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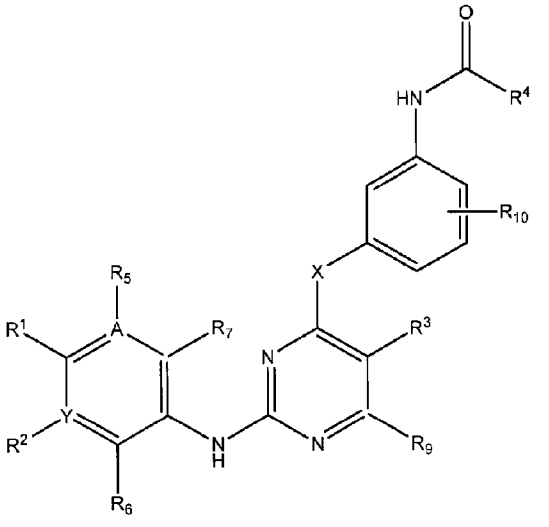
(54) **Titre : COMPOSES HETEROCYCLIQUES ET LEURS UTILISATIONS**
(54) **Title: HETEROCYCLIC COMPOUNDS AND USES THEREOF**



(Ia)

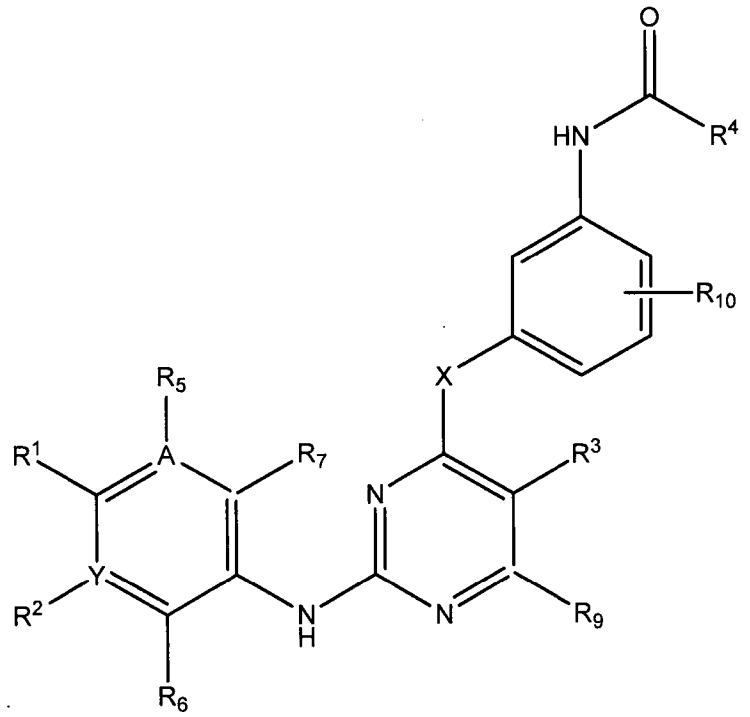
(57) **Abrégé/Abstract:**
The present invention relates to pharmaceutical compounds of Formula (Ia),

(see formula Ia)

and to compositions and methods of using these compounds for the treatment and/or prevention of a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, and in some embodiments diseases or disorders related to the dysregulation of kinase including EGFR (including HER), Alk, PDGFR, BLK, BMX/ETK, FLT3(D835Y), ITK, TEC, TXK, BTK, or JAK, and the respective pathways.

Abstract

The present invention relates to pharmaceutical compounds of Formula (Ia),



(Ia)

and to compositions and methods of using these compounds for the treatment and/or prevention of a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, and in some embodiments diseases or disorders related to the dysregulation of kinase including EGFR (including HER), Alk, PDGFR, BLK, BMX/ETK, FLT3(D835Y), ITK, TEC, TXK, BTK, or JAK, and the respective pathways.

