453). In some embodiments, an immunostimulatory agent is recombinant human interleukin 12 (rhIL-12). In some embodiments, an IL-15 based immunotherapeutic is heterodimeric IL-15 (hetIL-15, Novartis/Admune), a fusion complex composed of a synthetic form of endogenous IL-15 complexed to the soluble IL-15 binding protein IL-15 receptor alpha chain (IL15:sIL-15RA), which has been tested in Phase 1 clinical trials for melanoma, renal cell carcinoma, non-small cell lung cancer and head and neck squamous cell carcinoma (NCT02452268). In some embodiments, a recombinant human interleukin 12 (rhIL-12) is NM-IL-12 (Neumedicines, Inc.), NCT02544724, or NCT02542124.

[00324] In some embodiments, an immuno-oncology agent is selected from those descripted in Jerry L. Adams *et al.*, "Big opportunities for small molecules in immuno-oncology," Cancer Therapy **2015**, Vol. 14, pages 603-622, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is selected from the examples

described in Table 1 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule targeting an immuno-oncology target selected from those listed in Table 2 of Jerry L. Adams *et al.* In some embodiments, an immuno-oncology agent is a small molecule agent selected from those listed in Table 2 of Jerry L. Adams *et al.*

[00325] In some embodiments, an immuno-oncology agent is selected from the small molecule immuno-oncology agents described in Peter L. Toogood, "Small molecule immuno-oncology therapeutic agents," Bioorganic & Medicinal Chemistry Letters **2018**, Vol. 28, pages 319-329, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is an agent targeting the pathways as described in Peter L. Toogood.

[00326] In some embodiments, an immuno-oncology agent is selected from those described in Sandra L. Ross et al., "Bispecific T cell engager (BITE®) antibody constructs can mediate bystander tumor cell killing", PLoS ONE 12(8): e0183390, the content of which is incorporated herein by reference in its entirety. In some embodiments, an immuno-oncology agent is a bispecific T cell engager (BITE®) antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is a CD19/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct is an EGFR/CD3 bispecific antibody construct. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells, which release cytokines inducing upregulation of intercellular adhesion molecule 1 (ICAM-1) and FAS on bystander cells. In some embodiments, a bispecific T cell engager (BITE®) antibody construct activates T cells which result in induced bystander cell lysis. In some embodiments, the bystander cells are in solid tumors. In some embodiments, the bystander cells being lysed are in proximity to the BITE®-activated T cells. In some embodiment, the bystander cells comprises tumor-associated antigen (TAA) negative cancer cells. In some embodiment, the bystander cells comprise EGFR-negative cancer cells. In some embodiments, an immuno-oncology agent is an antibody which blocks the PD-L1/PD1 axis and/or CTLA4. In some embodiments, an immuno-oncology agent is an *ex vivo* expanded tumor-infiltrating T cell. In some embodiments, an immuno-oncology agent is a bispecific antibody construct or chimeric antigen receptors (CARs) that directly connect T cells with tumor-associated surface antigens (TAAs).

Exemplary Immune Checkpoint Inhibitors

[00327] In some embodiments, an immuno-oncology agent is an immune checkpoint inhibitor as described herein.

[00328] The term "checkpoint inhibitor" as used herein relates to agents useful in preventing cancer cells from avoiding the immune system of the patient. One of the major mechanisms of anti-tumor immunity subversion is known as "T-cell exhaustion," which results from chronic exposure to antigens that has led to up-regulation of inhibitory receptors. These inhibitory receptors serve as immune checkpoints in order to prevent uncontrolled immune reactions.

[00329] PD-1 and co-inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4, B and T Lymphocyte Attenuator (BTLA; CD272), T cell Immunoglobulin and Mucin domain-3 (Tim-3), Lymphocyte Activation Gene-3 (Lag-3; CD223), and others are often referred to as a checkpoint regulators. They act as molecular "gatekeepers" that allow extracellular information to dictate whether cell cycle progression and other intracellular signaling processes should proceed.

[00330] In some embodiments, an immune checkpoint inhibitor is an antibody to PD-1. PD-1 binds to the programmed cell death 1 receptor (PD-1) to prevent the receptor from binding to the inhibitory ligand PDL-1, thus overriding the ability of tumors to suppress the host anti-tumor immune response.

[00331] In one aspect, the checkpoint inhibitor is a biologic therapeutic or a small molecule. In another aspect, the checkpoint inhibitor is a monoclonal antibody, a humanized antibody, a fully human antibody, a fusion protein or a combination thereof. In a further aspect, the checkpoint inhibitor inhibits a checkpoint protein selected from CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an additional aspect, the checkpoint inhibitor interacts with a ligand of a checkpoint protein selected from CTLA-4, PDL1, PDL2, PDl, B7-H3, B7-H4, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD160, CGEN-15049, CHK 1, CHK2, A2aR, B-7 family ligands or a combination thereof. In an aspect, the checkpoint inhibitor is an immunostimulatory agent, a T cell growth factor, an interleukin, an antibody, a vaccine or a combination thereof. In a further aspect, the interleukin is IL-7 or IL-15. In a specific

aspect, the interleukin is glycosylated IL-7. In an additional aspect, the vaccine is a dendritic cell (DC) vaccine.

[00332] Checkpoint inhibitors include any agent that blocks or inhibits in a statistically significant manner, the inhibitory pathways of the immune system. Such inhibitors may include small molecule inhibitors or may include antibodies, or antigen binding fragments thereof, that bind to and block or inhibit immune checkpoint receptors or antibodies that bind to and block or inhibit immune checkpoint receptor ligands. Illustrative checkpoint molecules that can be targeted for blocking or inhibition include, but are not limited to, CTLA-4, PDL1, PDL2, PD1, B7-H3, B7-H4, BTLA, HVEM, GAL9, LAG3, TIM3, VISTA, KIR, 2B4 (belongs to the CD2 family of molecules and is expressed on all NK, γδ, and memory $CD8^+$ (αβ) T cells), CD160 (also referred to as BY55), CGEN-15049, CHK 1 and CHK2 kinases, A2aR, and various B-7 family ligands. B7 family ligands include, but are not limited to, B7- 1, B7-2, B7-DC, B7-H1, B7-H2, B7-H3, B7-H4, B7-H5, B7-H6 and B7-H7. Checkpoint inhibitors include antibodies, or antigen binding fragments thereof, other binding proteins, biologic therapeutics, or small molecules, that bind to and block or inhibit the activity of one or more of CTLA-4, PDL1, PDL2, PD1, BTLA, HVEM, TIM3, GAL9, LAG3, VISTA, KIR, 2B4, CD 160 and CGEN-15049. Illustrative immune checkpoint inhibitors include, but are not limited to, Tremelimumab (CTLA-4 blocking antibody), anti-OX40, PD-L1 monoclonal Antibody (Anti-B7-Hl; MEDI4736), MK-3475 (PD-1 blocker), Nivolumab (anti-PD1 antibody), CT-011 (anti-PD1 antibody), BY55 monoclonal antibody, AMP224 (anti-PDL1 antibody), BMS- 936559 (anti-PDL1 antibody), MPLDL3280A (anti-PDL1 antibody), MSB0010718C (anti-PDL1 antibody), and ipilimumab (anti-CTLA-4 checkpoint inhibitor). Checkpoint protein ligands include, but are not limited to PD-L1, PD-L2, B7-H3, B7-H4, CD28, CD86 and TIM-3.

[00333] In certain embodiments, the immune checkpoint inhibitor is selected from a PD-1 antagonist, a PD-L1 antagonist, and a CTLA-4 antagonist. In some embodiments, the checkpoint inhibitor is selected from the group consisting of nivolumab (OPDIVO®), ipilimumab (YERVOY®), and pembrolizumab (KEYTRUDA®). In some embodiments, the checkpoint inhibitor is selected from nivolumab (anti-PD-1 antibody, OPDIVO®, Bristol-Myers Squibb); pembrolizumab (anti-PD-1 antibody, KEYTRUDA®, Merck); ipilimumab (anti-CTLA-4

antibody, YERVOY®, Bristol-Myers Squibb); durvalumab (anti-PD-L1 antibody, IMFINZI®, AstraZeneca); and atezolizumab (anti-PD-L1 antibody, TECENTRIQ®, Genentech).

[00334] In some embodiments, the checkpoint inhibitor is selected from the group consisting of lambrolizumab (MK-3475), nivolumab (BMS-936558), pidilizumab (CT-011), AMP-224, MDX-1105, MEDI4736, MPDL3280A, BMS-936559, ipilimumab, lirlumab, IPH2101, pembrolizumab (KEYTRUDA®), and tremelimumab.

[00335] In some embodiments, an immune checkpoint inhibitor is REGN2810 (Regeneron), an anti-PD-1 antibody tested in patients with basal cell carcinoma (NCT03132636); NSCLC (NCT03088540); cutaneous squamous cell carcinoma (NCT02760498); lymphoma (NCT02651662); and melanoma (NCT03002376); pidilizumab (CureTech), also known as CT-011, an antibody that binds to PD-1, in clinical trials for diffuse large B-cell lymphoma and multiple myeloma; avelumab (BAVENCIO®, Pfizer/Merck KGaA), also known as MSB0010718C), a fully human IgG1 anti-PD-L1 antibody, in clinical trials for non-small cell lung cancer, Merkel cell carcinoma, mesothelioma, solid tumors, renal cancer, ovarian cancer, bladder cancer, head and neck cancer, and gastric cancer; or PDR001 (Novartis), an inhibitory antibody that binds to PD-1, in clinical trials for non-small cell lung cancer, melanoma, triple negative breast cancer and advanced or metastatic solid tumors. Tremelimumab (CP-675,206; Astrazeneca) is a fully human monoclonal antibody against CTLA-4 that has been in studied in clinical trials for a number of indications, including: mesothelioma, colorectal cancer, kidney cancer, breast cancer, lung cancer and non-small cell lung cancer, pancreatic ductal adenocarcinoma, pancreatic cancer, germ cell cancer, squamous cell cancer of the head and neck, hepatocellular carcinoma, prostate cancer, endometrial cancer, metastatic cancer in the liver, liver cancer, large B-cell lymphoma, ovarian cancer, cervical cancer, metastatic anaplastic thyroid cancer, urothelial cancer, fallopian tube cancer, multiple myeloma, bladder cancer, soft tissue sarcoma, and melanoma. AGEN-1884 (Agenus) is an anti-CTLA4 antibody that is being studied in Phase 1 clinical trials for advanced solid tumors (NCT02694822).

[00336] In some embodiments, a checkpoint inhibitor is an inhibitor of T-cell immunoglobulin mucin containing protein-3 (TIM-3). TIM-3 inhibitors that may be used in the present invention include TSR-022, LY3321367 and MBG453. TSR-022 (Tesaro) is an anti-TIM-3 antibody which is being studied in solid tumors (NCT02817633). LY3321367 (Eli Lilly) is an anti-TIM-3

antibody which is being studied in solid tumors (NCT03099109). MBG453 (Novartis) is an anti-TIM-3 antibody which is being studied in advanced malignancies (NCT02608268).

[00337] In some embodiments, a checkpoint inhibitor is an inhibitor of T cell immunoreceptor with Ig and ITIM domains, or TIGIT, an immune receptor on certain T cells and NK cells. TIGIT inhibitors that may be used in the present invention include BMS-986207 (Bristol-Myers Squibb), an anti-TIGIT monoclonal antibody (NCT02913313); OMP-313M32 (Oncomed); and anti-TIGIT monoclonal antibody (NCT03119428).

[00338] In some embodiments, a checkpoint inhibitor is an inhibitor of Lymphocyte Activation Gene-3 (LAG-3). LAG-3 inhibitors that may be used in the present invention include BMS-986016 and REGN3767 and IMP321. BMS-986016 (Bristol-Myers Squibb), an anti-LAG-3 antibody, is being studied in glioblastoma and gliosarcoma (NCT02658981). REGN3767 (Regeneron), is also an anti-LAG-3 antibody, and is being studied in malignancies (NCT03005782). IMP321 (Immutep S.A.) is an LAG-3-Ig fusion protein, being studied in melanoma (NCT02676869); adenocarcinoma (NCT02614833); and metastatic breast cancer (NCT00349934).

[00339] Checkpoint inhibitors that may be used in the present invention include OX40 agonists. OX40 agonists that are being studied in clinical trials include PF-04518600/PF-8600 (Pfizer), an agonistic anti-OX40 antibody, in metastatic kidney cancer (NCT03092856) and advanced cancers and neoplasms (NCT02554812; NCT05082566); GSK3174998 (Merck), an agonistic anti-OX40 antibody, in Phase 1 cancer trials (NCT02528357); MEDI0562 (Medimmune/AstraZeneca), an agonistic anti-OX40 antibody, in advanced solid tumors (NCT02318394 and NCT02705482); MEDI6469, an agonistic anti-OX40 antibody (Medimmune/AstraZeneca), in patients with colorectal cancer (NCT02559024), breast cancer (NCT01862900), head and neck cancer (NCT02274155) and metastatic prostate cancer (NCT01303705); and BMS-986178 (Bristol-Myers Squibb) an agonistic anti-OX40 antibody, in advanced cancers (NCT02737475).

[00340] Checkpoint inhibitors that may be used in the present invention include CD137 (also called 4-1BB) agonists. CD137 agonists that are being studied in clinical trials include utomilumab (PF-05082566, Pfizer) an agonistic anti-CD137 antibody, in diffuse large B-cell lymphoma (NCT02951156) and in advanced cancers and neoplasms (NCT02554812 and NCT05082566); urelumab (BMS-663513, Bristol-Myers Squibb), an agonistic anti-CD137

antibody, in melanoma and skin cancer (NCT02652455) and glioblastoma and gliosarcoma (NCT02658981); and CTX-471 (Compass Therapeutics), an agonistic anti-CD137 antibody in metastatic or locally advanced malignancies (NCT03881488).

[00341] Checkpoint inhibitors that may be used in the present invention include CD27 agonists. CD27 agonists that are being studied in clinical trials include varlilumab (CDX-1127, Celldex Therapeutics) an agonistic anti-CD27 antibody, in squamous cell head and neck cancer, ovarian carcinoma, colorectal cancer, renal cell cancer, and glioblastoma (NCT02335918); lymphomas (NCT01460134); and glioma and astrocytoma (NCT02924038).

[00342] Checkpoint inhibitors that may be used in the present invention include glucocorticoid-induced tumor necrosis factor receptor (GITR) agonists. GITR agonists that are being studied in clinical trials include TRX518 (Leap Therapeutics), an agonistic anti-GITR antibody, in malignant melanoma and other malignant solid tumors (NCT01239134 and NCT02628574); GWN323 (Novartis), an agonistic anti-GITR antibody, in solid tumors and lymphoma (NCT02740270); INCAGN01876 (Incyte/Agenus), an agonistic anti-GITR antibody, in advanced cancers (NCT02697591 and NCT03126110); MK-4166 (Merck), an agonistic anti-GITR antibody, in solid tumors (NCT02132754) and MEDI1873 (Medimmune/AstraZeneca), an agonistic hexameric GITR-ligand molecule with a human IgG1 Fc domain, in advanced solid tumors (NCT02583165).

[00343] Checkpoint inhibitors that may be used in the present invention include inducible T-cell co-stimulator (ICOS, also known as CD278) agonists. ICOS agonists that are being studied in clinical trials include MEDI-570 (Medimmune), an agonistic anti-ICOS antibody, in lymphomas (NCT02520791); GSK3359609 (Merck), an agonistic anti-ICOS antibody, in Phase 1 (NCT02723955); JTX-2011 (Jounce Therapeutics), an agonistic anti-ICOS antibody, in Phase 1 (NCT02904226).

[00344] Checkpoint inhibitors that may be used in the present invention include killer IgG-like receptor (KIR) inhibitors. KIR inhibitors that are being studied in clinical trials include lirilumab (IPH2102/BMS-986015, Innate Pharma/Bristol-Myers Squibb), an anti-KIR antibody, in leukemias (NCT01687387, NCT02399917, NCT02481297, NCT02599649), multiple myeloma (NCT02252263), and lymphoma (NCT01592370); IPH2101 (1-7F9, Innate Pharma) in myeloma (NCT01222286 and NCT01217203); and IPH4102 (Innate Pharma), an anti-KIR antibody that binds to three domains of the long cytoplasmic tail (KIR3DL2), in lymphoma (NCT02593045).

[00345] Checkpoint inhibitors that may be used in the present invention include CD47 inhibitors of interaction between CD47 and signal regulatory protein alpha (SIRPa). CD47/SIRPa inhibitors that are being studied in clinical trials include ALX-148 (Alexo Therapeutics), an antagonistic variant of (SIRPa) that binds to CD47 and prevents CD47/SIRPa-mediated signaling, in phase 1 (NCT03013218); TTI-621 (SIRPa-Fc, Trillium Therapeutics), a soluble recombinant fusion protein created by linking the N-terminal CD47-binding domain of SIRPa with the Fc domain of human IgG1, acts by binding human CD47, and preventing it from delivering its "do not eat" signal to macrophages, is in clinical trials in Phase 1 (NCT02890368 and NCT02663518); CC-90002 (Celgene), an anti-CD47 antibody, in leukemias (NCT02641002); and Hu5F9-G4 (Forty Seven, Inc.), in colorectal neoplasms and solid tumors (NCT02953782), acute myeloid leukemia (NCT02678338) and lymphoma (NCT02953509).

[00346] Checkpoint inhibitors that may be used in the present invention include CD73 inhibitors. CD73 inhibitors that are being studied in clinical trials include MEDI9447 (Medimmune), an anti-CD73 antibody, in solid tumors (NCT02503774); and BMS-986179 (Bristol-Myers Squibb), an anti-CD73 antibody, in solid tumors (NCT02754141).

[00347] Checkpoint inhibitors that may be used in the present invention include agonists of stimulator of interferon genes protein (STING, also known as transmembrane protein 173, or TMEM173). Agonists of STING that are being studied in clinical trials include MK-1454 (Merck), an agonistic synthetic cyclic dinucleotide, in lymphoma (NCT03010176); and ADU-S100 (MIW815, Aduro Biotech/Novartis), an agonistic synthetic cyclic dinucleotide, in Phase 1 (NCT02675439 and NCT03172936).

[00348] Checkpoint inhibitors that may be used in the present invention include CSF1R inhibitors. CSF1R inhibitors that are being studied in clinical trials include pexidartinib (PLX3397, Plexxikon), a CSF1R small molecule inhibitor, in colorectal cancer, pancreatic cancer, metastatic and advanced cancers (NCT02777710) and melanoma, non-small cell lung cancer, squamous cell head and neck cancer, gastrointestinal stromal tumor (GIST) and ovarian cancer (NCT02452424); and IMC-CS4 (LY3022855, Lilly), an anti-CSF-1R antibody, in pancreatic cancer (NCT03153410), melanoma (NCT03101254), and solid tumors (NCT02718911); and BLZ945 (4-[2((1R,2R)-2-hydroxycyclohexylamino)-benzothiazol-6-yloxyl]-pyridine-2-

carboxylic acid methylamide, Novartis), an orally available inhibitor of CSF1R, in advanced solid tumors (NCT02829723).

[00349] Checkpoint inhibitors that can be used in the present invention include NKG2A receptor inhibitors. NKG2A receptor inhibitors that are being studied in clinical trials include monalizumab (IPH2201, Innate Pharma), an anti-NKG2A antibody, in head and neck neoplasms (NCT02643550) and chronic lymphocytic leukemia (NCT02557516).

[00350] In some embodiments, the immune checkpoint inhibitor is selected from nivolumab, pembrolizumab, ipilimumab, avelumab, durvalumab, atezolizumab, or pidilizumab.

EXEMPLIFICATION

[00351] The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon.

Example 1: SPR Assays

MEK-RAF binding assay

[00352] Compound effects on binding affinity of MEK to BRAF or CRAF are followed by surface plasmon resonance (SPR) with single-cycle kinetic analysis. GST-BRAF or GST-CRAF is immobilized onto a chip and increasing concentrations of His-tagged MEK1 are flowed over the sensor chip. 500 mM ATP is added to the running buffer. The dissociation constant for MEK1 binding to either BRAF or CRAF is calculated in the absence and presence of compound. Instruments are carried out on a BIACORE 8K instrument. Sensorgrams are double-reference and DMSO corrected. Data is fit to a single-cycle kinetic model.

MEK-KSR binding assay

[00353] Compound effects on binding affinity of MEK to KSR1 or KSR2 are followed by surface plasmon resonance (SPR) with single-cycle kinetic analysis. GST-KSR1 or GST-KSR2 is immobilized onto a chip and increasing concentrations of His-tagged MEK1 are flowed over the sensor chip. 500 mM ATP is added to the running buffer. The dissociation constant for MEK1 binding to either BRAF or CRAF is calculated in the absence and presence of compound. Instruments are carried out on a BIACORE 8K instrument. Sensorgrams are double-reference and DMSO corrected. Data is fit to a single-cycle kinetic model.

MEK1/CRAF Stabilization

[00354] Anti-GST antibodies were immobilized to CM5 chips by amine coupling (GST capture kits from Cytiva). 1 μg/mL GST-CRAF protein (AA 306-548, N-terminal GST fusion, Carna Biosciences, Inc) was captured on this surface with a contact time of 200 seconds at a flow rate of 5 μL/min. Capture buffer was 1xPBS, pH 7.4, 10 mM $MgCl_2$, 1 mM DTT, 0.01% Tween-20 and 500 μM ATP. The capture level of CRAF was approximately 50 resonance units (RUs).

[00355] His-tagged MEK1 (± compound) was diluted in buffer containing 10 mM HEPES, pH 7.4, 150 mM NaCl, 10 mM $MgCl_2$, 1 mM DTT, 0.01% Tween-20, 500 μM ATP and 1% DMSO. Running buffer was 1xPBS, 10 mM $MgCl_2$, 1 mM DTT, 0.01% Tween-20, 500 μM ATP and 1% DMSO. MEK1 was serially diluted three-fold from the top doses of 200 nM with 3 μM compound solution for a total of 5 doses. In each cycle, association time was 60 seconds and dissociation time was 600 seconds with an extra wash of 50% DMSO. Analyte binding was collected at 15°C with a flow rate of 30 μL/min.

[00356] The K_D ratio is defined as the (K_D of CRAF-MEK1 binary complex)/(K_D of ternary complex).

Example 2: Immunoprecipitation Assay

[00357] Immunoprecipitation experiments are performed by plating about 450,000 HCT116 cells per well in 6-well plates. Cells are plated for 48 h so as to reach approximately 70% confluency before transfection. Then, 24 h after transfection, cells are treated with vehicle (0.1% DMSO) or a compound (about 200 nM) for 1 h. Cells are washed twice in cold PBS and then transferred to a pre-chilled tube in 0.6 ml of PBS solution. Cells are spun at 1,800*g* in a cold centrifuge for 10 min, and supernatant is aspirated. To lyse cells, pellets are resuspended in NP-40 buffer (50 mM Tris pH 7.8, 100 mM NaCl, 0.5% (v/v) NP-40, 10% (v/v) glycerol, 1 mM EDTA) supplemented with protease and phosphatase inhibitor cocktail (Thermo Fisher, 78440) and incubated on ice for 30 min. Lysates are centrifuged for 20 min at 2,100*g*, and supernatants are collected. Cleared lysates are quantified using BCA reagent (Pierce, 23225), with BSA as a standard. Five micrograms of rabbit anti-MEK1 antibody (Millipore-Sigma, 07-641), or rabbit IgG (Millipore Sigma, 12-370), is immobilized on 50 μl of Sepharose Protein A Resin (Thermo Fisher, 53139) and washed three times in 300 μl NP-40 buffer before initiating immunoprecipitations.

[00358] Next, for MEK1 immunoprecipitation, 250 μg of total cell lysate in a total volume of 0.6 ml is mixed with the pre-immobilized anti-MEK1 antibody pre-conjugated to Protein A resin. Samples are incubated at 4 °C on an end-over-end rotator for 4 h, followed by three washes in 0.6 ml volume of NP-40 buffer. Next, proteins are denatured and released from resin by the addition of 80 μl volume of 1× SDS sample buffer. Samples are boiled at 90 °C for 2 min, spun, and then applied to a 4–12% bis-tris glycine gel (Bio-Rad, 3450125) run in MOPS-SDS buffer (Thermo Fisher, NP0001) for 60 min at 150 V. Gels are then transferred onto nitrocellulose in 20% methanol in Tris-glycine buffer (95 V, 250 A). Transfers are confirmed using Ponceau red and then analyzed by western blot. Signals for MEK, Flag-tagged proteins, BRAF, and GAPDH are detected by enhanced chemiluminescence on a ChemDoc XRS+ imaging system (Biorad).

Example 3: Biological Assay for Inhibiting Mouse Xenograft Tumor Growth

[00359] Exemplary compounds having MEK inhibitory activity can be tested, alone or in combination with a second anti-cancer agent, such as a TEAD inhibitor or an ERK5 inhibitor, for ability to inhibit tumor growth in patient-derived mouse xenograft models of pancreatic cancer and lung cancer. Assay procedures are described below.

Procedures for Patient-Derived Mouse Xenograft (PDX) Tumor Growth Assay

[00360] Balb/c mice (6-8 weeks old) are inoculated subcutaneously in the right flank with a primary human tumor xenograft model tumor fragment (2-3 mm^3 in diameter) for tumor development. In one study, mice are inoculated with a human lung adenocarcinoma tumor model (MSCLC, ADC model LU6424) that harbors a BRAF mutation (LU6424); in a second study, mice are inoculated with a human pancreatic tumor model (adenosquamous carcinoma model PA6258) with a K-Ras G12D mutation (PA6258). When mean tumor volume reaches approximately 150-200 mm^3, animals are randomly allocated to appropriate treatment groups. Mice are treated with one of the following: (1) Vehicle control, (2) Exemplary MEK inhibitor alone, (3) Second anti-cancer agent alone, or (4) Combination of MEK inhibitor and second anti-cancer agent. Tumors are measured twice per week using calipers.

Example 4: Biological Assays

pERK HTRF assay

Assay Principle:

[00361] Human AsPc-1 cells or HCT-116 cells are seeded in 384-well culture plates and grown overnight. Cells are pretreated with compound (10-pt titration) for 4 hrs. Then, cell lysates are prepared and assayed for levels of phosphorylated ERK1/2 using a homogeneous TR-FRET assay.

3D CTG viability assay

Assay Principle:

CellTiter-Glo 3D cell viability assay is intended for determining cell viability in 3D cell spheroids. The assay reagent penetrates large spheroids and has increased lytic capacity. It measures ATP as an indicator of viability and generates a luminescent readout. Cell Titer-Glo 3D cell viability assay kit Promega G9683 was used.

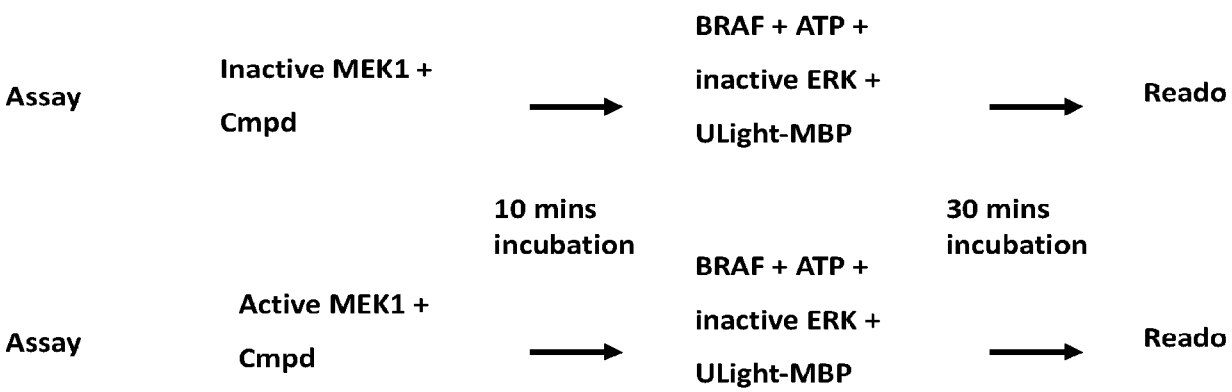
Generic protocol for NANOBRET

[00362] The protein:protein interaction of MEK1 and BRAF, MEK1 and CRAF, MEK1 and KSR1, and MEK1 and KSR2 are evaluated using a NANOBRET assay (Promega, Inc. Madison, Wisconsin). The full length open reading frames of each gene pair are either N-terminally or C-terminally fused with the open reading frames of either the NANOLUC® or HALOTAG® coding sequences. Once the vectors are synthesized, empiric evaluation of tag location for each pair determines the optimum signal window. The appropriate NANOLUC® and HALOTAG® chimeric gene fusions are transfected into HEK293 cells (or other cell lines) and cultured in white 96- or 384-well plates suitable for tissue culture and signal evaluation. Ikena compounds are dispensed to the transfected, live cells along with the necessary positive and negative controls. At discrete times the NANOBRET™ NANOLUC® substrate is added and donor and acceptor signals are measured on the Envision Multimode (or other capable instrument). Protein:protein interaction is evaluated by calculating the NANOBRET™ ratio by subtracting the NANOBRET™ ratios of the control samples from the experimental samples. Additionally, expression of these chimeric gene fusions in mammalian, bacterial or yeast protein expression systems can yield recombinant protein that can be used in an in vitro biochemical assay.

MEK1 Kinase Assay Protocol

Assay Principle:

It is a coupled assay which includes inactive ERK activation by MEK1 and phosphorylation of ULIGHT-MBP substrate. The phosphorylated substrate captured by an Eu-anti-phospho-substrate antibody, which brings the Eu chelate donor and ULIGHT acceptor dyes into close proximity. Upon excitation at 340 nm, the Eu chelate transfers its energy to the ULIGHT dye, resulting in a fluorescent light emission at 665 nm.



HCT116 ERK/pERK in-cell western assay

[00363] The In-Cell Western (ICW) Assay is a quantitative immunofluorescence assay performed in microplates (optimized for 96- or 384-well format) that combines the specificity of Western blotting with the replicability and throughput of ELISA.

[00364] In-Cell Western Assays are also called cytoblots, cell-based ELISA, In-Cell ELISA (ICE), and FACE (Fast Activated Cell-based ELISA). With In-Cell Western Assays, you can:

- Detect proteins in fixed and permeabilized cultured cells using target-specific primary antibodies and IRDYE® secondary antibodies
- Quantify two targets at 700 nm and 800 nm, using spectrally-distinct infrared dye conjugates
- Quickly, accurately measure relative protein levels in many samples
- Detect proteins in situ in a relevant cellular context

[00365] **Tables 2** and **3** show the activity of selected compounds in the assays described above. The compound numbers correspond to the compound numbers in **Table 1**. The activity is classified as A-D, wherein A represents $IC_{50} < 100$ nM; B represents 100 nM $\leq IC_{50} < 1$ uM; C represents 1 $\leq IC_{50} < 10$ uM; and D represents $IC_{50} \geq 10$ uM.

Table 2.

Compound	pERK AsPC-1 HTRF (4-hour): Average IC50 (nM)	pERK HCT-116 ICW (4-hour): Average IC50 (nM)	AsPC-1 CTG: Average IC50 (nM)
I-21	A	A	A
I-41	A	A	A
I-42	A	A	A
I-24	A	A	A
I-25	A	A	A
I-29	A	A	A
I-44	A	A	A
I-45	A	A	A
I-46	A	A	A
I-33	A	A	A
I-110 isomer 1	A	A	A
I-110 isomer 2	A	A	A
I-49	A	A	A
I-50	A	A	A
I-20	A	A	A
I-31	A	A	A
I-27 isomer 1	A	A	A
I-27 Isomer 2	A	A	A
I-54	D	C	
I-22	D	A	
I-55	A	A	

Table 3.

Compound	pERK HCT-116 ICW (4-hour): Average IC50 (nM)	pERK HCT-116 ICW (3-day): Average IC50 (nM)	pERK AsPC-1 HTRF (4-hour): Average IC50 (nM)	MEK1 HTRF: Average IC50 (nM)	AsPC-1 CTG: Average IC50 (nM)	HCT-116 ULA: Average IC50 (nM)
I-111	C		C		C	
I-109	A		A		A	
I-102	A		A		A	
I-82			A		A	
I-103			B		B	
I-54			C		C	
I-55	A	A	A		A	
I-22	D	D	D		D	
I-54	D	D	D		D	
I-52	A	A	A		A	
I-51	A	A	A		A	A
I-31	A	A	A		A	A
I-48	A	A	A	A	A	A
I-47	A	A	A	A	A	A
I-46	A	A	A	A	A	
I-29	A	A	A	A	A	
I-25	A	A	A	A	A	
I-24	A	A	A	A	A	
I-42	A	A	A	A	A	
I-41	A	A	A	A	A	
I-21	A	A	A	A	A	

I-33	A	A	A	A	A	
I-44	A	A	A	A	A	
I-20	A	A	A		A	
I-50	A	A	A		A	
I-49	A	A	A		A	
I-45	A	A	A	A	A	

[00366] **Table 4** shows the activity of selected compounds in the assays described above. The compound numbers correspond to the compound numbers in **Table 1**. The activity is classified as A-D, wherein A represents IC_{50} < 100 nM; B represents 100 nM ≤ IC_{50} < 1 uM; C represents 1 ≤ IC_{50} < 10 uM; and D represents IC_{50} ≥10 uM. The CRaf/MEK SPR: KD Ratio is classified as A-D, wherein A represents KD Ratio < 0.5; B represents 0.5 ≤ KD Ratio < 1; C represents 1 ≤ KD Ratio < 5; and D represents KD Ratio ≥5.

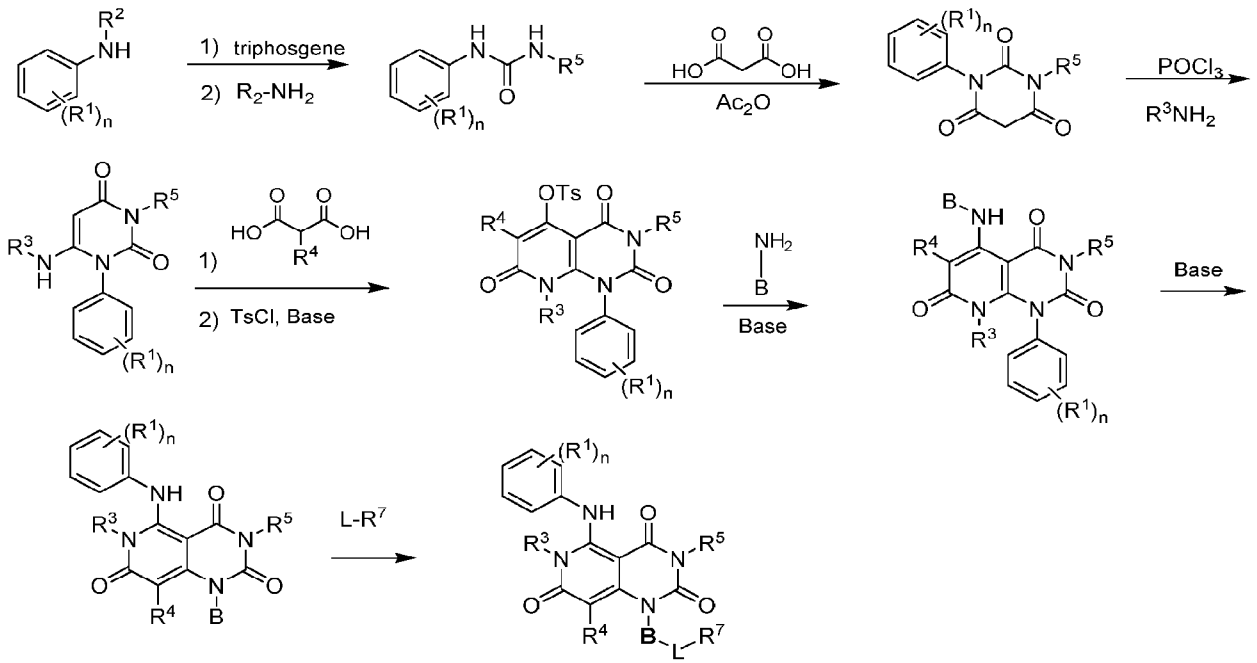
Table 4.

Compound	uMEK/BRAF HTRF: Average IC50 (nM)	pERK HCT-116 (G13D) ICW (4 hour): Average IC50 (nM)	CRaf/MEK SPR: KD Ratio
I-127	D	D	B
I-126	A	A	D
I-125	A	A	D
I-124	A	A	A
I-123	A	A	A
I-122	A	B	A
I-121	A	A	C
I-120	A	A	
I-119	A	A	A
I-118	A	A	A
I-117	A	A	C
I-28	A	A	C
I-116	B	C	

I-109	B	A	C
I-102	A	A	A
I-82	A		D
I-103	C	A	B
I-83	A		A
I-55		A	A
I-22	D	D	
I-54		D	
I-52	A	A	
I-51	A	A	A
I-31	A	A	A
I-20	A	A	
I-49	A	A	
I-48	A	A	A
I-47	A	A	C
I-33		A	C
I-46	A	A	B
I-45		A	
I-29	A	A	
I-115		A	D
I-25		A	D
I-114		A	A
I-24		A	
I-42	A	A	
I-41		A	
I-21	A	A	A
I-113	B	A	
I-112	A	A	D

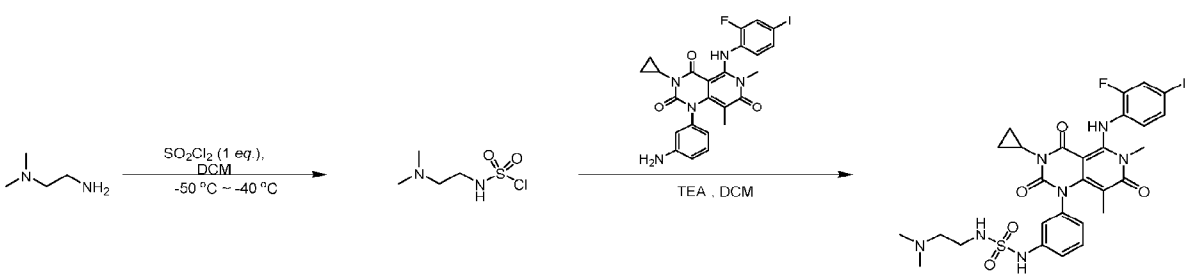
Example 5: Synthesis of Certain Compounds

General synthesis scheme

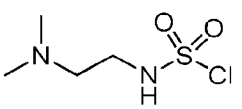


[00367] A general synthesis scheme for compounds as described herein is provided above. Additionally, synthesis procedures for certain exemplary compounds are provided below.

I-21



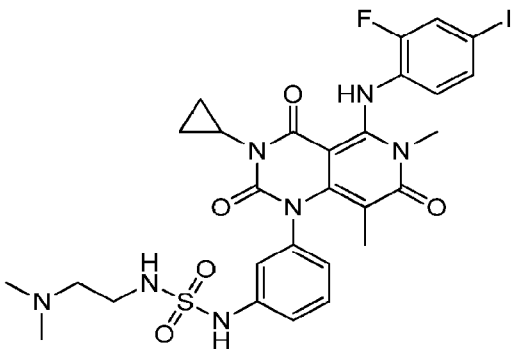
Step 1: ***N*-[2-(Dimethylamino)ethyl]sulfamoyl chloride**



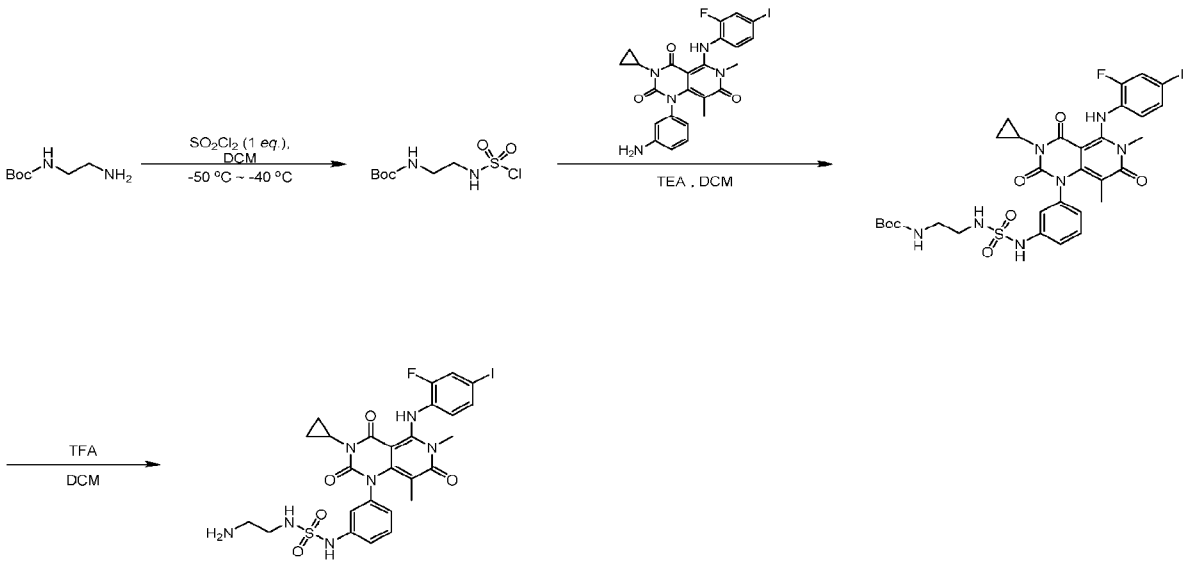
[00368] To a solution of sulfuryl chloride (1.53 g, 11.34 mmol, 1.13 mL, 1 eq) in DCM (50 mL) was added a solution of N',N'-dimethylethane-1,2-diamine (1 g, 11.34 mmol, 1.24 mL, 1 eq) and Et_3N (1.15 g, 11.34 mmol, 1.58 mL, 1 eq) in DCM (5 mL) dropwise under N_2 atmosphere at

-40~-50 °C. The mixture was stirred under N_2 atmosphere at -50 °C for 5 minutes to yield *N*-[2-(dimethylamino)ethyl]sulfamoyl chloride (75 g, crude) as a white suspension liquid, which was used in the next step without further purification.

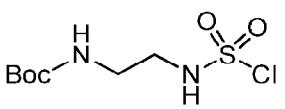
Step 2: **3-Cyclopropyl-1-[3-[2-(dimethylamino)ethylsulfamoylamino]phenyl]-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione**



[00369] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (60 mg, 104.65 μmol, 100% purity, 1 eq) and Et_3N (72.70 mg, 718.46 μmol, 0.1 mL, 6.87 eq) in DCM (10 mL) was added *N*-[2-(dimethylamino)ethyl]sulfamoyl chloride (6 g, 32.14 mmol, N/A purity, 307.17 eq) at 15 °C. The mixture was stirred at 15 °C for 5 minutes. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (0.05% NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 48%-78%, 10 min) and lyophilized to yield 3-cyclopropyl-1-[3-[2-(dimethylamino)ethylsulfamoylamino]phenyl]-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (14.69 mg, 19.82 μmol, 18.9% yield, 97.6% purity) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.68 (dd, J = 1.8, 10.1 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.45-7.38 (m, 1H), 7.26-7.20 (m, 2H), 7.08 (d, J = 7.8 Hz, 1H), 6.88 (t, J = 8.5 Hz, 1H), 3.22 (s, 3H), 3.12 (t, J = 6.9 Hz, 2H), 2.73 (tt, J = 3.8, 7.2 Hz, 1H), 2.51 (t, J = 6.9 Hz, 2H), 2.28 (s, 6H), 1.42 (s, 3H), 1.10-1.05 (m, 2H), 0.80-0.75 (m, 2H); ES-LCMS *m/z* 724.0 $[M+H]^+$.
I-41 & I-42

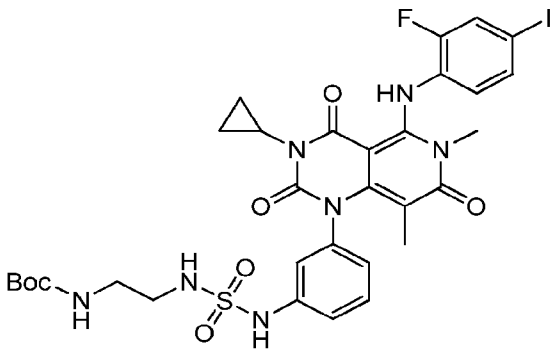


Step 1: ***tert*-Butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate**



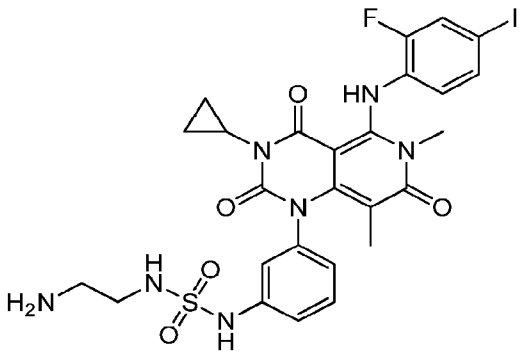
[00370] To a solution of sulfuryl chloride (850 mg, 6.30 mmol, 629.63 μL, 1.01 eq) and Et_3N (1.89 g, 18.73 mmol, 2.61 mL, 3 eq) in DCM (50 mL) was added a solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (1 g, 6.24 mmol, 980.39 μL, 1 eq) in DCM (5 mL) dropwise under N_2 atmosphere at -40~-50 °C. The mixture was stirred under N_2 atmosphere at -40~-50 °C for 5 minutes to yield *tert*-butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate (75 g, crude) as colorless liquid, which was used in the next step without further purification.