HETEROCYCLIC COMPOUNDS AND USES THEREOF

[0001] Field of the Invention

[0002] The field of this invention is compounds, pharmaceutical compositions and methods, especially as they are related to compositions and methods for the treatment of a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, and in some embodiments diseases or disorders related to the dysregulation of kinase such as, but not limited to, EGFR (including HER), Alk, PDGFR, BLK, BMX/ETK, BTK, FLT3 (D835Y), ITK, JAK such as JAK1, JAK2, JAK3, TEC and TXK, and the respective pathways.

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Background of the Invention

[0003] Protein kinases are a group of enzymes that regulate diverse, important biological processes including cell growth, proliferation, survival, invasion and differentiation, organ formation, tissue repair and regeneration, etc. Protein kinases exert their physiological functions through catalyzing the phsophorylation of protein and thereby modulating the cellular activities. Because protein kinases have profound effects on cells, their activities are highly regulated. Kinases are turned on or off by phosphorylation (sometimes by autophosphorylation), by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates. Dysfunctions in the activities of kinases, arising from genetic abnormalities or environmental factors, are known to be associated with many diseases. Several severe pathological states, including cancer and chronic inflammation, are associated with stimulation of intra-cellular signaling, and since kinases positively relay signaling events, their inhibition offers a powerful way to inhibit or control signal transduction cascades.

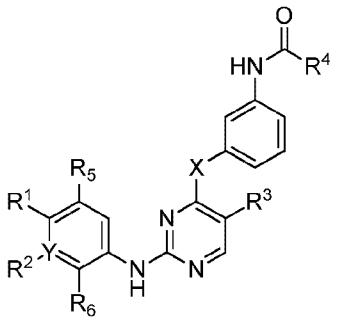
[0004] The epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans) is a member of the ErbB family of receptors, a subfamily of four closely related receptor tyrosine kinases: EGFR (ErbB-1), HER2/c-neu (ErbB-2), Her 3 (ErbB-3) and Her 4 (ErbB-4). EGFR is the cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands. Mutations affecting EGFR expression or activity could result in cancer. EGFR is reported deregulated in most solid tumor types, *i.e.*, lung cancer, breast cancer and brain tumor. It is estimated that mutations, amplifications or misregulations of EGFR or family members are implicated in about 30% of all epithelial cancers. Therapeutic approaches have been developed based on the inhibition of EGFR by either antibody drug or small molecular inhibitor drug, such as gefitinib and erlotinib. In the case of non small cell lung cancer, gefitinib and erlotinib have shown benefit for 10~40% of the patients. However, acquired resistant to gefitinib or erlotinib after a period of treatment become a major clinical problem. Research has confirmed that one main reason resistance developed is due to the present of the new mutation of T790M, which is the gatekeeper of EGFR. Subsequently, inhibitors can overcome this T790M have been developed and showed advantage in the clinical trial, such as BIBW2992. However, these T790M targeted EGFR inhibitor still has relative

inhibitory activity towards wild type EGFR which limit the clinical application. It is needed to further develop more efficient type of EGFR inhibitor which will target mutation only but not the wild type protein.

[0005] Other protein kinases that are useful targets for small molecule pharmaceuticals include B lymphoid tyrosine kinase (BLK), bone marrow kinase on the X chromosome (BMX/ETK), Bruton's tyrosine kinase (BTK), janus kinase 1 (JAK1), janus kinase 2 (JAK2), janus kinase 3 (JAK3), tyrosine kinase expressed in hepatocellular carcinoma (TEC), resting lymphocyte kinase (TXK, also known as RLK), FMS-like tyrosine kinase 3 (FLT3), and FLT3 (D835Y).