Step 2: ***tert*-Butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate**



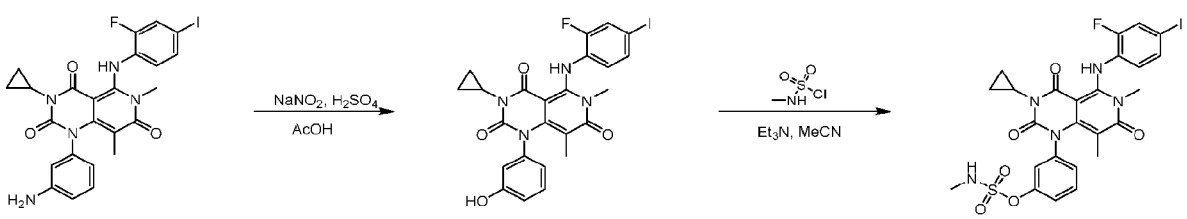
[00371] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (90 mg, 156.97 μmol, 100% purity, 1 eq) and Et_3N (145.40 mg, 1.44 mmol, 0.2 mL, 9.15 eq) in DCM (20 mL) was added *tert*-butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate (10 g, 38.65 mmol, N/A purity, 246.23 eq). The mixture was stirred at 15 °C for 10 minutes. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 3/4, R_f = 0.48) to yield the desired compound (100 mg). 50 mg of the desired compound (100 mg) was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 50%-80%, 10 min) and lyophilized to yield *tert*-butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate (16.07 mg, 20.07 μmol, 12.8% yield, 99.4% purity) as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.58 (dd, J = 1.8, 10.1 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.13 (dd, J = 1.4, 8.1 Hz, 1H), 7.00-6.95 (m, 1H), 6.78 (t, J = 8.5 Hz, 1H), 3.13 (s, 3H), 3.03-2.98 (m, 2H), 2.97-2.92 (m, 2H), 2.64 (tt, J = 3.8, 7.2 Hz, 1H), 1.33 (s, 9H), 1.32 (s, 3H), 1.02-0.96 (m, 2H), 0.71-0.66 (m, 2H); ES-LCMS *m/z* 796.1 $[M+H]^+$.

Step 3: **1-[3-(2-Aminoethylsulfamoylamino)phenyl]-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione**

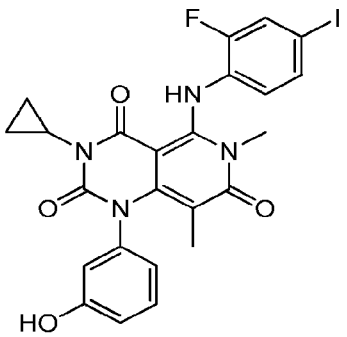


[00372] To a solution of *tert*-butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate (50 mg, 62.84 μmol, N/A purity, 1 eq) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 429.83 eq). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 45%-75%, 10 min) and lyophilized to yield 1-[3-(2-aminoethylsulfamoylamino)phenyl]-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (16.78 mg, 23.94 umol, 38.09% yield, 99.223% purity) was obtained as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.68 (dd, J = 1.8, 10.1 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.28-7.25 (m, 1H), 7.25-7.22 (m, 1H), 7.08-7.04 (m, 1H), 6.88 (t, J = 8.5 Hz, 1H), 3.22 (s, 3H), 3.06 (t, J = 6.1 Hz, 2H), 2.76-2.70 (m, 3H), 1.41 (s, 3H), 1.10-1.05 (m, 2H), 0.80-0.76 (m, 2H); ES-LCMS *m/z* 696.0 $[M+H]^+$.

I-24

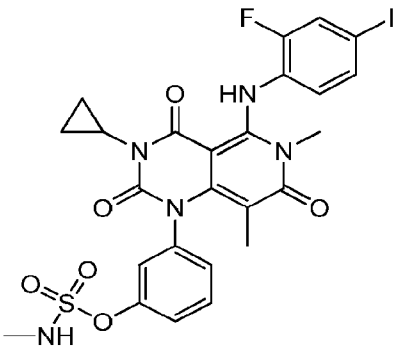


Step 1: **3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(3-hydroxyphenyl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



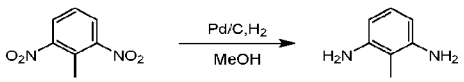
[00373] An aqueous solution of $NaNO_2$ (9.63 mg, 139.53 µmol, 2 eq) in H_2O (1 mL) was added to a solution of 1-(3-ainophenyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (40 mg, 69.76 µmol, 100.0% purity, 1 eq) in H_2SO_4 (0.25 mL) and H_2O (0.5 mL) at 0 °C. The reaction mixture was stirred for 30 minutes. AcOH (2 mL) was added. The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated under reduced pressure to remove most acetic acid. The residue was added addition sat aq $NaHCO_3$ until pH 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 1/1, R_f = 0.4) to yield 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(3-hydroxyphenyl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (35 mg, 55.45 µmol, 79.5% yield, 91.0% purity) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.30 (s, 1H), 7.53 (d, J = 9.3 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.29 (s, 1H), 6.84 (d, J = 7.8 Hz, 2H), 6.80 (s, 1H), 6.70 (t, J = 8.0 Hz, 1H), 5.59 (s, 1H), 3.21 (s, 3H), 2.75 (s, 1H), 1.44 (s, 3H), 1.16-1.10 (m, 2H), 0.86 (d, J = 16.8 Hz, 2H); ES-LCMS *m/z* 574.8 $[M+H]^+$.

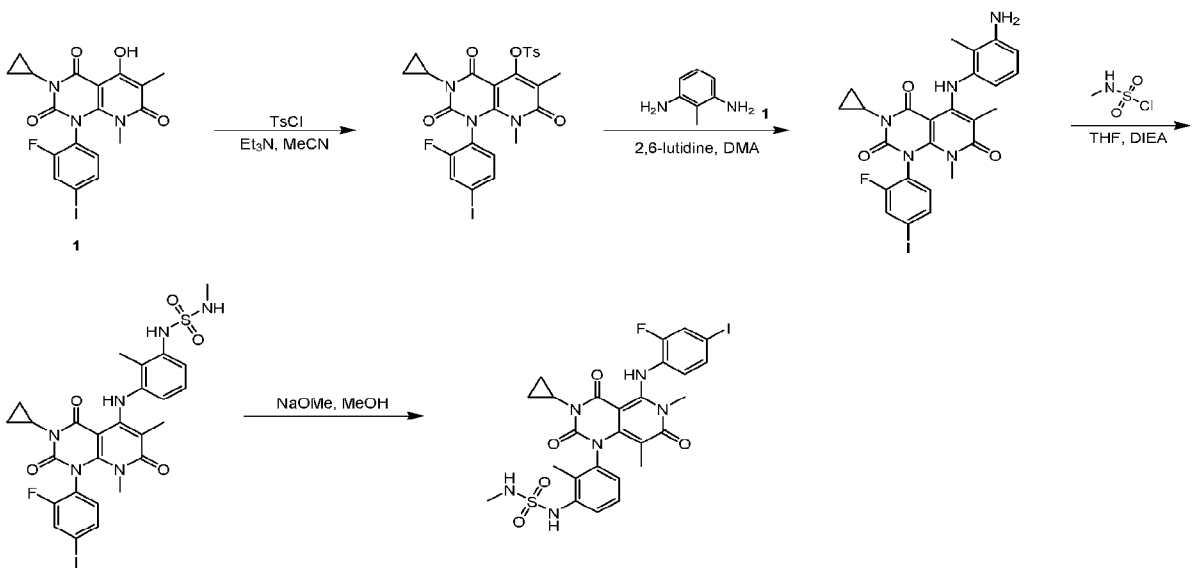
Step 2: **3-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl methylsulfamate**



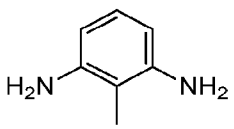
[00374] To a solution of 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(3-hydroxyphenyl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (25 mg, 55.45 µmol, 79.5% yield, 91.0% purity, 1 eq) in DCM (1 mL) was added *N*-methylsulfamoyl chloride (4.62 mg, 35.65 µmol, 0.9 eq) and Et_3N (12.02 mg, 118.83 µmol, 16.54 µL, 3 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was acidified by the addition of 0.1 *N* HCl and extracted with EtOAc (20 mL x 3). The organic layer was washed with brine (20 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water (0.05% NH_3H_2O + 10mM NH_4HCO_3)-ACN]; B%: 55%-85%, 10 min) and lyophilized to give desired compound (20 mg, purity 60.0%) as a white solid, which was further purified by preparative TLC (PE/EtOAc = 1/1, R_f = 0.38) to yield 3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl methylsulfamate (8.34 mg, 12.50 µmol, 31.6% yield, 100.0% purity) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.28 (s, 1H), 7.53 (dd, J = 1.7, 9.6 Hz, 1H), 7.49-7.45 (m, 2H), 7.34-7.29 (m, 2H), 7.25 (d, J = 2.3 Hz, 1H), 6.72 (t, J = 8.3 Hz, 1H), 4.80 (s, 1H), 3.21 (s, 3H), 2.96-2.91 (m, 3H), 2.80-2.71 (m, 1H), 1.40 (s, 3H), 1.16-1.11 (m, 2H), 0.83-0.77 (m, 2H); ES-LCMS *m/z* 668.0 $[M+H]^+$.

I-25



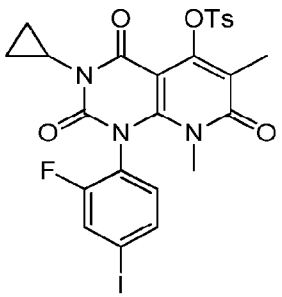


Step 1: **2-Methylbenzene-1,3-diamine**



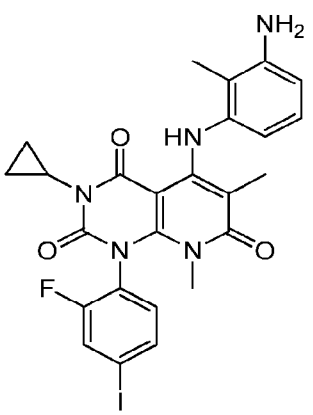
[00375] To a solution of 2-methyl-1,3-dinitro-benzene (2 g, 10.98 mmol, 1 eq) in MeOH (15 mL) was added Pd/C (1 g, 10.98 mmol, 10.0% purity, 1.00 eq) under Ar_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (30 psi) at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.37) to yield 2-methylbenzene-1,3-diamine (800 mg, 6.35 mmol, 57.9% yield, 97.0% purity) as a gray solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.67-7.15 (m, 1H), 6.89-6.81 (m, 2H), 6.22 (d, J = 7.8 Hz, 4H), 1.99 (s, 3H).

Step 2: **[3-Cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate**



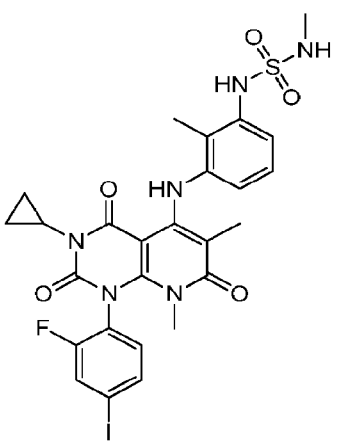
[00376] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (800 mg, 1.66 mmol, 100.0% purity, 1 eq) in MeCN (35 mL) was added 4-methylbenzenesulfonyl chloride (479.74 mg, 2.52 mmol, 1.52 eq) and Et_3N (581.30 mg, 5.74 mmol, 799.58 µL, 3.47 eq). The mixture was stirred under N_2 atmosphere at 15 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 2/1, R_f = 0.3) to yield [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (620 mg, 924.04 µmol, 55.8% yield, 95.0% purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 11.28 (s, 1H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.47 (s, 2H), 7.37-7.29 (m, 2H), 7.26-7.23 (m, 1H), 6.72 (t, *J* = 7.2 Hz, 1H), 4.95 (s, 1H), 3.21 (s, 3H), 2.93 (s, 3H), 2.74 (s, 1H), 1.40 (s, 3H), 1.27 (s, 2H), 1.14 (d, *J* = 6.1 Hz, 2H); ES-LCMS *m/z* 638.0 $[M+H]^+$.

Step 3: **5-(3-Amino-2-methyl-anilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione**



[00377] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (220 mg, 327.89 µmol, 95.0% purity, 1 eq) in DMA (2 mL) was added 2-methylbenzene-1,3-diamine (123.89 mg, 983.66 µmol, 97.0% purity, 3 eq) and 2,6-LUTIDINE (105.40 mg, 983.66 µmol, 114.56 µL, 3 eq). The mixture was stirred under microwave at 180 °C for 2 h. The mixture was diluted with water (20 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.05% HCl)-ACN];B%: 46%-76%, 10 min) and lyophilized to yield 5-(3-amino-2-methyl-anilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (58 mg, 88.65 µmol, 27.0% yield, 95.4% purity, HCl) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.16 (s, 1H), 7.70-7.59 (m, 2H), 7.14 (d, J = 7.8 Hz, 2H), 7.08-6.77 (m, 1H), 6.67(d, J = 6.1 Hz, 1H), 2.97 (s, 3H), 2.78 (s, 1H), 2.55 (s, 3H), 1.60 (s, 3H), 1.18 (d, J = 5.6 Hz, 2H), 0.83 (s, 2H); ES-LCMS *m/z* 588.1 $[M+H]^+$.

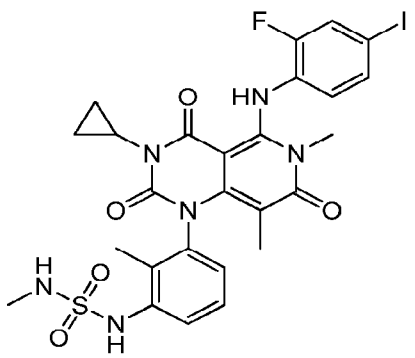
Step 4: **3-Cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[2-methyl-3-(methylsulfamoylamino)anilino]pyrido[2,3-*d*]pyrimidine-2,4,7-trione**



[00378] To a solution of 5-(3-amino-2-methyl-anilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (50 mg, 76.42 µmol, 95.4% purity, 1 eq, HCl) in DCM (1 mL) was added *N*-methylsulfamoyl chloride (8.91 mg, 68.78 µmol, 0.9 eq) and TEA (38.66 mg, 382.11 µmol, 53.18 µL, 5 eq). The mixture was stirred under N_2

atmosphere at 5°C for 1 h. The residue was added addition *sat. aq.* $NaHCO_3$ until pH 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by prep-TLC (SiO_2, PE/EtOAc = 1/1, R_f = 0.38) to yield 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[2-methyl-3-(methylsulfamoylamino)anilino]pyrido[2,3-*d*]pyrimidine-2,4,7-trione (50 mg, 70.19 μmol, 91.9% yield, 95.5% purity) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.11 (s, 1H), 7.63 (d, *J* = 9.5 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.25 (s, 1H), 4.50 (s, 1H), 4.12 (s, 1H), 2.96 (s, 3H), 2.85 (s, 1H), 2.79 (s, 3H), 2.74 (d, *J* = 4.6 Hz, 3H), 1.54 (s, 3H), 1.18 (d, *J* = 6.1 Hz, 2H), 0.83 (d, *J* = 5.4 Hz, 2H); ES-LCMS *m/z* 681.0 $[M+H]^+$.

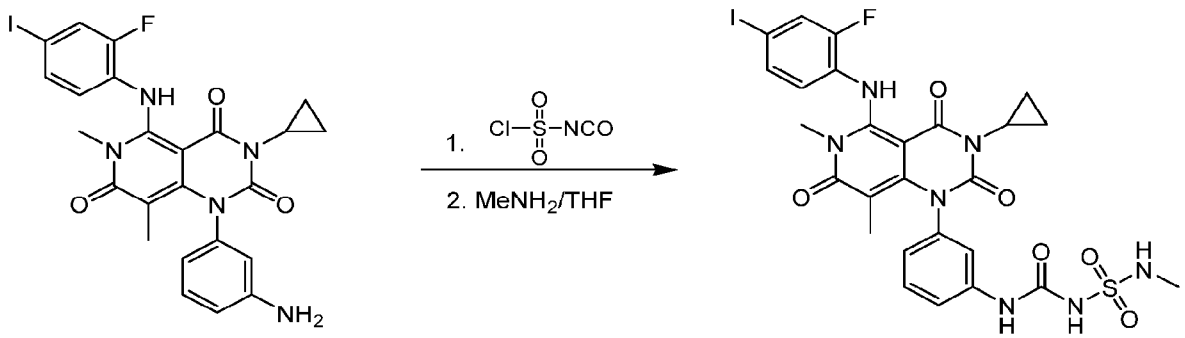
Step 5: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



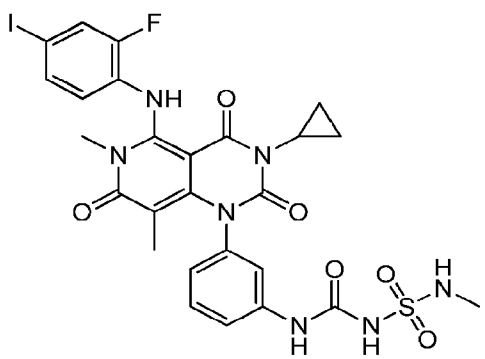
[00379] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[2-methyl-3-(methylsulfamoylamino)anilino]pyrido[2,3-*d*]pyrimidine-2,4,7-trione (30 mg, 42.11μmol, 95.5% purity, 1 eq) in THF (1 mL) was added a drop of NaOMe/MeOH (28 wt %, 42.11 μmol, 1 eq). The mixture was stirred at 25 °C for 1 h. The residue was added AcOH until pH to 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(0.05%HCl)-ACN]; B%: 50%-70%,10 min) and lyophilized to yield a product, which was added addition sat aq $NaHCO_3$ until pH = 7 and extracted with EtOAc (20 mL x 3), then the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 3-cyclopropyl-5-(2-

fluoro-4-iodo-anilino)-6,8-dimethyl-1-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (10.19 mg, 14.66 μmol, 34.8% yield, 97.9% purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.70-7.63 (m, 1H), 7.55 (*J* = 8.4, 12.8 Hz, 2H), 7.28 (*J* = 7.8 Hz, 1H), 7.06 (d, *J* = 7.1 Hz, 1H), 6.86 (t, *J* = 8.6 Hz, 1H), 3.20 (s, 3H), 2.74-2.69 (m, 1H), 2.67 (s, 3H), 2.24 (s, 3H), 1.27 (s, 3H), 1.07 (d, *J* − 7.1 Hz, 2H), 0.89-0.76 (m, 2H); ES-LCMS *m/z* 681.0 $[M+H]^+$.

I-29



Step 1: **1-[3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]-3-(methylsulfamoyl)urea**



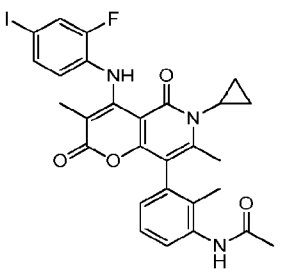
[00380] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (200 mg, 348.82 μmol, 1 eq) in THF (20 mL) was added *N*-(oxomethylene)sulfamoyl chloride (100 mg, 706.55 μmol, 61.35 μL, 2.03 eq) under N_2 atmosphere at -60 °C. The mixture was stirred under N_2 atmosphere at -60~ -20 °C for 0.5 h. $MeNH_2$ (235 mg, 3.48 mmol, 100% purity, 9.98 eq, HCl) and Et_3N (352.97 mg, 3.49 mmol, 485.52 μL, 10 eq) was added. The mixture was warmed to 25 °C slowly and stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to yield a residue which was

purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (0.05%HCl)-ACN]; B%: 50%-70%, 10 min) and lyophilized. The residue was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 25%-55%, 10 min) and lyophilized to yield 1-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]-3-(methylsulfamoyl)urea (18.94 mg, 25.86 μmol, 7.4% yield, 96.9% purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.70-7.52 (m, 3H), 7.40 (d, J = 4.6 Hz, 2H), 7.08 (d, J = 3.2 Hz, 1H), 6.86 (t, J = 8.6 Hz, 1H), 3.20 (s, 3H), 2.75-2.65 (m, 4H), 1.40 (s, 3H), 1.10-1.00 (m, 2H), 0.80-0.70(m, 2H); ES-LCMS *m/z* 710.0 $[M+H]^+$.

I-44

1

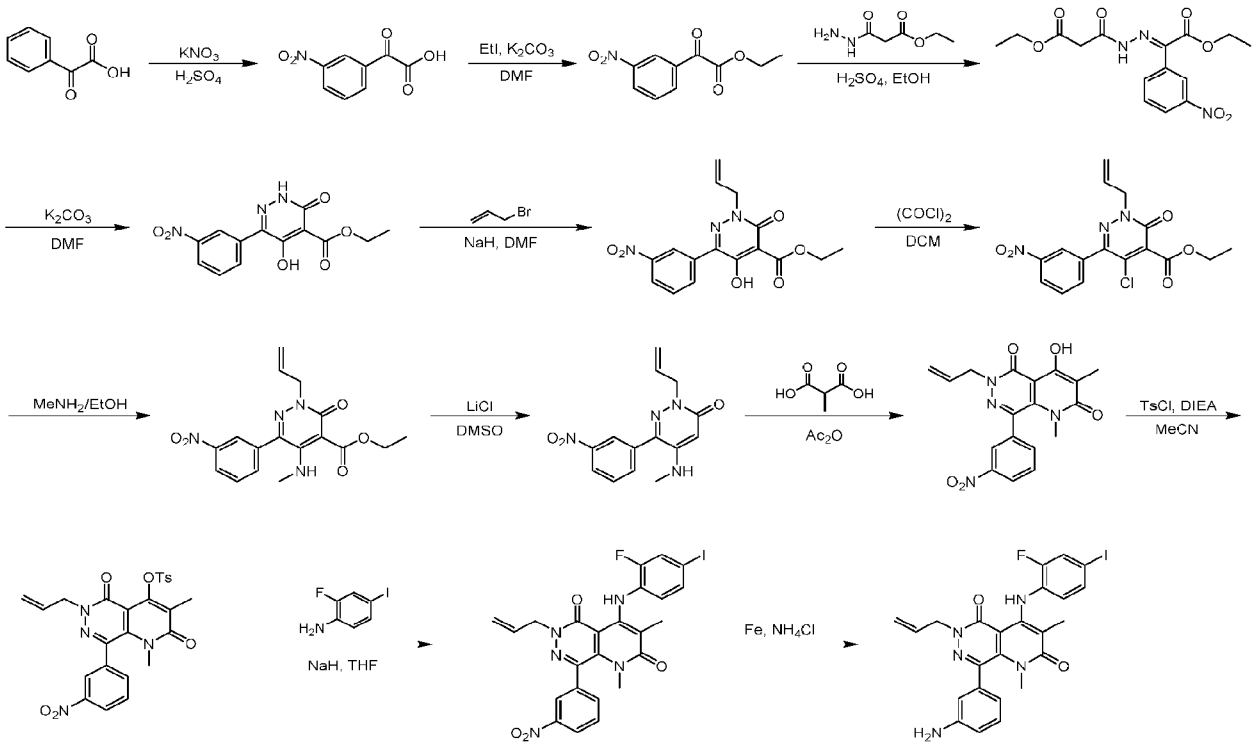
Step 1: ***N*-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-2,5-dioxo-pyrano[3,2-c]pyridin-8-yl]-2-methyl-phenyl]acetamide**



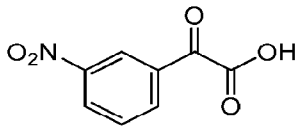
[00381] To a stirred solution of 8-(3-amino-2-methyl-phenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-pyrano[3,2-c]pyridine-2,5-dione (20 mg, 31.50 μmol, 90.0% purity, 1 eq) and TEA (9.56 mg, 94.51 μmol, 13.15 μL, 3 eq) in DCM (2 mL) was added acetyl chloride (4.95 mg, 63.01 μmol, 4.50 μL, 2 eq). The reaction mixture was stirred at 0 °C for 1 h under N_2

atmosphere. The reaction mixture was quenched by addition *sat. aq.* $NaHCO_3$ (15 mL) at 0 °C and extracted with DCM (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (PE/EtOAc = 0/1, TLC: PE/EtOAc = 0/1, R_f = 0.45), followed by lyophilization to yield *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-2,5-dioxo-pyrano[3,2-c]pyridin-8-yl]-2-methyl-phenyl]acetamide (13.71 mg, 22.31 µmol, 70.8% yield, 99.8% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.32 (s, 1H), 9.40 (s, 1H), 7.72 (d, J = 10.3 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.26 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.88 (t, J = 8.7 Hz, 1H), 3.04 (d, J = 4.2 Hz, 1H), 2.24 (s, 3H), 2.08 (s, 3H), 1.95 (s, 3H), 1.45 (s, 3H), 1.21 (d, J = 8.1 Hz, 2H), 0.97-0.88 (m, 2H); ES-LCMS *m/z* 614.0 $[M+H]^+$.

I-45

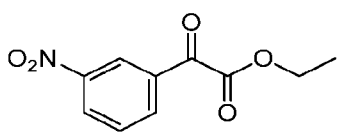


Step 1: **2-(3-Nitrophenyl)-2-oxo-acetic acid**



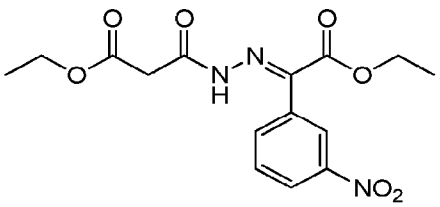
[00382] To a solution of 2-oxo-2-phenyl-acetic acid (51 g, 339.70 mmol, 1 eq) in H_2SO_4 (80 mL) was added KNO_3 (41.21 g, 407.64 mmol, 1.2 eq) at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was poured into ice water (1.6 L) and extracted with EtOAc (400 mL x 3). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-(3-nitrophenyl)-2-oxo-acetic acid (66 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (t, J = 1.8 Hz, 1H), 8.56 (td, J = 1.2, 8.2 Hz, 1H), 8.41-8.37 (m, 1H), 7.89 (t, J = 8.0 Hz, 1H).

Step 2: **Ethyl 2-(3-nitrophenyl)-2-oxo-acetate**



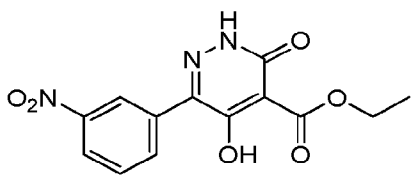
[00383] To a solution of 2-(3-nitrophenyl)-2-oxo-acetic acid (66 g, 338.24 mmol, 1 eq) in DMF (700 mL) was added K_2CO_3 (121.54 g, 879.42 mmol, 2.6 eq). After stirred at 20 °C for 2h, iodoethane (263.77 g, 1.69 mol, 135.26 mL, 5 eq) was added dropwise. The mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into water (800 mL), extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1, TLC: PE/EtOAc = 5/1, R_f = 0.45) to yield ethyl 2-(3-nitrophenyl)-2-oxo-acetate (35.5 g, 143.16 mmol, 42.3% yield, 90.0% purity) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.90 (s, 1H), 8.54-8.47 (m, 1H), 8.40 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H).

Step 3: **Ethyl 3-[(2*E*)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate**



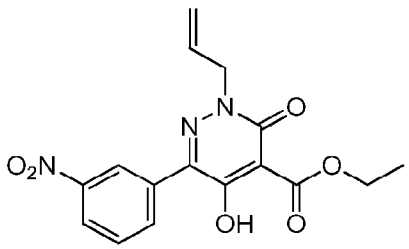
[00384] To a solution of ethyl 2-(3-nitrophenyl)-2-oxo-acetate (22.5 g, 90.73 mmol, 1 eq) in EtOH (120 mL) was added H_2SO_4 (2.29 g, 23.33 mmol, 1.24 mL, 0.25 eq) and ethyl 3-hydrazino-3-oxo-propanoate (13.79 g, 94.36 mmol, 1.04 eq). The mixture was stirred at 90 °C for 2 h. The solvent was removed to yield a residue which was diluted with water (200 mL) and extracted with EtOAc (300 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield ethyl 3-[(2*E*)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate (30 g, crude, E/Z mixture) as a yellow oil. ES-LCMS *m/z* 352.2 $[M+H]^+$.

Step 4: **Ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate**



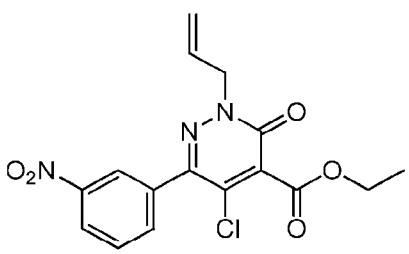
[00385] To a solution of ethyl 3-[(2*E*)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate (30 g, 85.39 mmol, E/Z mixture, 1 eq) in DMF (300 mL) was added K_2CO_3 (6.49 g, 46.97 mmol, 0.55 eq). The mixture was stirred at 80 °C for 3 h. The mixture was cooled to ambient temperature and poured into 3N HCl (600 mL). The precipitated solid was collected by filtration to give a residue which was added MeOH (50 mL), and stirred at 15 °C for 2 h. The slurry was filtered, and the cake was rinsed with MeOH (3 x 3 mL). The solid was collected and dried in vacuo to yield ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate (8.3 g, 24.47 mmol, 28.7% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 13.23 (s, 1H), 8.58-8.53 (m, 1H), 8.30 (td, J = 1.2, 7.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ES-LCMS *m/z* 306.1 $[M+H]^+$.

Step 5: **Ethyl 2-allyl-5-hydroxy-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate**



[00386] To a solution of ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (3 g, 8.85 mmol, 1 eq) in DMF (40 mL) was added NaH (707.63 mg, 17.69 mmol, 60.0% purity, 2 eq) and stirred at 20 °C for 30 min. The solution was cooled to -10 °C, 3-bromoprop-1-ene (1.12 g, 9.29 mmol, 1.05 eq) was added dropwise. The reaction temperature was slowly warmed up to 20 °C and stirred at 20 °C for 1 h. The reaction mixture was quenched by addition water (60 mL) and extracted with EtOAc (80 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield ethyl 2-allyl-5-hydroxy-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (3 g, 7.82 mmol, 88.4% yield, 90.0% purity) as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.57 (s, 1H), 8.30 (d, J = 1.5, 8.3 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 5.98 (td, J = 5.5, 10.9, 16.8 Hz, 1H), 5.24-5.15 (m, 2H), 4.70 (d, J = 5.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ES-LCMS m/z 346.0 $[M+H]^+$.

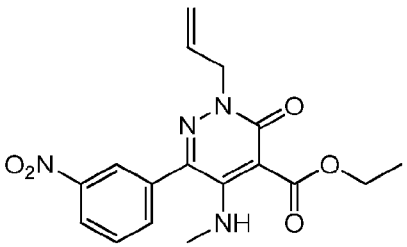
Step 6: **Ethyl 2-allyl-5-chloro-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate**



[00387] To a solution of ethyl 2-allyl-5-hydroxy-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (3 g, 7.82 mmol, 1 eq) in DCM (40 mL) was added $(COCl)_2$ (9.92 g, 78.19 mmol, 6.84 mL, 10 eq). The mixture was stirred at 35 °C for 3 h. The solvent was removed to yield ethyl 2-allyl-5-chloro-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (3 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.46 (t, J = 1.8 Hz, 1H), 8.37-8.33 (m, 1H), 7.91 (d, J

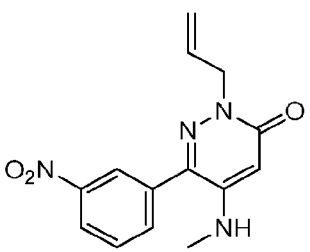
= 1.0, 7.8 Hz, 1H), 7.68 (t, *J* = 7.9 Hz, 1H), 6.01 (td, *J* = 6.2, 10.3, 16.9 Hz, 1H), 5.41-5.27 (m, 2H), 4.82 (d, *J* = 6.4 Hz, 2H), 4.49 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H); ES-LCMS *m/z* 364.1, 366.1 $[M+H]^+$.

Step 7: **Ethyl 2-allyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate**



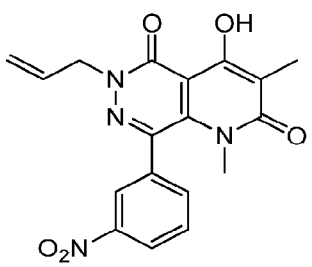
[00388] To a solution of ethyl 2-allyl-5-chloro-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (3 g, 6.60 mmol, 1 eq) in DCM (30 mL) was added $MeNH_2$ (13.66 g, 131.96 mmol, 30.0% purity, 20 eq) at 0 °C. The mixture was stirred at 0 °C for 5 h. The reaction mixture was quenched by addition water (50 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (PE/EtOAc = 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.24) to yield ethyl 2-allyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (2.2 g, 5.53 mmol, 83.7% yield, 90.0% purity) as a yellow solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.38-8.32 (m, 1H), 8.29 (t, *J* = 1.7 Hz, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.83-7.76 (m, 1H), 6.24 (d, *J* = 5.1 Hz, 1H), 5.98-5.84 (m, 1H), 5.21-5.07 (m, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.24 (q, *J* = 7.1 Hz, 2H), 2.66 (d, *J* = 5.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H); ES-LCMS *m/z* 359.1 $[M+H]^+$.

Step 8: **2-Allyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one**



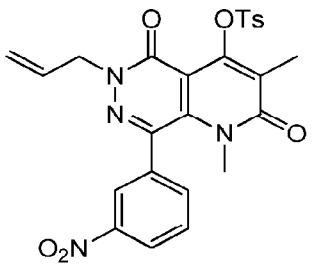
[00389] To a solution of ethyl 2-allyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (1.5 g, 3.77 mmol, 1 eq) in DMSO (20 mL) was added LiCl (3.19 g, 75.35 mmol, 20 eq). The mixture was stirred at 180 °C for 6 h. The mixture was diluted with water (40 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 1/2, TLC: PE/EtOAc = 1/2, R_f = 0.25) to yield 2-allyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (1.2 g, 3.35 mmol, 89.0% yield, 80.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, J = 1.7 Hz, 1H), 8.34-8.29 (m, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.70 (t, J = 7.9 Hz, 1H), 6.09-5.94 (m, 1H), 5.86 (s, 1H), 5.28-5.17 (m, 2H), 4.73 (d, J = 4.6 Hz, 2H), 4.29 (s, 1H), 2.85-2.79 (m, 3H); ES-LCMS *m/z* 287.1 $[M+H]^+$.

Step 9: **6-Allyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione**



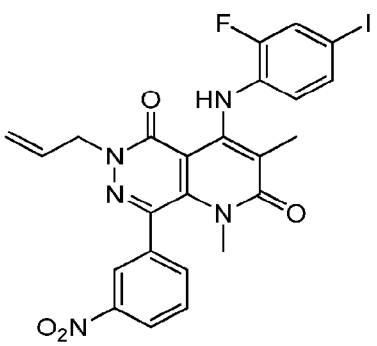
[00390] To a solution of 2-allyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (1.2 g, 3.35 mmol, 1 eq) in Ac2O (20 mL) was added 2-methylpropanedioic acid (1.19 g, 10.06 mmol, 3 eq). The mixture was stirred at 110 °C for 2 h. The solvent was removed to yield a residue which was purified by preparative TLC (PE/EtOAc = 1/1, TLC: PE/EtOAc = 1/1, Rf = 0.40), followed by lyophilization to yield 6-allyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (1.1 g, 2.45 mmol, 73.0% yield, 82.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.50-8.27 (m, 2H), 7.83-7.60 (m, 2H), 6.10-5.92 (m, 1H), 5.39-5.31 (m, 2H), 4.86 (d, J = 6.1 Hz, 2H), 3.08 (s, 3H), 2.15 (s, 3H); ES-LCMS *m/z* 369.1 $[M+H]^+$.

Step 10: **[6-Allyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate**



[00391] To a solution of 6-allyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (1.1 g, 2.45 mmol, 1 eq) in ACN (20 mL) was added DIEA (1.58 g, 12.24 mmol, 2.13 mL, 5 eq) and 4-methylbenzenesulfonyl chloride (933.71 mg, 4.90 mmol, 2 eq). The mixture was stirred at 60 °C for 1 h. The mixture was diluted with water (50 mL) and extracted with EtOAc (60 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.35) to yield [6-allyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate (1.2 g, 1.88 mmol, 76.9% yield, 82.0% purity) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.41-8.30 (m, 2H), 7.97 (d, J = 8.3 Hz, 2H), 7.79-7.66 (m, 2H), 7.41 (d, J = 8.3 Hz, 2H), 6.10-5.94 (m, 1H), 5.40-5.22 (m, 2H), 4.84 (d, J = 6.1 Hz, 2H), 3.09 (s, 3H), 2.50 (s, 3H), 1.89 (s, 3H); ES-LCMS m/z 523.1 $[M+H]^+$.

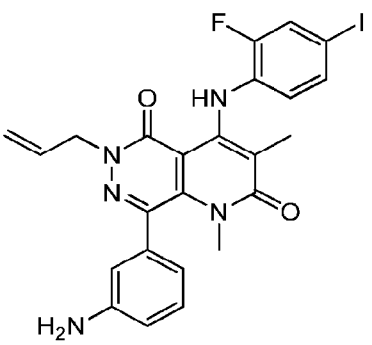
Step 11: **6-Allyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione**



[00392] To a solution of 2-fluoro-4-iodo-aniline (647.80 mg, 2.73 mmol, 2.49 eq) in THF (10 mL) was added NaH (175.74 mg, 4.39 mmol, 60.0% purity, 4 eq) and stirred at 0 °C for 30 min, [6-allyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-

methylbenzenesulfonate (700 mg, 1.10 mmol, 1 eq) was added at 0 °C. The reaction temperature was slowly warmed up to 25 °C and stirred at 25 °C for 3 h. The reaction mixture was quenched by addition water (30 mL) and extracted with EtOAc (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.43) to yield 6-allyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (150 mg, 217.08 µmol, 19.7% yield, 85.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.72 (s, 1H), 8.42-8.39 (m, 1H), 8.36 (td, J = 1.8, 7.8 Hz, 1H), 7.77-7.66 (m, 2H), 7.46 (dd, J = 1.8, 10.0 Hz, 1H), 7.38 (d, J = 8.7 Hz, 1H), 6.57 (t, J = 8.5 Hz, 1H), 6.04 (td, J = 6.1, 10.4, 16.9 Hz, 1H), 5.39-5.28 (m, 2H), 4.86 (d, J = 6.0 Hz, 2H), 3.08 (s, 3H), 1.82 (s, 3H); ES-LCMS *m/z* 588.0 $[M+H]^+$.

Step 10: **6-Allyl-8-(3-aminophenyl)-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione**



[00393] To a solution of 6-allyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (130 mg, 188.14 µmol, 1 eq) in EtOH (1.5 mL) and H_2O (1.5 mL) was added NH_4Cl (100.64 mg, 1.88 mmol, 10 eq) and Fe (52.53 mg, 940.68 µmol, 5 eq). The mixture was stirred at 90 °C for 3 h. The reaction mixture was filtered to remove the insoluble. The filter liquor was concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: $AgNO_3$_silica 150*25mm*15um; mobile phase: [Heptane-EtOH (0.1%NH_3H_2O)]; B%: 0%-80%, 9min), followed by lyophilization to yield 6-allyl-8-(3-aminophenyl)-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-

d]pyridazine-2,5-dione (80.27 mg, 144.02 μmol, 76.6% yield, 100.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.81 (s, 1H), 7.44 (d, J = 1.8, 10.1 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 6.84-6.70 (m, 3H), 6.53 (t, J = 8.5 Hz, 1H), 6.04 (td, J = 6.0, 10.5, 17.0 Hz, 1H), 5.37-5.24 (m, 2H), 4.85 (d, J = 4.9 Hz, 2H), 3.83 (s, 2H), 3.16 (s, 3H), 1.81 (s, 3H); ES-LCMS *m/z* 557.9 $[M+H]^+$.

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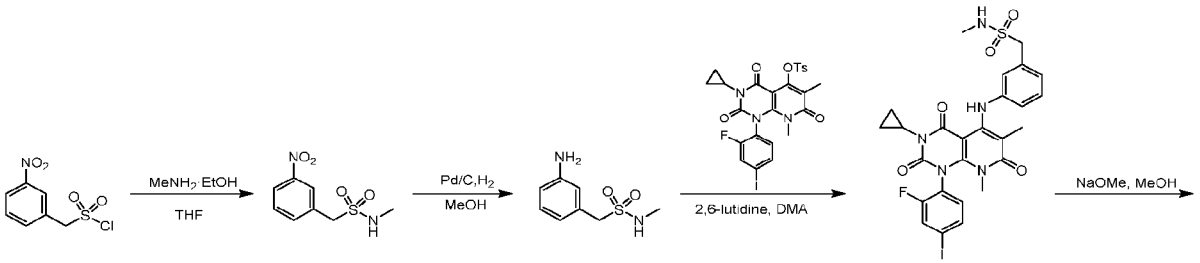
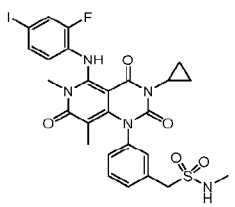
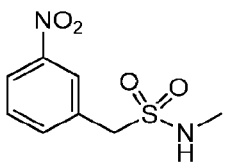




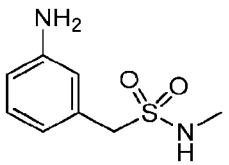
Step 1: **4-Methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide**



[00394] To a solution of (3-nitrophenyl)methanesulfonyl chloride (500 mg, 2.12 mmol, 1 eq) in THF (1 mL) was added DIEA (548.47 mg, 4.24 mmol, 739.17 μL, 2 eq) and $MeNH_2$.EtOH (197.69 mg, 6.37 mmol, 212.18 μL, 3 eq). The mixture was stirred at 25 °C for 1 h. The mixture was quenched with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic phase was washed with $NaHCO_3$ (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 2/1, R_f = 0.4) to yield 4-methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide (200 mg, 861.19 μmol,

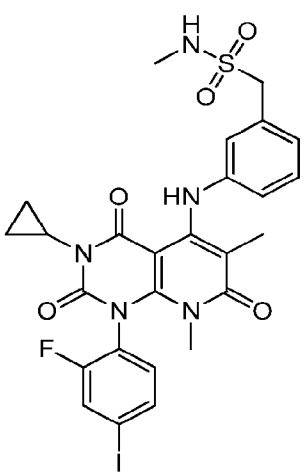
40.6% yield, 99.1% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32-8.20 (m, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.64-7.58 (m, 1H), 4.35 (s, 2H), 4.27-4.13 (m, 1H), 2.79 (d, J = 5.4 Hz, 3H).

Step 2: **1-(3-Aminophenyl)-*N*-methylmethanesulfonamide**



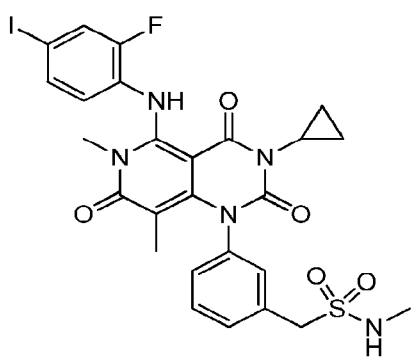
[00395] To a solution of 4-methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide (200 mg, 861.19 µmol, 99.1%, 1 eq) in MeOH (2 mL) was added Pd/C (200 mg, 861.19 µmol, 10.0%, 1 eq) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to yield 1-(3-aminophenyl)-*N*-methyl-methanesulfonamide (180 mg, 853.90 µmol, 99.2% yield, 95.0% purity) as a yellow solid, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.22-7.17 (m, 1H), 7.17-7.14 (m, 1H), 6.75-6.73 (m, 2H), 6.71-6.67 (m, 2H), 6.66-6.57 (m, 1H), 4.18 (s, 2H), 2.02 (s, 3H).

Step 3: **1-(3-((3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide**



[00396] To a solution of 1-(3-aminophenyl)-*N*-methyl-methanesulfonamide (150 mg, 711.58 µmol, 95.0%, 1.91 eq) in DMA (3 mL) was added 2,6-lutidine (119.77 mg, 1.12 mmol, 130.19 µL, 3 eq) and [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (250 mg, 372.60 µmol, 90.0%, 1 eq). The mixture was stirred under microwave (2 bar) at 140 °C for 3 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30 mm*5 um; mobile phase: [water (HCl) - ACN]; B%: 46%-66%, 10 min) and lyophilized to yield a product, which was added addition sat aq $NaHCO_3$ until pH = 7 and extracted with EtOAc (20 mL x 3), then the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-(3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide (45 mg, 58.55 µmol, 15.7% yield, 86.6% purity) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.85 (dd, *J* = 1.8, 9.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.22-7.14 (m, 2H), 7.08-6.99 (m, 2H), 4.33 (s, 2H), 2.95 (s, 3H), 2.82-2.76 (m, 1H), 2.69 (s, 3H), 1.67 (s, 3H), 1.16-1.09 (m, 2H), 0.81 (d, *J* = 2.6 Hz, 2H); ES-LCMS *m/z* 666.0 $[M+H]^+$.