Disclosure of the Invention

[0006] In one aspect, the present disclosure provides for a heterocyclic compound having a structure according to Formula I:



(I)

wherein

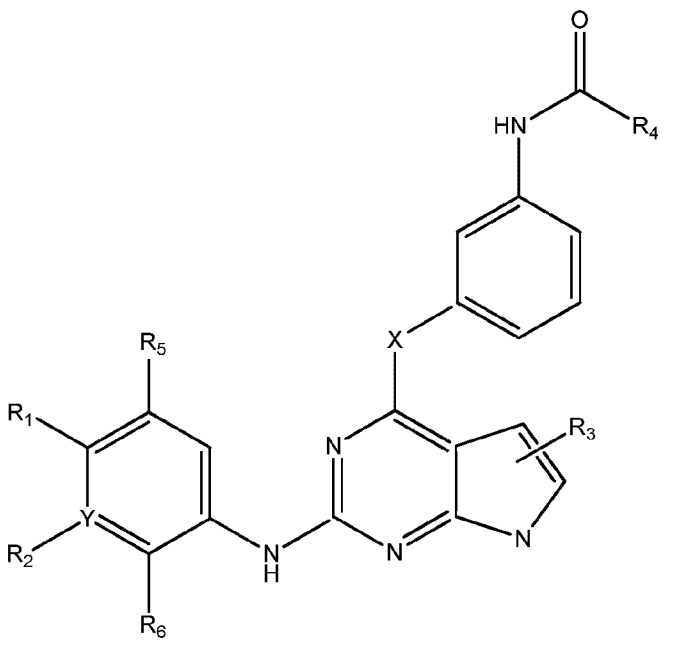
R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo;

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;
R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;
R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;
R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or
R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or
R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,
Y is CH optionally substituted with halo, or N,
wherein at least one of R^2, R^3, R^5 and R^6 is not H;
or a pharmaceutically acceptable salt thereof.

[0007] In another aspect, the present disclosure provides for a heterocyclic compound having a structure according to Formula II:



(II)

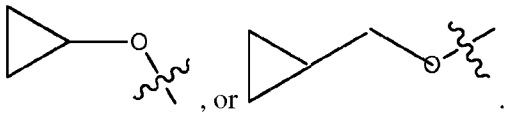
wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

NR^eR^f wherein R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo; or

OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,


, or

.

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

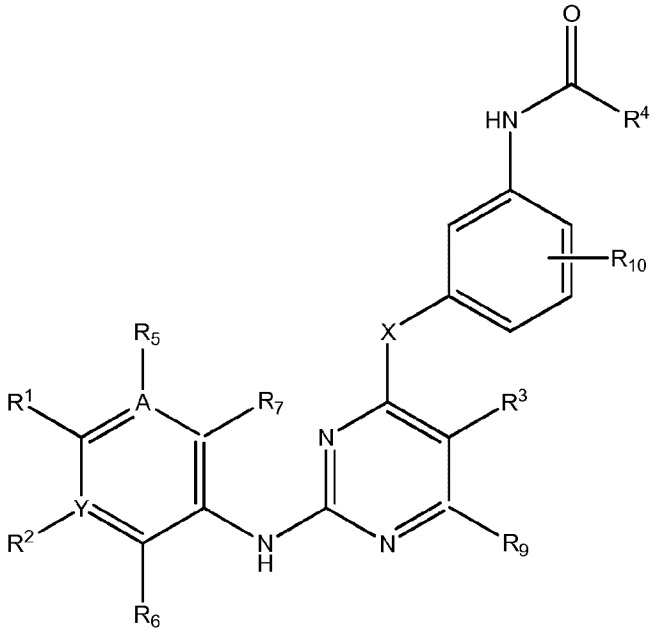
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,

Y is CH optionally substituted with halo, or N,

or a pharmaceutically acceptable salt thereof.

[0008] In still another aspect, the present disclosure provides for a heterocyclic compound having a structure according to Formula Ia:



(Ia)

wherein

R^1 is H, or

NR^cR^d wherein

R^c is H, C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring, said C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12}

are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, and

R^d is H, C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring, said C_{1-4} alkyl, C_{1-4} alkenyl or 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl; or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4; or

$O(CH_2)_mSO_2(CH_2)_nH$, wherein m is 1-4 and n is 1-4;

R^2 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^3 is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^5 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^6 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy; or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^7 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^9 is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^{10} is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl; or

R^1 and R^5 are part of 3-7 member cyclic ring, said 3-7 member cyclic being optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic being optionally substituted with R_8CO,

wherein R_8 is C_{1-4} alkyl, or said 3-7 member cyclic being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl, said C_{1-4} alkyl further optionally substituted with halo, OZ, or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl, or one or more members of said 3-7 member cyclic ring is optionally part of a carbonyl group or a sulfonyl group; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$;

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo;

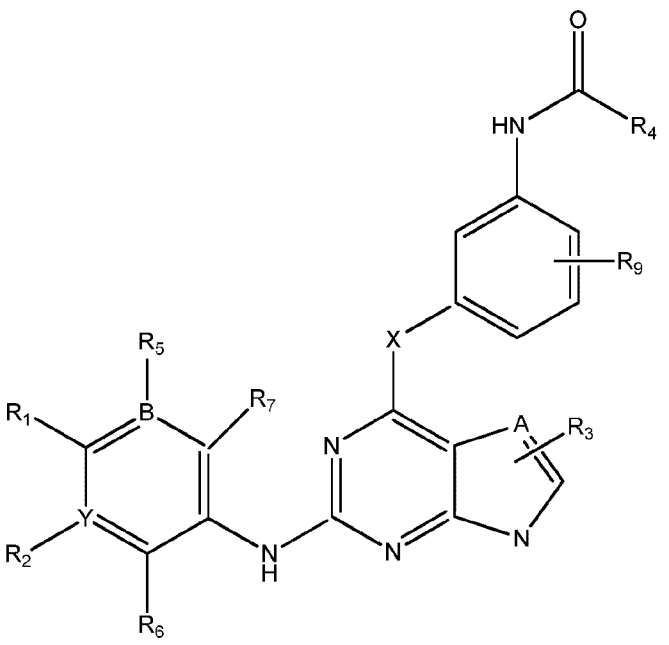
Y is C, CH optionally substituted with halo, or N;

A is C, CH optionally substituted with halo or N; and

wherein at least one of R^2, R^3, R^5 and R^6 is not H;

or a pharmaceutically acceptable salt thereof.

[0009] In yet another aspect, the present disclosure provides for a heterocyclic compound having a structure according to Formula IIa:



(IIa)

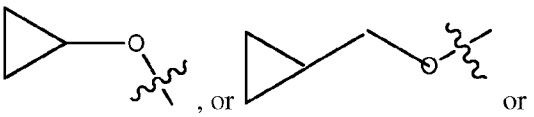
wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, said 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are H or C_{1-4} alkyl; or

NR^eR^f wherein R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo; or

OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,



3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl;

R^2 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^3 is absent, H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^5 is absent, H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^7 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^9 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl; or
R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl; or
R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently are H or C_{1-4} alkyl,; or
R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl;
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$;
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo;
Y is C, CH optionally substituted with halo, or N;
A is C, CH optionally substituted with halo, or N; and
B is C, CH optionally substituted with halo, or N,
or a pharmaceutically acceptable salt thereof.

[0010] The compound described above can be used for any suitable purpose. In some embodiments, the compound described above can be used in therapy.

[0011] In still another aspect, the present disclosure provides for a pharmaceutical composition comprising a compound described above admixed with at least one pharmaceutically acceptable carrier or excipient.

[0012] In yet another aspect, the present disclosure provides for a method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, or lupus, which comprises administering to a subject in need thereof an effective amount of a compound described above or a pharmaceutical composition described above.

[0013] In yet another aspect, the present disclosure provides for a use of a compound described above for the manufacture of a medicament.