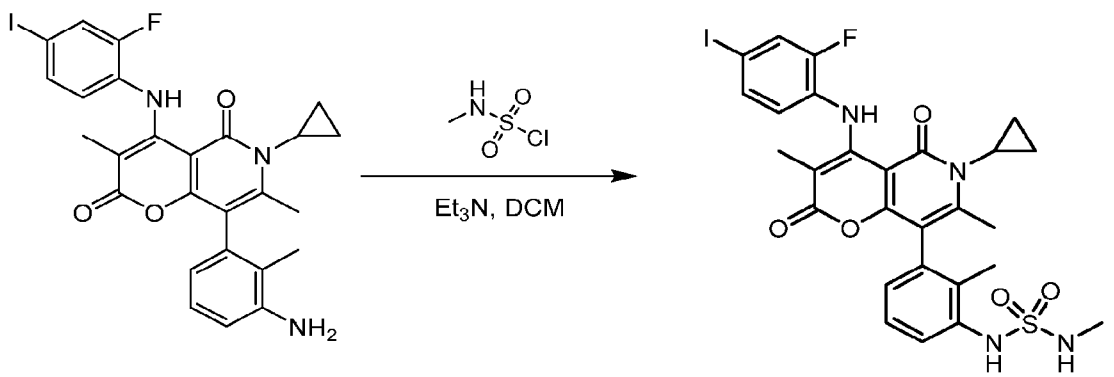
Step 4: **1-(3-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonamide**



[00397] To a solution of 1-(3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide (45 mg, 58.15 µmol, 86.0%, 1 eq) in THF (1 mL) was added a drop

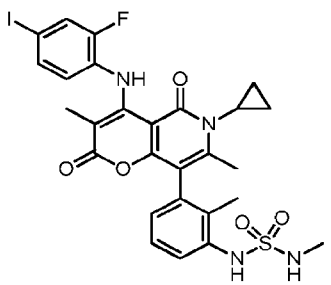
of NaOMe/MeOH (20 wt%, 58.15 μmol, 1 eq). The mixture was stirred under N_2 atmosphere at 25 °C for 1 h. The residue was added AcOH until pH = 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 53%-83%, 10 min) and lyophilized to yield 1-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonamide (10.01 mg, 14.96 μmol, 25.7% yield, 99.4% purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, *J* = 1.7, 10.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.51-7.47 (m, 2H), 7.43 (s, 1H), 7.39 (dd, *J* = 3.2, 5.6 Hz, 1H), 6.86 (t, *J* = 8.4 Hz, 1H), 4.37 (s, 2H), 3.20 (s, 3H), 2.76-2.69 (m, 1H), 2.67 (s, 3H), 1.34 (s, 3H), 1.08-1.03 (m, 2H), 0.81-0.74 (m, 2H); ES-LCMS *m/z* 666.1 $[M+H]^+$.

I-33



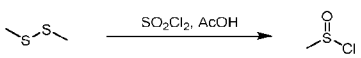
1

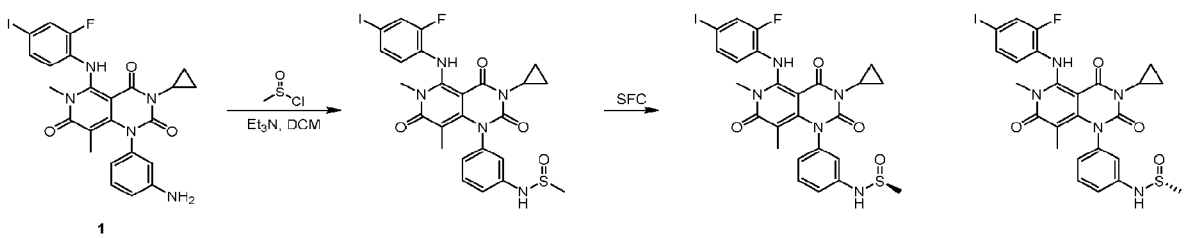
Step 1: **6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-8-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrano[3,2-c]pyridine-2,5-dione**



[00398] To a stirred solution of 8-(3-amino-2-methyl-phenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-pyrano[3,2-c]pyridine-2,5-dione (50 mg, 70.01 μmol, 80% purity, 1 eq) and TEA (28.34 mg, 280.02 μmol, 38.98 μL, 4 eq) in DCM (2 mL) was added *N*-methylsulfamoyl chloride (18.14 mg, 140.01 μmol, N/A purity, 2 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h under N_2 atmosphere. The reaction mixture was quenched by addition *sat. aq.* $NaHCO_3$ (30 mL) at 0 °C and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative *HPLC* (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 53%-83%,10min), followed by lyophilization to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-8-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrano[3,2-c]pyridine-2,5-dione (6.22 mg, 9.36 μmol, 13.4% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.30 (s, 1H), 8.82 (s, 1H), 7.71 (d, J = 1.7, 10.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.14 (q, J = 4.9 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 8.7 Hz, 1H), 3.03 (s, 1H), 2.55 (d, J = 5.1 Hz, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.43 (s, 3H), 1.23-1.17 (m, 2H), 0.96-0.84 (m, 2H); ES-LCMS *m/z* 665.0 $[M+H]^+$.

I-47 & I-48



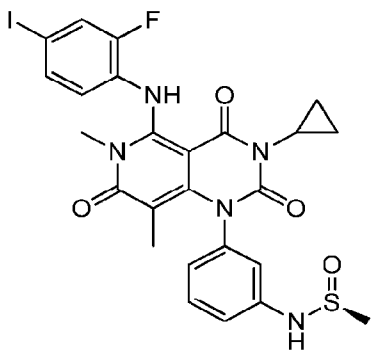


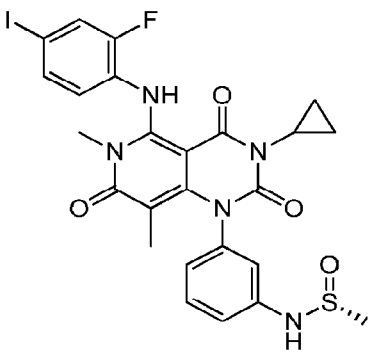
1

Step 1: **Methanesulfinyl chloride**

[00399] To a mixture of (methyldisulfanyl)methane (5.07 g, 53.82 mmol, 4.83 mL, 1 eq) and AcOH (6.46 g, 107.64 mmol, 6.16 mL, 2 eq) was added sulfuryl chloride (21.79 g, 161.47 mmol, 16.14 mL, 3 eq) dropwise under N_2 atmosphere at -20 °C. The mixture was stirred under N_2 atmosphere at -20 °C for 2 h. The mixture was warmed to 20 °C slowly and stirred under N_2 atmosphere at 20 °C for 1 h and at 35 °C for 1 h. The mixture was concentrated under reduced pressure to yield methanesulfinyl chloride (10.6 g, crude) as colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.38 (s, 3H).

Step 2: **(*S*)-*N*-[3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide** and **(*R*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide**





[00400] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (200 mg, 348.82 μmol, 100% purity, 1 eq) and Et_3N (363.50 mg, 3.59 mmol, 0.5 mL, 10.30 eq) in DCM (10 mL) was added methanesulfinyl chloride (200 mg, 2.03 mmol, N/A purity, 5.82 eq). The mixture was stirred at 25 °C for 0.5 h. TLC (PE/EtOAc = 2/3, R_f = 0.15) showed the starting material was almost consumed. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 0/1, TLC: PE/EtOAc = 2/3, R_f = 0.15) to yield *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (200 mg, 91.9% purity) as a white solid. The product (160 mg) was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) to give

desired compound as a white solid, which was further separated by SFC (column: DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); mobile phase: [0.1% NH_3H_2O EtOH]; B%: 45%-45%) to yield peak 1 and peak 2. Peak 1 was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 43%-73%, 11 min), followed by lyophilization to yield (*S*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (13.75 mg, 20.91 μmol, 9.0% yield, 96.6% purity, SFC: R_t = 4.554, ee = 100%, $[\alpha]^{27.8}_D$ = -36.364 (MeOH, c = 0.011 g/100 mL)) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, J = 1.8, 10.1 Hz, 1H), 7.59-7.54 (m, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.17-7.08 (m, 2H), 7.05-7.00 (m, 1H), 6.86 (t, J = 8.5 Hz, 1H), 3.20 (s, 3H), 2.84 (s, 3H), 2.71 (tt, J = 3.8, 7.2 Hz, 1H), 1.40 (s, 3H), 1.10-1.00 (m, 2H), 0.79-0.70 (m, 2H); ES-LCMS *m/z* 636.1 $[M+H]^+$. Peak 2 was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) to give desired compound as a white solid, which was further separated by SFC (column: DAICEL CHIRALCEL OD-H (250mm*30mm,5um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 45%-45%, min), followed by lyophilization to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 11 min), followed by lyophilization to yield (*R*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (12.41 mg, 19.05 μmol, 8.2% yield, 97.6% purity, SFC: R_t = 4.991, ee = 89.18%, $[\alpha]^{27.7}_D$ = +107.692 (MeOH, c = 0.013 g/100 mL)) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, J = 1.8, 10.2 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.17-7.10 (m, 2H), 7.02 (dd, J = 1.1, 8.0 Hz, 1H), 6.86 (t, J = 8.5 Hz, 1H), 3.20 (s, 3H), 2.84 (s, 3H), 2.71 (tt, J = 3.7, 7.2 Hz, 1H), 1.40 (s, 3H), 1.08-1.03 (m, 2H), 0.78-0.73 (m, 2H); ES-LCMS *m/z* 636.0 $[M+H]^+$.

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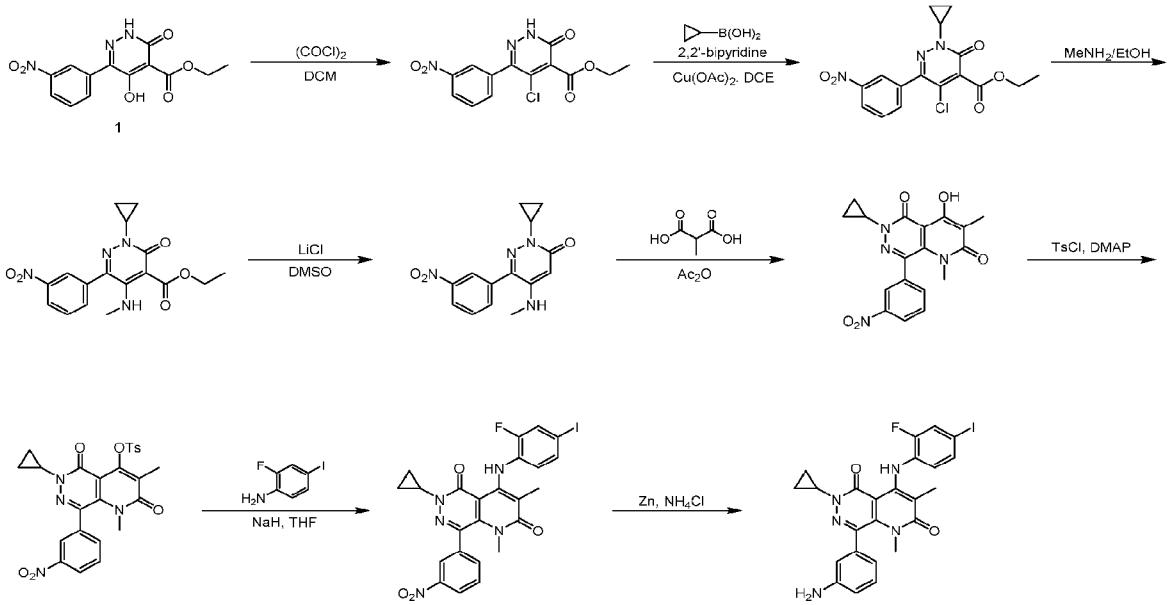

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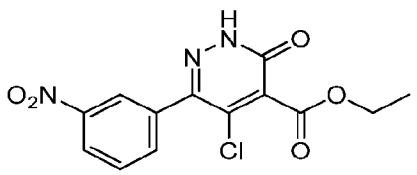
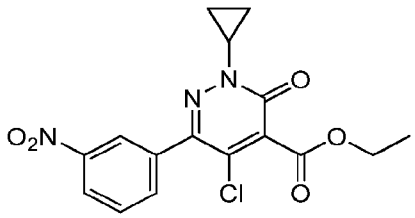
Step 1: **Ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate**



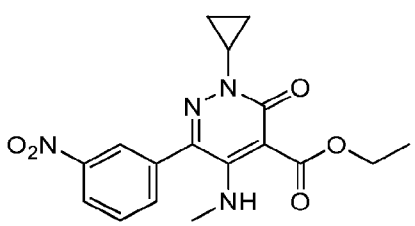
[00401] To a solution of ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate (2.5 g, 7.37 mmol, 1 eq) in DCM (30 mL) was added $(COCl)_2$ (935.60 mg, 7.37 mmol, 645.24 μL, 1 eq). The mixture was stirred at 35 °C for 3 h. The reaction mixture was quenched by addition water (30 mL) and extracted with DCM (40 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was added MeOH (5 mL), and stirred at 25 °C for 2 h. The slurry was filtered, and the cake was rinsed with PE (2 x 3 mL). The solid was collected and dried in vacuo to yield ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (1.9 g, 5.69 mmol, 77.2% yield, 97.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.67 (s, 1H), 8.48 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.74-7.66 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ES-LCMS *m/z* 324.0, 326.0 $[M+H]^+$.

Step 2: **Ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate**



[00402] A mixture of ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (1.4 g, 4.20 mmol, 1 eq), cyclopropylboronic acid (720.75 mg, 8.39 mmol, 2 eq), 2-(2-pyridyl)pyridine (1.64 g, 10.49 mmol, 2.5 eq), Na_2CO_3 (533.60 mg, 5.03 mmol, 1.2 eq) and $Cu(OAc)_2$ (914.43 mg, 5.03 mmol, 1.2 eq) in DCE (20 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 70 °C for 24 h under N_2 atmosphere. The reaction mixture was diluted with water (100 mL) and extracted with DCM (60 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.43) to yield ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (400 mg, 989.69 μmol, 23.6% yield, 90.0% purity) as a yellow gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.42 (d, J = 1.8 Hz, 1H), 8.35 (td, J = 1.1, 8.3 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.70-7.65 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.22 (t, J = 4.0, 7.6 Hz, 1H), 1.43 (t, J = 7.2 Hz, 3H), 1.22-1.16 (m, 2H), 1.13-1.06 (m, 2H); ES-LCMS *m/z* 364.0, 366.0 $[M+H]^+$.

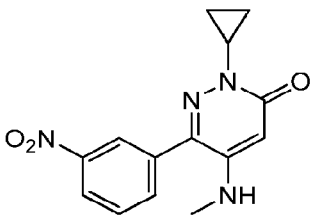
Step 3: **Ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate**



[00403] To a solution of ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (400 mg, 989.69 μmol, 1 eq) in DCM (3 mL) was added $MeNH_2$ (1.02 g, 9.90 mmol, 30.0% purity, 10 eq) at 0 °C. The mixture was stirred at 20 °C for 2 h. The solvent was

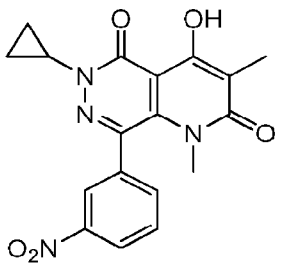
removed to yield ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (300 mg, 669.74 μmol, 67.7% yield, 80.0% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.33-8.30 (m, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.70-7.66 (m, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.02-3.95 (m, 1H), 2.69 (d, J = 5.3 Hz, 3H), 1.44 (t, J = 7.1 Hz, 2H), 1.46-1.42 (m, 1H), 1.03-0.94 (m, 4H); ES-LCMS m/z 359.1 $[M+H]^+$.

Step 4: **2-Cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one**



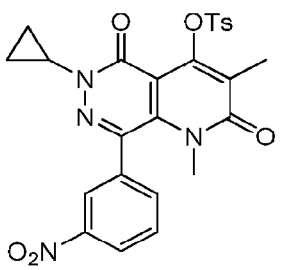
[00404] To a solution of ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (300 mg, 669.74 μmol, 1 eq) in DMSO (5 mL) was added LiCl (283.93 mg, 6.70 mmol, 10 eq). The mixture was stirred at 150 °C for 8 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (40 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 0/1, TLC: PE/EtOAc = 0/1, R_f = 0.15) to yield 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (200 mg, 628.74 μmol, 93.9% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38-8.27 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.73-7.66 (m, 1H), 5.92 (s, 1H), 4.03 (t, J = 3.9, 7.5 Hz, 1H), 2.83 (d, J = 3.4 Hz, 3H), 1.09-0.93 (m, 4H); ES-LCMS m/z 287.1 $[M+H]^+$.

Step 5: **6-Cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione**



[00405] To a solution of 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (200 mg, 628.74 µmol, 1 eq) in Ac_2O (3 mL) was added 2-methylpropanedioic acid (222.74 mg, 1.89 mmol, 152.56 µL, 3 eq). The mixture was stirred at 110 °C for 2 h. The solvent was removed to yield a residue which was purified by preparative TLC (PE/EtOAC = 3/1, TLC: PE/EtOAC = 3/1, R_f = 0.24) to yield 6-cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (200 mg, 434.38 µmol, 69.1% yield, 80.0% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.80 (s, 1H), 8.37 (td, J = 2.2, 7.0 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 7.72-7.68 (m, 2H), 4.16-4.09 (m, 1H), 3.06 (s, 3H), 2.16 (s, 3H), 1.20-1.15 (m, 2H), 1.15-1.09 (m, 2H); ES-LCMS *m/z* 369.0 $[M+H]^+$.

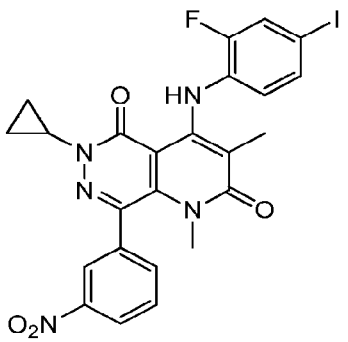
Step 6: **[6-Cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate**



[00406] To a solution of 6-cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (200 mg, 434.38 µmol, 1 eq) in DCM (8 mL) was added DIEA (561.40 mg, 4.34 mmol, 756.61 µL, 10 eq) and 4-methylbenzenesulfonyl chloride (414.06 mg, 2.17 mmol, 5 eq). The mixture was stirred at 50 °C for 12 h. The solvent was removed to yield a residue which was purified by preparative TLC (PE/EtOAC = 3/1, TLC: PE/EtOAC = 3/1, R_f = 0.24) to yield [6-cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate (200 mg, 371.27 µmol, 85.5% yield, 97.0% purity) as a yellow

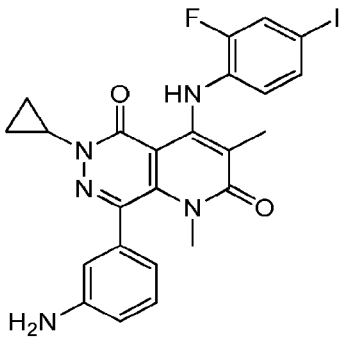
solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38-8.30 (m, 2H), 7.98 (d, J = 8.3 Hz, 2H), 7.77-7.63 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.22-4.06 (m, 1H), 3.08 (s, 3H), 2.49 (s, 3H), 1.85 (s, 3H), 1.12-1.01 (m, 4H); ES-LCMS m/z 523.1 $[M+H]^+$.

Step 7: **6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione**



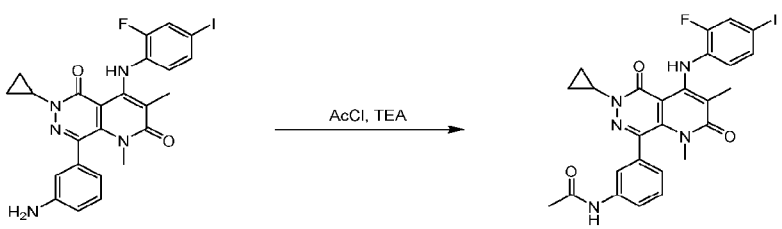
[00407] To a solution of 2-fluoro-4-iodo-aniline (263.99 mg, 1.11 mmol, 3 eq) in THF (3 mL) was added NaH (89.10 mg, 2.23 mmol, 60.0% purity, 6 eq) and stirred at 0 °C for 30 min, then [6-cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate (200 mg, 371.27 µmol, 1 eq) was added at 0 °C. The reaction temperature was slowly warmed up to 25 °C and stirred at 25 °C for 1 h. The reaction mixture was quenched by addition water (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (PE/EtOAC = 1/1, TLC: PE/EtOAC = 1/1, R_f = 0.35) to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (100 mg, 156.64 µmol, 42.2% yield, 92.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.78 (s, 1H), 8.44-8.27 (m, 2H), 7.75-7.65 (m, 2H), 7.46 (d, J = 1.8, 10.0 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.56 (t, J = 8.5 Hz, 1H), 4.10-4.01 (m, 1H), 3.07 (s, 3H), 1.82 (s, 3H), 1.19-1.07 (m, 4H); ES-LCMS m/z 588.0 $[M+H]^+$.

Step 8: **8-(3-Aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione**



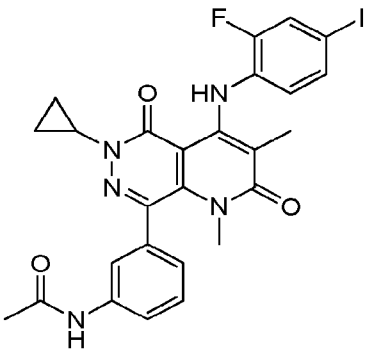
[00408] To a solution of 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (100 mg, 156.64 μmol, 1 eq) in EtOH (1.5 mL), H_2O (1.5 mL) and THF (1.5 mL) was added NH_4Cl (83.79 mg, 1.57 mmol, 10 eq) and Fe (43.74 mg, 783.19 μmol, 5 eq). The mixture was stirred at 90 °C for 3 h. The reaction mixture was filtered to remove the insoluble. The filter liquor was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 64%-94%,10min), followed by lyophilization to yield 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (55.23 mg, 99.09 μmol, 63.3% yield, 100.0% purity) as a yellow solid. ^{1}H NMR (400MHz, CD_3OD) δ ppm 7.55 (d, J = 1.8, 10.3 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 1.5, 8.0 Hz, 1H), 6.79-6.76 (m, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.64 (t, J = 8.6 Hz, 1H), 4.04 (t, J = 3.9, 7.5 Hz, 1H), 3.13 (s, 3H), 1.76 (s, 3H), 1.17-1.11 (m, 2H), 1.07-0.99 (m, 2H); ES-LCMS m/z 558.0 $[M+H]^+$.

I-50



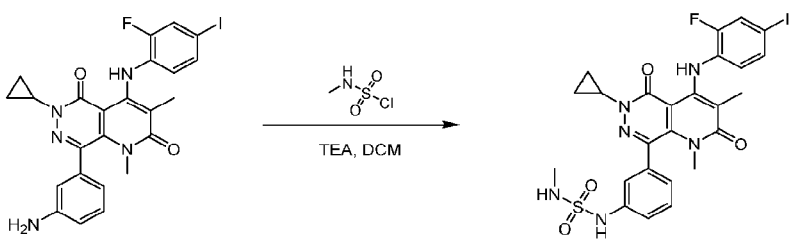
1

Step 1: ***N*-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]acetamide**



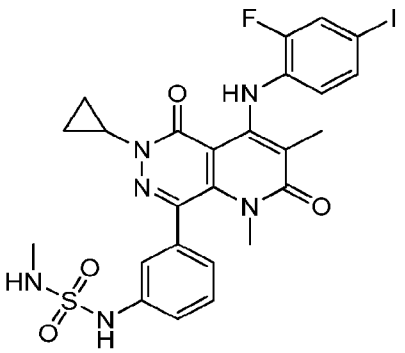
[00409] To a solution of 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (20 mg, 35.88 μmol, 1 eq) in DCM (3 mL) was added acetyl chloride (5.63 mg, 71.77 μmol, 5.12 μL, 2 eq) and TEA (14.52 mg, 143.53 μmol, 19.98 μL, 4 eq). The mixture was stirred at 25 °C for 1 h. The solvent was removed to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 55%-85%,10min), followed by lyophilization to yield *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]acetamide (7.96 mg, 13.28 μmol, 37.0% yield, 100.0 purity) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.76 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 1.7, 10.3 Hz, 1H), 7.49-7.40 (m, 2H), 7.20 (d, J = 7.6 Hz, 1H), 6.64 (t, J = 8.6 Hz, 1H), 4.05 (t, J = 3.8, 7.5 Hz, 1H), 3.09 (s, 3H), 2.14 (s, 3H), 1.76 (s, 3H), 1.17-1.09 (m, 2H), 1.09-1.00 (m, 2H); ES-LCMS *m/z* 600.0 $[M+H]^+$.

I-20



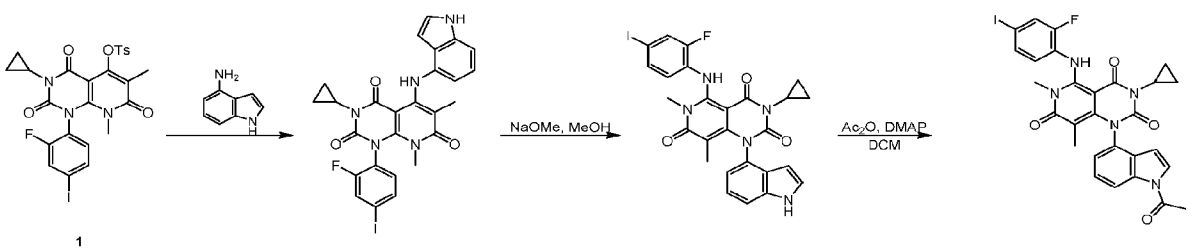
1

Step 1: **6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-[3-(methylsulfamoylamino)phenyl]pyrido[2,3-d]pyridazine-2,5-dione**



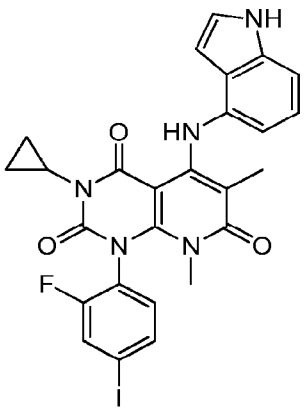
[00410] To a solution of 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (20 mg, 35.88 μmol, 1 eq) in DCM (2 mL) was added TEA (3.63 mg, 35.88 μmol, 4.99 μL, 1 eq) and *N*-methylsulfamoyl chloride (9.30 mg, 71.77 μmol, 2 eq). The mixture was stirred at 0 °C for 1 h. The solvent was removed to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 51%-81%,10min), followed by lyophilization to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-[3-(methylsulfamoylamino)phenyl]pyrido[2,3-d]pyridazine-2,5-dione (7.62 mg, 11.46 μmol, 31.9% yield, 97.9% purity) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.55 (d, J = 1.8, 10.3 Hz, 1H), 7.49-7.40 (m, 2H), 7.33-7.26 (m, 2H), 7.18 (d, J = 7.6 Hz, 1H), 6.65 (t, J = 8.6 Hz, 1H), 4.05 (t, J = 3.9, 7.5 Hz, 1H), 3.09 (s, 3H), 2.61 (s, 3H), 1.77 (s, 3H), 1.18-1.10 (m, 2H), 1.09-0.99 (m, 2H); ES-LCMS *m/z* 651.0 $[M+H]^+$.

I-31



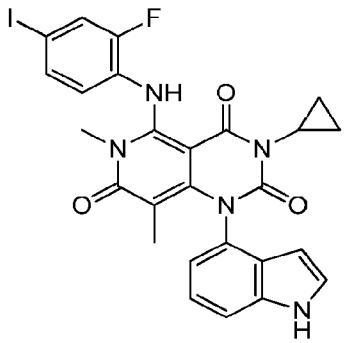
1

Step 1: **5-((1*H*-Indol-4-yl)amino)-3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione**



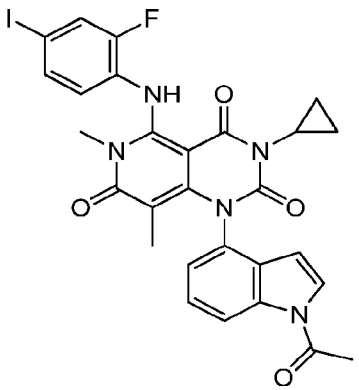
[00411] A mixture of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (400 mg, 564.78 μmol, 90.0%, 1 eq), 1*H*-indol-4-amine (111.96 mg, 847.17 μmol, 1.5 eq), Xphos Pd G_2 (24.30 mg, 28.24 μmol, 0.05 eq) and Xphos (29.62 mg, 62.13 μmol, 0.11 eq) in 1,4-dioxane (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred under N_2 atmosphere at 130 °C for 6 h. The mixture was duilted with water (30 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic phase was concentrated in vacuum to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.26) to yield 5-((1*H*-indol-4-yl)amino)-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (230 mg, 346.51 μmol, 61.4% yield, 90.0% purity) as a green solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 11.21 (s, 1H), 10.45 (s, 1H), 7.95 (dd, J = 1.8, 9.5 Hz, 1H), 7.74 (dd, J = 1.7, 8.4 Hz, 1H), 7.34 (t, J = 2.7 Hz, 1H), 7.28 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 6.46-6.38 (m, 2H), 2.75 (s, 3H), 2.70-2.65 (m, 1H), 2.07 (s, 3H), 1.02-0.98 (m, 2H), 0.69-0.64 (m, 2H); ES-LCMS *m/z* 598.0 $[M+H]^+$.

Step 2: **3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



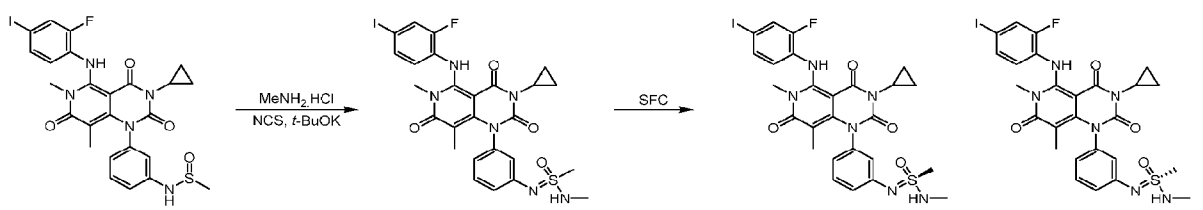
[00412] To a solution of 5-((1*H*-indol-4-yl)amino)-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (100 mg, 150.66 μmol, 90.0%, 1 eq) was added a drop of NaOMe/MeOH (20 wt %, 58.15 μmol, 1 eq) in THF (2 mL). The mixture was stirred at 25 °C for 2 h. The residue was added AcOH until pH 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.3) to yield 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (40 mg, 56.92 μmol, 37.8% yield, 85.0%) as a green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.29 (s, 1H), 11.12 (s, 1H), 7.84-7.73 (m, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 2.6 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.01-6.88 (m, 2H), 6.22 (s, 1H), 3.07 (s, 3H), 2.68-2.62 (m, 1H), 2.07 (s, 3H), 0.96-0.93 (m, 2H), 0.75-0.64 (m, 2H); ES-LCMS *m/z* 598.0 $[M+H]^+$.

Step 3: **1-(1-Acetyl-1*H*-indol-4-yl)-3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



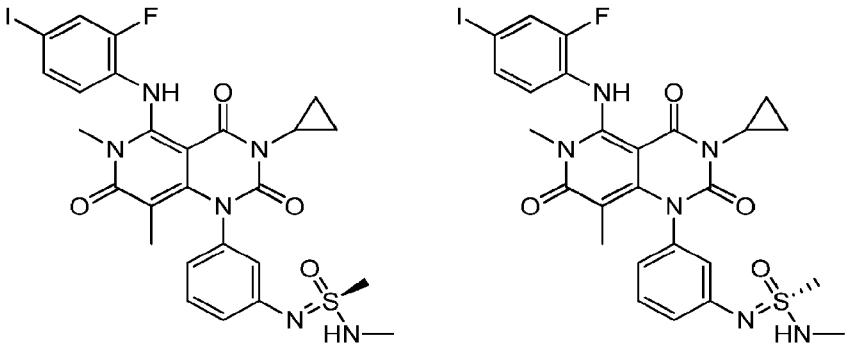
[00413] To a solution of 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (20 mg, 28.46 μmol, 85.0%, 1 eq) in DCM (2 mL) was added Ac_2O (2.91 mg, 28.46 μmol, 2.67 μL, 1 eq) and DMAP (10.43 mg, 85.37 μmol, 3 eq). The mixture was stirred at 0 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue which was by preparative HPLC (column: Boston Green ODS 150*30 mm*5 um; mobile phase: [water (NH_3H_2O+NH_4HCO_3)-ACN]; B%: 55%-85%, 10 min) and lyophilized to yield 1-(1-acetyl-1*H*-indol-4-yl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (9.66 mg, 15.03 μmol, 52.8% yield, 99.5%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 8.48 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 3.9 Hz, 1H), 7.66 (d, J = 10.3 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.40 (t, J = 8.2 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.88 (t, J = 8.6 Hz, 1H), 6.55 (d, J = 3.9 Hz, 1H), 3.20 (s, 3H), 2.73 (s, 1H), 2.69 (s, 3H), 1.11 (s, 3H), 1.07 (d, J = 5.6 Hz, 2H), 0.80 (d, J = 3.9 Hz, 2H); ES-LCMS *m/z* 640.1 $[M+H]^+$.

I-51 & I-52



Step 1: **(*S*)-*N*'-(3-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonimidamide** and **(*R*)-*N*'-(3-(3-cyclopropyl-5-((2-fluoro-4-**

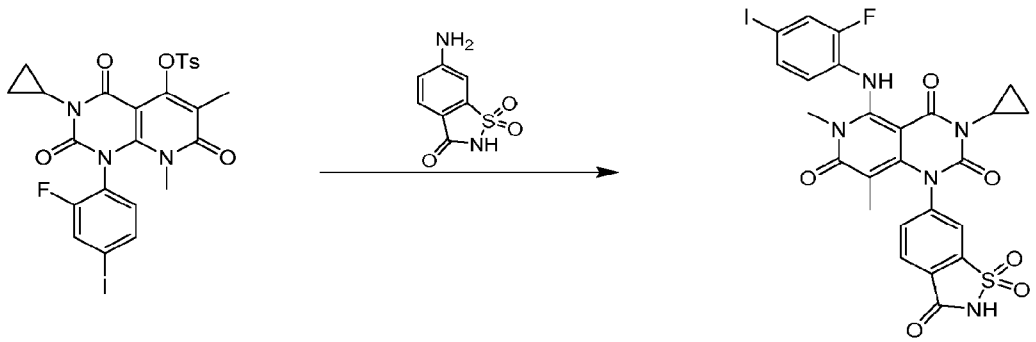
iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonimidamide



[00414] To a solution of *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (100 mg, 135.81 μmol, 86.3% purity, 1 eq), $MeNH_2$ (32 mg, 473.95 μmol, 100% purity, 3.49 eq, HCl) and *t*-BuOK (1 M, 1 mL, 7.36 eq) in MeCN (20 mL) was added NCS (25 mg, 187.22 μmol, 1.38 eq) under N_2 atmosphere at 25 °C. The mixture was stirred under N_2 atmosphere at 25 °C for 12 h. The reaction mixture was diluted with H_2O (50 mL) and extracted with EtOAc (50 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 0/1, TLC: PE/EtOAc = 1/2, R_f = 0.20). The desired fraction was concentrated under reduced pressure to yield a residue which was separated by SFC (column: (s,s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [0.1%NH_3H_2O/MeOH]; B%: 60%-60%) to yield peak 1 and peak 2. Peak 1 was concentrated under reduced pressure to yield a residue which was dissolved in MeCN (10 mL) and water (10 mL) and lyophilized to yield (*S*)-*N*'-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonimidamide (5.32 mg, 8.01 μmol, 5.9% yield, 100.0% purity, SFC: R_t = 5.680, ee = 100%, $[\alpha]^{29.3}_D$ = -5.26 (MeOH, c = 0.114 g/100 mL)). ^1H NMR (500 MHz, CD_3OD) δ ppm 7.67 (dd, *J* = 1.8, 10.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 8.5 Hz, 1H), 3.22 (s, 3H), 3.12 (s, 3H), 2.74-2.72 (m, 1H), 2.70 (s, 3H), 1.43 (s, 3H), 1.10-1.05 (m, 2H), 0.79-0.75 (m, 2H); ES-LCMS *m/z* 665.1 $[M+H]^+$. Peak 2 was concentrated under reduced pressure to yield a residue which was dissolved in MeCN (10 mL) and water (10 mL) and lyophilized to yield (*R*)-

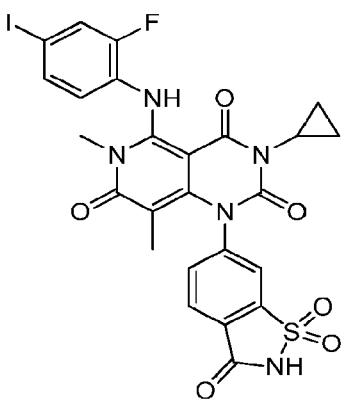
N'-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-d]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonimidamide (5.85 mg, 8.80 μmol, 6.5% yield, 100.0% purity, SFC: R_t = 6.804, ee = 100%, $[\alpha]^{29.4}_D$ = +18.28 (MeOH, c = 0.186 g/100 mL)) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.67 (dd, *J* = 1.8, 10.1 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.33-7.28 (m, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.06 (s, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.87 (t, *J* = 8.5 Hz, 1H), 3.22 (s, 3H), 3.12 (s, 3H), 2.75-2.72 (m, 1H), 2.70 (s, 3H), 1.43 (s, 3H), 1.10-1.05 (m, 2H), 0.79-0.75 (m, 2H); ES-LCMS *m/z* 665.0 $[M+H]^+$.

I-54



1

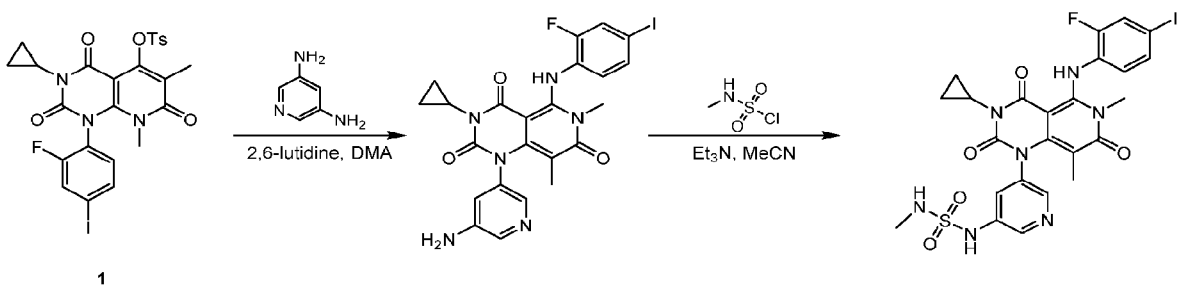
Step 1: **3-Cyclopropyl-1-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



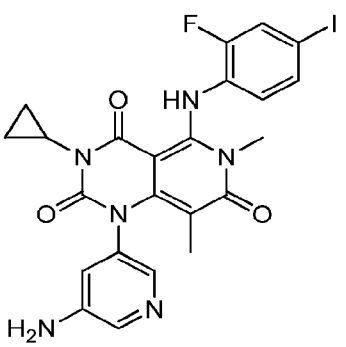
[00415] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (200 mg, 307.49 μmol, 98.0%, 1 eq) in DMF (3 mL) was added Cs_2CO_3 (200.37 mg, 614.98 μmol, 2.5 eq) and 6-amino-1,1-

dioxo-1,2-benzothiazol-3-one (121.89 mg, 614.98 μmol, 2 eq). The mixture was stirred at 130 °C for 6 h. The mixture was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um;mobile phase: [water (HCl)-ACN];B%: 44%-64%, 10 min) and lyophilized to yield 3-cyclopropyl-1-(1,1-dioxido-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yl)-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (6.74 mg, 9.69 μmol, 3.15% yield, 95.4% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.42 (s, 1H), 8.00 (s, 1H), 7.67 (s, 1H), 7.60 (s, 2H), 7.44-7.35 (m, 2H), 7.01 (s, 1H), 3.41 (s, 3H), 2.84-2.75 (m, 1H), 1.53 (s, 3H), 1.31-1.12 (m, 2H), 0.91-0.79 (m, 2H); ES-LCMS *m/z* 664.0 $[M+H]^+$.

I-22



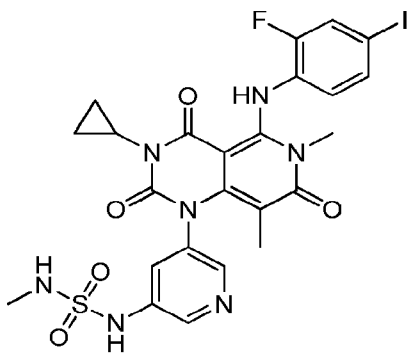
Step 1: **1-(5-Aminopyridin-3-yl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



[00416] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (250 mg, 384.36 μmol, 98.0%, 1 eq) in DMF (5 mL) was added pyridine-3,5-diamine (50.33 mg, 461.24 μmol, 1.2 eq) and 2,6-LUTIDINE (102.96 mg, 960.91 μmol, 111.91 μL, 2.5 eq). The mixture was stirred under N_2 atmosphere at 140 °C for 6 h. The reaction mixture was diluted with H_2O (20 mL), extracted

with DCM:IPA (3:1, 30 ml) and the organic layer was concentrated under reduced pressure to yield 1-(5-aminopyridin-3-yl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (150 mg, 261.17 µmol, 68.0% yield, 100.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.08-7.93 (m, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.26 (d, J = 18.1 Hz, 2H), 7.19-7.09 (m, 1H), 6.85 (s, 1H), 6.51 (s, 1H), 6.48 (s, 1H), 4.89 (s, 1H), 2.83 (s, 3H), 2.37-2.25 (m, 1H), 1.79 (s, 3H), 0.96 (s, 2H), 0.57 (d, J = 14.7 Hz, 2H); ES-LCMS *m/z* 575.1 $[M+H]^+$.

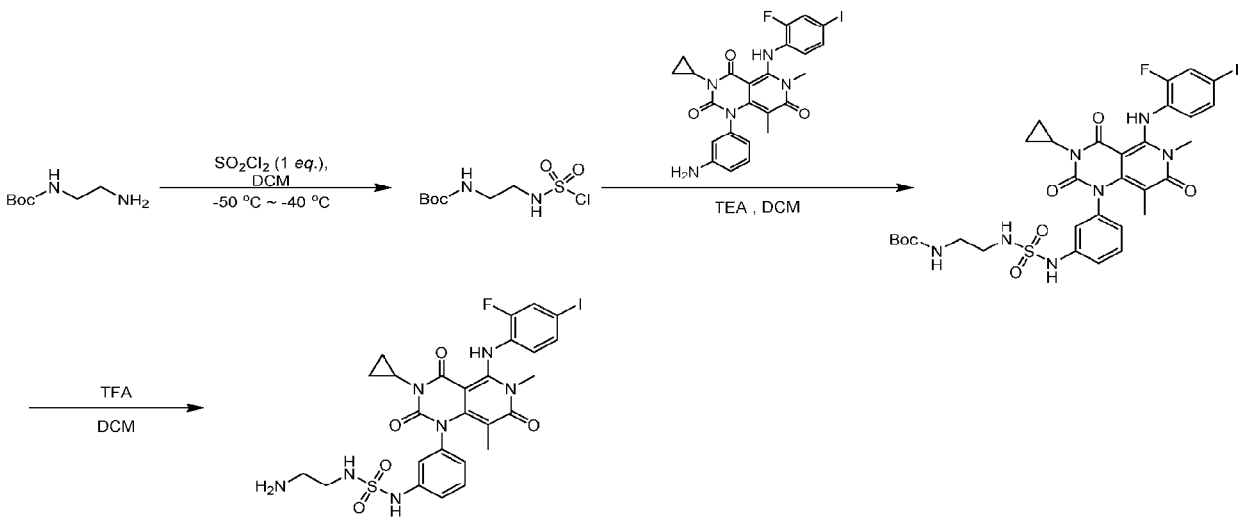
Step 2: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[5-(methylsulfamoylamino)-3-pyridyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



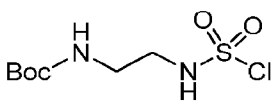
[00417] To a solution of 1-(5-aminopyridin-3-yl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (95 mg, 165.41 µmol, 100.0%, 1 eq) in DCM (5 mL) was added *N*-methylsulfamoyl chloride (32.15 mg, 248.11 µmol, N/A, 1.5 eq) and TEA (50.21 mg, 496.22 µmol, 69.07 µL, 3 eq). The mixture was stirred under N_2 atmosphere at 0 °C for 3 h. The reaction mixture was diluted with H_2O (20 mL), extracted with DCM (30 mL x 3) and the organic layer was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O + NH_4HCO_3)-ACN];B%: 20%-50%, 10 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[5-(methylsulfamoylamino)-3-pyridyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (16.52 mg, 24.67 µmol, 14.9% yield, 99.7% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.99 (ddd, J = 1.6, 4.9, 9.3 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.38-7.26 (m, 2H), 7.18-7.04 (m, 2H), 6.05 (d,

J = 15.5 Hz, 2H), 5.47 (s, 1H), 2.82 (d, J = 2.1 Hz, 3H), 2.39-2.35 (m, 3H), 2.33 (d, J = 1.8 Hz, 1H), 1.77 (d, J = 1.9 Hz, 3H), 1.00-0.91 (m, 2H), 0.58 (s, 2H); ES-LCMS *m/z* 668.0 $[M+H]^+$.

I-41 and I-42

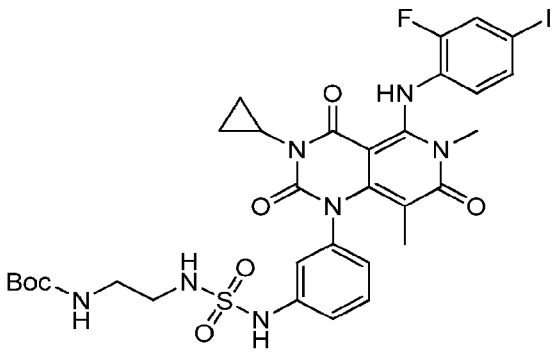


Step 1: ***tert*-Butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate**



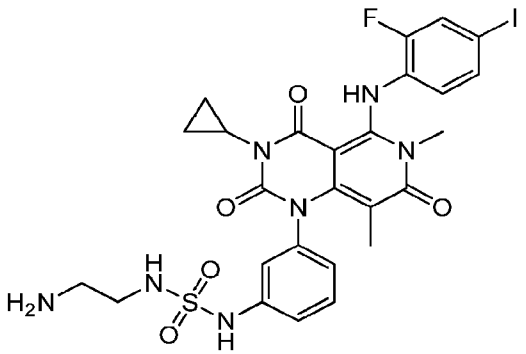
[00418] To a solution of sulfuryl chloride (850 mg, 6.30 mmol, 629.63 μL, 1.01 eq) and Et_3N (1.89 g, 18.73 mmol, 2.61 mL, 3 eq) in DCM (50 mL) was added a solution of *tert*-butyl *N*-(2-aminoethyl)carbamate (1 g, 6.24 mmol, 980.39 μL, 1 eq) in DCM (5 mL) dropwise under N_2 atmosphere at -40~-50 °C. The mixture was stirred under N_2 atmosphere at -40~-50 °C for 5 minutes to yield *tert*-butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate (75 g, crude) as colorless liquid, which was used in the next step without further purification.

Step 2: ***tert*-Butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate**



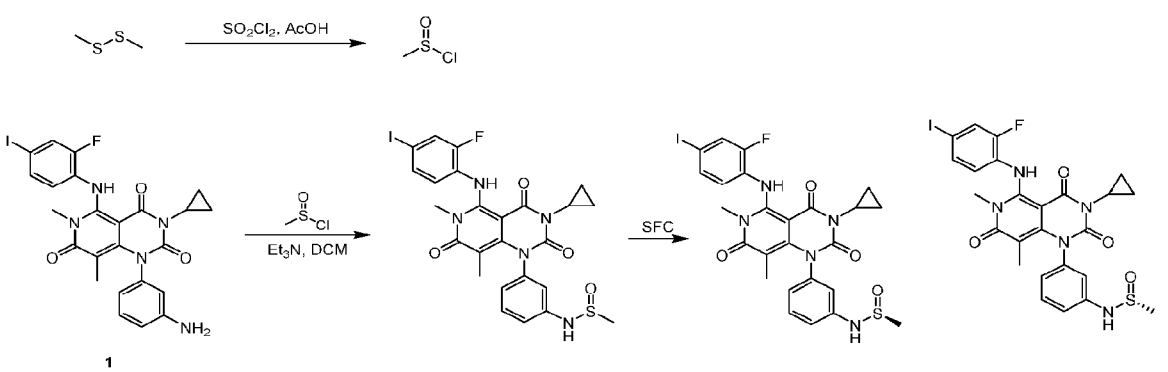
[00419] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (90 mg, 156.97 μmol, 100% purity, 1 eq) and Et_3N (145.40 mg, 1.44 mmol, 0.2 mL, 9.15 eq) in DCM (20 mL) was added *tert*-butyl *N*-[2-(chlorosulfonylamino)ethyl]carbamate (10 g, 38.65 mmol, N/A purity, 246.23 eq). The mixture was stirred at 15 °C for 10 minutes. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 3/4, R_f = 0.48) to yield the desired compound (100 mg). 50 mg of the desired compound (100 mg) was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (10mM NH4HCO3)-ACN]; B%: 50%-80%, 10 min) and lyophilized to yield *tert*-butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate (16.07 mg, 20.07 μmol, 12.8% yield, 99.4% purity) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.58 (dd, J = 1.8, 10.1 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.17 (s, 1H), 7.13 (dd, J = 1.4, 8.1 Hz, 1H), 7.00-6.95 (m, 1H), 6.78 (t, J = 8.5 Hz, 1H), 3.13 (s, 3H), 3.03-2.98 (m, 2H), 2.97-2.92 (m, 2H), 2.64 (tt, J = 3.8, 7.2 Hz, 1H), 1.33 (s, 9H), 1.32 (s, 3H), 1.02-0.96 (m, 2H), 0.71-0.66 (m, 2H); ES-LCMS *m/z* 796.1 $[M+H]^+$.

Step 3: **1-[3-(2-Aminoethylsulfamoylamino)phenyl]-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione**



[00420] To a solution of *tert*-butyl *N*-[2-[[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]sulfamoylamino]ethyl]carbamate (50 mg, 62.84 μmol, N/A purity, 1 eq) in DCM (2 mL) was added TFA (3.08 g, 27.01 mmol, 2 mL, 429.83 eq). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (0.05%NH_3H_2O+10mM NH_4HCO_3)-ACN]; B%: 45%-75%, 10 min) and lyophilized to yield 1-[3-(2-aminoethylsulfamoylamino)phenyl]-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (16.78 mg, 23.94 umol, 38.09% yield, 99.223% purity) was obtained as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.68 (dd, J = 1.8, 10.1 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.28-7.25 (m, 1H), 7.25-7.22 (m, 1H), 7.08-7.04 (m, 1H), 6.88 (t, J = 8.5 Hz, 1H), 3.22 (s, 3H), 3.06 (t, J = 6.1 Hz, 2H), 2.76-2.70 (m, 3H), 1.41 (s, 3H), 1.10-1.05 (m, 2H), 0.80-0.76 (m, 2H); ES-LCMS *m/z* 696.0 $[M+H]^+$.

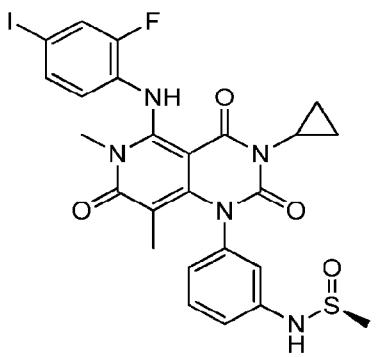
I-47 and I-48

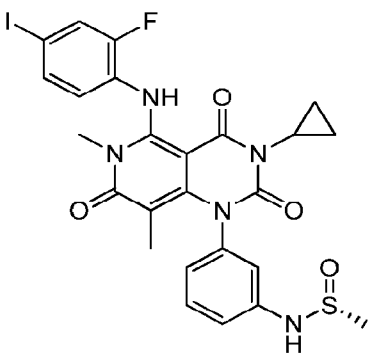


Step 1: **Methanesulfinyl chloride**

[00421] To a mixture of (methyldisulfanyl)methane (5.07 g, 53.82 mmol, 4.83 mL, 1 eq) and AcOH (6.46 g, 107.64 mmol, 6.16 mL, 2 eq) was added sulfuryl chloride (21.79 g, 161.47 mmol, 16.14 mL, 3 eq) dropwise under N_2 atmosphere at -20 °C. The mixture was stirred under N_2 atmosphere at -20 °C for 2 h. The mixture was warmed to 20 °C slowly and stirred under N_2 atmosphere at 20 °C for 1 h and at 35 °C for 1 h. The mixture was concentrated under reduced pressure to yield methanesulfinyl chloride (10.6 g, crude) as colorless oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.38 (s, 3H).

Step 2: **(*S*)-*N*-[3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide** and **(*R*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide**

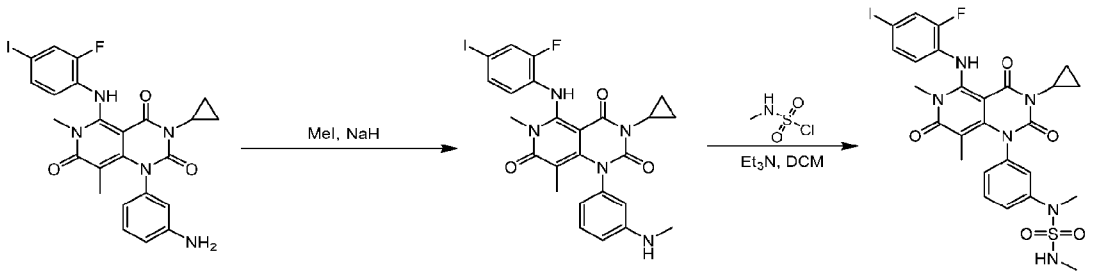




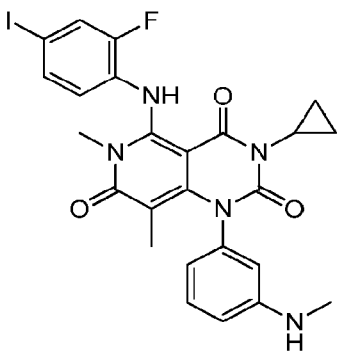
[00422] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (200 mg, 348.82 μmol, 100% purity, 1 eq) and Et_3N (363.50 mg, 3.59 mmol, 0.5 mL, 10.30 eq) in DCM (10 mL) was added methanesulfinyl chloride (200 mg, 2.03 mmol, N/A purity, 5.82 eq). The mixture was stirred at 25 °C for 0.5 h. TLC (PE/EtOAc = 2/3, R_f = 0.15) showed the starting material was almost consumed. The reaction mixture was concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 0/1, TLC: PE/EtOAc = 2/3, R_f = 0.15) to yield *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (200 mg, 91.9% purity) as a white

solid. The product (160 mg) was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) to give desired compound as a white solid, which was further separated by SFC (column: DAICEL CHIRALCEL OD-H (250mm*30mm, 5um); mobile phase: [0.1% NH_3H_2O EtOH]; B%: 45%-45%) to yield peak 1 and peak 2. Peak 1 was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 43%-73%, 11 min), followed by lyophilization to yield (*S*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (13.75 mg, 20.91 μmol, 9.0% yield, 96.6% purity, SFC: R_t = 4.554, ee = 100%, $[\alpha]^{27.8}_D$ = -36.364 (MeOH, c = 0.011 g/100 mL)) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, J = 1.8, 10.1 Hz, 1H), 7.59-7.54 (m, 1H), 7.39 (t, J = 8.1 Hz, 1H), 7.17-7.08 (m, 2H), 7.05-7.00 (m, 1H), 6.86 (t, J = 8.5 Hz, 1H), 3.20 (s, 3H), 2.84 (s, 3H), 2.71 (tt, J = 3.8, 7.2 Hz, 1H), 1.40 (s, 3H), 1.10-1.00 (m, 2H), 0.79-0.70 (m, 2H); ES-LCMS *m/z* 636.1 $[M+H]^+$. Peak 2 was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) to give desired compound as a white solid, which was further separated by SFC (column: DAICEL CHIRALCEL OD-H (250mm*30mm,5um); mobile phase: [0.1% NH_3H_2O ETOH]; B%: 45%-45%, min), followed by lyophilization to yield a residue which was purified by preparative HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 11 min), followed by lyophilization to yield (*R*)-*N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]phenyl]methanesulfinamide (12.41 mg, 19.05 μmol, 8.2% yield, 97.6% purity, SFC: R_t = 4.991, ee = 89.18%, $[\alpha]^{27.7}_D$ = +107.692 (MeOH, c = 0.013 g/100 mL)) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, J = 1.8, 10.2 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.17-7.10 (m, 2H), 7.02 (dd, J = 1.1, 8.0 Hz, 1H), 6.86 (t, J = 8.5 Hz, 1H), 3.20 (s, 3H), 2.84 (s, 3H), 2.71 (tt, J = 3.7, 7.2 Hz, 1H), 1.40 (s, 3H), 1.08-1.03 (m, 2H), 0.78-0.73 (m, 2H); ES-LCMS *m/z* 636.0 $[M+H]^+$.

I-55

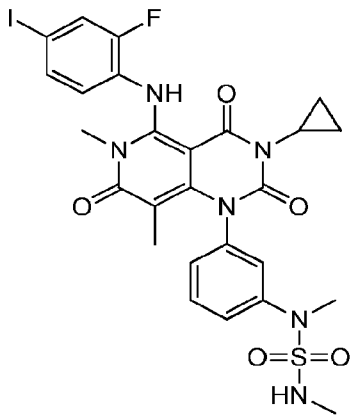


Step 1: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione**



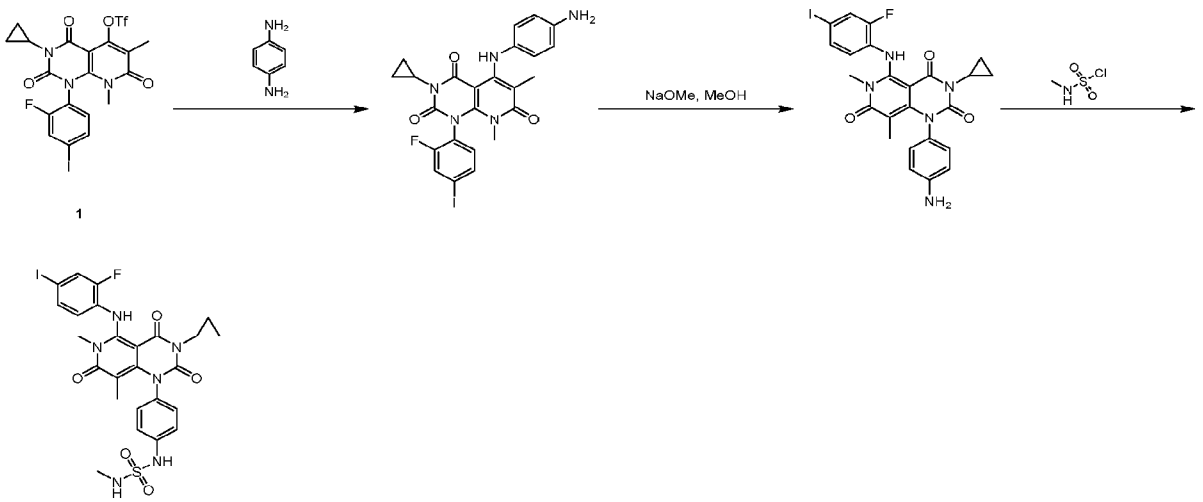
[00423] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (100 mg, 174.41 μmol, 100% purity, 1 eq) in THF (5 mL) was added NaH (40 mg, 1.00 mmol, 60% purity, 5.73 eq). The mixture was stirred at 25 °C for 0.5 h. MeI (30 mg, 211.36 μmol, 13.16 μL, 1.21 eq) was added. The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 49%-69%, 10 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (6 mg, 9.87 μmol, 5.7% yield, 96.6% purity) as an off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.68 (dd, J = 1.8, 10.2 Hz, 1H), 7.66-7.62 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.47-7.40 (m, 2H), 6.90 (t, J = 8.5 Hz, 1H), 3.22 (s, 3H), 3.10 (s, 3H), 2.74 (tt, J = 3.7, 7.2 Hz, 1H), 1.37 (s, 3H), 1.11-1.06 (m, 2H), 0.81-0.76 (m, 2H); ES-LCMS *m/z* 588.1 $[M+H]^+$.

Step 2: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-[methyl(methylsulfamoyl)amino]phenyl]-2,4,7-trioxo-pyrido[4,3-d]pyrimidine**



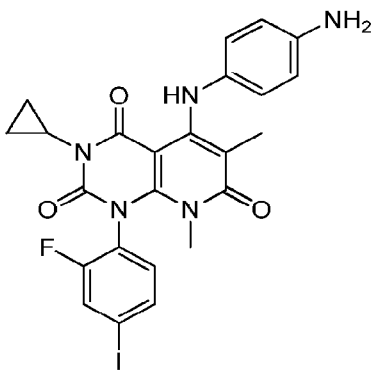
[00424] To a solution of 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (5 mg, 8.22 μmol, 96.6% purity, 1 eq) and DIEA (22.26 mg, 172.23 μmol, 30 μL, 20.95 eq) in DCM (5 mL) was added *N*-methylsulfamoyl chloride (10 mg, 77.18 μmol, 9.39 eq) at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 54%-74%, 10 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-[methyl(methylsulfamoyl)amino]phenyl]-2,4,7-trioxo-pyrido[4,3-d]pyrimidine (1.58 mg, 2.28 μmol, 27.8% yield, 98.3% purity) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 11.24 (s, 1H), 7.68 (dd, J = 1.3, 10.3 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.48-7.44 (m, 1H), 7.34-7.25 (m, 1H), 6.88 (dt, J = 2.5, 8.5 Hz, 1H), 3.27 (s, 3H), 3.22 (d, J = 2.9 Hz, 3H), 2.73 (tt, J = 3.7, 7.2 Hz, 1H), 2.65 (s, 3H), 1.39 (s, 3H), 1.13-1.02 (m, 2H), 0.83-0.75 (m, 2H); ES-LCMS *m/z* 680.9 $[M+H]^+$.

I-82



1

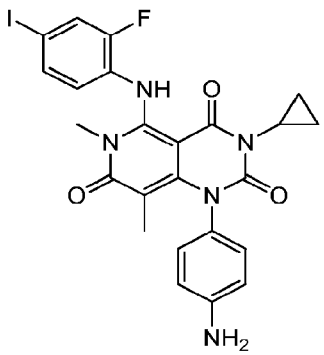
Step 1: ***tert*-Butyl 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione**



[00425] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] trifluoromethanesulfonate (300 mg, 482.70 μmol, 99.0%, 1 eq) in DMF (2 mL) was added 2,6-lutidine (155.17 mg, 1.45 mmol, 168.66 μL, 3 eq) and benzene-1,4-diamine (78.30 mg, 724.05 μmol, 1.5 eq). The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 2/1, TLC: PE/EtOAc = 2/1, R_f = 0.20) to yield *tert*-butyl 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (200 mg, 327.89 μmol, 67.9% yield, 94.0% purity) as a brown solid. ^{1}H NMR (400 MHz,

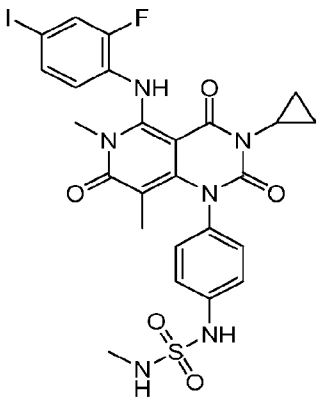
DMSO-d_6) δ ppm 10.16-10.03 (m, 1H), 8.04-7.87 (m, 1H), 7.77-7.60 (m, 1H), 7.32-7.13 (m, 1H), 6.85-6.65 (m, 2H), 6.63-6.45 (m, 2H), 5.24-4.99 (m, 2H), 2.73-2.67 (m, 3H), 1.51-1.34 (m, 3H), 1.09-0.89 (m, 2H), 0.76-0.56 (m, 2H); ES-LCMS *m/z* 574.1 $[M+H]^+$.

Step 2: ***tert*-Butyl 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



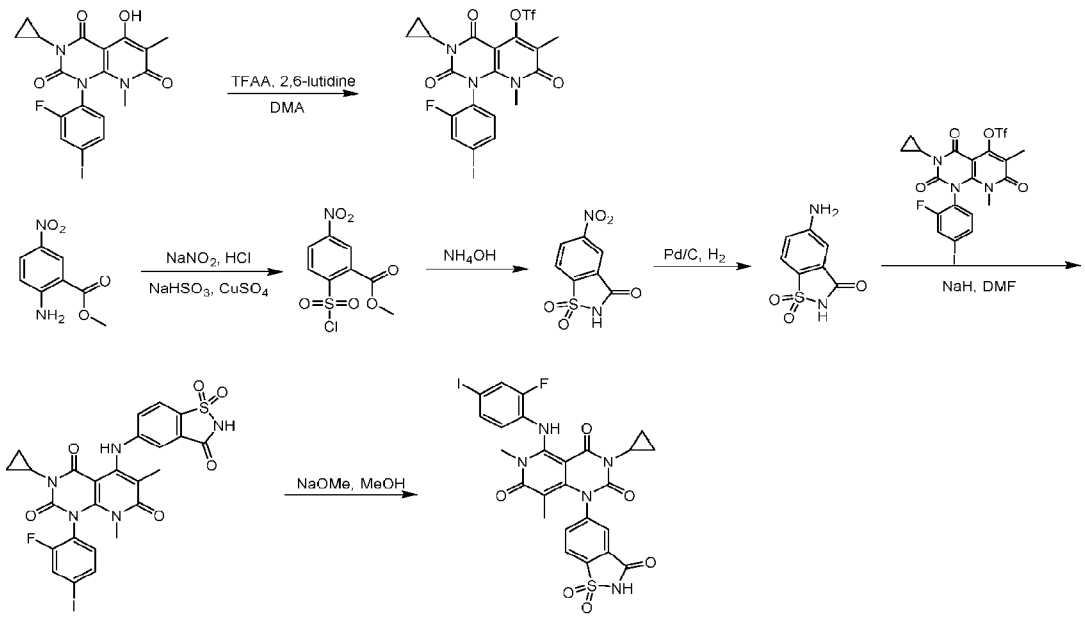
[00426] A mixture of 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (100 mg, 163.95 μmol, 1 eq) and NaOMe/MeOH (163.95 μmol, 11 μL, 30.0%, 1 eq) in THF (0.3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched by addition AcOH (0.1 mL), and then diluted with H_2O (20 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (DCM/MeOH = 10/1, TLC: DCM/MeOH= 10/1, R_f= 0.80) to yield *tert*-butyl 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (90 mg, 67.50 μmol, 41.2% yield, 43.0% purity) as a yellow solid. ES-LCMS *m/z* 574.0 $[M+H]^+$.

Step 3: ***tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[4-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione**

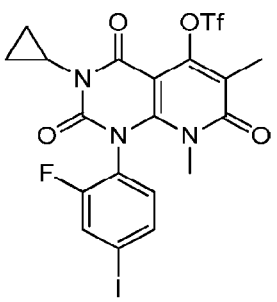


[00427] To a solution of 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (43.00 mg, 75.00 μmol, 1 eq) in DCM (1 mL) was added TEA (15.18 mg, 149.99 μmol, 20.88 μL, 2 eq) and *N*-methylsulfamoyl chloride (9.72 mg, 75.00 μmol, 1 eq). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 56%-76%, 12 min), followed by lyophilization to yield *tert*-butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[4-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (8.77 mg, 13.16 μmol, 17.6% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.23-10.93 (m, 1H), 10.00-9.81 (m, 1H), 7.90-7.70 (m, 1H), 7.59-7.52 (m, 1H), 7.50-7.44 (m, 1H), 7.29-7.23 (m, 2H), 7.22-7.15 (m, 2H), 6.99-6.82 (m, 1H), 3.12-3.01 (m, 3H), 2.63-2.57 (m, 1H), 2.47-2.44 (m, 3H), 1.22 (s, 3H), 0.99-0.91 (m, 2H), 0.72-0.57 (m, 2H); ES-LCMS *m/z* 667.0 $[M+H]^+$.

I-83



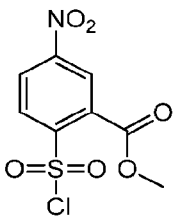
Step 1: **3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate**



[00428] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (3.2 g, 6.62 mmol, 1 eq) and 2,6-lutidine (1.21 g, 11.26 mmol, 1.31 mL, 1.7 eq) in DCM (20 mL) was added dropwise trifluoromethylsulfonyl trifluoromethanesulfonate (3.74 g, 13.24 mmol, 2.19 mL, 2 eq) at 0 °C over 30 min. And then, the mixture was stirred at 25 °C under N_2 atmosphere for 12 h. The reaction mixture was successively with the saturated aqueous $NaHCO_3$(40 mL x 3), 1N HCl (40 mL x 3) and extracted with DCM (50 mL x 3). The organic layer was washed with brine (50 mL x 3) and dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from EtOAc/DCM = 100/1 to 8/1, TLC: PE/EtOAc = 1/1, R_f

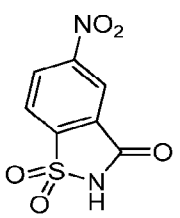
= 0.3) to yield 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate (4 g, 6.43 mmol, 97.1% yield, 98.9% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.95 (dd, J = 1.8, 9.4 Hz, 1H), 7.72 (dd, J = 1.3, 8.4 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 2.76 (s, 3H), 2.71-2.65 (m, 1H), 2.01 (s, 3H), 1.08-0.98 (m, 2H), 0.68-0.58 (m, 2H); ES-LCMS *m/z* 615.9 $[M+H]^+$.

Step 2: **Methyl 2-chlorosulfonyl-5-nitro-benzoate**



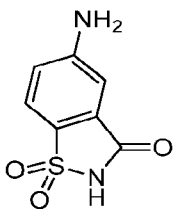
[00429] To a solution of methyl 2-amino-5-nitro-benzoate (5 g, 25.49 mmol, 1 eq) in HCl (12 M, 80 mL, 37.66 eq) was added a solution of $NaNO_2$ (1.76 g, 25.49 mmol, 1 eq) in H_2O (5 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 15 min and a solution of $NaHSO_3$ (23.9 g, 229.67 mmol, 9.01 eq) in H_2O (50 mL) was added, followed by $CuSO_4$ (406.83 mg, 2.55 mmol, 0.1 eq) at 0 °C, the mixture was stirred at 0 °C for 45 min. The mixture was diluted with water (100 mL) and extracted with EtOAc (80 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 5/1, TLC: PE/EtOAc = 3/1, R_f = 0.51) to yield methyl 2-chlorosulfonyl-5-nitro-benzoate (5.6 g, 18.02 mmol, 70.7% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.58 (d, J = 2.3 Hz, 1H), 8.54 (d, J = 2.3, 8.7 Hz, 1H), 8.40 (d, J = 8.7 Hz, 1H), 4.06 (s, 3H).

Step 3: **5-Nitro-1,1-dioxo-1,2-benzothiazol-3-one**



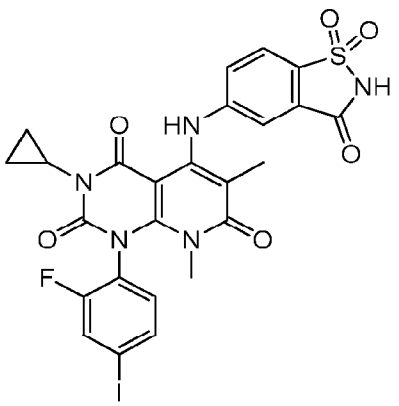
[00430] A mixture of methyl 2-chlorosulfonyl-5-nitro-benzoate (5.6 g, 18.02 mmol, 90.0%, 1 eq) in $NH_3 \cdot H_2O$ (54.60 g, 436.23 mmol, 60 mL, 28.0% purity, 24.21 eq) was stirred at 25 °C for 16 h. TLC (PE/EtOAc = 1/1, R_f = 0.04) indicated the starting material was consumed completely and one new spot formed. The mixture was adjusted pH to 2 with HCl (12 M) diluted with water (150 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 5-nitro-1,1-dioxo-1,2-benzothiazol-3-one (3.7 g, 14.59 mmol, 80.9% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.88 (d, J = 2.0 Hz, 1H), 8.76 (d, J = 2.0, 8.4 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H).

Step 4: **5-Amino-1,1-dioxo-1,2-benzothiazol-3-one**



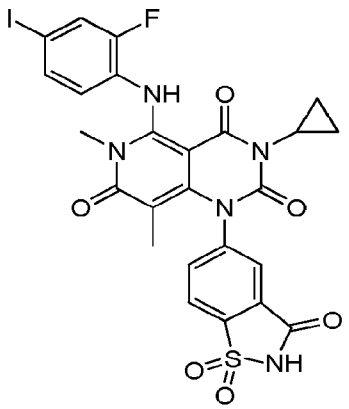
[00431] To a solution of Pd/C (3 g, 14.59 mmol, 10% purity, 1 eq) in THF (50 mL) was added 5-nitro-1,1-dioxo-1,2-benzothiazol-3-one (3.7 g, 14.59 mmol, 90.0%, 1 eq) under N_2. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 12 h. The reaction mixture was filtered and the filter was concentrated to yield a residue which was added EtOAc/MeOH (10/1, 10 mL), and stirred at 25 °C for 2 h. The slurry was filtered, and the cake was rinsed with EtOAc (2 x 3 mL). The solid was collected and dried in vacuo to yield 5-amino-1,1-dioxo-1,2-benzothiazol-3-one (2.8 g, 13.42 mmol, 91.9% yield, 95.0% purity) as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.67 (d, J = 8.4 Hz, 1H), 7.02-6.90 (m, 2H).

Step 5: **3-Cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[(1,1,3-trioxo-1,2-benzothiazol-5-yl)amino]pyrido[2,3-d]pyrimidine-2,4,7-trione**



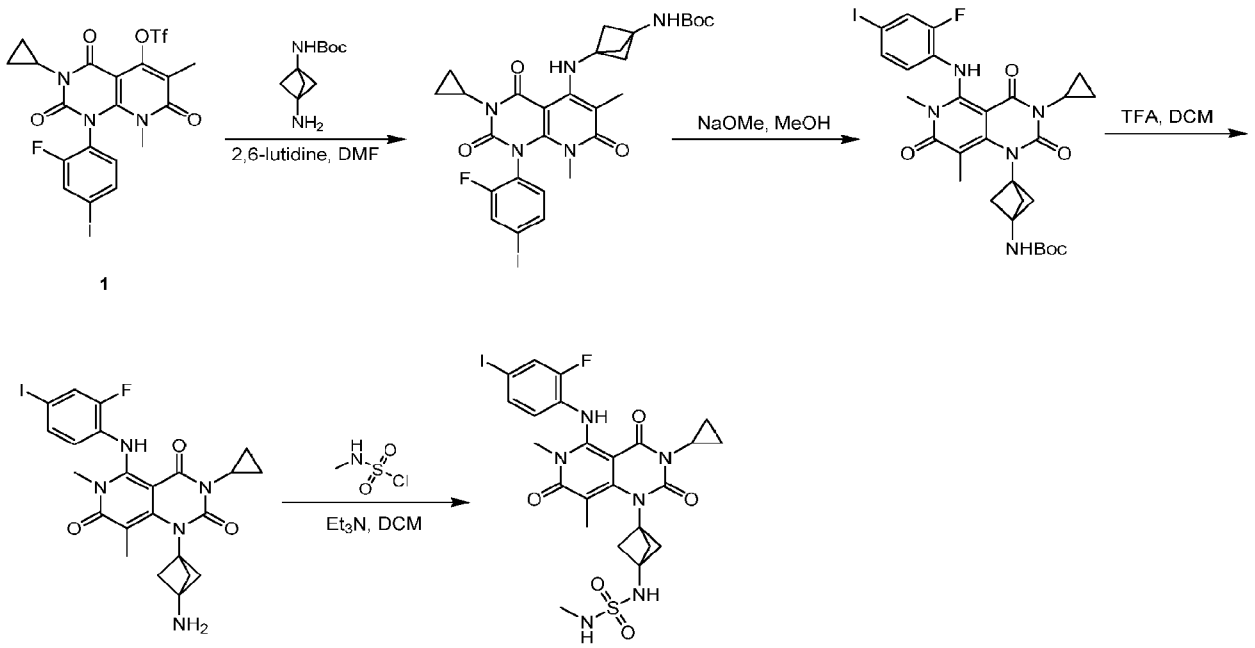
[00432] To a solution of 5-amino-1,1-dioxo-1,2-benzothiazol-3-one (134.81 mg, 646.16 μmol, 95.0%, 2.01 eq) in DMF (3 mL) was added NaH (51.44 mg, 1.29 mmol, 60.0% purity, 4 eq) and stirred at 0 °C for 30 min, [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl] trifluoromethanesulfonate (200 mg, 321.47 μmol, 98.9%, 1 eq) was added at 0 °C. The reaction temperature was slowly warmed up to 25 °C and stirred at 25 °C for 3 h. The reaction mixture was quenched by addition water (40 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 28%-58%,10min), followed by lyophilization to yield 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[(1,1,3-trioxo-1,2-benzothiazol-5-yl)amino]pyrido[2,3-d]pyrimidine-2,4,7-trione (25 mg, 37.68 μmol, 11.7% yield, 100.0% purity) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.93 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 10.2 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 6.89 (t, J = 8.5 Hz, 1H), 3.21 (s, 3H), 2.76-2.68 (m, 1H), 1.34 (s, 3H), 1.10-1.01 (m, 2H), 0.81-0.73 (m, 2H); ES-LCMS *m/z* 663.9 $[M+H]^+$.

Step 6: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-(1,1,3-trioxo-1,2-benzothiazol-5-yl)pyrido[4,3-d]pyrimidine-2,4,7-trione**

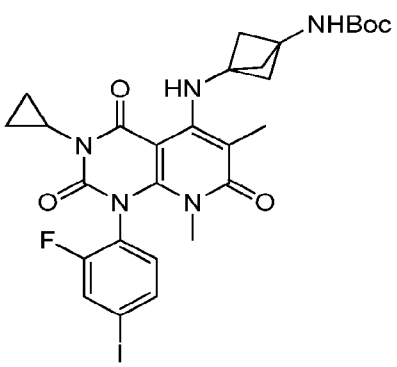


[00433] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-5-[(1,1,3-trioxo-1,2-benzothiazol-5-yl)amino]pyrido[2,3-d]pyrimidine-2,4,7-trione (20 mg, 30.15 µmol, 1 eq) in THF (0.5 mL) was added NaOMe (5.82 mg, 30.15 µmol, 28.0% purity, 1 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 29%-59%, 10min), followed by lyophilization to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-(1,1,3-trioxo-1,2-benzothiazol-5-yl)pyrido[4,3-d]pyrimidine-2,4,7-trione (2.99 mg, 4.46 µmol, 14.8% yield, 99.0% purity) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.06 (s, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.73 (s, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 10.4 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 6.70 (t, J = 8.3 Hz, 1H), 3.07 (s, 3H), 2.64 (s, 1H), 1.18 (s, 3H), 1.02 (d, J = 6.1 Hz, 2H), 0.70 (s, 2H); ES-LCMS *m/z* 663.9 $[M+H]^+$.

[00434] I-102



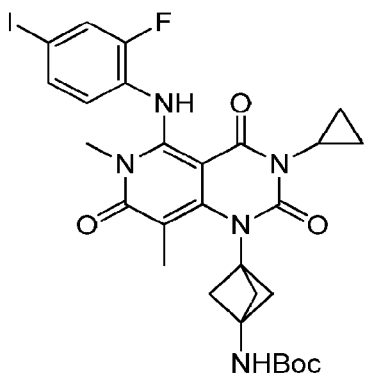
Step 1: ***tert*-Butyl *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate**



[00435] To a solution of *N*-[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl] trifluoromethanesμLfonate (300 mg, 482.70 μmol, 99.0%, 1 eq) in DMF (8 mL) was added 2,6-lutidine (155.17 mg, 1.45 mmol, 168.66 μL, 3 eq) and *tert*-butyl *N*-(3-amino-1-bicyclo[1.1.1]pentanyl)carbamate (143.55 mg, 724.05 μmol, 1.5). The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with

brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 2/1, TLC: PE/EtOAc = 2/1, R_f = 0.20) to yield *tert*-butyl *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate (200 mg, 292.4 μmol, 60.6% yield, 97.0% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.02-7.87 (m, 1H), 7.76-7.63 (m, 1H), 7.54 (s, 1H), 7.25-7.13 (m, 1H), 2.74-2.67 (m, 3H), 2.67-2.61 (m, 1H), 2.18-2.07 (m, 6H), 1.99-1.93 (m, 3H), 1.43-1.31 (m, 9H), 1.08-0.94 (m, 2H), 0.73-0.59 (m, 2H); ES-LCMS *m/z* 664.5 $[M+H]^+$.

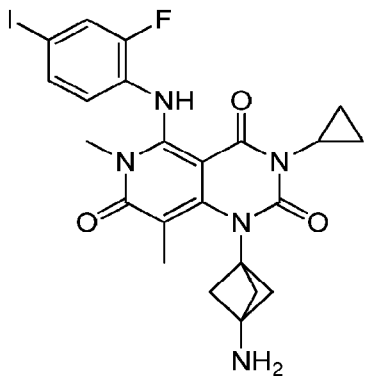
Step 2: ***tert*-Butyl *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-*d*]pyrimidin-1-yl]-1-bicyclo[1.1.1]pentanyl]carbamate**



[00436] A mixture of *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate (100 mg, 146.20 μmol, 97.0%, 1 eq) and NaOMe/MeOH (19.40 mg, 20 μL, 30.0%, 1.00 eq) in THF (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched by addition CH_3COOH (0.1 mL), and then diluted with H_2O (20 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue, which was purified by preparative TLC (PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.30) to yield *tert*-butyl *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-*d*]pyrimidin-1-yl]-1-bicyclo[1.1.1]pentanyl]carbamate (50

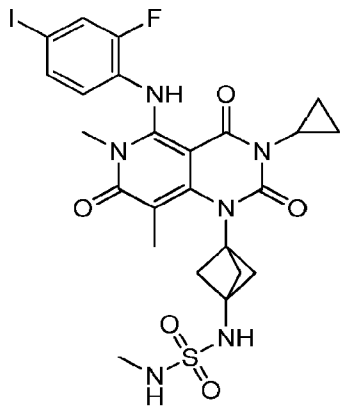
mg, 67.8 µmol, 46.4% yield, 90.0% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.36-10.16 (m, 1H), 7.83-7.68 (m, 1H), 7.65-7.55 (m, 1H), 7.54-7.48 (m, 1H), 6.96-6.82 (m, 1H), 3.08-3.06 (m, 3H), 2.59-2.54 (m, 3H), 2.44-2.39 (m, 2H), 2.23-2.18 (m, 2H), 2.03-2.01 (m, 3H), 1.39-1.35 (m, 9H), 0.93-0.84 (m, 2H), 0.63-0.39 (m, 2H); ES-LCMS *m/z* 664.0 $[M+H]^+$.

Step 3: ***tert*-Butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



[00437] To a solution of *tert*-butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (50 mg, 67.82 µmol, 90.0%, 1 eq) in DCM (1 mL) was added TFA (462.00 mg, 4.05 mmol, 0.3 mL, 59.74 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to yield a residue pressure to yield *tert*-butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (30 mg, 44.29 µmol, 65.3% yield, 100.0% purity, TFA) was obtained as a white solid which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.31 (s, 1H), 8.69 (s, 2H), 7.76 (dd, J=1.8, 10.2 Hz, 1H), 7.53 (d, J=8.5 Hz, 1H), 6.90 (t, J=8.5 Hz, 1H), 3.06 (s, 3H), 2.65-2.62 (m, 1H), 2.52-2.51 (m, 6H), 2.01 (s, 3H), 0.94-0.85 (m, 2H), 0.67-0.34 (m, 2H); ES-LCMS *m/z* 564.1 $[M+H]^+$.

Step 3: ***tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsµLfamoylamino)-1-bicyclo[1.1.1]pentanyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



[00438] To a solution of 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (30 mg, 44.29 µmol, 100.0%, 1 eq, TFA) in DCM (4 mL) was added TEA (10.78 mg, 106.50 µmol, 14.82 µL, 2 eq) and *N*-methylsµLfamoyl chloride (6.90 mg, 53.25 µmol, 1 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to yield a residue pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 51%-71%, 12 min), followed by lyophilization to yield product, followed by lyophilization to yield *tert*-butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)-1-bicyclo[1.1.1]pentanyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (12.23 mg, 18.63 µmol, 42.1% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.26 (s, 1H), 7.85 (s, 1H), 7.76 (dd, J = 1.8, 10.3 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 6.88 (t, J = 8.6 Hz, 1H), 6.76 (q, J = 5.0 Hz, 1H), 3.06 (s, 3H), 2.57-2.54 (m, 1H), 2.52 (s, 1H), 2.42 (d, J = 5.0 Hz, 6H), 2.23 (s, 3H), 2.02 (s, 3H), 0.88 (s, 2H), 0.67-0.32 (m, 2H); ES-LCMS m/z 657.0 [M+H]+.

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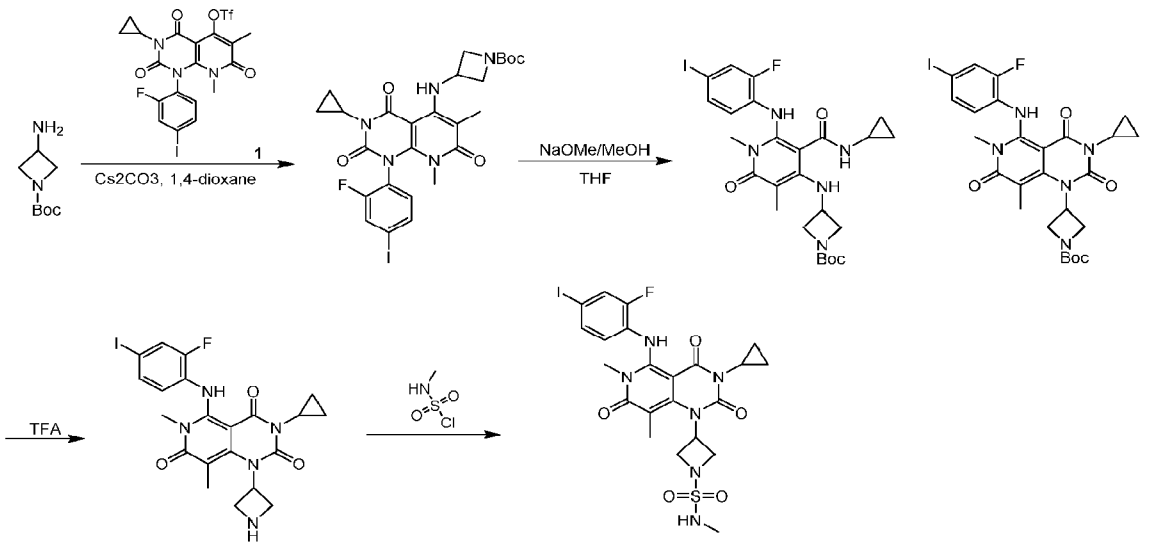
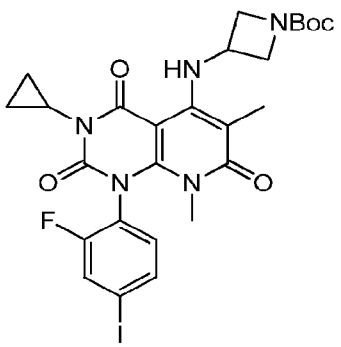


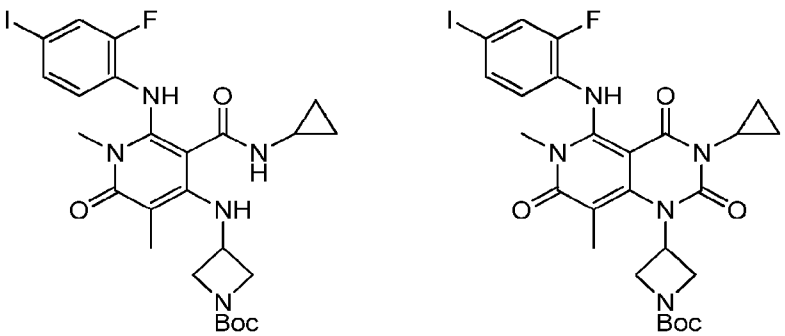
Step 1: ***tert*-Butyl 3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl]amino]azetidine-1-carboxylate**



[00439] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl] trifluoromethanesulfonate (400 mg, 642.95 μmol, 98.9% purity, 1 eq) and *tert*-butyl 3-aminoazetidine-1-carboxylate (221.46 mg, 1.29 mmol, 2 eq) in 1,4-dioxane (8 mL) was added Cs_2CO_3 (628.45 mg, 1.93 mmol, 3 eq). The mixture was stirred at 40 °C for 3 h. TLC (petroleum ether: EtOAc=1:1, R_f = 0.4) showed that new point was formed and start material was consumed completely. The reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (PE/EtOAc = 1/1.5, TLC: PE/EtOAc = 1/1, R_f = 0.40) to yield *tert*-butyl 3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-

pyrido[2,3-d]pyrimidin-5-yl]amino]azetidine-1-carboxylate (150 mg, 223.55 μmol, 34.8% yield, 95.0% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.19 (d, J = 6.4 Hz, 1H), 7.61 (dd, J = 8.8, 15.6 Hz, 2H), 6.89 (t, J = 8.0 Hz, 1H), 4.56-4.46 (m, 1H), 4.27 (td, J = 8.4, 13.2 Hz, 2H), 3.92 (dt, J = 5.2, 9.2 Hz, 2H), 2.89 (s, 3H), 2.79-2.71 (m, 1H), 2.04 (s, 3H), 1.46 (s, 9H), 1.22-1.15 (m, 2H), 0.86-0.78 (m, 2H); ES-LCMS *m/z* 638.0 $[M+H]^+$.

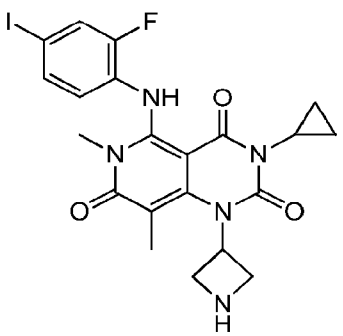
Step 2: ***tert*-Butyl 3-[[3-(cyclopropylcarbamoyl)-2-(2-fluoro-4-iodo-anilino)-1,5-dimethyl-6-oxo-4-pyridyl]amino]azetidine-1-carboxylate** and ***tert*-butyl 3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]azetidine-1-carboxylate**



[00440] To a solution of NaOMe (13.42 mg, 74.52 μmol, 0.5 mL, 30% purity, 1 eq) in THF (30 mL) was added *tert*-butyl 3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl]amino]azetidine-1-carboxylate (50 mg, 74.52 μmol, 95% purity, 1 eq) at 0 °C. The mixture was stirred at 0 °C for 1 h. TLC (petroleum ether: EtOAc=3:1, R_f = 0.7) showed that new point was formed and start material was consumed completely. The reaction mixture was quenched by addition of AcOH (1 mL) and stirred at 0 °C for 10 min. The mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by preparative TLC (PE/EtOAc = 2/1 , TLC: PE/EtOAc = 3/1, R_f = 0.70) to yield *tert*-butyl 3-[[3-(cyclopropylcarbamoyl)-2-(2-fluoro-4-iodo-anilino)-1,5-dimethyl-6-oxo-4-pyridyl]amino]azetidine-1-carboxylate (20 mg, 31.07 μmol, 41.7% yield, 95.0% purity) and *tert*-butyl 3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]azetidine-1-carboxylate (20 mg, 29.81 μmol, 40.0% yield, 95.0% purity) as a

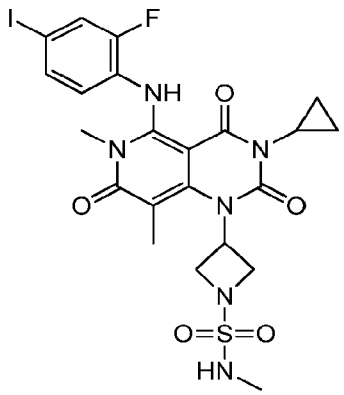
white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.87 (s, 1H), 7.50 (dd, J = 1.5, 9.5 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 6.68 (t, J = 8.5 Hz, 1H), 4.75 (quin, J=6.5 Hz, 1H), 4.26 - 4.15 (m, 4H), 3.19 - 3.12 (m, 3H), 2.71 (tt, J=4.0, 7.0 Hz, 1H), 2.03 (s, 3H), 1.43 (s, 9H), 1.10 (q, J = 7.0 Hz, 2H), 0.73-0.67 (m, 2H); ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.83 (s, 1H), 7.42 (dd, J = 2.0, 10.0 Hz, 1H), 7.30 (d, J − 8.5 Hz, 1H), 7.14 (d, J − 2.0 Hz, 1H), 6.35 (t, J − 8.5 Hz, 1H), 4.61 (d, J − 10.0 Hz, 1H), 4.21 (dd, J = 8.0, 9.0 Hz, 2H), 3.73 (dd, J = 5.0, 9.5 Hz, 2H), 3.25 (s, 3H), 2.74 (dt, J = 3.5, 7.0 Hz, 1H), 2.08 (s, 3H), 2.04 (s, 3H), 1.44 (s, 9H), 0.80-0.75 (m, 2H), 0.38-0.32 (m, 2H); ES-LCMS m/z 612.1 $[M+H]^+$; ES-LCMS m/z 638.0 $[M+H]^+$.