[0014] In yet another aspect, the present disclosure provides for a combination for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject, which combination comprises an effective amount of a compound described above, or a pharmaceutically acceptable salt thereof, and an effective amount of a second prophylactic or therapeutic agent for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, a n autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject.

[0015] In yet another aspect, the present disclosure provides for a method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject, which methods comprises administering to a subject in need thereof an effective amount of the combination described above.

[0016] In yet another aspect, the present disclosure provides for a method for inhibiting an activity of a Bruton's tyrosine kinase (Btk or BTK) or a Janus kinase (JAK), EGFR (including HER), Alk, PDGFR, BLK, BMX/ETK, FLT3(D835Y), ITK, TEC, TXK, and the respective pathways, in a cell or subject, which methods comprises administering to a cell or subject in need thereof an effective amount of a compound described above, or a pharmaceutical composition described above, or a combination described above.

Brief Description of the Drawings

[0017] Figure 1 shows reduction of the Btk Tyr223 phosphorylation in Ramos cells by exemplary compounds. Figure 1A shows reduction of the Btk Tyr223 phosphorylation in Ramos cells by PCI-32765 (Ibrutinib). Figure 1B shows reduction of the Btk Tyr223 phosphorylation in Ramos cells by Compound No. I-1. Figure 1C shows reduction of the Btk Tyr223 phosphorylation in Ramos cells by Compound No. I-2.

[0018] Figure 2 shows that compounds I-1 and I-2 irreversibly inhibited the BTK phosphorylation in Ramos cells.

[0019] Figure 3 shows dose-dependent inhibition of the BTK phosphorylation in Ramos cells by compound I-1.

[0020] Figure 4A-4N show exemplary western blotting image IC_{50} curves from several compounds, while PCI-32765 served as positive Btk inhibitor.

[0021] Figure 5A and 5B show that compounds I-1 and I-2 inhibited the Btk phosphorylation in Ramos cells after 8 hours of removal.

[0022] Figure 6A-6L show exemplary Btk Target Site Occupancy ELISA assay results from several compounds.

Description of Selected Embodiments

General Definitions:

[0023] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. If a definition set forth in this section is contrary to or otherwise inconsistent with a definition set forth in a patent, application, or other publication that is cited herein, the definition set forth in this section prevails over the definition in the cited reference.

[0024] As used herein, "a" or "an" means "at least one" or "one or more".

[0025] The term "alkyl" as used herein refers to saturated hydrocarbon groups in a straight, branched, or cyclic configuration or any combination thereof, and particularly contemplated alkyl groups include those having ten or less carbon atoms, especially 1-6 carbon atoms and

lower alkyl groups having 1-4 carbon atoms. Exemplary alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tertiary butyl, pentyl, isopentyl, hexyl, cyclopropylmethyl, etc.

[0026] Alkyl groups can be unsubstituted, or they can be substituted to the extent that such substitution makes sense chemically. Typical substituents include, but are not limited to, halo, =O, =N-CN, =N-OR^a, =NR^a, -OR^a, -NR^a_2, -SR^a, -SO_2R^a, -$SO_2NR^a_2$, -$NR^aSO_2R^a$, -$NR^aCONR^a_2$, -NR^aCOOR^a, -NR^aCOR^a, -CN, -$COOR^a$, -$CONR^a_2$, -$OOCR^a$, -COR^a, and -NO_2, wherein each R^a is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C3-C8 heterocyclyl, C4-C10 heterocyclyclalkyl, C1-C8 acyl, C2-C8 heteroacyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, or C5-C10 heteroaryl, and each R^a is optionally substituted with halo, =O, =N-CN, =N-OR^b, =NR^b, OR^b, NR^b_2, SR^b, SO_2R^b, $SO_2NR^b_2$, $NR^bSO_2R^b$, $NR^bCONR^b_2$, NR^bCOOR^b, NR^bCOR^b, CN, $COOR^b$, $CONR^b_2$, $OOCR^b$, COR^b, and NO_2, wherein each R^b is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C3-C8 heterocyclyl, C4-C10 heterocyclyclalkyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl. Alkyl, alkenyl and alkynyl groups can also be substituted by C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl, each of which can be substituted by the substituents that are appropriate for the particular group. Where a substituent group contains two R^a or R^b groups on the same or adjacent atoms (*e.g.*, -NR^b2, or –NR^b-C(O) R^b), the two R^a or R^b groups can optionally be taken together with the atoms in the substituent group to which are attached to form a ring having 5-8 ring members, which can be substituted as allowed for the R^a or R^b itself, and can contain an additional heteroatom (N, O or S) as a ring member.