Step 3: **1-(Azetidin-3-yl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione**



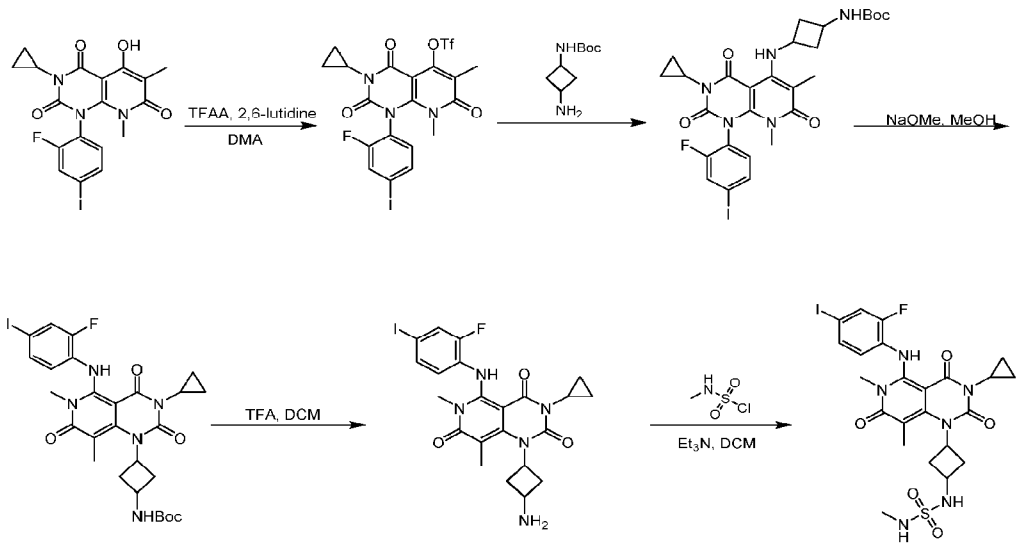
[00441] To a solution of *tert*-butyl 3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]azetidine-1-carboxylate (20 mg, 29.81 μmol, 95.0% purity, 1 eq) in DCM (5 mL) was added TFA (1.54 g, 13.51 mmol, 1 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated to yield 1-(azetidin-3-yl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (16 mg, 28.29 μmol, 94.9% yield, 95.0% purity) as a white solid, which was used directly in the next step without further purification. ES-LCMS m/z 538.0 $[M+H]^+$.

Step 4: **3-[3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]-*N*-methyl-azetidine-1-sulfonamide**

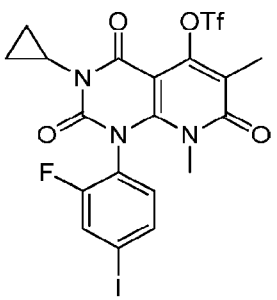


[00442] To a solution of 1-(azetidin-3-yl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (16 mg, 28.29 μmol, 95% purity, 1 eq) in DCM (5 mL) was added Et_3N (8.59 mg, 84.86 μmol, 11.81 μL, 3 eq) and *N*-methylsulfamoyl chloride (3.67 mg, 28.29 μmol, 1 eq) under N_2 atmosphere at 0 °C. The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition of H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue, which was purified by preparative HPLC (column: Welch Xtimate C18 150 * 25 mm * 5 μm; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 36%-66%,11min) to yield 3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-d]pyrimidin-1-yl]-*N*-methyl-azetidine-1-sulfonamide (6.76 mg, 10.47 μmol, 37.0% yield, 100.0% purity) as a white solid. ^1H NMR (500 MHz, CD_3OD) δ ppm 7.64 (d, J = 10.0 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 6.84 (t, J = 8.5 Hz, 1H), 4.95 (d, J = 7.5 Hz, 1H), 4.08 (quin, J = 8.0 Hz, 4H), 3.18 (s, 3H), 2.72-2.67 (m, 4H), 2.05 (s, 3H), 1.03 (q, J = 7.0 Hz, 2H), 0.68-0.62 (m, 2H); ES-LCMS *m/z* 630.9 $[M+H]^+$.

I-109



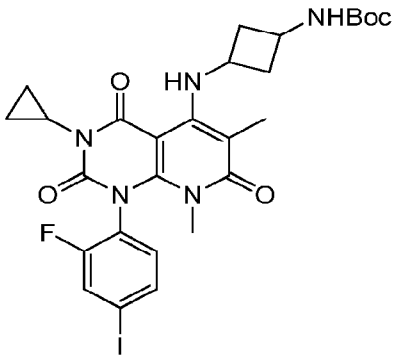
Step 1: **3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate**



[00443] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (5 g, 10.35 mmol, 1 eq) and 2,6-lutidine (1.88 g, 17.59 mmol, 2.05 mL, 1.7 eq) in DCM (35 mL) was added dropwise trifluoromethylsulfonyl trifluoromethanesulfonate (5.84 g, 20.69 mmol, 3.41 mL, 2 eq) at 0 °C over 30 min. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched with the saturated aqueous $NaHCO_3$ (40 mL x 3), extracted with DCM (50 mL x 3). The organic layer was washed with 1N HCl (40 mL x 3) and brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from EtOAc/DCM = 100/1 to 8/1, TLC: PE/EtOAc = 1/1, R_f = 0.3) to yield 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate (4 g, 6.43 mmol, 97.1% yield,

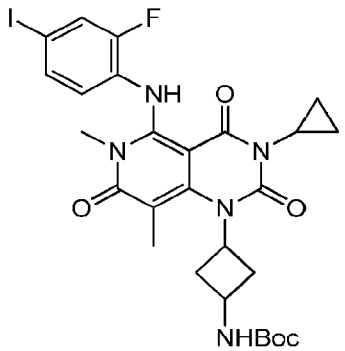
98.9% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.95 (dd, J = 1.2, 9.5 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 2.76 (s, 3H), 2.70-2.66 (m, 1H), 2.01 (s, 3H), 1.08-0.98 (m, 2H), 0.62 (t, J = 11.9 Hz, 2H); ES-LCMS m/z 615.9 $[M+H]^+$.

Step 2: ***tert*-Butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate**



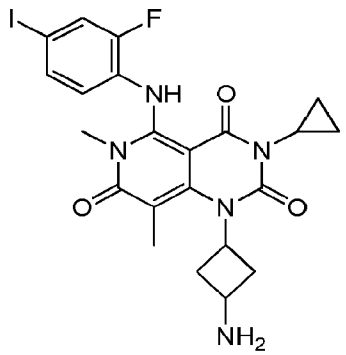
[00444] A mixture of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate (350 mg, 563.15 µmol, 99.0%, 1 eq), *tert*-butyl *N*-(3-aminocyclobutyl)carbamate (115.38 mg, 619.46 µmol, 1.1 eq) and Cs_2CO_3 (550.45 mg, 1.69 mmol, 3 eq) in DMF (5 mL) was stirred at 40 °C for 1 h, then the mixture was stirred under N_2 atmosphere at 25 °C for 4 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (40 mL x 3), and washed with brine (40 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by prep-TLC (SiO_2, PE/EtOAc = 1/1, R_f = 0.3) to yield *tert*-butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate (200 mg, 255.42 µmol, 45.4% yield, 83.2% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 (d, J = 6.6 Hz, 1H), 7.88 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.16-7.11 (m, 1H), 4.27 (d, J = 6.4 Hz, 1H), 3.87-3.41 (m, 1H), 2.62 (s, 3H), 2.35-2.09 (m, 4H), 1.95 (s, 3H), 1.93 (s, 1H), 1.34 (s, 9H), 0.99 (s, 2H), 0.65 (s, 2H); ES-LCMS m/z 652.1 $[M+H]^+$.

Step 3: ***tert*-Butyl (3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate**



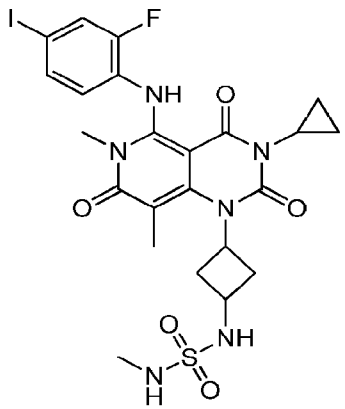
[00445] To a solution of *tert*-butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate (150 mg, 191.57 μmol, 83.2%, 1 eq) in THF (30 mL) was added NaOMe/MeOH (191.57 μmol, 0.25 mL, 30%, 1 eq) at 0 °C under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 25 °C for 0.5 h. The residue was added the CH_3COOH to pH = 7 and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the residue which was purified by prep-TLC (SiO_2, PE/EtOAc = 1:1, R_{f1} = 0.3) to yield *tert*-butyl(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate (30 mg, 32.56 μmol, 17.0% yield, 70.7% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.99-10.67 (m, 1H), 7.51 (d, J = 9.6 Hz, 1H), 7.45-7.41 (m, 1H), 6.68-6.61 (m, 1H), 4.09-3.93 (m, 1H), 3.76 (s, 3H), 3.53-3.41 (m, 1H), 3.17 (s, 3H), 3.12-2.99 (m, 1H), 2.79-2.70 (m, 2H), 2.48-2.24 (m, 2H), 1.45 (s, 9H), 1.18-1.07 (m, 2H), 0.92-0.86 (m, 2H); ES-LCMS m/z 652.1 [M+H]+.

[00446] Step 4: **1-(3-Aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**



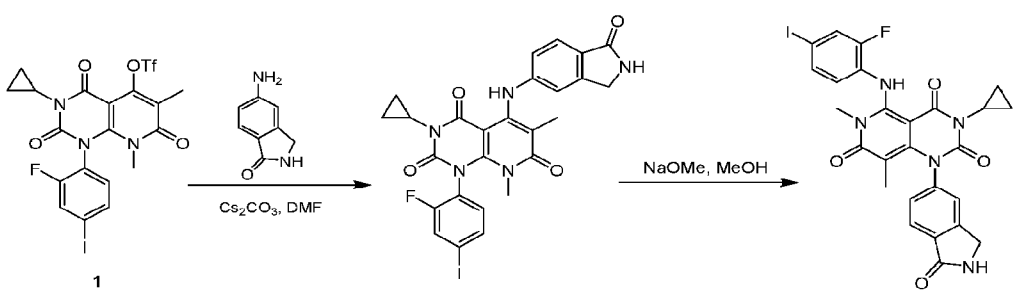
[00447] To a solution of *tert*-butyl (3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate (30 mg, 32.56 μmol, 70.7%, 1 eq) in DCM (2 mL) was added TFA (616.00 mg, 5.40 mmol, 0.4 mL, 165.94 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was diluted with H_2O (10 mL), extracted with DCM (30 mL x 3) and washed with brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-(3-aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (30 mg, 31.56 μmol, 96.9% yield, 70.0% purity, TFA) as yellow oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.62 (d, *J* = 10.5 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 6.87-6.74 (m, 1H), 5.33 (s, 2H), 4.16 (d, *J* = 7.0 Hz, 1H), 3.43 (d, *J* = 1.5 Hz, 1H), 3.16 (s, 3H), 2.72 (s, 2H), 2.64 (s, 1H), 2.28-2.18 (m, 2H), 1.27 (s, 3H), 1.04-0.99 (m, 2H), 0.90-0.88 (m, 2H); ES-LCMS m/z 552.1 [M+H]+.

Step 5: **3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)cyclobutyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione**

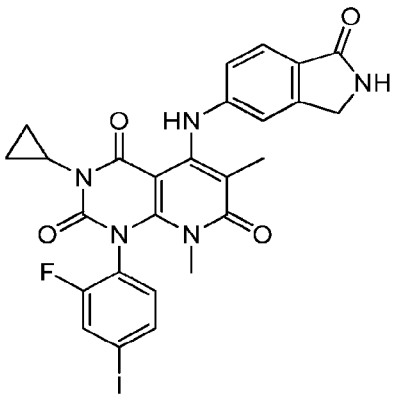


[00448] To a solution of 1-(3-aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (30 mg, 31.56 μmol, 70.0%, 1 eq, TFA) in DCM (2 mL) was added TEA (9.58 mg, 94.68 μmol, 13.18 μL, 3 eq) and *N*-methylsulfamoyl chloride (4.50 mg, 34.72 μmol, 1.1 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL), extracted with DCM (20 mL x 3). The organic layer was concentrated under reduced pressure, which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 45%-70%, 11 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)cyclobutyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (3.13 mg, 4.81 μmol, 15.3% yield, 99.1% purity) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.64 (dd, J = 1.8, 10.0 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.82 (t, J = 8.5 Hz, 1H), 4.29-4.20 (m, 1H), 3.51-3.47 (m, 1H), 3.18 (s, 3H), 2.87-2.82 (m, 2H), 2.67 (td, J = 3.4, 7.1 Hz, 1H), 2.58 (s, 3H), 2.44-2.37 (m, 2H), 2.08 (s, 3H), 1.05-0.98 (m, 2H), 0.66-0.62 (m, 2H); ES-LCMS *m/z* 645.0 $[M+H]^+$.

[00449] I-111

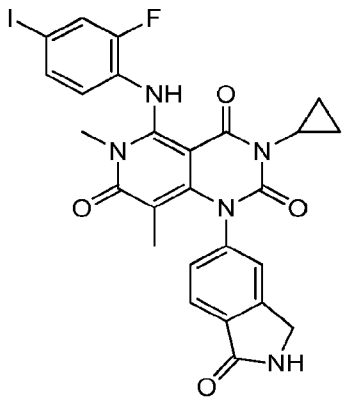


Step 1: **3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione**



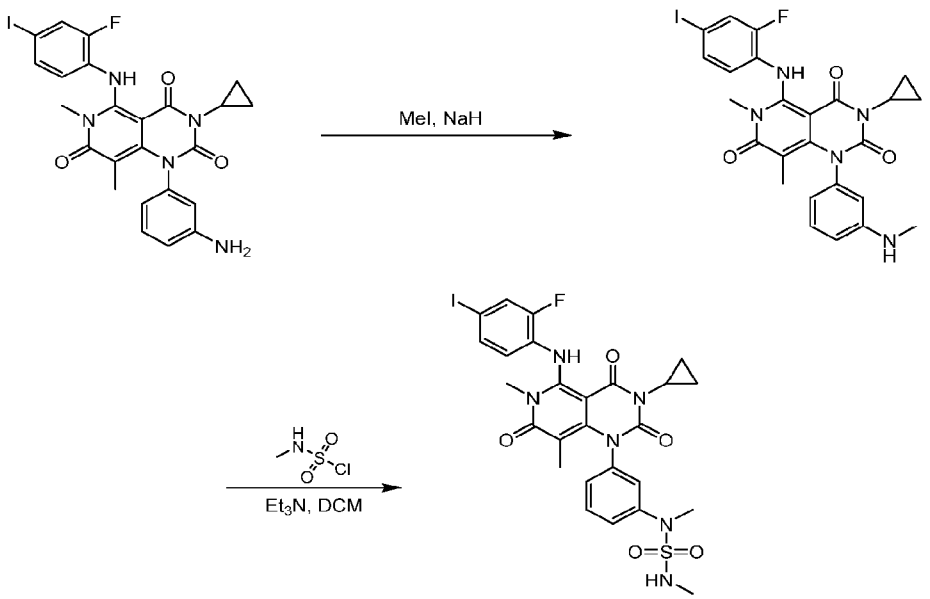
[00450] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] trifluoromethanesulfonate (200 mg, 321.80 µmol, 99.0%, 1 eq) in DMF (3 mL) was added 5-aminoisoindolin-1-one (47.68 mg, 321.80 µmol, 1 eq) and Cs_2CO_3 (314.54 mg, 965.39 µmol, 3 eq). The mixture was stirred at 60 °C for 3 h. The reaction mixture was diluted with H_2O (30 mL), extracted with DCM (40 mL x 3) and the organic layer was concentrated under reduced pressure, which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) and lyophilized to yield 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (120 mg, 193.09 µmol, 60.0% yield, 98.7% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.90-7.83 (m, 1H), 7.73-7.63 (m, 1H), 7.45 (d, J = 8.9 Hz, 1H), 6.79-6.62 (m, 2H), 6.06 (d, J = 6.6 Hz, 2H), 4.70-4.56 (m, 2H), 4.46 (d, J = 15.9 Hz, 1H), 3.38 (s, 3H), 2.52 (s, 1H), 2.50 (s, 3H), 2.07 (d, J = 1.5 Hz, 1H), 0.94-0.83 (m, 2H), 0.67-0.45 (m, 2H); ES-LCMS m/z 614.0 [M+H]+.

Step 2: **3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(1-oxoisoindolin-5-yl)pyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione**

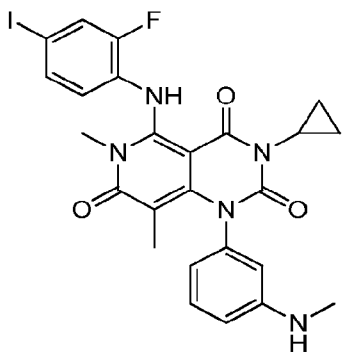


[00451] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (30 mg, 48.27 μmol, 98.7%, 1 eq) in THF (30 mL) was added MeONa/MeOH (48.27 μmol, 0.1 mL, 30%, 1 eq) at 0°C under N_2 atmosphere. The resulting mixture was stirred under N_2 atmosphere at 25°C for 20 min. The residue was added the CH_3COOH to pH = 7 and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure, which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(TFA)-ACN]; B%: 38%-58%, 12 min) and lyophilized to yield 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(1-oxoisoindolin-5-yl)pyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (3.84 mg, 6.26 μmol, 13.0% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.01 (s, 1H), 8.46 (s, 1H), 7.87 (dd, J = 1.5, 9.4 Hz, 1H), 7.70-7.63 (m, 2H), 7.27-7.22 (m, 1H), 7.21-7.17 (m, 2H), 4.34 (s, 2H), 3.11 (s, 3H), 2.33 (d, J = 1.8 Hz, 1H), 1.29 (s, 3H), 0.95 (d, J = 7.0 Hz, 2H), 0.67-0.57 (m, 2H); ES-LCMS m/z 613.9 [M+H]+.

Synthesis of 3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-[methyl(methylsulfamoyl)amino]phenyl]-2,4,7-trioxo-pyrido[4,3-d]pyrimidine (I-55)



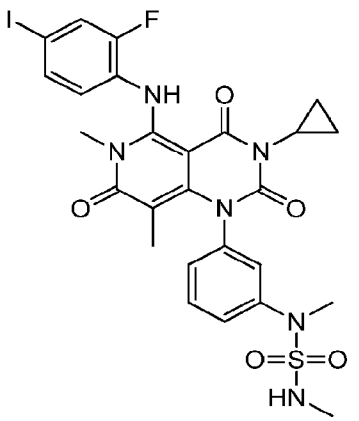
Step 1: 3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione



[00452] To a solution of 1-(3-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (100 mg, 174.41 µmol, 100% purity, 1 eq) in THF (5 mL) was added NaH (40 mg, 1.00 mmol, 60% purity, 5.73 eq). The mixture was stirred at 25 °C for 0.5 h. MeI (30 mg, 211.36 µmol, 13.16 µL, 1.21 eq) was added. The mixture was stirred at 25 °C for 12 h. The reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 49%-69%, 10 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-

(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (6 mg, 9.87 μmol, 5.7% yield, 96.6% purity) as an off-white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.68 (dd, J = 1.8, 10.2 Hz, 1H), 7.66-7.62 (m, 1H), 7.60 (d, J = 8.4 Hz, 1H), 7.50 (t, J = 1.9 Hz, 1H), 7.47-7.40 (m, 2H), 6.90 (t, J = 8.5 Hz, 1H), 3.22 (s, 3H), 3.10 (s, 3H), 2.74 (tt, J = 3.7, 7.2 Hz, 1H), 1.37 (s, 3H), 1.11-1.06 (m, 2H), 0.81-0.76 (m, 2H); ES-LCMS m/z 588.1 $[M+H]^+$.

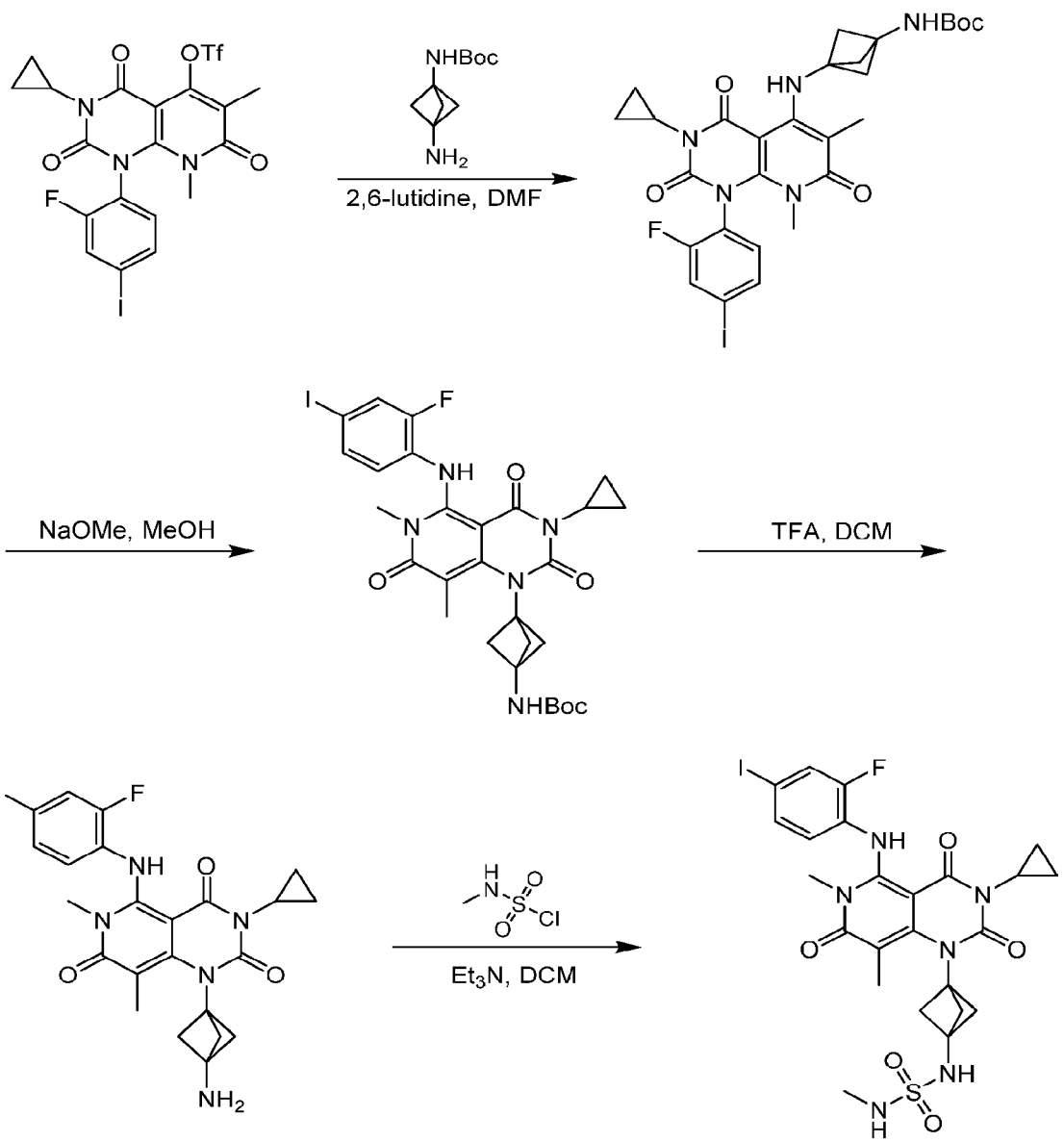
Step 2: 3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-[methyl(methylsulfamoyl)amino]phenyl]-2,4,7-trioxo-pyrido[4,3-d]pyrimidine



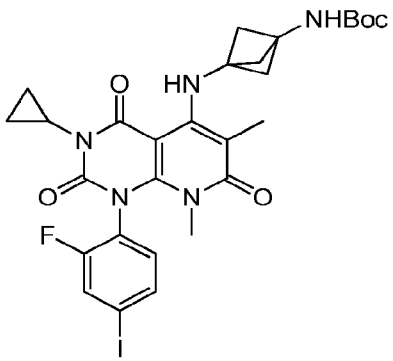
[00453] To a solution of 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylamino)phenyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (5 mg, 8.22 μmol, 96.6% purity, 1 eq) and DIEA (22.26 mg, 172.23 μmol, 30 μL, 20.95 eq) in DCM (5 mL) was added *N*-methylsulfamoyl chloride (10 mg, 77.18 μmol, 9.39 eq) at 0 °C. The mixture was stirred at 0 °C for 10 minutes. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 54%-74%, 10 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-[methyl(methylsulfamoyl)amino]phenyl]-2,4,7-trioxo-pyrido[4,3-d]pyrimidine (1.58 mg, 2.28 μmol, 27.8% yield, 98.3% purity) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 11.24 (s, 1H), 7.68 (dd, J = 1.3, 10.3 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.53-7.48 (m, 2H), 7.48-7.44 (m, 1H), 7.34-7.25 (m, 1H), 6.88 (dt, J = 2.5, 8.5 Hz, 1H), 3.27 (s, 3H), 3.22 (d, J = 2.9 Hz, 3H), 2.73

(tt, J = 3.7, 7.2 Hz, 1H), 2.65 (s, 3H), 1.39 (s, 3H), 1.13-1.02 (m, 2H), 0.83-0.75 (m, 2H); ES-LCMS m/z 680.9 $[M+H]^+$.

Synthesis of ***tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsµLfamoylamino)-1-bicyclo[1.1.1]pentanyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione** (I-102)

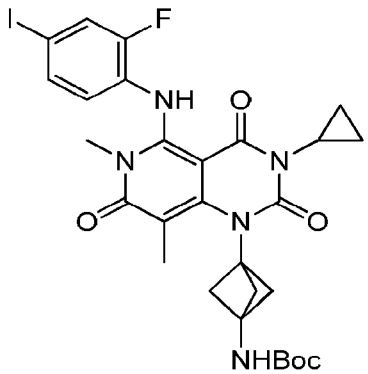


Step 1: *tert*-Butyl *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate



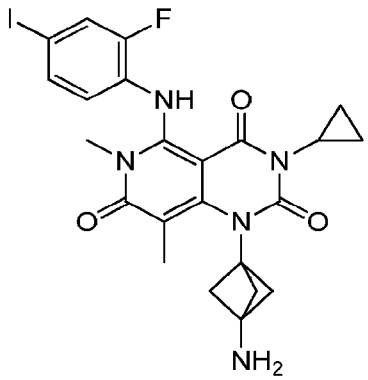
[00454] To a solution of *N*-[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-d]pyrimidin-5-yl] trifluoromethanesµlfonate (300 mg, 482.70 µmol, 99.0%, 1 eq) in DMF (8 mL) was added 2,6-lutidine (155.17 mg, 1.45 mmol, 168.66 µL, 3 eq) and *tert*-butyl *N*-(3-amino-1-bicyclo[1.1.1]pentanyl)carbamate (143.55 mg, 724.05 µmol, 1.5). The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 2/1, TLC: PE/EtOAc = 2/1, R_f = 0.20) to yield *tert*-butyl *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate (200 mg, 292.4 µmol, 60.6% yield, 97.0% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.02-7.87 (m, 1H), 7.76-7.63 (m, 1H), 7.54 (s, 1H), 7.25-7.13 (m, 1H), 2.74-2.67 (m, 3H), 2.67-2.61 (m, 1H), 2.18-2.07 (m, 6H), 1.99-1.93 (m, 3H), 1.43-1.31 (m, 9H), 1.08-0.94 (m, 2H), 0.73-0.59 (m, 2H); ES-LCMS *m/z* 664.5 $[M+H]^+$.

Step 2: *tert*-Butyl *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-*d*]pyrimidin-1-yl]-1-bicyclo[1.1.1]pentanyl]carbamate



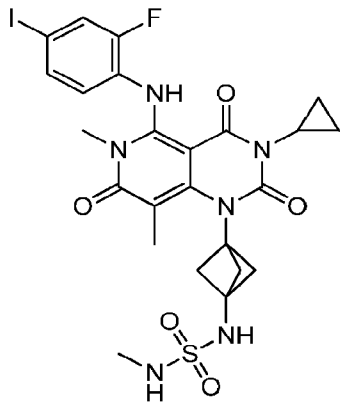
[00455] A mixture of *N*-[3-[[3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl]amino]-1-bicyclo[1.1.1]pentanyl]carbamate (100 mg, 146.20 μmol, 97.0%, 1 eq) and NaOMe/MeOH (19.40 mg, 20 μL, 30.0%, 1.00 eq) in THF (3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched by addition CH_3COOH (0.1 mL), and then diluted with H_2O (20 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue, which was purified by preparative TLC (PE/EtOAc = 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.30) to yield *tert*-butyl *N*-[3-[3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-2,4,7-trioxo-pyrido[4,3-*d*]pyrimidin-1-yl]-1-bicyclo[1.1.1]pentanyl]carbamate (50 mg, 67.8 μmol, 46.4% yield, 90.0% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.36-10.16 (m, 1H), 7.83-7.68 (m, 1H), 7.65-7.55 (m, 1H), 7.54-7.48 (m, 1H), 6.96-6.82 (m, 1H), 3.08-3.06 (m, 3H), 2.59-2.54 (m, 3H), 2.44-2.39 (m, 2H), 2.23-2.18 (m, 2H), 2.03-2.01 (m, 3H), 1.39-1.35 (m, 9H), 0.93-0.84 (m, 2H), 0.63-0.39 (m, 2H); ES-LCMS *m/z* 664.0 $[M+H]^+$.

Step 3: *tert*-Butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione



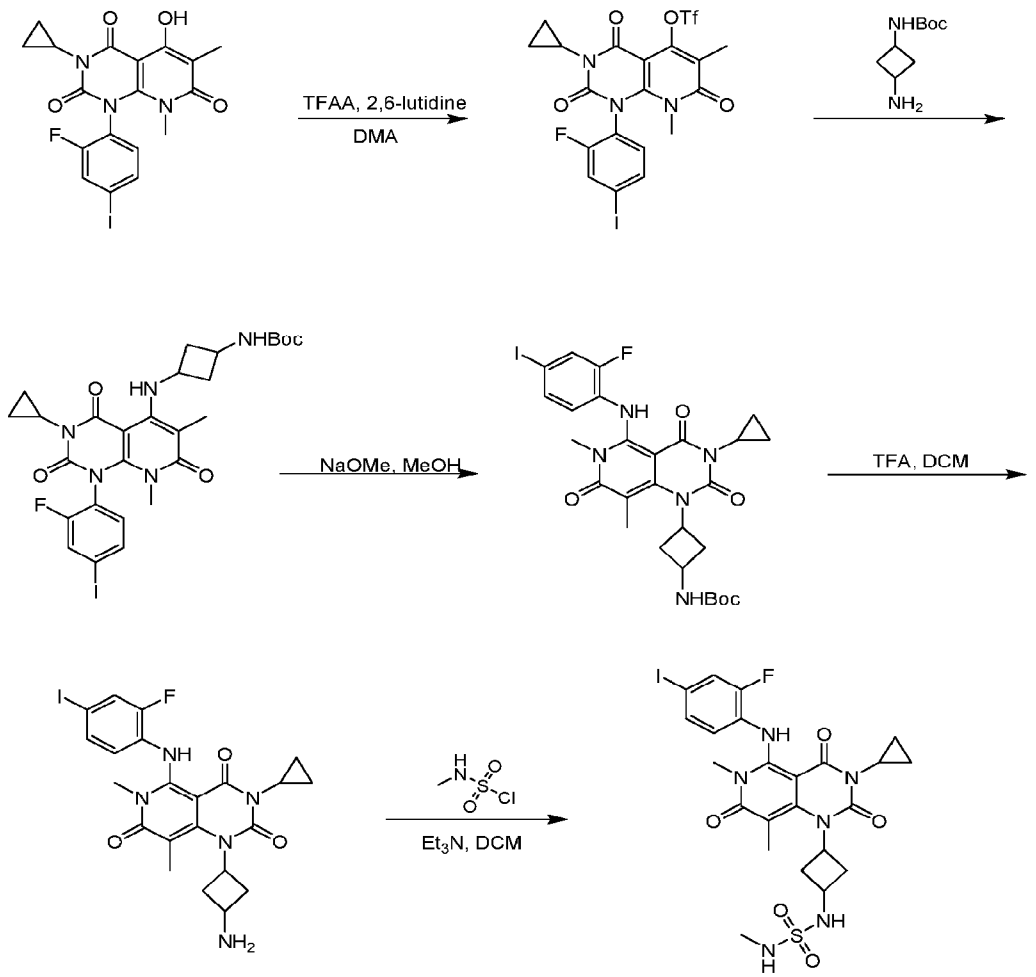
[00456] To a solution of *tert*-butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (50 mg, 67.82 µmol, 90.0%, 1 eq) in DCM (1 mL) was added TFA (462.00 mg, 4.05 mmol, 0.3 mL, 59.74 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to yield a residue pressure to yield *tert*-butyl 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (30 mg, 44.29 µmol, 65.3% yield, 100.0% purity, TFA) was obtained as a white solid which was used in the next step without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.31 (s, 1H), 8.69 (s, 2H), 7.76 (dd, J=1.8, 10.2 Hz, 1H), 7.53 (d, J=8.5 Hz, 1H), 6.90 (t, J=8.5 Hz, 1H), 3.06 (s, 3H), 2.65-2.62 (m, 1H), 2.52-2.51 (m, 6H), 2.01 (s, 3H), 0.94-0.85 (m, 2H), 0.67-0.34 (m, 2H); ES-LCMS *m/z* 564.1 $[M+H]^+$.

Step 3: *tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsµLfamoylamino)-1-bicyclo[1.1.1]pentanyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione

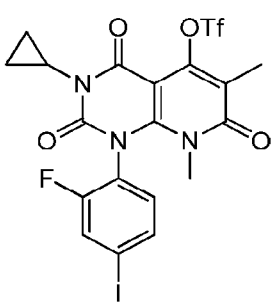


[00457] To a solution of 1-(3-amino-1-bicyclo[1.1.1]pentanyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-d]pyrimidine-2,4,7-trione (30 mg, 44.29 µmol, 100.0%, 1 eq, TFA) in DCM (4 mL) was added TEA (10.78 mg, 106.50 µmol, 14.82 µL, 2 eq) and *N*-methylsµLfamoyl chloride (6.90 mg, 53.25 µmol, 1 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated to yield a residue pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 51%-71%, 12 min), followed by lyophilization to yield product, followed by lyophilization to yield *tert*-butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)-1-bicyclo[1.1.1]pentanyl]pyrido[4,3-d]pyrimidine-2,4,7-trione (12.23 mg, 18.63 µmol, 42.1% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.26 (s, 1H), 7.85 (s, 1H), 7.76 (dd, J = 1.8, 10.3 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 6.88 (t, J = 8.6 Hz, 1H), 6.76 (q, J = 5.0 Hz, 1H), 3.06 (s, 3H), 2.57-2.54 (m, 1H), 2.52 (s, 1H), 2.42 (d, J = 5.0 Hz, 6H), 2.23 (s, 3H), 2.02 (s, 3H), 0.88 (s, 2H), 0.67-0.32 (m, 2H); ES-LCMS m/z 657.0 [M+H]+.

Synthesis of 3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)cyclobutyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (I-109)



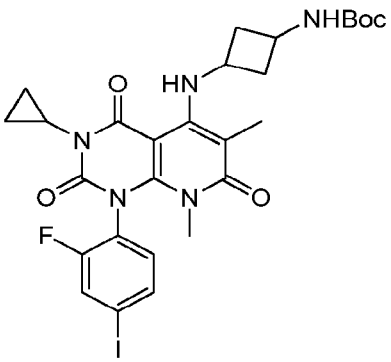
Step 1: 3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate



[00458] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-5-hydroxy-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (5 g, 10.35 mmol, 1 eq) and 2,6-lutidine (1.88 g, 17.59 mmol, 2.05 mL, 1.7 eq) in DCM (35 mL) was added dropwise trifluoromethylsulfonyl

trifluoromethanesulfonate (5.84 g, 20.69 mmol, 3.41 mL, 2 eq) at 0 °C over 30 min. The mixture was stirred at 25 °C for 12 h under N_2 atmosphere. The reaction mixture was quenched with the saturated aqueous $NaHCO_3$ (40 mL x 3), extracted with DCM (50 mL x 3). The organic layer was washed with 1N HCl (40 mL x 3) and brine (50 mL x 3), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from EtOAc/DCM = 100/1 to 8/1, TLC: PE/EtOAc = 1/1, R_f = 0.3) to yield 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate (4 g, 6.43 mmol, 97.1% yield, 98.9% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.95 (dd, J = 1.2, 9.5 Hz, 1H), 7.72 (d, J = 8.6 Hz, 1H), 7.30 (t, J = 8.1 Hz, 1H), 2.76 (s, 3H), 2.70-2.66 (m, 1H), 2.01 (s, 3H), 1.08-0.98 (m, 2H), 0.62 (t, J = 11.9 Hz, 2H); ES-LCMS *m/z* 615.9 $[M+H]^+$.

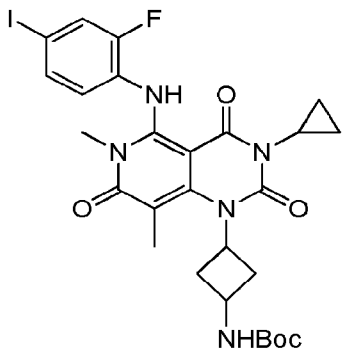
Step 2: *tert*-Butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate



[00459] A mixture of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl trifluoromethanesulfonate (350 mg, 563.15 μmol, 99.0%, 1 eq), *tert*-butyl *N*-(3-aminocyclobutyl)carbamate (115.38 mg, 619.46 μmol, 1.1 eq) and Cs_2CO_3 (550.45 mg, 1.69 mmol, 3 eq) in DMF (5 mL) was stirred at 40 °C for 1 h, then the mixture was stirred under N_2 atmosphere at 25 °C for 4 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (40 mL x 3), and washed with brine (40 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by prep-TLC (SiO_2, PE/EtOAc = 1/1, R_f = 0.3) to yield *tert*-butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-

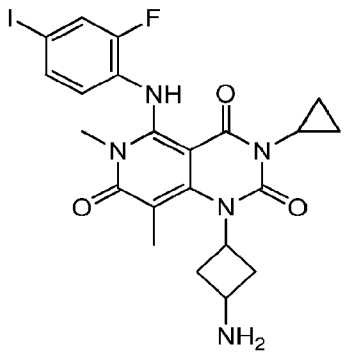
hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate (200 mg, 255.42 μmol, 45.4% yield, 83.2% purity) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 (d, J = 6.6 Hz, 1H), 7.88 (d, J = 9.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 7.8 Hz, 1H), 7.16-7.11 (m, 1H), 4.27 (d, J = 6.4 Hz, 1H), 3.87-3.41 (m, 1H), 2.62 (s, 3H), 2.35-2.09 (m, 4H), 1.95 (s, 3H), 1.93 (s, 1H), 1.34 (s, 9H), 0.99 (s, 2H), 0.65 (s, 2H); ES-LCMS *m/z* 652.1 $[M+H]^+$.

Step 3: *tert*-Butyl (3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate



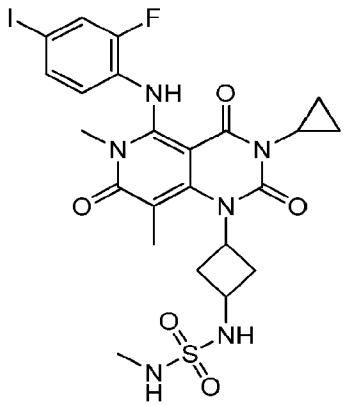
[00460] To a solution of *tert*-butyl (3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)cyclobutyl)carbamate (150 mg, 191.57 μmol, 83.2%, 1 eq) in THF (30 mL) was added NaOMe/MeOH (191.57 μmol, 0.25 mL, 30%, 1 eq) at 0 °C under N_2 atmosphere. The mixture was stirred under N_2 atmosphere at 25 °C for 0.5 h. The residue was added the CH_3COOH to pH = 7 and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the residue which was purified by prep-TLC (SiO_2, PE/EtOAc = 1:1, R_{f1} = 0.3) to yield *tert*-butyl(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate (30 mg, 32.56 μmol, 17.0% yield, 70.7% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.99-10.67 (m, 1H), 7.51 (d, J = 9.6 Hz, 1H), 7.45-7.41 (m, 1H), 6.68-6.61 (m, 1H), 4.09-3.93 (m, 1H), 3.76 (s, 3H), 3.53-3.41 (m, 1H), 3.17 (s, 3H), 3.12-2.99 (m, 1H), 2.79-2.70 (m, 2H), 2.48-2.24 (m, 2H), 1.45 (s, 9H), 1.18-1.07 (m, 2H), 0.92-0.86 (m, 2H); ES-LCMS m/z 652.1 [M+H]+.

Step 4: 1-(3-Aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione



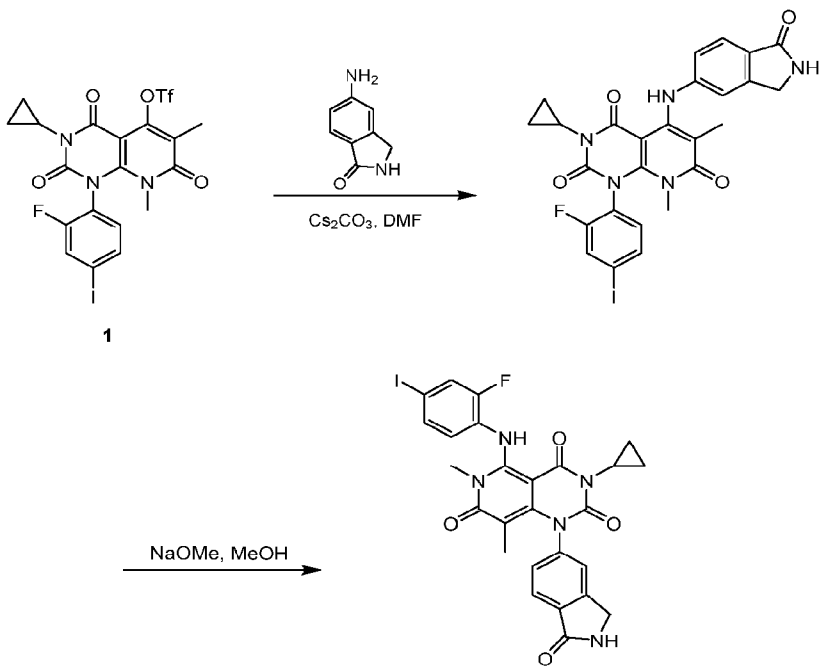
[00461] To a solution of *tert*-butyl (3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)cyclobutyl)carbamate (30 mg, 32.56 µmol, 70.7%, 1 eq) in DCM (2 mL) was added TFA (616.00 mg, 5.40 mmol, 0.4 mL, 165.94 eq). The mixture was stirred at 25 °C for 0.5 h. The reaction mixture was diluted with H_2O (10 mL), extracted with DCM (30 mL x 3) and washed with brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-(3-aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (30 mg, 31.56 µmol, 96.9% yield, 70.0% purity, TFA) as yellow oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.62 (d, *J* = 10.5 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 6.87-6.74 (m, 1H), 5.33 (s, 2H), 4.16 (d, *J* = 7.0 Hz, 1H), 3.43 (d, *J* = 1.5 Hz, 1H), 3.16 (s, 3H), 2.72 (s, 2H), 2.64 (s, 1H), 2.28-2.18 (m, 2H), 1.27 (s, 3H), 1.04-0.99 (m, 2H), 0.90-0.88 (m, 2H); ES-LCMS m/z 552.1 [M+H]+.

Step 5: 3-Cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)cyclobutyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione

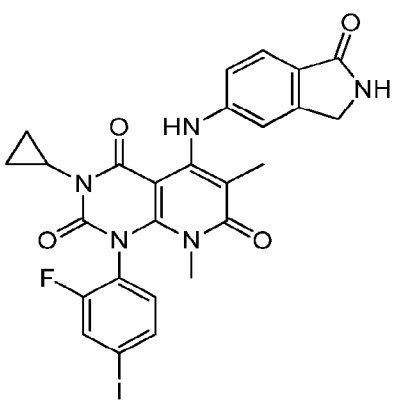


[00462] To a solution of 1-(3-aminocyclobutyl)-3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (30 mg, 31.56 μmol, 70.0%, 1 eq, TFA) in DCM (2 mL) was added TEA (9.58 mg, 94.68 μmol, 13.18 μL, 3 eq) and *N*-methylsulfamoyl chloride (4.50 mg, 34.72 μmol, 1.1 eq). The mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL), extracted with DCM (20 mL x 3). The organic layer was concentrated under reduced pressure, which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(NH_4HCO_3)-ACN]; B%: 45%-70%, 11 min) and lyophilized to yield 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[3-(methylsulfamoylamino)cyclobutyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (3.13 mg, 4.81 μmol, 15.3% yield, 99.1% purity) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.64 (dd, J = 1.8, 10.0 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 6.82 (t, J = 8.5 Hz, 1H), 4.29-4.20 (m, 1H), 3.51-3.47 (m, 1H), 3.18 (s, 3H), 2.87-2.82 (m, 2H), 2.67 (td, J = 3.4, 7.1 Hz, 1H), 2.58 (s, 3H), 2.44-2.37 (m, 2H), 2.08 (s, 3H), 1.05-0.98 (m, 2H), 0.66-0.62 (m, 2H); ES-LCMS *m/z* 645.0 $[M+H]^+$.

Synthesis of **3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(1-oxoisoindolin-5-yl)pyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione** (I-116)



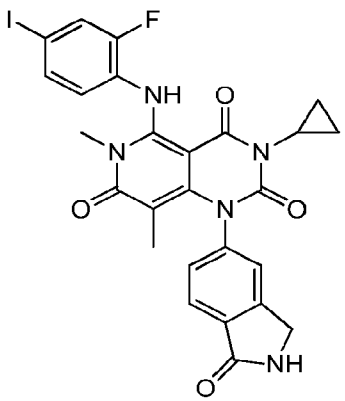
Step 1: 3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione



[00463] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] trifluoromethanesulfonate (200 mg, 321.80 μmol, 99.0%, 1 eq) in DMF (3 mL) was added 5-aminoisoindolin-1-one (47.68 mg, 321.80 μmol, 1 eq) and Cs_2CO_3 (314.54 mg, 965.39 μmol, 3 eq). The mixture was stirred at 60 °C for 3 h. The reaction mixture was diluted with H_2O (30 mL), extracted with DCM (40 mL x 3) and the organic layer was concentrated under reduced pressure, which was purified by preparative HPLC (column:

Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 40%-70%, 10 min) and lyophilized to yield 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (120 mg, 193.09 μmol, 60.0% yield, 98.7% purity) as a white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 7.90-7.83 (m, 1H), 7.73-7.63 (m, 1H), 7.45 (d, J = 8.9 Hz, 1H), 6.79-6.62 (m, 2H), 6.06 (d, J = 6.6 Hz, 2H), 4.70-4.56 (m, 2H), 4.46 (d, J = 15.9 Hz, 1H), 3.38 (s, 3H), 2.52 (s, 1H), 2.50 (s, 3H), 2.07 (d, J = 1.5 Hz, 1H), 0.94-0.83 (m, 2H), 0.67-0.45 (m, 2H); ES-LCMS m/z 614.0 [M+H]+.

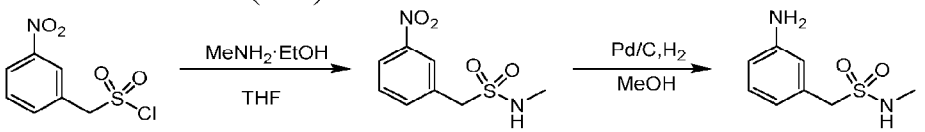
Step 2: 3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(1-oxoisoindolin-5-yl)pyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione

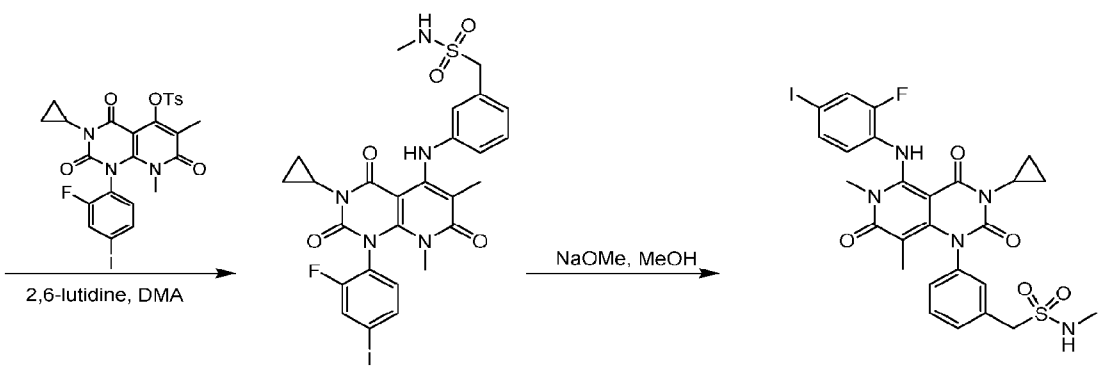


[00464] To a solution of 3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-5-((1-oxoisoindolin-5-yl)amino)pyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (30 mg, 48.27 μmol, 98.7%, 1 eq) in THF (30 mL) was added MeONa/MeOH (48.27 μmol, 0.1 mL, 30%, 1 eq) at 0°C under N_2 atmosphere. The resulting mixture was stirred under N_2 atmosphere at 25°C for 20 min. The residue was added the CH_3COOH to pH = 7 and extracted with EtOAc (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure, which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(TFA)-ACN]; B%: 38%-58%, 12 min) and lyophilized to yield 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-1-(1-oxoisoindolin-5-yl)pyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (3.84 mg, 6.26 μmol, 13.0% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.01 (s, 1H), 8.46 (s, 1H), 7.87

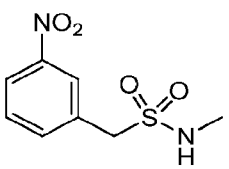
(dd, J = 1.5, 9.4 Hz, 1H), 7.70-7.63 (m, 2H), 7.27-7.22 (m, 1H), 7.21-7.17 (m, 2H), 4.34 (s, 2H), 3.11 (s, 3H), 2.33 (d, J = 1.8 Hz, 1H), 1.29 (s, 3H), 0.95 (d, J = 7.0 Hz, 2H), 0.67-0.57 (m, 2H); ES-LCMS m/z 613.9 [M+H]+.

Synthesis of **1-(3-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonamide** (I-46)





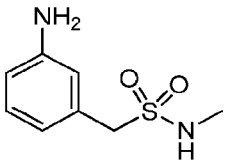
Step 1: **4-Methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide**



[00465] To a solution of (3-nitrophenyl)methanesulfonyl chloride (500 mg, 2.12 mmol, 1 eq) in THF (1 mL) was added DIEA (548.47 mg, 4.24 mmol, 739.17 µL, 2 eq) and $MeNH_2$.EtOH (197.69 mg, 6.37 mmol, 212.18 µL, 3 eq). The mixture was stirred at 25 °C for 1 h. The mixture was quenched with water (30 mL) and extracted with DCM (30 mL x 3). The combined organic phase was washed with $NaHCO_3$ (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuum to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 2/1, R_f = 0.4) to yield 4-methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide (200 mg, 861.19 µmol, 40.6% yield, 99.1% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.32-8.20 (m,

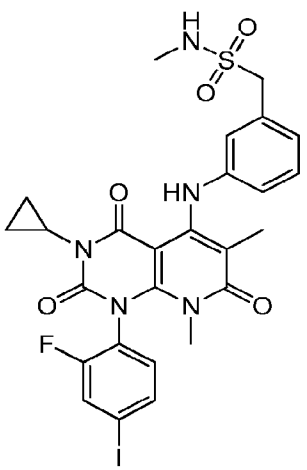
2H), 7.79 (d, J = 7.6 Hz, 1H), 7.64-7.58 (m, 1H), 4.35 (s, 2H), 4.27-4.13 (m, 1H), 2.79 (d, J = 5.4 Hz, 3H).

Step 2: **1-(3-Aminophenyl)-*N*-methylmethanesulfonamide**



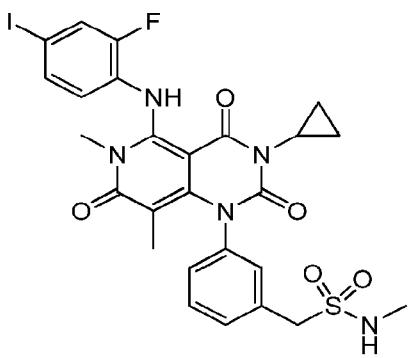
[00466] To a solution of 4-methylbenzenesulfonate *N*-methyl-1-(3-nitrophenyl)methanesulfonamide (200 mg, 861.19 µmol, 99.1%, 1 eq) in MeOH (2 mL) was added Pd/C (200 mg, 861.19 µmol, 10.0%, 1 eq) under N_2 atmosphere. The suspension was degassed under vacuum and purged with H_2 several times. The mixture was stirred under H_2 (15 psi) at 25 °C for 1 h. The reaction mixture was filtered and concentrated under reduced pressure to yield 1-(3-aminophenyl)-*N*-methyl-methanesulfonamide (180 mg, 853.90 µmol, 99.2% yield, 95.0 % purity) as a yellow solid, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.22-7.17 (m, 1H), 7.17-7.14 (m, 1H), 6.75-6.73 (m, 2H), 6.71-6.67 (m, 2H), 6.66-6.57 (m, 1H), 4.18 (s, 2H), 2.02 (s, 3H).

Step 3: **1-(3-((3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide**



[00467] To a solution of 1-(3-aminophenyl)-*N*-methyl-methanesulfonamide (150 mg, 711.58 µmol, 95.0%, 1.91 eq) in DMA (3 mL) was added 2,6-lutidine (119.77 mg, 1.12 mmol, 130.19 µL, 3 eq) and [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] 4-methylbenzenesulfonate (250 mg, 372.60 µmol, 90.0%, 1 eq). The mixture was stirred under microwave (2 bar) at 140 °C for 3 h. The mixture was diluted with water (30 mL) and extracted with ethyl acetate (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30 mm*5 um; mobile phase: [water (HCl) - ACN]; B%: 46%-66%, 10 min) and lyophilized to yield a product, which was added addition sat aq $NaHCO_3$ until pH = 7 and extracted with EtOAc (20 mL x 3), then the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield 1-(3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide (45 mg, 58.55 µmol, 15.7% yield, 86.6% purity) as a yellow solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.85 (dd, *J* = 1.8, 9.5 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.22-7.14 (m, 2H), 7.08-6.99 (m, 2H), 4.33 (s, 2H), 2.95 (s, 3H), 2.82-2.76 (m, 1H), 2.69 (s, 3H), 1.67 (s, 3H), 1.16-1.09 (m, 2H), 0.81 (d, *J* = 2.6 Hz, 2H); ES-LCMS *m/z* 666.0 $[M+H]^+$.

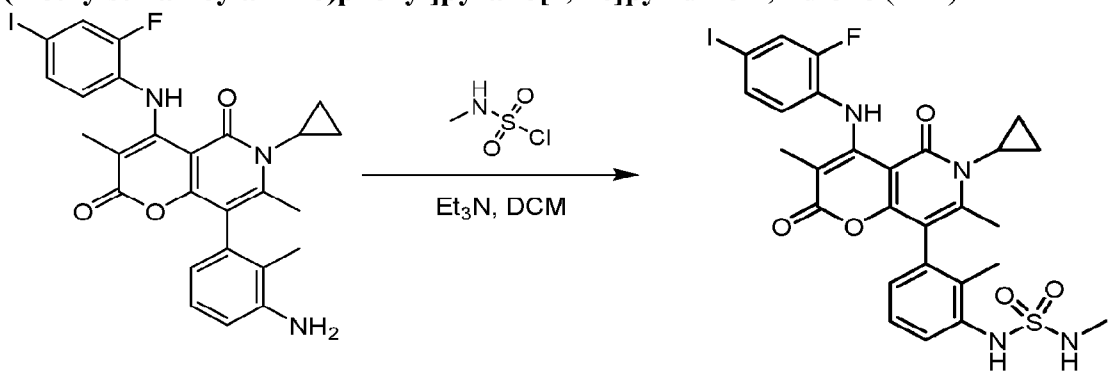
Step 4: **1-(3-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonamide**



[00468] To a solution of 1-(3-((3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidin-5-yl)amino)phenyl)-*N*-methylmethanesulfonamide (45 mg, 58.15 µmol, 86.0%, 1 eq) in THF (1 mL) was added a drop

of NaOMe/MeOH (20 wt%, 58.15 μmol, 1 eq). The mixture was stirred under N_2 atmosphere at 25 °C for 1 h. The residue was added AcOH until pH = 7 and extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 53%-83%, 10 min) and lyophilized to yield 1-(3-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)phenyl)-*N*-methylmethanesulfonamide (10.01 mg, 14.96 μmol, 25.7% yield, 99.4% purity) as a white solid. ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.66 (dd, *J* = 1.7, 10.3 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.51-7.47 (m, 2H), 7.43 (s, 1H), 7.39 (dd, *J* = 3.2, 5.6 Hz, 1H), 6.86 (t, *J* = 8.4 Hz, 1H), 4.37 (s, 2H), 3.20 (s, 3H), 2.76-2.69 (m, 1H), 2.67 (s, 3H), 1.34 (s, 3H), 1.08-1.03 (m, 2H), 0.81-0.74 (m, 2H); ES-LCMS *m/z* 666.1 $[M+H]^+$.

Synthesis of **6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-8-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrano[3,2-c]pyridine-2,5-dione** (I-33)



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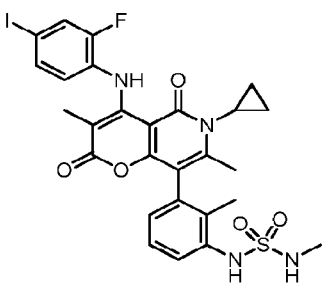
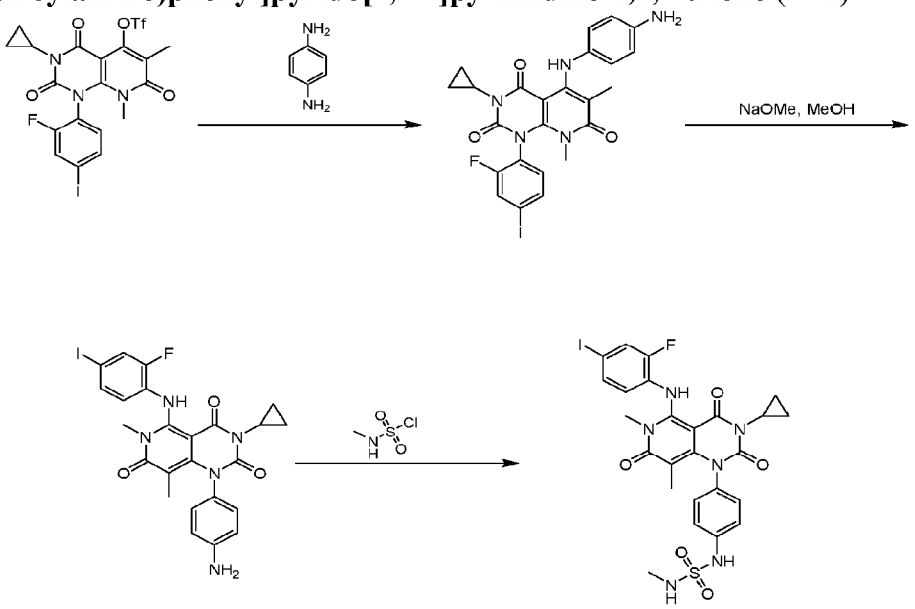
Step 1: **6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-8-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrano[3,2-c]pyridine-2,5-dione**

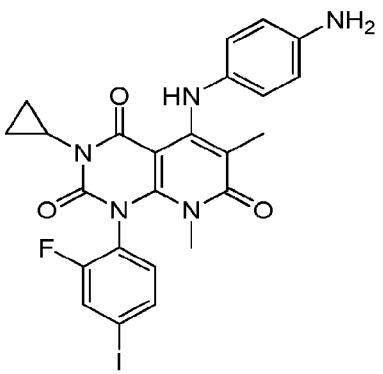


[00469] To a stirred solution of 8-(3-amino-2-methyl-phenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-pyrano[3,2-c]pyridine-2,5-dione (50 mg, 70.01 μmol, 80% purity, 1 eq) and TEA (28.34 mg, 280.02 μmol, 38.98 μL, 4 eq) in DCM (2 mL) was added *N*-methylsulfamoyl chloride (18.14 mg, 140.01 μmol, N/A purity, 2 eq) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h under N_2 atmosphere. The reaction mixture was quenched by addition *sat. aq.* $NaHCO_3$ (30 mL) at 0 °C and extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative *HPLC* (column: Boston Prime C18 150*30mm*5um;mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN];B%: 53%-83%,10min), followed by lyophilization to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-3,7-dimethyl-8-[2-methyl-3-(methylsulfamoylamino)phenyl]pyrano[3,2-c]pyridine-2,5-dione (6.22 mg, 9.36 μmol, 13.4% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.30 (s, 1H), 8.82 (s, 1H), 7.71 (d, J = 1.7, 10.3 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 7.7 Hz, 1H), 7.14 (q, J = 4.9 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 8.7 Hz, 1H), 3.03 (s, 1H), 2.55 (d, J = 5.1 Hz, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.43 (s, 3H), 1.23-1.17 (m, 2H), 0.96-0.84 (m, 2H); ES-LCMS *m/z* 665.0 $[M+H]^+$.

Synthesis of ***tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[4-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione** (I-82)

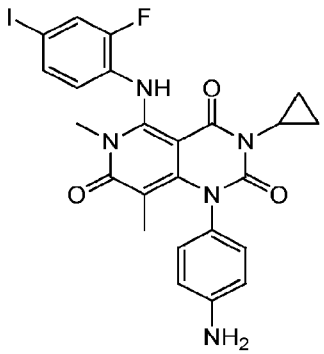


Step 1: ***tert*-Butyl 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione**



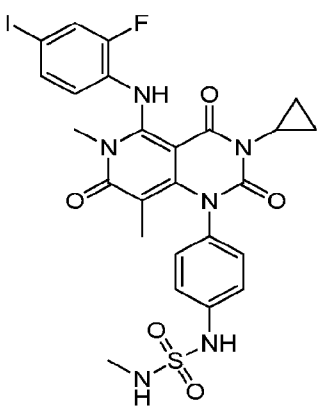
[00470] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] trifluoromethanesulfonate (300 mg, 482.70 μmol, 99.0%, 1 eq) in DMF (2 mL) was added 2,6-lutidine (155.17 mg, 1.45 mmol, 168.66 μL, 3 eq) and benzene-1,4-diamine (78.30 mg, 724.05 μmol, 1.5 eq). The mixture was stirred at 60 °C for 2 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 2/1, TLC: PE/EtOAc = 2/1, R_f = 0.20) to yield *tert*-butyl 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (200 mg, 327.89 μmol, 67.9% yield, 94.0% purity) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 10.16-10.03 (m, 1H), 8.04-7.87 (m, 1H), 7.77-7.60 (m, 1H), 7.32-7.13 (m, 1H), 6.85-6.65 (m, 2H), 6.63-6.45 (m, 2H), 5.24-4.99 (m, 2H), 2.73-2.67 (m, 3H), 1.51-1.34 (m, 3H), 1.09-0.89 (m, 2H), 0.76-0.56 (m, 2H); ES-LCMS *m/z* 574.1 $[M+H]^+$.

Step 2: ***tert*-Butyl 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione**



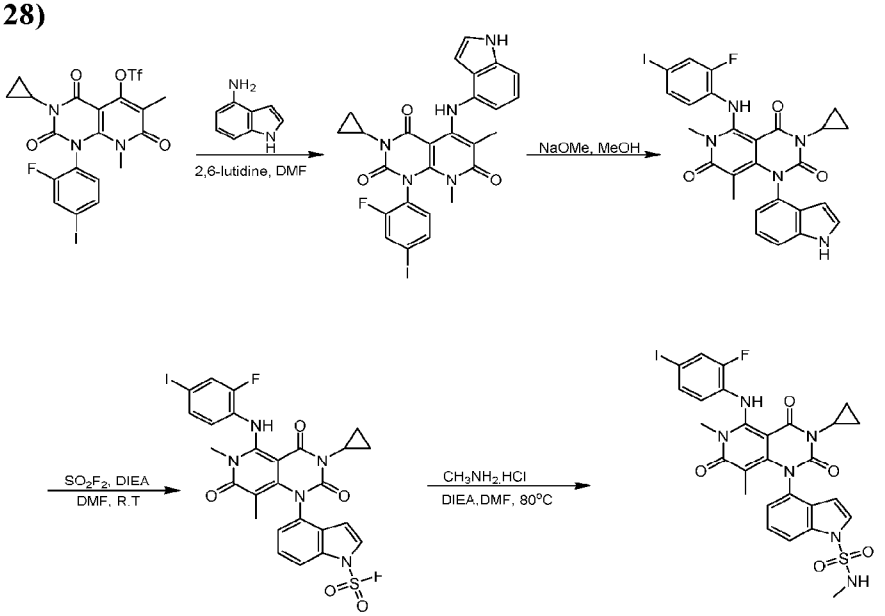
[00471] A mixture of 5-(4-aminoanilino)-3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-pyrido[2,3-*d*]pyrimidine-2,4,7-trione (100 mg, 163.95 μmol, 1 eq) and NaOMe/MeOH (163.95 μmol, 11 μL, 30.0%, 1 eq) in THF (0.3 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 25 °C for 1 h under N_2 atmosphere. The reaction mixture was quenched by addition AcOH (0.1 mL), and then diluted with H_2O (20 mL), and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (DCM/MeOH = 10/1, TLC: DCM/MeOH= 10/1, R_f= 0.80) to yield *tert*-butyl 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (90 mg, 67.50 μmol, 41.2% yield, 43.0% purity) as a yellow solid. ES-LCMS *m/z* 574.0 $[M+H]^+$.

Step 3: *tert*-Butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[4-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione

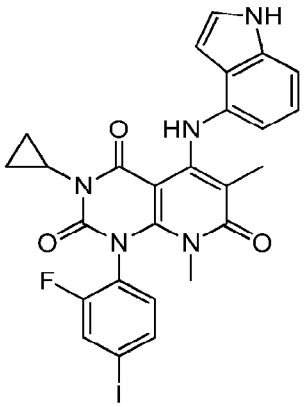


[00472] To a solution of 1-(4-aminophenyl)-3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-pyrido[4,3-*d*]pyrimidine-2,4,7-trione (43.00 mg, 75.00 μmol, 1 eq) in DCM (1 mL) was added TEA (15.18 mg, 149.99 μmol, 20.88 μL, 2 eq) and *N*-methylsulfamoyl chloride (9.72 mg, 75.00 μmol, 1 eq). The mixture was stirred at 0 °C for 1 h. The reaction mixture was quenched by addition H_2O (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 56%-76%, 12 min), followed by lyophilization to yield *tert*-butyl 3-cyclopropyl-5-(2-fluoro-4-iodo-anilino)-6,8-dimethyl-1-[4-(methylsulfamoylamino)phenyl]pyrido[4,3-*d*]pyrimidine-2,4,7-trione (8.77 mg, 13.16 μmol, 17.6% yield, 100.0% purity) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.23-10.93 (m, 1H), 10.00-9.81 (m, 1H), 7.90-7.70 (m, 1H), 7.59-7.52 (m, 1H), 7.50-7.44 (m, 1H), 7.29-7.23 (m, 2H), 7.22-7.15 (m, 2H), 6.99-6.82 (m, 1H), 3.12-3.01 (m, 3H), 2.63-2.57 (m, 1H), 2.47-2.44 (m, 3H), 1.22 (s, 3H), 0.99-0.91 (m, 2H), 0.72-0.57 (m, 2H); ES-LCMS *m/z* 667.0 $[M+H]^+$.

Synthesis of 4-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-*N*-methyl-1*H*-indole-1-sulfonamide (I-28)

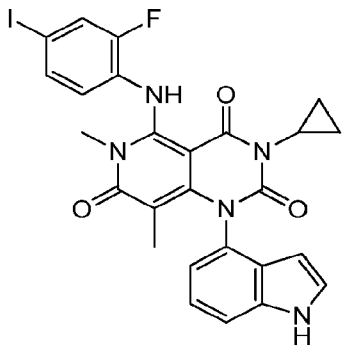


Step 1: 5-((1*H*-Indol-4-yl)amino)-3-Cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione



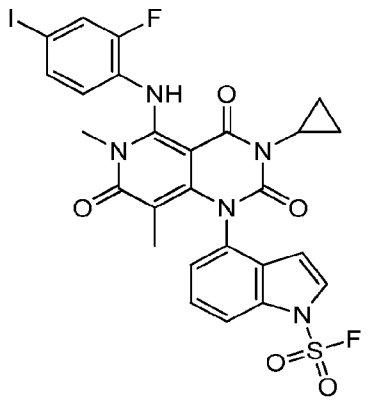
[00473] To a solution of [3-cyclopropyl-1-(2-fluoro-4-iodo-phenyl)-6,8-dimethyl-2,4,7-trioxo-pyrido[2,3-*d*]pyrimidin-5-yl] trifluoromethanesulfonate (1.2 g, 1.92 mmol, 98.6%, 1 eq) in DMF (5 mL) was added 1*H*-indol-4-amine (254.15 mg, 1.92 mmol, 1 eq) and 2,6-LUTIDINE (618.14 mg, 5.77 mmol, 671.90 μL, 3 eq). The mixture was stirred under microwave at 60 °C for 8 h. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (50 mL x 3), and washed with brine (40 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 100/1 to 1/1, TLC: PE/EtOAc = 1/1, R_f = 0.2) to yield 5-((1*H*-indol-4-yl)amino)-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (900 mg, 1.40 mmol, 72.9% yield, 93.0% purity) as a gray green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.22 (s, 1H), 10.46 (s, 1H), 7.95 (d, J = 9.4 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.58-7.49 (m, 1H), 7.34 (d, J = 2.5 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.03-7.00 (m, 2H), 6.40 (d, J = 7.4 Hz, 1H), 2.75 (s, 3H), 2.67 (dd, J = 3.3, 6.8 Hz, 1H), 1.45 (s, 3H), 0.99 (d, J = 6.7 Hz, 2H), 0.67 (m, 2H); ES-LCMS *m/z* 598.0 $[M+H]^+$.

Step 2: 3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione



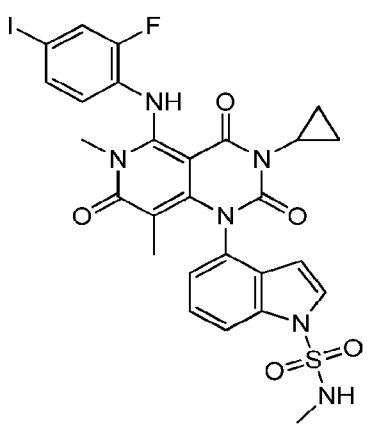
[00474] To a solution of 5-((1*H*-indol-4-yl)amino)-3-cyclopropyl-1-(2-fluoro-4-iodophenyl)-6,8-dimethylpyrido[2,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,8*H*)-trione (500 mg, 701.82 μmol, 83.9%, 1 eq) in THF (30 mL) was added NaOMe/MeOH (701.82 μmol, 0.1 mL, 30.0%, 1 eq). The mixture was stirred under N_2 atmosphere at 25 °C for 0.5 h. The residue was added the CH_3COOH to pH = 7 and extracted with EtOAc (40 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (PE/EtOAc = 1/1, TLC: PE/EtOAC = 1/1, R_f = 0.3) to yield 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (330 mg, 469.55 μmol, 66.9% yield, 85.0% purity) as a gray green solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 11.29 (s, 1H), 11.12 (s, 1H), 7.79 (dd, J = 1.7, 10.4 Hz, 1H), 7.59-7.52 (m, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.38 (t, J = 2.7 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.98-6.89 (m, 2H), 6.22 (s, 1H), 3.07 (s, 3H), 2.68-2.59 (m, 1H), 0.96 (s, 3H), 0.95-0.88 (m, 2H), 0.70 (d, J = 4.1 Hz, 2H); ES-LCMS *m/z* 598.0 $[M+H]^+$.

Step 3: 4-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-1*H*-indole-1-sulfonyl fluoride



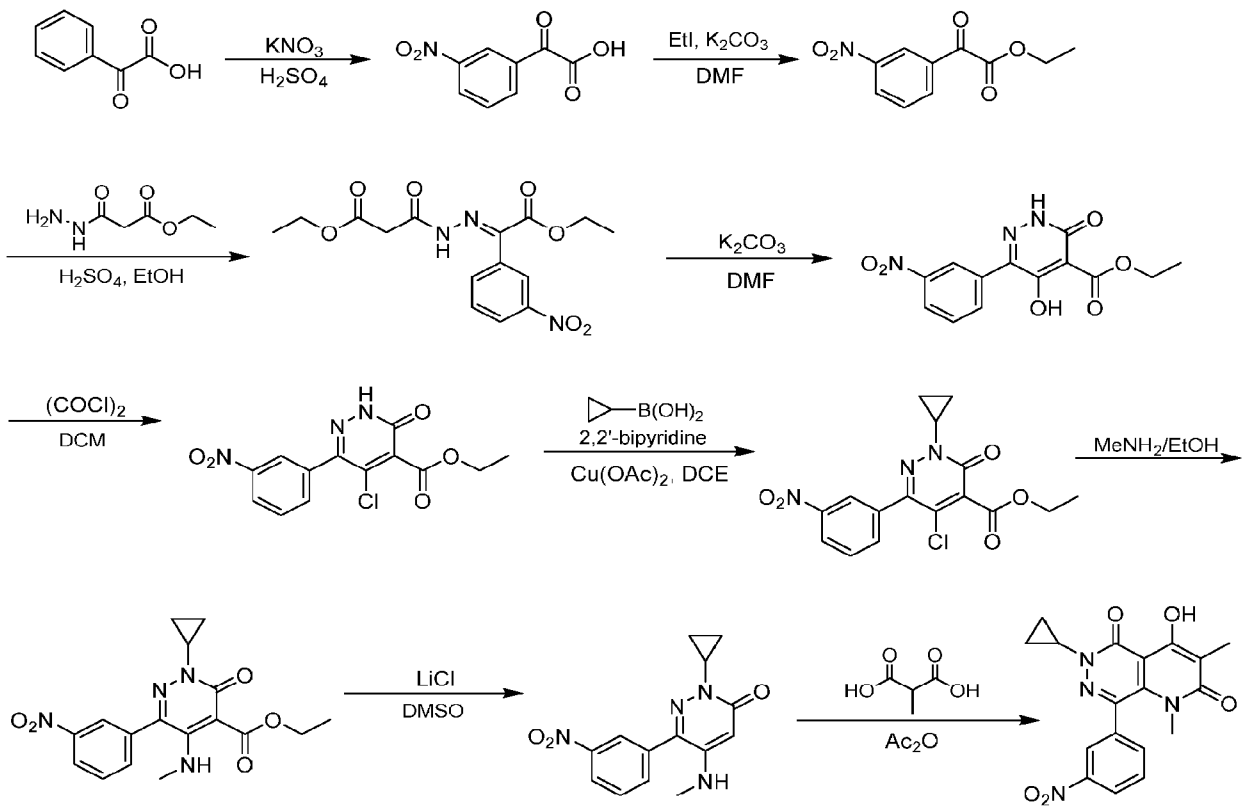
[00475] To a solution of 3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-1-(1*H*-indol-4-yl)-6,8-dimethylpyrido[4,3-*d*]pyrimidine-2,4,7(1*H*,3*H*,6*H*)-trione (100 mg, 142.29 µmol, 85.0%, 1 eq) in DCM (4 mL) was added DIEA (110.34 mg, 853.73 µmol, 148.70 µL, 6 eq). The suspension was degassed under vacuum and purged with N_2 several times. The mixture was stirred under F_2O_2S (15 Psi) at 25 °C for 24 h. The mixture was concentrated under reduced pressure to yield the residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 70%-90%, 10 min) and lyophilized to yield 4-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-1*H*-indole-1-sulfonyl fluoride (20 mg, 29.44 µmol, 20.7% yield, N/A purity) as a white solid. ES-LCMS m/z 679.9 [M+H]+.

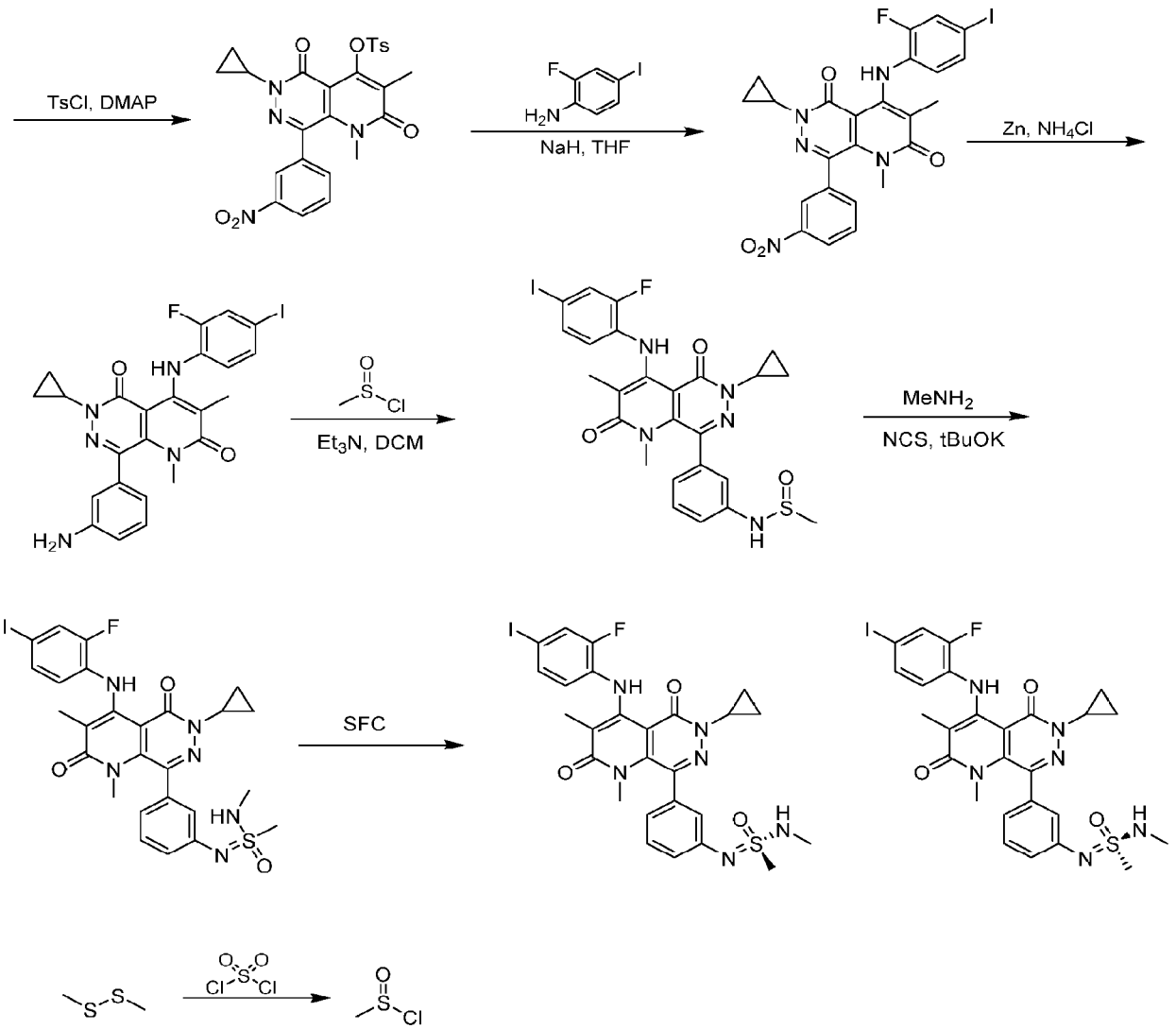
Step 4: 4-(3-Cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-*N*-methyl-1*H*-indole-1-sulfonamide



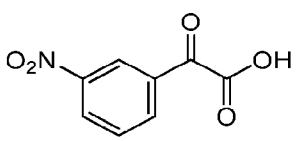
[00476] To a solution of 4-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-1H-indole-1-sulfonyl fluoride (20 mg, 29.44 μmol, N/A, 1 eq) in DMF (2 mL) was added DIEA (49.46 mg, 382.67 μmol, 66.65 μL, 13 eq) and methanamine;hydrochloride (39.75 mg, 588.73 μmol, 20 eq). The mixture was stirred at 80 °C for 12 h. The reaction mixture was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water(HCl)-ACN]; B%: 60%-80%, 10min) and lyophilized to yield 4-(3-cyclopropyl-5-((2-fluoro-4-iodophenyl)amino)-6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-*d*]pyrimidin-1(2*H*)-yl)-*N*-methyl-1*H*-indole-1-sulfonamide (2.51 mg, 3.64 μmol, 12.4% yield, 100.0% purity) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 11.37 (s, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.56-7.51 (m, 2H), 7.47 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.19 (d, J = 7.6 Hz, 1H), 6.72 (t, J = 8.2 Hz, 1H), 6.46-6.31 (m, 1H), 4.88 (d, J = 5.0 Hz, 1H), 3.21 (s, 3H), 2.83-2.70 (m, 1H), 2.64 (d, J = 5.3 Hz, 3H), 1.27 (d, J = 6.1 Hz, 2H), 1.15 (s, 3H), 0.89-0.83 (m, 2H); ES-LCMS m/z 691.0 [M+H]+.

Synthesis of (*S*)-*N'*-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-N-methylmethanesulfonimidamide & (*R*)-*N'*-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-N-methylmethanesulfonimidamide (I-119 & I-120)


KNO3
H2SO4
EtI, K2CO3
DMF
H2SO4, EtOH
K2CO3
DMF
(COCl)2
DCM
B(OH)2
2,2'-bipyridine
Cu(OAc)2, DCE
MeNH2/EtOH
LiCl
DMSO
Ac2O



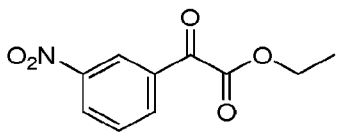
Step 1: 2-(3-Nitrophenyl)-2-oxo-acetic acid



[00477] To a solution of 2-oxo-2-phenyl-acetic acid (51 g, 339.70 mmol, 1 *eq*) in H_2SO_4 (80 mL) was added KNO_3 (41.21 g, 407.64 mmol, 1.2 *eq*) at 0 °C. The mixture was stirred at 25 °C for 16 h. The reaction mixture was poured into ice water (1.6 L) and extracted with EtOAc (400 mL x 3). The combined organic phases were washed with brine (300 mL), dried over anhydrous

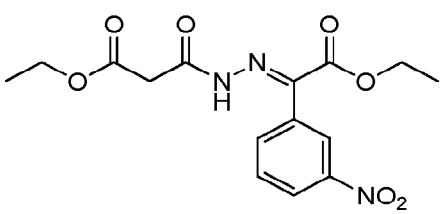
Na_2SO_4, filtered and concentrated under reduced pressure to yield 2-(3-nitrophenyl)-2-oxo-acetic acid (66 g, crude) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (t, J = 1.8 Hz, 1H), 8.56 (td, J = 1.2, 8.2 Hz, 1H), 8.41-8.37 (m, 1H), 7.89 (t, J = 8.0 Hz, 1H).

Step 2: Ethyl 2-(3-nitrophenyl)-2-oxo-acetate



[00478] To a solution of 2-(3-nitrophenyl)-2-oxo-acetic acid (66 g, 338.24 mmol, 1 *eq*) in DMF (700 mL) was added K_2CO_3 (121.54 g, 879.42 mmol, 2.6 *eq*). After stirred at 20 °C for 2h, iodoethane (263.77 g, 1.69 mol, 135.26 mL, 5 *eq*) was added dropwise. The mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into water (800 mL), extracted with EtOAc (500 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 10/1, TLC: PE/EtOAc = 5/1, R_f = 0.45) to yield ethyl 2-(3-nitrophenyl)-2-oxo-acetate (35.5 g, 143.16 mmol, 42.3% yield, 90.0% purity) as a yellow oil. ^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.90 (s, 1H), 8.54-8.47 (m, 1H), 8.40 (d, J = 7.8 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 4.50 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H).

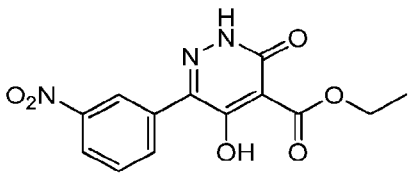
Step 3: Ethyl 3-[(2E)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate



[00479] To a solution of ethyl 2-(3-nitrophenyl)-2-oxo-acetate (22.5 g, 90.73 mmol, 1 *eq*) in EtOH (120 mL) was added H_2SO_4 (2.29 g, 23.33 mmol, 1.24 mL, 0.25 *eq*) and ethyl 3-hydrazino-3-oxo-propanoate (13.79 g, 94.36 mmol, 1.04 *eq*). The mixture was stirred at 90 °C for 2 h. The solvent was removed to yield a residue which was diluted with water (200 mL) and extracted with EtOAc (300 mL x 3). The combined organic phases were washed with brine (100

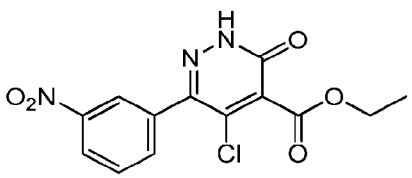
mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to yield ethyl 3-[(2E)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate (30 g, crude, E/Z mixture) as a yellow oil. ES-LCMS *m/z* 352.2 $[M+H]^+$.

Step 4: Ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate



[00480] To a solution of ethyl 3-[(2E)-2-[2-ethoxy-1-(3-nitrophenyl)-2-oxo-ethylidene]hydrazino]-3-oxo-propanoate (30 g, 85.39 mmol, E/Z mixture, 1 *eq*) in DMF (300 mL) was added K_2CO_3 (6.49 g, 46.97 mmol, 0.55 *eq*). The mixture was stirred at 80 °C for 3 h. The mixture was cooled to ambient temperature and poured into 3N HCl (600 mL). The precipitated solid was collected by filtration to give a residue which was added MeOH (50 mL), and stirred at 15 °C for 2 h. The slurry was filtered, and the cake was rinsed with MeOH (3 x 3 mL). The solid was collected and dried in vacuo to yield ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (8.3 g, 24.47 mmol, 28.7% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (400MHz, DMSO-d_6) δ ppm 13.23 (s, 1H), 8.58-8.53 (m, 1H), 8.30 (td, J = 1.2, 7.2 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 7.76 (t, J = 8.1 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ES-LCMS *m/z* 306.1 $[M+H]^+$.

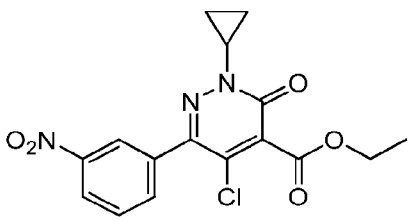
Step 5: Ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate



[00481] To a solution of ethyl 4-hydroxy-3-(3-nitrophenyl)-6-oxo-1*H*-pyridazine-5-carboxylate (2.5 g, 7.37 mmol, 1 eq) in DCM (30 mL) was added $(COCl)_2$ (935.60 mg, 7.37 mmol, 645.24 µL, 1 eq). The mixture was stirred at 35 °C for 3 h. The reaction mixture was quenched by addition water (30 mL) and extracted with DCM (40 mL x 3). The combined

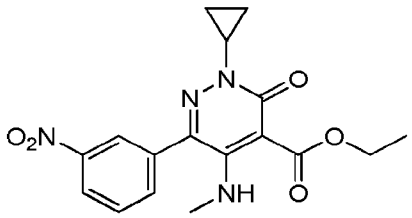
organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was added MeOH (5 mL), and stirred at 25 °C for 2 h. The slurry was filtered, and the cake was rinsed with PE (2 x 3 mL). The solid was collected and dried in vacuo to yield ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (1.9 g, 5.69 mmol, 77.2% yield, 97.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.67 (s, 1H), 8.48 (s, 1H), 8.38 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.74-7.66 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ES-LCMS m/z 324.0, 326.0 $[M+H]^+$.

Step 6: Ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate



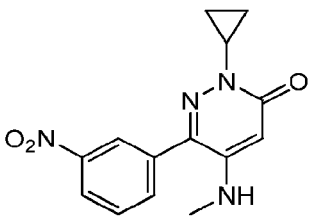
[00482] A mixture of ethyl 4-chloro-3-(3-nitrophenyl)-6-oxo-1H-pyridazine-5-carboxylate (1.4 g, 4.20 mmol, 1 eq), cyclopropylboronic acid (720.75 mg, 8.39 mmol, 2 eq), 2-(2-pyridyl)pyridine (1.64 g, 10.49 mmol, 2.5 eq), Na_2CO_3 (533.60 mg, 5.03 mmol, 1.2 eq) and $Cu(OAc)_2$ (914.43 mg, 5.03 mmol, 1.2 eq) in 1,4-dioxane (20 mL) was degassed and purged with N_2 for 3 times and the mixture was stirred at 70 °C for 24 h under N_2 atmosphere. The reaction mixture was diluted with water (100 mL) and extracted with DCM (60 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 3/1, TLC: PE/EtOAc = 3/1, R_f = 0.43) to yield ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (400 mg, 989.69 µmol, 23.6% yield, 90.0% purity) as a yellow gum. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.42 (d, J = 1.8 Hz, 1H), 8.35 (td, J = 1.1, 8.3 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.70-7.65 (m, 1H), 4.51 (q, J = 7.1 Hz, 2H), 4.22 (t, J = 4.0, 7.6 Hz, 1H), 1.43 (t, J = 7.2 Hz, 3H), 1.22-1.16 (m, 2H), 1.13-1.06 (m, 2H); ES-LCMS m/z 364.0, 366.0 $[M+H]^+$.

Step 7: Ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate



[00483] To a solution of ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (400 mg, 989.69 μmol, 1 eq) in DCM (3 mL) was added $MeNH_2$ (1.02 g, 9.90 mmol, 30.0% purity, 10 eq) at 0 °C. The mixture was stirred at 20 °C for 2 h. The solvent was removed to yield ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (300 mg, 669.74 μmol, 67.7% yield, 80.0% purity) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.33-8.30 (m, 2H), 7.79 (d, J = 7.6 Hz, 1H), 7.70-7.66 (m, 1H), 4.43 (q, J = 7.1 Hz, 2H), 4.02-3.95 (m, 1H), 2.69 (d, J = 5.3 Hz, 3H), 1.44 (t, J = 7.1 Hz, 2H), 1.46-1.42 (m, 1H), 1.03-0.94 (m, 4H); ES-LCMS *m/z* 359.1 $[M+H]^+$.

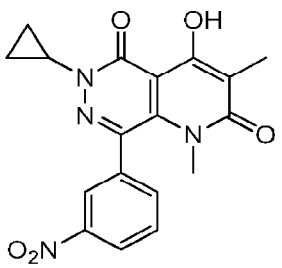
Step 8: 2-Cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one



[00484] To a solution of ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxo-pyridazine-4-carboxylate (300 mg, 669.74 μmol, 1 eq) in DMSO (5 mL) was added LiCl (283.93 mg, 6.70 mmol, 10 eq). The mixture was stirred at 150 °C for 8 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (40 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 0/1, TLC: PE/EtOAc = 0/1, R_f = 0.15) to yield 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (200 mg, 628.74 μmol, 93.9% yield, 90.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38-8.27 (m, 2H), 7.83 (d, J = 7.6

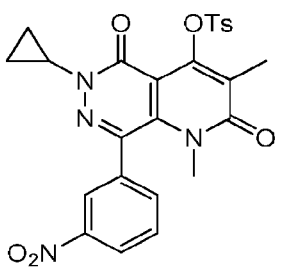
Hz, 1H), 7.73-7.66 (m, 1H), 5.92 (s, 1H), 4.03 (t, J = 3.9, 7.5 Hz, 1H), 2.83 (d, J = 3.4 Hz, 3H), 1.09-0.93 (m, 4H); ES-LCMS *m/z* 287.1 $[M+H]^+$.

Step 9: 6-Cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione



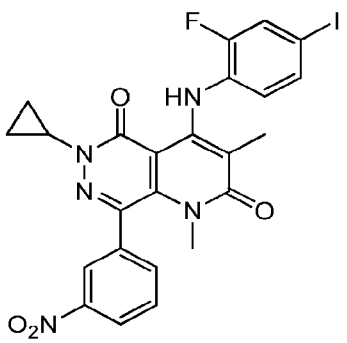
[00485] To a solution of 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)pyridazin-3-one (200 mg, 628.74 µmol, 1 eq) in Ac_2O (3 mL) was added 2-methylpropanedioic acid (222.74 mg, 1.89 mmol, 152.56 µL, 3 eq). The mixture was stirred at 110 °C for 2 h. The solvent was removed to yield a residue which was purified by preparative TLC (PE/EtOAC = 3/1, TLC: PE/EtOAC = 3/1, R_f = 0.24) to yield 6-cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (200 mg, 434.38 µmol, 69.1% yield, 80.0% purity) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.80 (s, 1H), 8.37 (td, J = 2.2, 7.0 Hz, 1H), 8.33 (d, J = 1.5 Hz, 1H), 7.72-7.68 (m, 2H), 4.16-4.09 (m, 1H), 3.06 (s, 3H), 2.16 (s, 3H), 1.20-1.15 (m, 2H), 1.15-1.09 (m, 2H); ES-LCMS *m/z* 369.0 $[M+H]^+$.

Step 10: [6-Cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate



[00486] To a solution of 6-cyclopropyl-4-hydroxy-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (200 mg, 434.38 µmol, 1 eq) in DCM (8 mL) was added DIEA (561.40 mg, 4.34 mmol, 756.61 µL, 10 eq) and 4-methylbenzenesulfonyl chloride (414.06 mg, 2.17 mmol, 5 eq). The mixture was stirred at 50 °C for 12 h. The solvent was removed to yield a residue which was purified by preparative TLC (PE/EtOAC − 3/1, TLC: PE/EtOAC − 3/1, R_f − 0.24) to yield [6-cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate (200 mg, 371.27 µmol, 85.5% yield, 97.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38-8.30 (m, 2H), 7.98 (d, J = 8.3 Hz, 2H), 7.77-7.63 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.22-4.06 (m, 1H), 3.08 (s, 3H), 2.49 (s, 3H), 1.85 (s, 3H), 1.12-1.01 (m, 4H); ES-LCMS m/z 523.1 $[M+H]^+$.

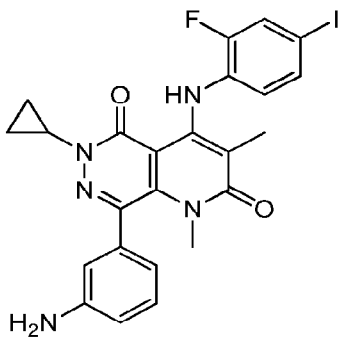
Step 11: 6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione



[00487] To a solution of 2-fluoro-4-iodo-aniline (263.99 mg, 1.11 mmol, 3 eq) in THF (3 mL) was added NaH (89.10 mg, 2.23 mmol, 60.0% purity, 6 eq) and stirred at 0 °C for 30 min, then [6-cyclopropyl-1,3-dimethyl-8-(3-nitrophenyl)-2,5-dioxo-pyrido[2,3-d]pyridazin-4-yl] 4-methylbenzenesulfonate (200 mg, 371.27 µmol, 1 eq) was added at 0 °C. The reaction temperature was slowly warmed up to 25 °C and stirred at 25 °C for 1 h. The reaction mixture was quenched by addition water (20 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (PE/EtOAC = 1/1, TLC: PE/EtOAC = 1/1, R_f = 0.35) to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (100 mg, 156.64 µmol, 42.2%

yield, 92.0% purity) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.78 (s, 1H), 8.44-8.27 (m, 2H), 7.75-7.65 (m, 2H), 7.46 (d, J = 1.8, 10.0 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 6.56 (t, J = 8.5 Hz, 1H), 4.10-4.01 (m, 1H), 3.07 (s, 3H), 1.82 (s, 3H), 1.19-1.07 (m, 4H); ES-LCMS *m/z* 588.0 $[M+H]^+$.

Step 12: 8-(3-Aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione

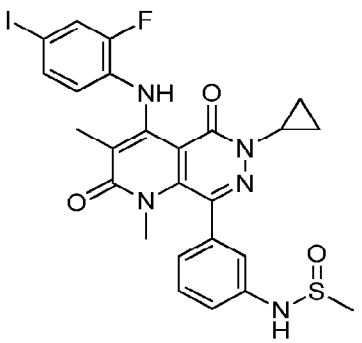


[00488] To a solution of 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (100 mg, 156.64 µmol, 1 eq) in EtOH (1.5 mL), H_2O (1.5 mL) and THF (1.5 mL) was added NH_4Cl (83.79 mg, 1.57 mmol, 10 eq) and Fe (43.74 mg, 783.19 µmol, 5 eq). The mixture was stirred at 90 °C for 3 h. The reaction mixture was filtered to remove the insoluble. The filter liquor was concentrated under reduced pressure to give a residue. The residue was purified by preparative HPLC (column: Boston Prime C18 150*30mm*5um; mobile phase: [water(NH_3H_2O+NH_4HCO_3)-ACN]; B%: 64%-94%,10min), followed by lyophilization to yield 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (55.23 mg, 99.09 µmol, 63.3% yield, 100.0% purity) as a yellow solid. ^{1}H NMR (400MHz, CD_3OD) δ ppm 7.55 (d, J = 1.8, 10.3 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.21 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 1.5, 8.0 Hz, 1H), 6.79-6.76 (m, 1H), 6.71 (d, J = 7.7 Hz, 1H), 6.64 (t, J = 8.6 Hz, 1H), 4.04 (t, J = 3.9, 7.5 Hz, 1H), 3.13 (s, 3H), 1.76 (s, 3H), 1.17-1.11 (m, 2H), 1.07-0.99 (m, 2H); ES-LCMS *m/z* 558.0 $[M+H]^+$.

Step 13: Methanesulfinyl chloride

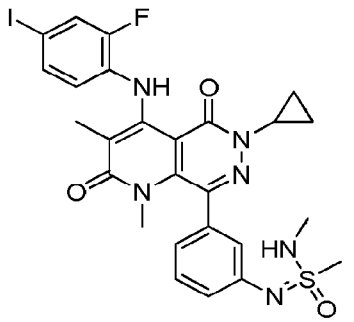
[00489] To a solution of (methyldisulfanyl)methane (5.35 g, 56.79 mmol, 5.10 mL, 1 eq) in AcOH (6.82 g, 113.59 mmol, 6.50 mL, 2 eq) was added SO_2Cl_2 (20.27 g, 170.38 mmol, 12.36 mL, 3 eq) at -20 °C under N_2. The mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated to yield crude methanesulfinyl chloride (8.9 g, crude) as light yellow oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 3.39 (s, 3H).

Step 14: *N*-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]methanesulfinamide



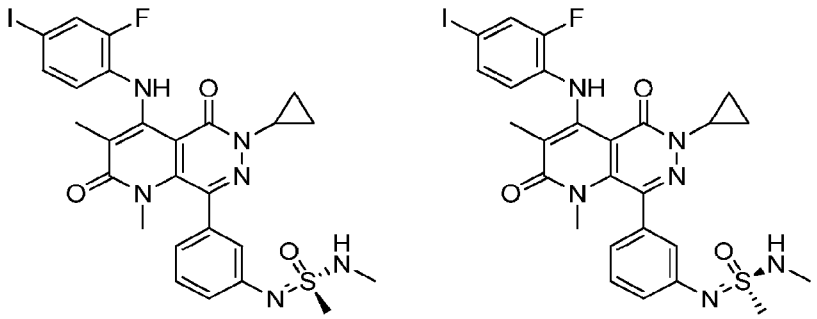
[00490] To a solution of 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (500 mg, 897.09 μmol, 100%, 1 eq) in DCM (30 mL) was added DIEA (907.77 mg, 7.02 mmol, 1.22 mL, 7.83 eq) and methanesulfinyl chloride (176.82 mg, 1.79 mmol, 2 eq). The mixture was stirred at 20 °C for 1 h. TLC (PE/EtOAc = 1/1, R_f = 0.07) indicated the starting material was consumed completely and one new spot formed. The reaction mixture was concentrated to yield a residue which was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 0/1, TLC: PE/EtOAc = 1/1, R_f = 0.07) to yield *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]methanesulfinamide (350 mg, 553.72 μmol, 61.7% yield, 98.0% purity) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 10.85 (br s, 1H), 7.48-7.33 (m, 3H), 7.23-7.02 (m, 3H), 6.54 (t, J = 7.8 Hz, 1H), 6.33 (br s, 1H), 4.05 (br s, 1H), 3.11 (s, 3H), 2.87 (s, 3H), 1.82 (s, 3H), 1.25-1.05 (m, 4H); ES-LCMS *m/z* 620.2 $[M+H]^+$.

Step 15: 6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-[3-[[methyl-(methylamino)-oxo-λ6-sulfanylidene]amino]phenyl]pyrido[2,3-d]pyridazine-2,5-dione



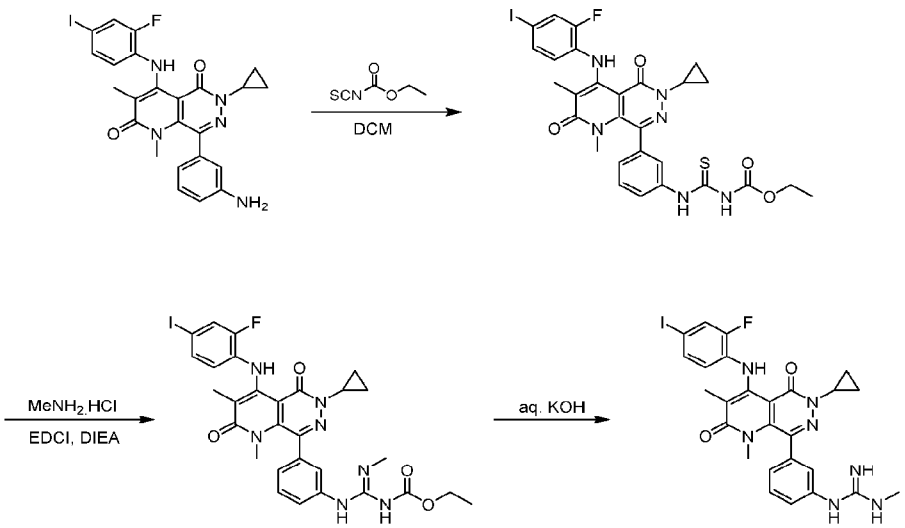
[00491] To a solution of N-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]methanesulfinamide (150 mg, 237.31 μmol, 98%, 1 eq) and $MeNH_2$ (0.35 g, 3.72 mmol, 33%, 15.67 eq) in MeCN (45 mL) was added *t*-BuOK (1 M, 1.42 mL, 6 eq), followed by the addition of NCS (126.75 mg, 949.23 umol, 4 eq) at -20 °C under N_2. The mixture was stirred at 20 °C for 3 h. TLC (PE/EtOAc = 0/1, R_f = 0.28) indicated the starting material was consumed completely and one new spot formed. The reaction mixture was quenched by addition of water (50 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue. The residue was purified by flash silica gel chromatography (from PE/EtOAc = 1/0 to 0/1, TLC: PE/EtOAc = 0/1, R_f = 0.28) to yield 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-[3-[[methyl-(methylamino)-oxo-λ6-sulfanylidene]amino]phenyl]pyrido[2,3-d]pyridazine-2,5-dione (80 mg, 109.79 μmol, 46.2% yield, 89.0% purity) as a white solid. ES-LCMS *m/z* 649.2 $[M+H]^+$.

Step 16: (*S*)-*N'*-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-N-methylmethanesulfonimidamide & (*R*)-*N'*-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-N-methylmethanesulfonimidamide

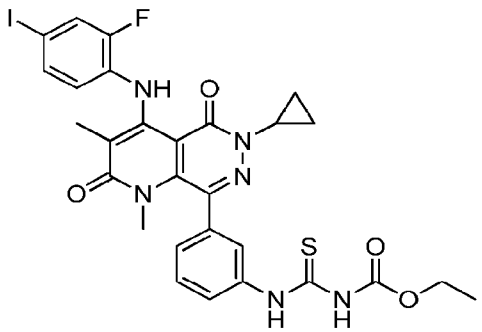


[00492] 6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-8-[3-[[methyl-(methylamino)-oxo-λ6-sulfanylidene]amino]phenyl]pyrido[2,3-d]pyridazine-2,5-dione (80 mg, 109.79 μmol, 89%, 1 eq) was separated by SFC (AD_IPA_DEA_5_40_4ML_4MIN_5CM). The Desired fraction was concentrated to yield a residue, and followed by lyophilization to yield Peak 1: (*S*)-*N*'-(3-(6-cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-N-methylmethanesulfonimidamide (20.27 mg, 30.91 μmol, 28.1% yield, 98.9% purity) (ee=100%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.58-7.52 (m, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.19 (d, J – 7.8 Hz, 1H), 7.15 (s, 1H), 7.07 (d, J – 7.5 Hz, 1H), 6.65 (t, J – 8.5 Hz, 1H), 4.05 (td, J – 3.6, 7.4 Hz, 1H), 3.12 (d, J – 7.0 Hz, 6H), 2.72 (s, 3H), 1.77 (s, 3H), 1.14 (d, J – 2.7 Hz, 2H), 1.03 (d, J = 5.2 Hz, 2H); ES-LCMS *m/z* 649.2 $[M+H]^+$. Peak 2: (*R*)-*N*'-(3-(6-cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-d]pyridazin-8-yl)phenyl)-*N*-methylmethanesulfonimidamide (20.68 mg, 31.67 μmol, 28.8% yield, 99.3% purity) (ee=100%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD) δ ppm 7.55 (dd, J = 1.8, 10.3 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.15 (s, 1H), 7.07 (d, J = 6.7 Hz, 1H), 6.65 (t, J = 8.6 Hz, 1H), 4.05 (tt, J = 3.9, 7.5 Hz, 1H), 3.18-3.06 (m, 6H), 2.72 (s, 3H), 1.77 (s, 3H), 1.20-1.09 (m, 2H), 1.07-0.98 (m, 2H); ES-LCMS *m/z* 649.2 $[M+H]^+$.

Synthesis of 1-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-3-methyl-guanidine (I-122)



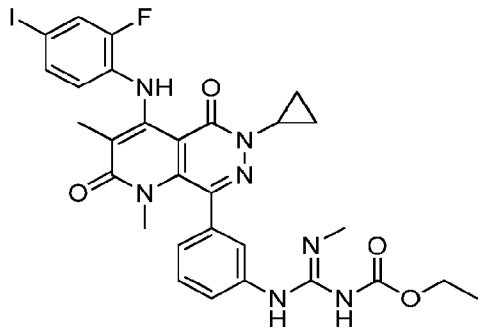
Step 1: Ethyl *N*-[[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]carbamothioyl]carbamate



[00493] A solution of 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-d]pyridazine-2,5-dione (300 mg, 538.25 µmol, 100.0%, 1 eq) and ethyl *N*-(thioxomethylene)carbamate (155.31 mg, 1.18 mmol, 2.2 eq) in DCM (10 mL) was stirred at 15 °C for 12 h. The mixture was added PE, filtered and concentrated under reduced pressure to yield ethyl *N*-[[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]carbamothioyl]carbamate (330 mg, 460.12 µmol, 85.5% yield, 96.0% purity) as a yellow solid, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 11.58 (s, 1H), 10.83 (br s, 1H), 8.12 (s, 1H), 7.86 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.9 Hz, 1H), 7.45 (d, J = 9.9 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 7.30-7.27 (m, 1H), 6.54 (t, J = 8.5 Hz, 1H), 4.32 (q, J = 7.0 Hz, 2H), 4.06 (tt, J = 3.9, 7.4 Hz, 1H),

3.17 (s, 3H), 1.82 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H), 1.19-1.14 (m, 2H), 1.10-1.04 (m, 2H); ES-LCMS m/z 689.2 $[M+H]^+$.

Step 2: Ethyl *N*-[(*Z*)-*N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-*N'*-methyl-carbamimidoyl]carbamate

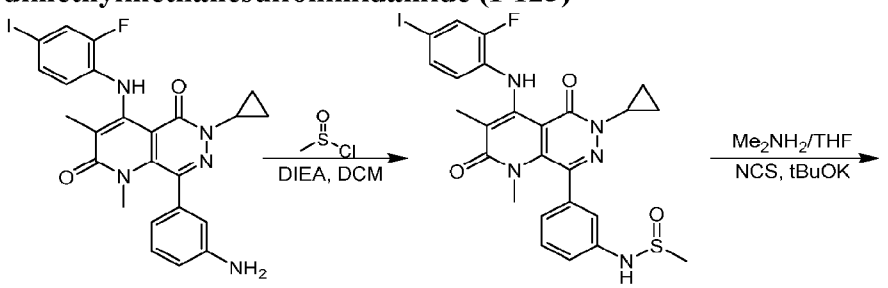


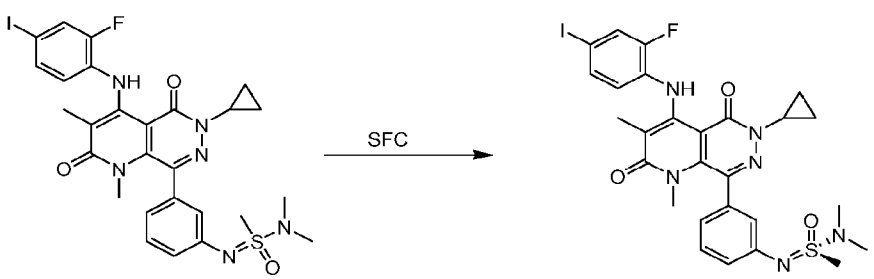
[00494] To a solution of ethyl *N*-[[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]carbamothioyl]carbamate (270 mg, 376.47 µmol, 96.0% purity, 1 eq), DIEA (316.25 mg, 2.45 mmol, 426.22 µL, 6.5 eq) and methanamine;hydrochloride (101.67 mg, 1.51 mmol, 4 eq) in DCM (20 mL) was added EDCI (288.67 mg, 1.51 mmol, 4 eq) at 0 °C. The mixture was stirred at 15°C for 12 h. TLC (DCM/MeOH = 10/1, R_f = 0.50) indicated starting material was consumed completely. The mixture was diluted with water (30 mL) and extracted with DCM (20 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by flash silica gel chromatography (from DCM/MeOH = 100/1 to 50/1, TLC: DCM/MeOH = 10/1, R_f = 0.50) to yield ethyl *N*-[(*Z*)-*N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-*N'*-methyl-carbamimidoyl]carbamate (260 mg, 371.71 µmol, 98.7% yield, 98.0% purity) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 10.81 (s, 1H), 7.54-7.18 (m, 6H), 6.53 (t, J = 8.5 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 4.08-4.00 (m, 1H), 3.10 (s, 3H), 2.97 (d, J = 4.6 Hz, 3H), 1.81 (s, 3H), 1.37-1.29 (m, 3H), 1.18-1.11 (m, 2H), 1.11-1.04 (m, 2H); ES-LCMS m/z 686.1 $[M+H]^+$.

Step 3: 1-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-3-methyl-guanidine

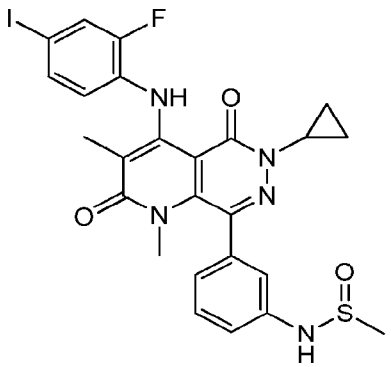
[00495] To a solution of ethyl *N*-[(*Z*)-*N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-*N*'-methyl-carbamimidoyl]carbamate (100 mg, 142.96 μmol, 98.0% purity, 1 eq) in EtOH (4 mL) was added KOH (2 M, 1.14 mL, 16 eq). The mixture was stirred at 40 °C for 12 h. The mixture was concentrated under reduced pressure to yield a residue which was purified by preparative HPLC (column: Boston Green ODS 150*30mm*5um; mobile phase: [water (FA)-ACN]; B%: 26%-46%, 12 min), followed by lyophilization to yield 1-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-d]pyridazin-8-yl]phenyl]-3-methyl-guanidine (15.28 mg, 23.17 μmol, 16.2% yield, 100.0% purity, FA) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64-7.59 (m, 1H), 7.56 (d, J = 10.4 Hz, 1H), 7.47 (d, J = 8.2 Hz, 2H), 7.44-7.34 (m, 2H), 6.66 (t, J = 8.5 Hz, 1H), 4.13-4.01 (m, 1H), 3.10 (s, 3H), 2.94 (s, 3H), 1.77 (s, 3H), 1.16-1.09 (m, 2H), 1.08-1.02 (m, 2H); ES-LCMS *m/z* 614.1 $[M+H]^+$.

Synthesis of (*S*)-*N*'-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide (I-123)



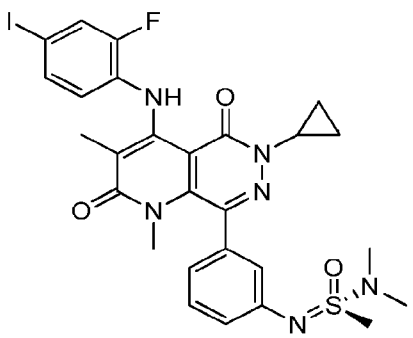


Step 1: *N*-[3-[6-Cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-*d*]pyridazin-8-yl]phenyl]methanesulfinamide



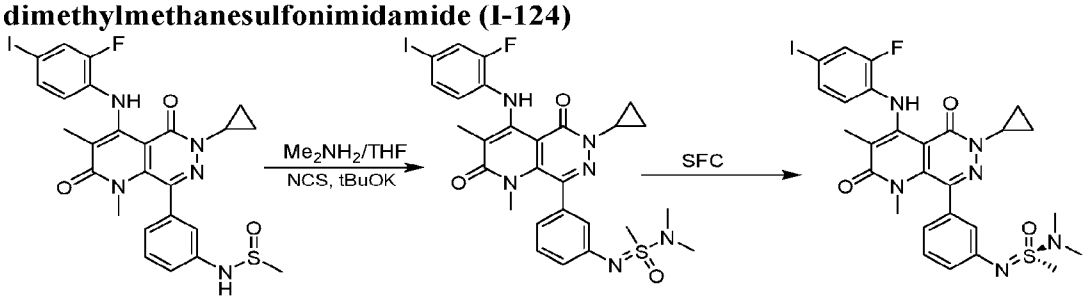
[00496] A mixture of 8-(3-aminophenyl)-6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-pyrido[2,3-*d*]pyridazine-2,5-dione (100 mg, 179.42 µmol, 100.0%, 1 eq), methanesulfinyl chloride (26.52 mg, 269.13 µmol, N/A, 1.5 eq) and DIEA (69.57 mg, 538.25 µmol, 93.75 µL, 3 eq) in DCM (2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 0 °C for 10 min under N_2 atmosphere. The reaction mixture was washed with the saturated $NaHCO_3$ (30 mL) solution, extracted with DCM (30 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-*d*]pyridazin-8-yl]phenyl]methanesulfinamide (110 mg, 163.37 µmol, 91.1% yield, 92.0% purity) as a yellow solid which was used directly in the next step without further purification. ES-LCMS m/z 620.0 $[M+H]^+$.

Step 2: (*S*)-*N*'-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide

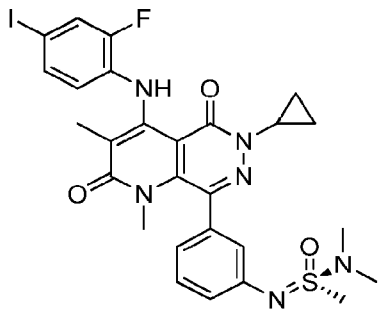


[00497] To a solution of *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-*d*]pyridazin-8-yl]phenyl]methanesulfinamide (110 mg, 163.37 μmol, 92.0%, 1 eq) in MeCN (30 mL) was added *N*-methylmethanamine (2 M, 816.86 μL, 10 eq) and t-BuOK (1 M, 1.31 mL, 8 eq) followed by the addition of NCS (141.80 mg, 1.06 mmol, 6.5 eq). The mixture was stirred under N_2 atmosphere at 40 °C for 12 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (TLC: PE/EtOAc = 2/3, R_f = 0.2). The desired fraction was concentrated under reduced pressure to yield a residue which was separated by chiral SFC (column: DAICEL CHIRALPAK AD(column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O/ETOH]; B%: 40%-40%) to yield peak 1 and peak 2. Peak 1 was concentrated under reduced pressure to yield a residue which was dissolved in MeCN (20 mL) and water (20 mL) and lyophilized to yield (*S*)-*N*'-(3-(6-cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide (18.06 mg, 27.26 μmol, 16.7% yield, 100.0% purity, SFC: R_t = 5.737, ee = 100.0%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.87 (s, 1H), 7.45 (dd, J = 1.8, 10.0 Hz, 1H), 7.35 (d, J = 9.7 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.14-6.97 (m, 2H), 6.53 (t, J = 8.5 Hz, 1H), 4.05 (s, 1H), 3.12 (s, 3H), 2.99 (s, 3H), 2.91 (s, 6H), 1.81 (s, 3H), 1.19-1.13 (m, 2H), 1.09-1.01 (m, 2H); ES-LCMS m/z 663.1 $[M+H]^+$.

Synthesis of (*R*)-*N*'-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide (I-124)

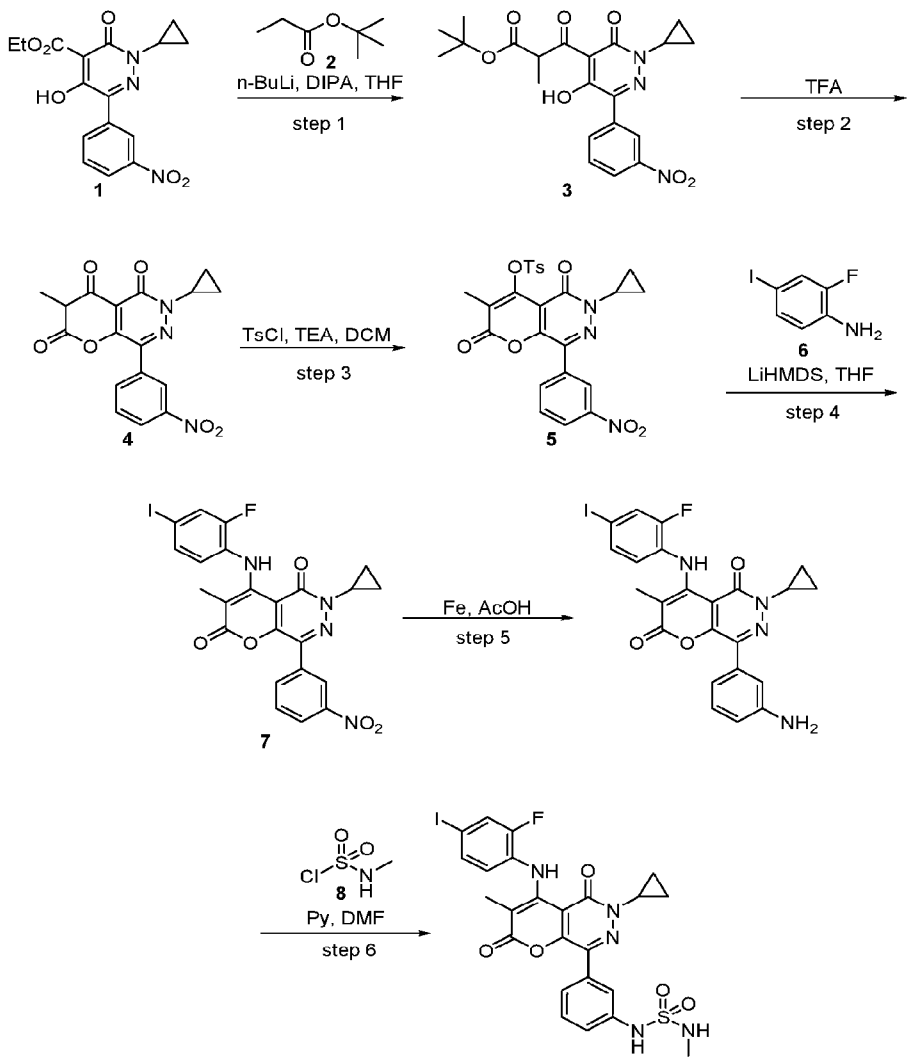


Step 1: (*R*)-*N*'-(3-(6-Cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide

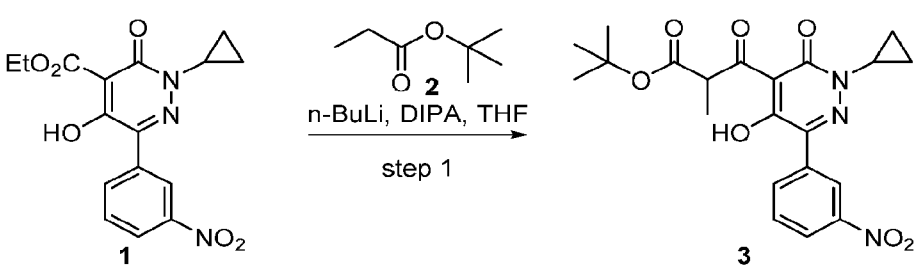


[00498] To a solution of *N*-[3-[6-cyclopropyl-4-(2-fluoro-4-iodo-anilino)-1,3-dimethyl-2,5-dioxo-pyrido[2,3-*d*]pyridazin-8-yl]phenyl]methanesulfinamide (110 mg, 163.37 μmol, 92.0%, 1 eq) in MeCN (30 mL) was added *N*-methylmethanamine (2 M, 816.86 μL, 10 eq) and t-BuOK (1 M, 1.31 mL, 8 eq) followed by the addition of NCS (141.80 mg, 1.06 mmol, 6.5 eq). The mixture was stirred under N_2 atmosphere at 40 °C for 12 h. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL x 3). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield a residue which was purified by preparative TLC (TLC: PE/EtOAc = 2/3, R_f = 0.2). The desired fraction was concentrated under reduced pressure to yield a residue which was separated by chiral SFC (column: DAICEL CHIRALPAK AD(column: DAICEL CHIRALPAK AD(250mm*30mm,10um); mobile phase: [0.1%NH_3H_2O/ETOH]; B%: 40%-40%) to yield peak 1 and peak 2. Peak 2 was concentrated under reduced pressure to yield a residue which was dissolved in MeCN (20 mL) and water (20 mL) and lyophilized to yield (*R*)-*N*'-(3-(6-cyclopropyl-4-((2-fluoro-4-iodophenyl)amino)-1,3-dimethyl-2,5-dioxo-1,2,5,6-tetrahydropyrido[2,3-*d*]pyridazin-8-yl)phenyl)-*N*,*N*-dimethylmethanesulfonimidamide (19.63 mg, 28.75 μmol, 17.6% yield, 97.0% purity, SFC: R_t = 6.270, ee = 97.7%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.87 (s, 1H), 7.45 (dd, *J* =1.8, 10.0 Hz, 1H), 7.35 (d, *J* = 9.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.14-6.98 (m, 2H), 6.53 (t, *J* = 8.5 Hz, 1H), 4.04 (d, *J* = 3.6 Hz, 1H), 3.12 (s, 3H), 2.99 (s, 3H), 2.91 (s, 6H), 1.81 (s, 3H), 1.18-1.13 (m, 2H), 1.08-1.02 (m, 2H); ES-LCMS m/z 663.1 $[M+H]^+$.

Synthesis of 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methyl-8-{3-[(methylsulfamoyl)amino]phenyl}pyrano[2,3-d]pyridazine-2,5-dione (I-129)

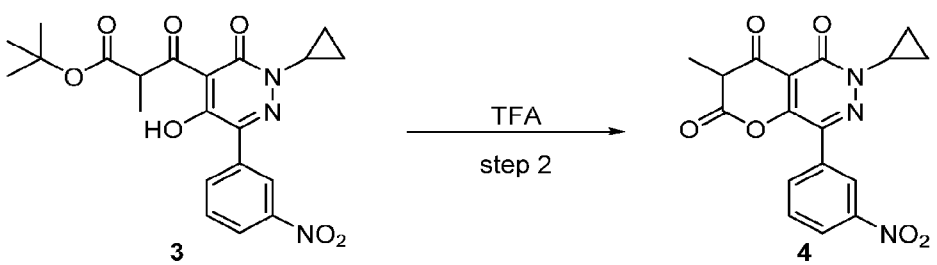

EtO2C
HO
NO2
1
2
n-BuLi, DIPA, THF
step 1
3
TFA
step 2
4
TsCl, TEA, DCM
step 3
OTs
5
I
F
NH2
6
LiHMDS, THF
step 4
NH
7
Fe, AcOH
step 5
Cl
S
N
H
8
Py, DMF
step 6

Step 1


EtO2C
HO
NO2
1
2
n-BuLi, DIPA, THF
step 1
3

[00499] To a solution of DIPA (10.55 g, 104.26 mmol, 6.00 equiv) in THF (20.00 mL) was added n-BuLi (41.70 mL, 104.26 mmol, 6.00 equiv) dropwised at -78 °C under N_2 atmosphere. The reaction mixture was stirred at -50 °C for 0.5 hr. A solution of tert-butyl propionate (6.79 g, 52.13 mmol, 3.00 equiv) in THF (20.00 mL) was added dropwise to previous reaction mixture at -78 °C and stirred for another 1 hr at -78 °C. Then a solution of ethyl 2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (6.00 g, 17.38 mmol, 1.00 equiv) in THF (120.00 mL) was added dropwise at -78 °C and the mixture was stirred for another 2 hrs at -50 °C. The reaction was quenched with sat. NH_4Cl (500 mL), and then extracted with EtOAc (2 x 200 mL). The combined organic was washed with brine (400 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum to afford tert-butyl 3-[2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazin-4-yl]-2-methyl-3-oxopropanoate (6.00 g, crude) as a yellow solid.

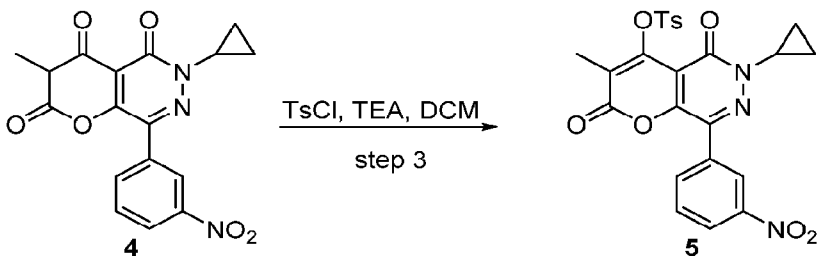
Step 2



3 4

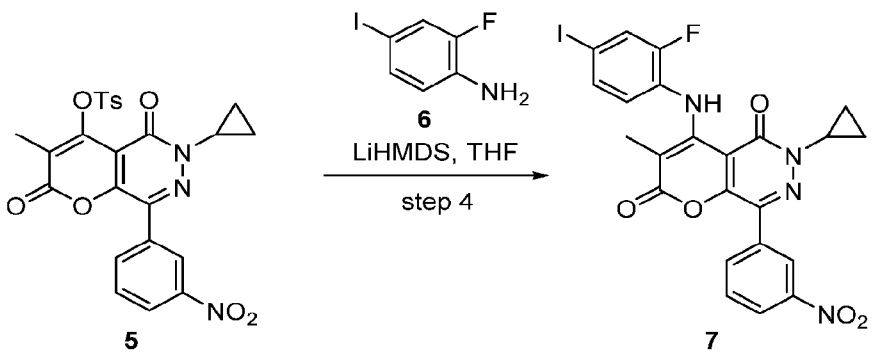
[00500] In a 100-mL round bottom flask, a solution of tert-butyl 3-[2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazin-4-yl]-2-methyl-3-oxopropanoate (6.00 g, 13.97 mmol, 1.00 equiv) in TFA (50.00 mL) was stirred at 60 °C for 3 hrs. The reaction mixture was concentrated under vacuum to yield a crude product which was directly purified by flash chromatography (PE:EA=1:1) to afford 6-cyclopropyl-3-methyl-8-(3-nitrophenyl)-3H-pyrano[2,3-d]pyridazine-2,4,5-trione (1.70 g, 34.27%) as a yellow solid.

Step 3



[00501] To a solution of 6-cyclopropyl-4-hydroxy-3-methyl-8-(3-nitrophenyl)pyrano[2,3-d]pyridazine-2,5-dione (1.70 g, 4.79 mmol, 1.00 equiv) and TEA (1.33 mL, 9.57 mmol, 2.00 equiv) in DCM (20.00 mL) was added a solution of TsCl (1.09 g, 5.72 mmol, 1.20 equiv) in DCM (20.00 mL) dropwised at 0 °C. The mixture was stirred at 25 °C for 16 hrs. The reaction mixture was treated by the addition of 100.00 mL H_2O and extracted with EA (3 x 100.00 mL). The combined organic layers were washed with brine (150.00 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a crude product which was directly purified by flash chromatography (PE:EA=3:1) to afford 6-cyclopropyl-3-methyl-8-(3-nitrophenyl)-2,5-dioxopyrano[2,3-d]pyridazin-4-yl 4-methylbenzenesulfonate (1.70 g, 51.55%) as a yellow solid.

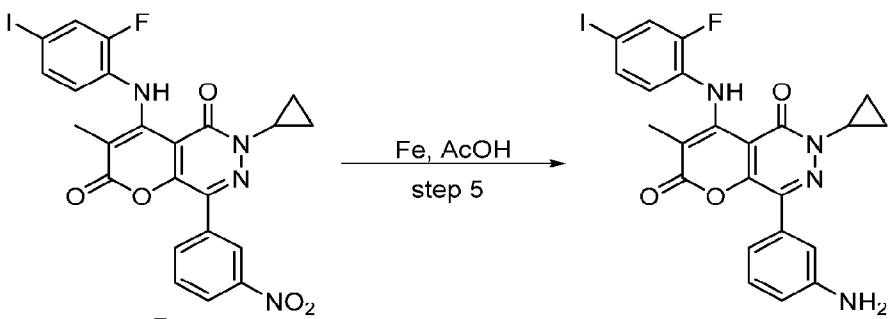
Step 4



[00502] To a solution of 2-fluoro-4-iodoaniline (2.85 g, 12.01 mmol, 3.60 equiv) in THF (30.00 mL) was added LiHMDS (10.01 mL, 10.01 mmol, 3.00 equiv) dropwise at -78 °C and stirred at -78 °C for 0.5 hrs. Then a solution of 6-cyclopropyl-3-methyl-8-(3-nitrophenyl)-2,5-dioxopyrano[2,3-d]pyridazin-4-yl 4-methylbenzenesulfonate (1.70 g, 3.34 mmol, 1.00 equiv) in THF (30.00 mL) was dropwise added to the reaction at -78 °C and stirred at -78

°C for 0.5 hrs. The reaction mixture was treated by the addition of Sat.NH_4Cl (150.00 mL) and extracted with EA (3 x 100.00 mL). The combined organic layers were washed with brine (150.00 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a crude product which was directly purified by flash chromatography (PE:EA=5:1) to afford 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methyl-8-(3-nitrophenyl)pyrano[2,3-d]pyridazine-2,5-dione (1.41 g, 73.58%) as a yellow solid.

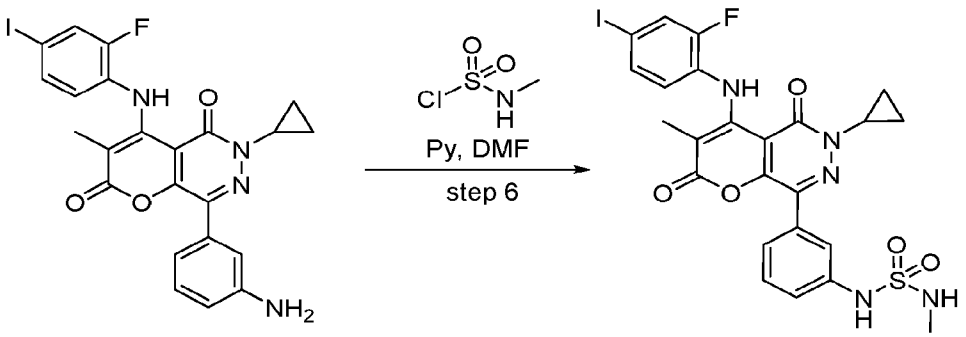
Step 5



7

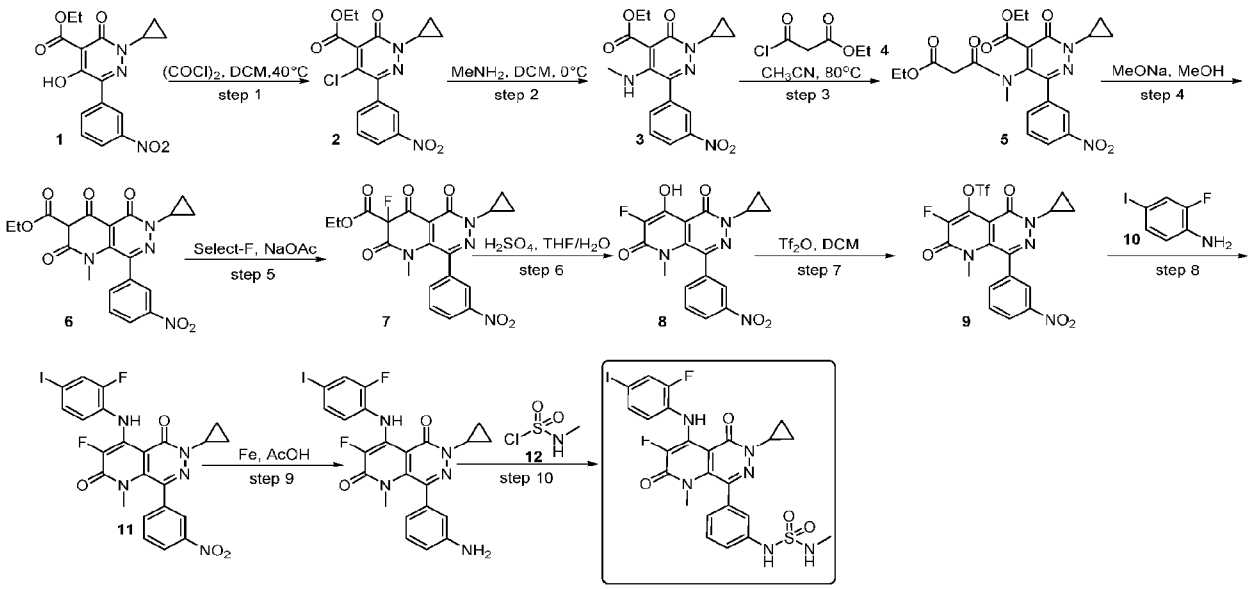
[00503] To a solution of 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methyl-8-(3-nitrophenyl)pyrano[2,3-d]pyridazine-2,5-dione (1.06 g, 1.85 mmol, 1.00 equiv) in AcOH (20.00 mL) was added Fe (1.03 g, 18.5 mmol, 10.00 equiv) at 25 °C and stirred at 50 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 50.00 mL Sat.$NaHCO_3$ and extracted with EA (3 x 50.00 mL). The combined organic layers were washed with brine (50.00 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methyl-8-(3-nitrophenyl)pyrano[2,3-d]pyridazine-2,5-dione (0.78 g, 73.58%) as a yellow solid, which was directly used in next step without further purification.

Step 6

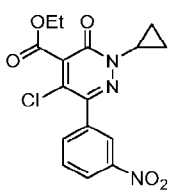


[00504] To a solution of 8-(3-aminophenyl)-6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methylpyrano[2,3-d]pyridazine-2,5-dione (0.24 g, 0.44 mmol, 1.00 equiv) and Pyridine (0.11 g, 1.32 mmol, 3.00 equiv) in DMF (1.50 mL) was dropwise added N-methylsulfamoyl chloride (0.09 g, 0.66 mmol, 1.50 equiv) in CH_3CN (1.50 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 0.5 hrs. The reaction mixture was treated by the addition of 20.00 mL H_2O and extracted with EA (3 x 30.00 mL). The combined organic layers were washed with brine (50.00 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give a crude product which was directly purified by Prep-HPLC (Column: Welch Xtimate C18 ExRS, 250 mm, 10μm; Mobile Phase A: Water (0.05%$NH_3.H_2O$), Mobile Phase B: ACN; Flow rate: 90 mL/min; Gradient: 90% B to 90% B in 10 min, 90% B; Wave Length: 254 nm; RT1(min): 7; Number Of Runs: 5) to afford 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-3-methyl-8-{3-[(methylsulfamoyl)amino]phenyl}pyrano[2,3-d]pyridazine-2,5-dione (62 mg, 33.09%) as a yellow solid. LCMS: (ES, m/z) $[M+H]^+$: 638.1. ^1H NMR: (400 MHz, DMSO-d_6): δ 7.72 - 7.71 (m, 1H), 7.63 - 7.60 (m, 1H), 7.57 - 7.50 (m, 2H), 7.46 - 7.42 (m, 1H), 7.35 - 7.32 (m, 1H), 6.92 (t, J=8.4 Hz, 1H), 4.20 - 4.16 (m, 1H), 2.62 (s, 3H), 1.65 (s, 3H), 1.25 - 1.23 (m, 2H), 1.11 - 1.06 (m, 2H).

Synthesis of 6-cyclopropyl-3-fluoro-4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-8-{3-[(methylsulfamoyl)amino]phenyl}pyrido[2,3-d]pyridazine-2,5-dione (I-128)

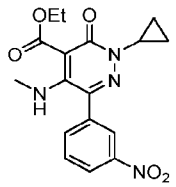


Step 1



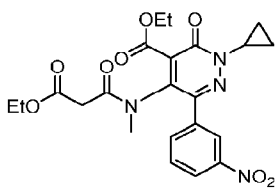
[00505] To a stirred solution of ethyl 2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazine -4-carboxylate (3.5 g, 1.45 mmol, 1.0 equiv) in DCM (30 mL) was added $(COCl)_2$ (12.9 g, 14.48 mmol, 10 equiv) and DMF (0.7 mL, 1.30 mmol, 0.9 equiv) dropwise at room temperature. The resulting mixture was stirred for 1 h at 40°C. The solvent and excess oxalyl dichloride were removed under reduced pressure. The residue was layered with DCM (50 mL) and H_2O (30mL), the water layer was extracted with DCM (2*30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (5.3 g, crude) as a brown oil. ES-LCMS *m/z* 364.0 $[M+H]^+$

Step 2



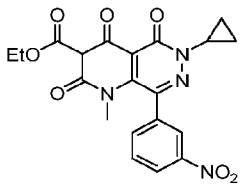
[00506] To a stirred solution of ethyl 5-chloro-2-cyclopropyl-6-(3-nitrophenyl)-3-oxopyridazine-4- carboxylate (4 g, 11.00 mmol, 1.0 equiv) in DCM (40 mL) was added CH_3NH_2/THF (45 mL, 90.00 mmol, 8.18 equiv) dropwise at 0 °C. The resulting mixture was stirred for additional 4 h at room temperature. The solvent was removed under reduced pressure. The residue was diluted in H_2O (100 mL) and extracted with DCM (3 x 100mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxopyridazine-4 -carboxylate (5.06 g, crude) as a brown yellow solid. ES-LCMS *m/z* 359.2 $[M+H]^+$

Step 3



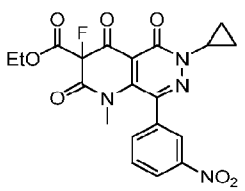
[00507] To a stirred solution of ethyl 2-cyclopropyl-5-(methylamino)-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (3.6 g, 10.05 mmol, 1.0 equiv) in ACN (36 mL) was added ethyl 3-chloro-3-oxopropanoate (3.6 mL) in portions at room temperature. The resulting mixture was stirred for additional 2 h at 80°C. The reaction mixture was cooled and quenched by pouring into water/ice (150 mL). The resulting mixture was extracted with EtOAc (3 x 150mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / THF (5:1) to afford ethyl 2-cyclopropyl-5-(3-ethoxy-N-methyl-3-oxopropanamido)- 6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (4.42 g, 93%) as a brown solid. ES-LCMS *m/z* 473.2 $[M+H]^+$

Step 4



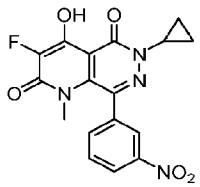
[00508] To a stirred solution of ethyl 2-cyclopropyl-5-(3-ethoxy-N-methyl-3-oxopropanamido) -6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (4.4 g, 9.31 mmol, 1.0 equiv) in MeOH (45 mL) was added sodium methoxide (1.0 g, 18.63 mmol, 2.0 equiv) in portions at 0°C under air atmosphere. The resulting mixture was stirred for additional 1 h at 0°C. The resulting mixture was concentrated and acidified to pH 4 with 1N HCl (aq.), then extracted with EtOAc (3 x 50mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 6-cyclopropyl-1-methyl-8-(3-nitrophenyl)-2,4,5-trioxo-3H-pyrido[2,3-d]pyridazine-3-carboxylate (3.7 g, 92%) as a brown solid. ES-LCMS *m/z* 427.2 $[M+H]^+$

Step 5



[00509] To a stirred solution of ethyl 6-cyclopropyl-1-methyl-8-(3-nitrophenyl)-2,4,5-trioxo -3H-pyrido[2,3-d]pyridazine-3-carboxylate acetate (3.1 g, 6.16 mmol, 1.0 equiv) and sodium acetate (1.0 g, 12.31 mmol, 2.0 equiv) in ACN (35 mL) was added Selectfluor (3.3 g, 9.23 mmol, 1.5 equiv) in portions at 0°C under air atmosphere. The resulting mixture was stirred for additional 3 h at 0°C. The reaction was quenched by the addition of water/ice (5mL) at 0°C, then extracted with EtOAc (3 x 10mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford ethyl 6-cyclopropyl-3-fluoro-1-methyl-8-(3-nitrophenyl)-2,4,5-trioxopyrido[2,3-d]pyridazine-3-carboxylate (2.4 g, 88%) as a yellow solid. ES-LCMS *m/z* 445.1 $[M+H]^+$.

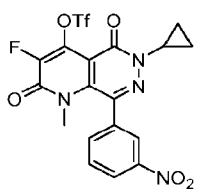
Step 6



[00510] To a stirred solution of ethyl 6-cyclopropyl-3-fluoro-1-methyl-8-(3-nitrophenyl)-2,4,5- trioxopyrido[2,3-d] pyridazine-3-carboxylate (2.4 g, 5.45 mmol, 1.0 equiv) in THF (25 mL) was added H_2SO_4 (24 mL) dropwise at room temperature under air atmosphere. The resulting mixture was stirred for 3 h at 90°C. Then THF was removed, the residue was diluted with water (10 mL) and extracted with DCM (3 x 20mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / THF (5:1) to afford 6-cyclopropyl-3-fluoro- 4-hydroxy-1-methyl-8-(3-nitrophenyl) pyrido[2,3-d] pyridazine-2,5-dione (1.1 g, 54%) as a yellow solid. ES-LCMS *m/z* 373.1 $[M+H]^+$.

[00511] ^1H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 8.44 - 8.41 (m, 1H), 8.40 - 8.34 (m, 1H), 8.04 - 7.98 (m, 1H), 7.87 - 7.79 (m, 1H), 3.78-3.70 (m, 1H), 2.93 (s, 3H), 1.10 - 1.07 (m, 2H), 1.07 - 1.04 (m, 2H).

Step 7



[00512] To a stirred solution of 6-cyclopropyl-3-fluoro-4-hydroxy-1-methyl-8-(3-nitrophenyl) pyrido[2,3-d] pyridazine-2,5-dione (1.1 g, 2.96 mmol, 1.0 equiv) and pyridine (0.7 g, 8.87 mmol, 3.0 equiv) in DCM (10 mL), Tf_2O (1.7 g, 5.91 mmol, 2.0 equiv) in DCM (2 mL) was added dropwise at 0°C. The resulting mixture was stirred for 0.5 h at room temperature. The mixture was diluted with water (10 mL) and extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE / THF (5:1) to afford 6-cyclopropyl-3-fluoro-1-methyl-8- (3-

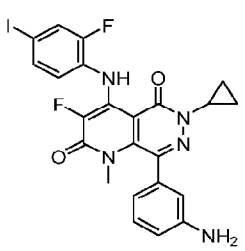
nitrophenyl)-2,5-dioxopyrido[2,3-d] pyridazin-4-yl trifluoromethanesulfonate (460 mg, 30%) as a yellow solid. ES-LCMS *m/z* 505.1 $[M+H]^+$.

[00513] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 (s, 1H), 8.39 - 8.32 (m, 1H), 8.10 - 8.03 (m, 1H), 7.88 - 7.79 (m, 1H), 4.10-4.0 (m, 1H), 2.97 (s, 3H), 1.49 - 1.22 (m, 2H), 0.94 - 0.76 (m, 2H).

Step 8

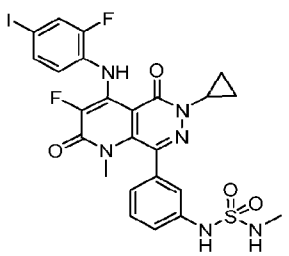
[00514] To a stirred solution of 2-fluoro-4-iodoaniline (648 mg, 2.74 mmol, 3.0 equiv) in THF (2 mL) were added LDA (2M in THF) (1.82ml, 3.65 mmol, 4.0 equiv) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 30 min at 0°C under nitrogen atmosphere. To the above mixture was added 6-cyclopropyl-3-fluoro- 1-methyl-8-(3-nitrophenyl)-2,5-dioxopyrido[2,3-d]pyridazin-4-yl trifluoromethanesulfonate (460 mg, 0.91 mmol, 1.0 equiv) in THF (3 mL) dropwise at 0°C. The resulting mixture was stirred for additional 30 min at room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of water (20 mL) at 0°C, extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (2:1) to afford 6-cyclopropyl-3-fluoro-4-[(2-fluoro-4-iodophenyl)amino]- 1-methyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (210 mg, 39%) as a white solid. ES-LCMS *m/z* 592.0 $[M+H]^+$.

Step 9



[00515] To a stirred solution of 6-cyclopropyl-3-fluoro-4-[(2-fluoro-4- iodophenyl)amino]-1-methyl-8-(3-nitrophenyl)pyrido[2,3-d]pyridazine-2,5-dione (240 mg, 0.40 mmol, 1.0 equiv) in AcOH (5 mL) was added Fe (226 mg, 4.06 mmol, 10 equiv) in portions at rt.. The resulting mixture was stirred for 30 min at 60°C under nitrogen atmosphere. The reaction was monitored by LCMS. The resulting mixture was cooled to room temperature, diluted with water (20 mL), neutralized to pH 7 with saturated $NaHCO_3$ (aq.), extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography, eluted with PE/EA (1:1) to afford 8-(3-aminophenyl)-6-cyclopropyl-3-fluoro-4-[(2-fluoro-4-iodophenyl)amino]-1-methylpyrido[2,3-d]pyridazine-2,5-dione (150 mg, 66%) as a white solid. ES-LCMS *m/z* 562.0 $[M+H]^+$.

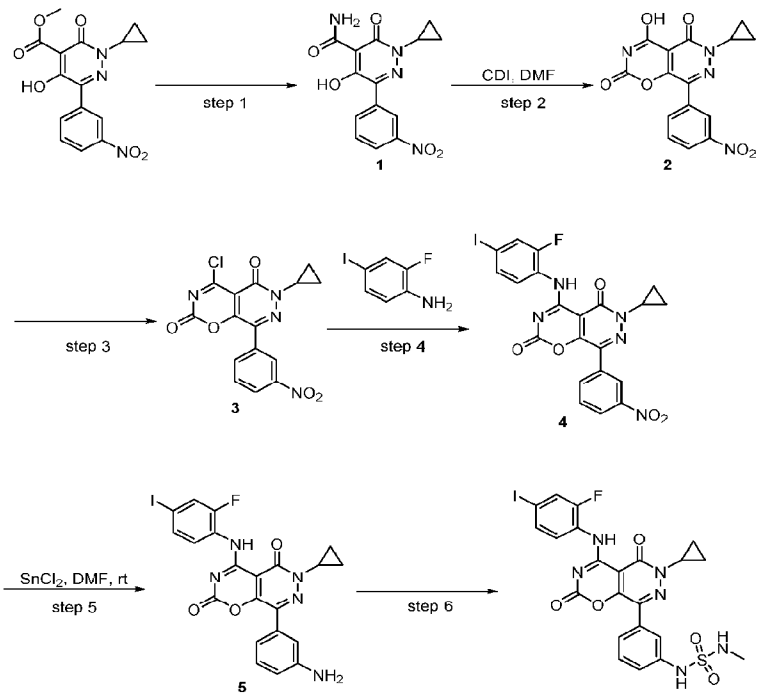
Step 10



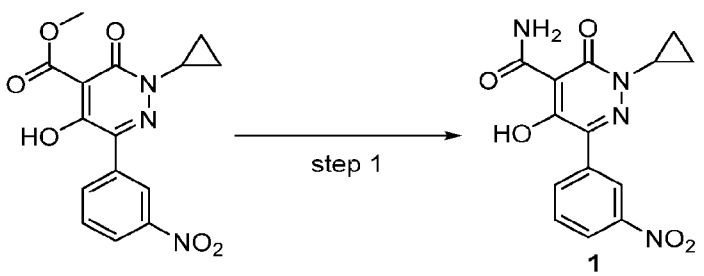
[00516] To a stirred solution of 8-(3-aminophenyl)-6-cyclopropyl-3-fluoro -4-[(2-fluoro-4-iodophenyl)amino]-1-methylpyrido[2,3-d]pyridazine-2,5-dione (150 mg, 0.27 mmol, 1.0 equiv) and Et_3N (81 mg, 0.80 mmol, 3.0 equiv) in DCM (1.5 mL) was added N-methylsulfamoyl chloride (69 mg, 0.53 mmol, 2.0 equiv) in DCM (0.5 mL) dropwise at 0°C under nitrogen atmosphere. The resulting mixture was stirred for 1 h at room temperature. The reaction was monitored by LCMS. The reaction was quenched by the addition of water (20 mL) at 0°C, extracted with EtOAc (3 x 20mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The crude product (200 mg) was purified by Prep-HPLC with the following conditions (Complete Non-WJ SC Hardware 50 mm x 40 cm, 7 μm, 40 - 60 % 18 min, NH_3 H_2O+NH_4HCO_3/CAN, 80 mL/min flash) to afford 6-cyclopropyl-3-fluoro-4-[(2-fluoro-4-iodophenyl)amino]-1-methyl-8-{3-[(methylsulfamoyl)amino]phenyl}pyrido[2,3-d]pyridazine-2,5-dione (68.4 mg, 39%) as a white solid. ES-LCMS *m/z* 655.0 $[M+H]^+$.

[00517] ^{1}H NMR(400 MHz, DMSO-d6) δ 10.92 (d, J = 2.6 Hz, 1H), 9.87 (s, 1H), 7.76 - 7.68 (m, 1H), 7.59 - 7.52 (m, 1H), 7.46 - 7.35 (m, 2H), 7.30 - 7.22 (m, 2H), 7.20 - 7.13 (m, 1H), 7.06 - 6.96 (m, 1H), 4.03 - 3.93 (m, 1H), 2.93 (s, 3H), 2.47 (d, J = 4.8 Hz, 3H), 1.06 - 0.99 (m, 4H).

Synthesis of 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-8-{3-[(methylsulfamoyl)amino]phenyl}pyridazino[4,5-e][1,3]oxazine-2,5-dione (I-127)



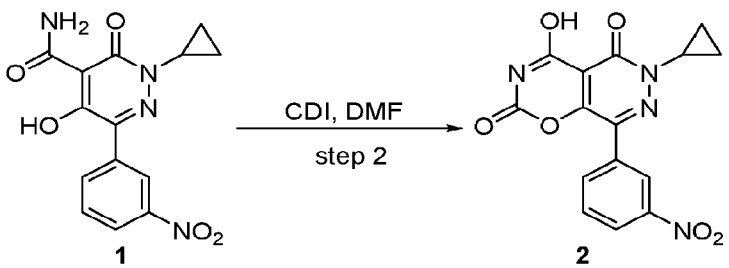
Step 1



[00518] A mixture of methyl 2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxylate (5 g, 15.093 mmol, 1 equiv) and NH_3*H_2O (10 mL, 256.805 mmol, 17.12 equiv) in 1,4-dioxane (40 mL) was stirred for 2 h at 80°C. The resulting mixture was concentrated under

reduced pressure and purified by trituration with ethyl ether (30 mL). This resulted in 2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxamide (4.6 g, 96.37%) as a light brown solid.

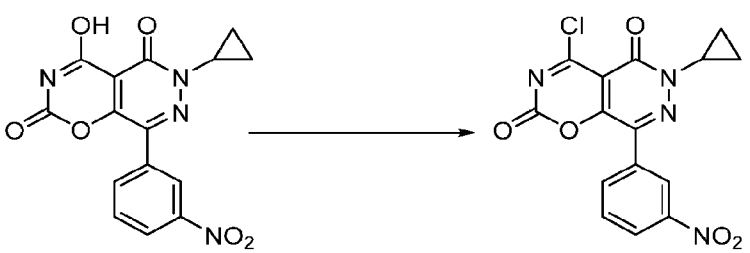
Step 2



1 2

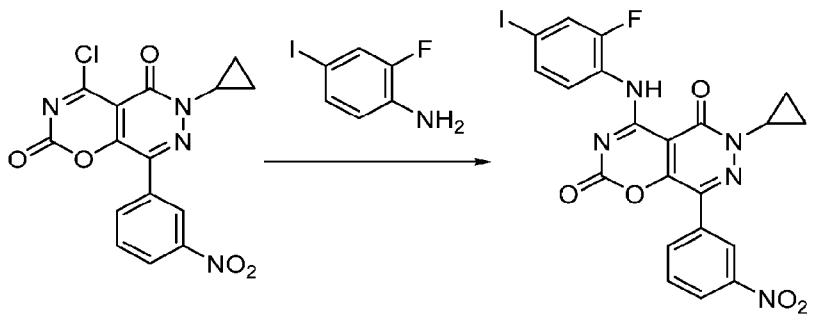
[00519] A mixture of 2-cyclopropyl-5-hydroxy-6-(3-nitrophenyl)-3-oxopyridazine-4-carboxamide (4.6 g, 14.544 mmol, 1 equiv) and CDI (3.54 g, 21.816 mmol, 1.5 equiv) in DMF was stirred at room temperature overnight. The precipitated solids were collected by filtration and washed with MeOH (3x20 mL). This resulted in 6-cyclopropyl-4-hydroxy-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (4.2 g, 84.37%) as a yellow solid.

Step 3



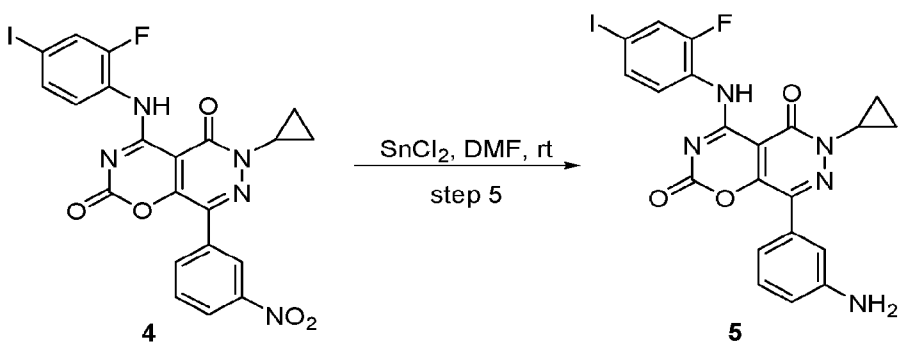
[00520] A mixture of 6-cyclopropyl-4-hydroxy-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (4.2 g, 12.271 mmol, 1 equiv) and PCl_5 (5.11 g, 24.542 mmol, 2 equiv) in DCE was stirred for 2 h at 80 °C under nitrogen atmosphere. The solvent was removed under reduced pressure to afford 4-chloro-6-cyclopropyl-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (6 g, crude) as a yellow solid. The crude product was used in next step directly without further purification.

Step 4



[00521] A mixture of 2-fluoro-4-iodoaniline (5.91 g, 24.951 mmol, 1.5 equiv) and 4-chloro-6-cyclopropyl-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (6 g, 16.634 mmol, 1 equiv) in acetonitrile was stirred for 2 h at room temperature under nitrogen atmosphere. The precipitated solids were collected by filtration and washed with ACN (3x10 mL). The collected solid was purified by trituration with MeOH (20 mL). This resulted in 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (3.8 g, 55.15%) as a yellow solid.

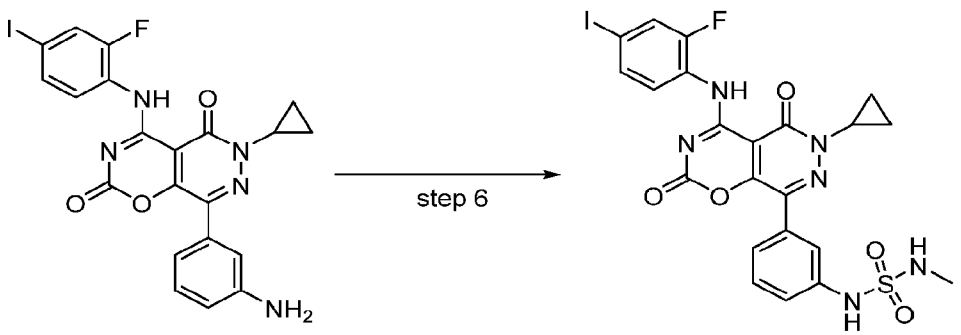
Step 5



4 5

[00522] A mixture of 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-8-(3-nitrophenyl)pyridazino[4,5-e][1,3]oxazine-2,5-dione (250 mg, 0.445 mmol, 1 equiv) and $SnCl_2$ (2.54 g, 13.230 mmol, 29.73 equiv) in DMF (10 mL) was stirred at room temperature overnight. The resulting solution was diluted with EtOAc (50 mL) and washed with 3x 20 mL of water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. This resulted in 8-(3-aminophenyl)-6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]pyridazino[4,5-e][1,3]oxazine-2,5-dione (280 mg, crude) as a yellow green solid.

Step 6



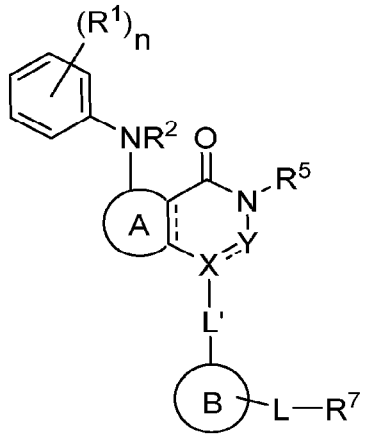
[00523] To a stirred solution of 8-(3-aminophenyl)-6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]pyridazino[4,5-e][1,3]oxazine-2,5-dione (280 mg, 0.527 mmol, 1 equiv) and pyridine (125.06 mg, 1.581 mmol, 3 equiv) in DMF(2.8 mL), N-methylsulfamoyl chloride (102.42 mg, 0.790 mmol, 1.5 equiv) in ACN (1 mL) was added dropwise at 0°C. The resulting mixture was stirred for 30 min at room temperature, then diluted with EtOAc (2*20 mL). The combined organic phase was washed with 3x20 mL of water and concentrated under vacuum. The residue was purified by Prep-HPLC (Column: Welch Ultimate XB-C18, 50*250 mm, 10μm; Mobile Phase A: Water (0.1% FA), Mobile Phase B: ACN; Flow rate: 90 mL/min; Gradient: 30% B to 65% B in 12 min, 65% B in 9 min; Wave Length: 254 nm.) to afford 6-cyclopropyl-4-[(2-fluoro-4-iodophenyl)amino]-8-{3-[(methylsulfamoyl)amino]phenyl}pyridazino[4,5-e][1,3]oxazine-2,5-dione (66.9 mg, 20.33%) as an off-white solid. LCMS: (ES, m/z) $[M+H]^+$: 625.1. ^{1}H NMR: (300 MHz, DMSO-d_6) δ 12.02 (br, s, 1H), 9.93 (br, s, 1H), 8.29-8.18 (m, 1H), 7.92-7.82 (m, 1H), 7.76-7.67 (m, 1H), 7.58 (s, 1H), 7.50-7.42 (m, 2H), 7.41-7.28 (m, 2H), 4.24-4.13 (m, 1H), 2.50 (s, 3H), 1.19-1.05 (m, 4H).

[00524] While a number of embodiments of this invention are described, it is apparent that the 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 application and appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

What is claimed is:

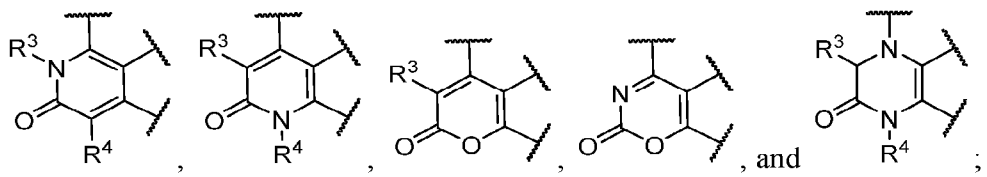
1. A compound of Formula **I'**:



(I')

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is selected from:



each ==== independently represents a single bond or a double bond;

each R^1 is independently H, halogen, -CN, or optionally substituted C_{1-6} aliphatic;

X is C, CH, or N;

Y is CR^6, C(O), or N;

L' is a covalent bond, -O-, $-C(R^9)_2-$, or $-NR^8-$;

each of R^2, R^5, and R^8 is independently H or optionally substituted C_{1-6} aliphatic;

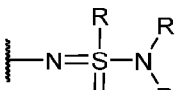
each of R^3, R^4, R^6, and R^9 is independently H, halogen, or optionally substituted C_{1-6} aliphatic;

Ring B is an optionally substituted ring selected from a 3-8 membered monocyclic carbocyclic ring, a 3-8 membered monocyclic heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a 5-11 membered bicyclic carbocyclic ring, a 5-11 membered

bicyclic heterocyclic ring having 1-5 heteroatoms independently selected from N, O, or S, a phenyl ring, a 5-6 membered monocyclic heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S, a 8-11 membered bicyclic aromatic ring, and a 8-11 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S;

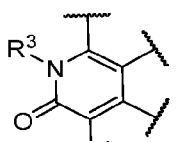
L is a covalent bond or a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -S-, -N(R)-, $-N^{+}(R)_2$-, -CH(R)-, -CH(OR)-, -CH(SR)-, –CH(N(R)$_2$)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -S(O)$_2$-, -(CH$_2$-CH$_2$-O)$_{1-10}$-, -S(O)-, -N(R)-C(O)-, -N(R)-S(O)$_2$-, -C(O)-N(R)-, -S(O)$_2$-N(R)-, -P(O)(OR)-, or -Cy-;

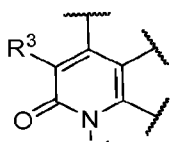
each -Cy- is independently an optionally substituted ring selected from a 3-7 membered carbocyclic ring, a 3-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from N, O, or S, a phenyl ring, and a 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S;

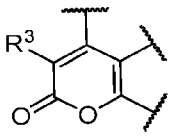
R^7 is R, -CN, -S(O)$_2$-N(R)$_2$, -NR-S(O)$_2$-R, -P(O)(OR)-N(R)$_2$, -C(=N-R)-N(R)$_2$, -C(=N-OR)-N(R)$_2$, -C(O)-R, -S(O)-R, -N(R)$_2$, -OR, -SR, or  ;

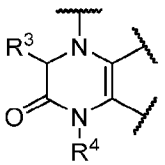
each R is independently H, -CN, or optionally substituted C_{1-6} aliphatic; and

n is 0, 1, 2, 3, 4, or 5.

2. The compound of claim 1, wherein Ring A is  .

3. The compound of claim 1, wherein Ring A is  .

4. The compound of claim 1, wherein Ring A is  .

5. The compound of claim 1, wherein Ring A is  .

6. The compound of any one of claims 1-5, wherein each R^1 is independently halogen.

7. The compound of any one of claims 1-6, wherein R^2 is H.

8. The compound of any one of claims 1-7, wherein R^3 is optionally substituted C_{1-6} alkyl.

9. The compound of any one of claims 1-8, wherein R^4 is optionally substituted C_{1-6} alkyl.

10. The compound of any one of claims 1-9, wherein R^5 is optionally substituted 3, 4, 5, or 6 membered saturated or unsaturated carbocyclyl.

11. The compound of any one of claims 1-10, wherein R^6 is optionally substituted C_{1-6} alkyl.

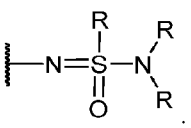
12. The compound of any one of claims 1-11, wherein Ring B is an optionally substituted phenyl ring.

13. The compound of any one of claims 1-11, wherein Ring B is an optionally substituted 5-6 membered heteroaromatic ring having 1-3 heteroatoms independently selected from N, O, or S.

14. The compound of any one of claims 1-11, wherein Ring B is an optionally substituted 8-10 membered bicyclic heteroaromatic ring having 1-5 heteroatoms independently selected from N, O, or S.

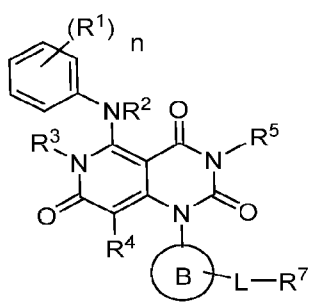
15. The compound of any one of claims 1-14, wherein L is a C_{1-10} bivalent straight or branched hydrocarbon chain wherein 1, 2, or 3 methylene units of the chain are independently and optionally replaced with -O-, -N(R)-, -CH(R)-, -C(=N-R)-, -C(=N-OR)-, -C(O)-, -$S(O)_2$-, -P(O)(OR)-, or -Cy-.

16. The compound of any one of claims 1-15, wherein -Cy- is an optionally substituted 3, 4, 5, 6, or 7 membered heterocyclic ring having 1, 2, or 3 heteroatoms independently selected from N, O, or S.

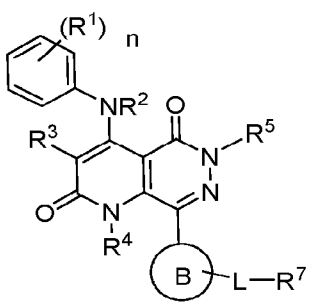
17. The compound of any one of claims 1-16, wherein R^7 is -CN, -$S(O)_2$-$N(R)_2$, -NR-$S(O)_2$-R, -P(O)(OR)-$N(R)_2$, -C(=N-R)-$N(R)_2$, -C(=N-OR)-$N(R)_2$, -OR, or  .

18. The compound of any one of claims 1-17, wherein n is 2.

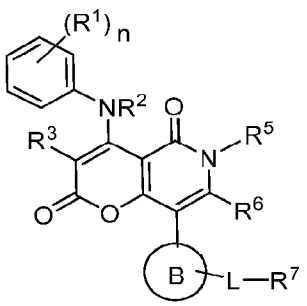
19. The compound of any one of claims 1-18, wherein the compound is a compound of Formulae **(II)**, **(III)**, or **(IV)**:



(II)



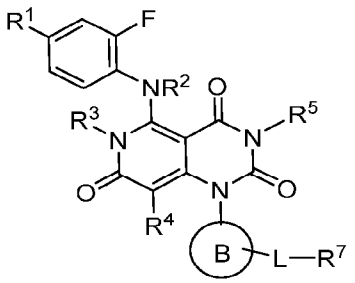
(III)



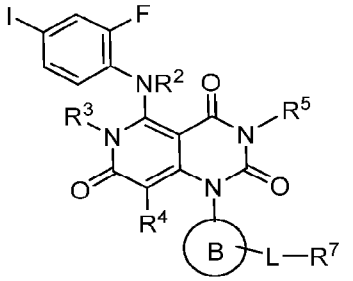
(IV)

or a pharmaceutically acceptable salt thereof.

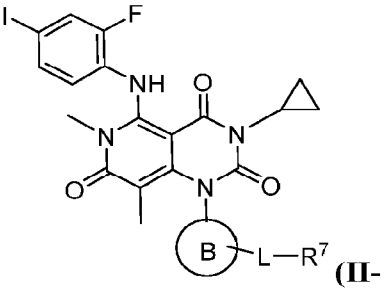
20. The compound of any one of claims 1-19, wherein the compound is a compound selected from Formulae **(II-a)** to **(II-o)**, **(III-a)** to **(III-e)**, and **(IV-a)** to **(IV-e)**:



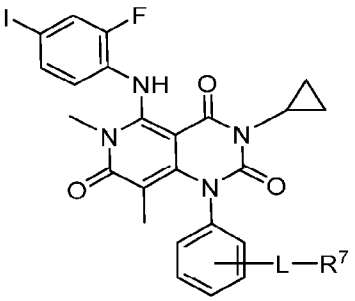
(II-a)



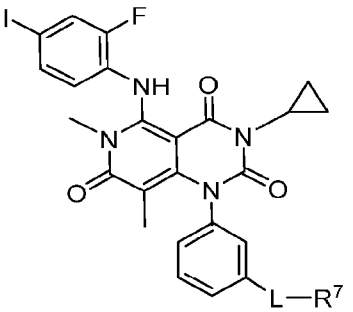
(II-b)



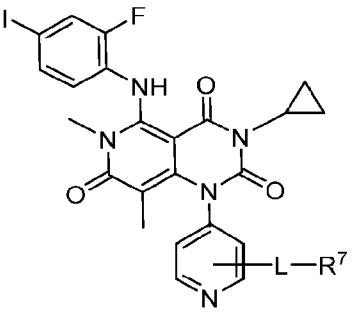
(II-c)



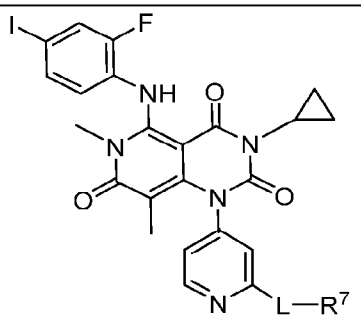
(II-d)



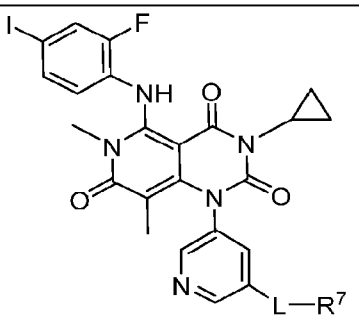
(II-e)



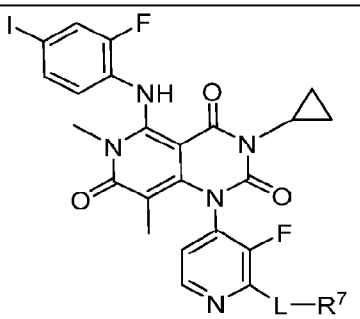
(II-f)



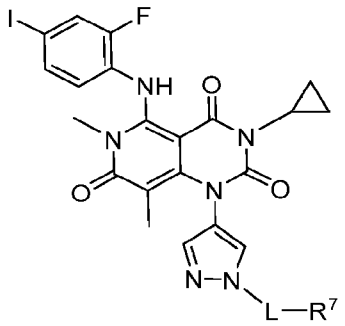
(II-g)



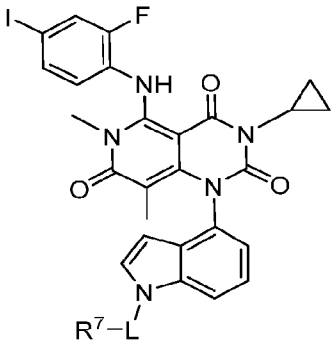
(II-h)



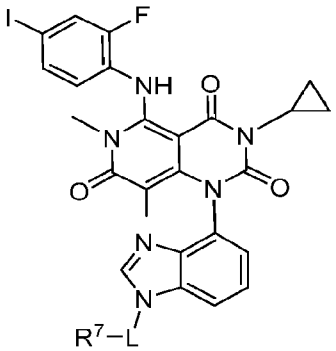
(II-i)



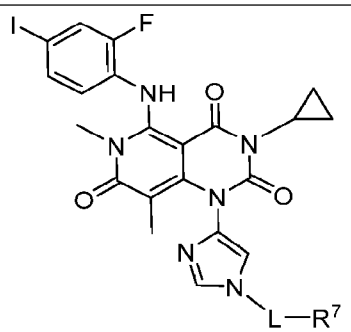
(II-j)



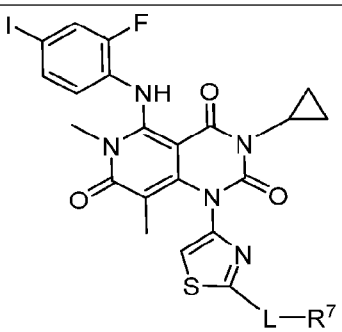
(II-k)



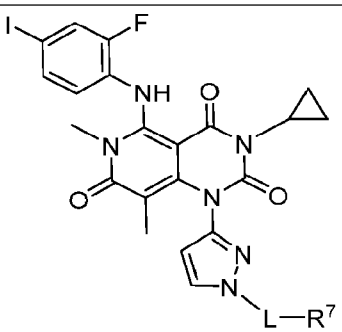
(II-l)



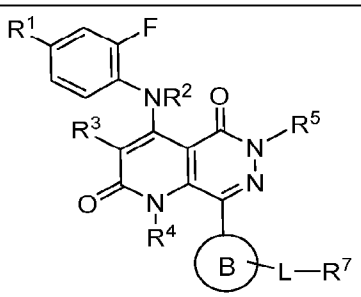
(II-m)



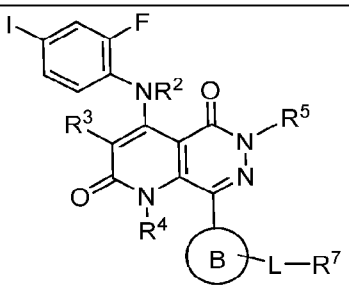
(II-n)



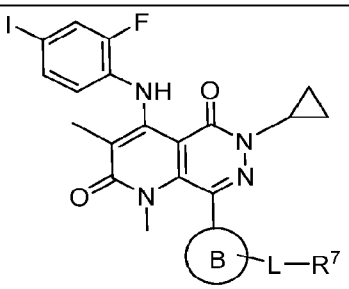
(II-o)



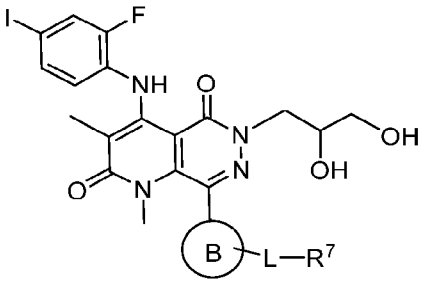
(III-a)



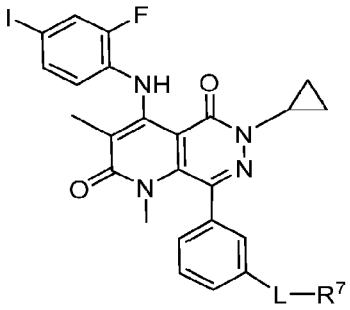
(III-b)



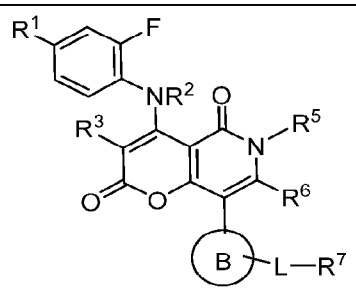
(III-c)



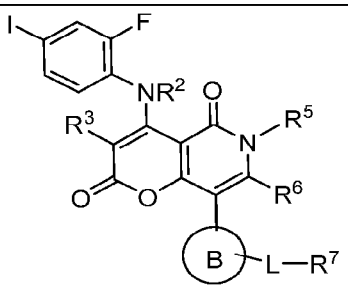
(III-d)



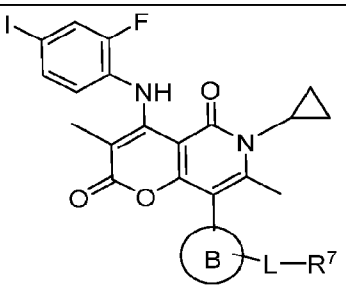
(III-e)



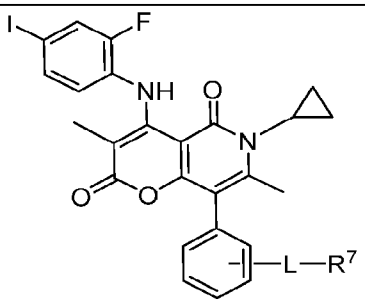
(IV-a)



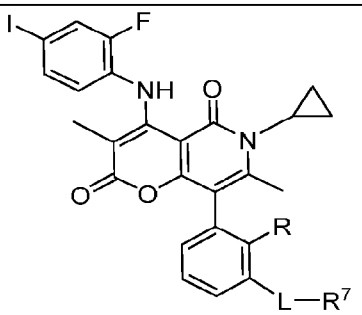
(IV-b)



(IV-c)



(IV-d)



(IV-e)

or a pharmaceutically acceptable salt thereof.

21. The compound of any one of claims 1-20, wherein the compound is selected from the compounds in Table 1.

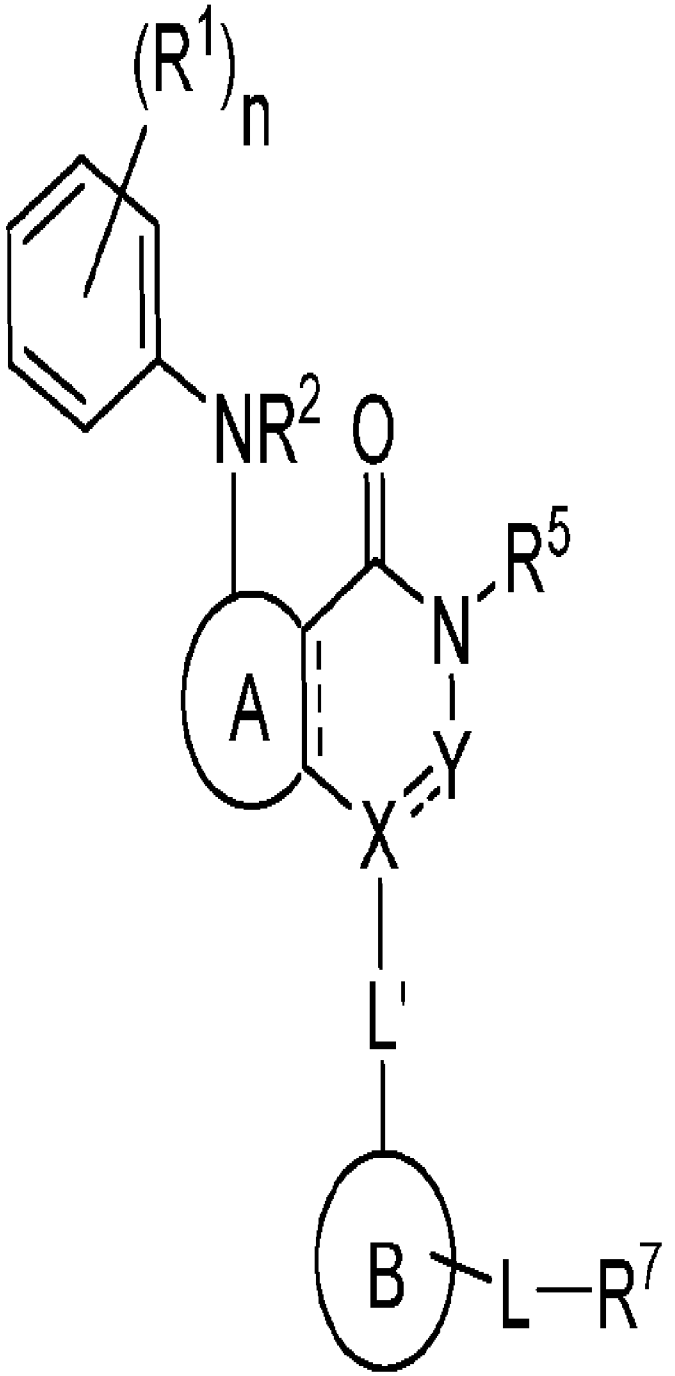
22. A pharmaceutical composition comprising the compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

23. A method of treating a disorder mediated by MEK, comprising administering a therapeutically effective amount of a compound of any one of claims 1-21, or a pharmaceutical composition of claim 22, to a subject in need thereof to treat the disorder.

24. The method of claim 23, wherein the disorder is cancer.

25. A method for treating a cancer in a patient, comprising administering the compound of any one of claims 1-21, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition of claim 22, to the patient.

26. A method of inhibiting MEK activity, comprising contacting MEK or a KSR-MEK complex or a RAF-MEK complex with an effective amount of a compound of any one of claims 1-21, or a pharmaceutical composition of claim 22, to inhibit MEK activity.



(I')