[0027] The term "alkenyl" as used herein refers to an alkyl as defined above having at least two carbon atoms and at least one carbon-carbon double bond. Thus, particularly contemplated alkenyl groups include straight, branched, or cyclic alkenyl groups having two to ten carbon atoms (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, etc.) or 5-10 atoms for cyclic alkenyl groups. Alkenyl groups are optionally substituted by groups suitable for alkyl groups as set forth herein.

[0028] Similarly, the term "alkynyl" as used herein refers to an alkyl or alkenyl as defined above and having at least two (preferably three) carbon atoms and at least one carbon-carbon triple bond. Especially contemplated alkynyls include straight, branched, or cyclic alkynes having two to ten total carbon atoms (*e.g.*, ethynyl, propynyl, butynyl, cyclopropylethynyl, etc.). Alkynyl groups are optionally substituted by groups suitable for alkyl groups as set forth herein.

[0029] The term "cycloalkyl" as used herein refers to a cyclic alkane (*i.e.*, in which a chain of carbon atoms of a hydrocarbon forms a ring), preferably including three to eight carbon atoms. Thus, exemplary cycloalkanes include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Cycloalkyls also include one or two double bonds, which form the "cycloalkenyl" groups. Cycloalkyl groups are optionally substituted by groups suitable for alkyl groups as set forth herein.

[0030] The term "aryl" or "aromatic moiety" as used herein refers to an aromatic ring system, which may further include one or more non-carbon atoms. These are typically 5-6 membered isolated rings, or 8-10 membered bicyclic groups, and can be substituted. Thus, contemplated aryl groups include (*e.g.*, phenyl, naphthyl, etc.) and pyridyl. Further contemplated aryl groups may be fused (*i.e.*, covalently bound with 2 atoms on the first aromatic ring) with one or two 5- or 6-membered aryl or heterocyclic group, and are thus termed "fused aryl" or "fused aromatic".

[0031] Aromatic groups containing one or more heteroatoms (typically N, O or S) as ring members can be referred to as heteroaryl or heteroaromatic groups. Typical heteroaromatic groups include monocyclic C5-C6 aromatic groups such as pyridyl, pyrimidyl, pyrazinyl, thienyl, furanyl, pyrrolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, and imidazolyl and the fused bicyclic moieties formed by fusing one of these monocyclic groups with a phenyl ring or with any of the heteroaromatic monocyclic groups to form a C8-C10 bicyclic group such as indolyl, benzimidazolyl, indazolyl, benzotriazolyl, isoquinolyl, quinolyl, benzothiazolyl, benzofuranyl, pyrazolopyridyl, pyrazolopyrimidyl, quinazolinyl, quinoxalinyl, cinnolinyl, and the like. Any monocyclic or fused ring bicyclic system which has the characteristics of aromaticity in terms of electron distribution throughout the ring system is included in this definition. It also includes bicyclic groups where at least the ring which is directly attached to the remainder of the molecule has the characteristics of aromaticity. Typically, the ring systems contain 5-12 ring member atoms.

[0032] As also used herein, the terms "heterocycle", "cycloheteroalkyl", and "heterocyclic moieties" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, wherein the ring includes at least one atom other than a carbon atom as a ring member. Particularly contemplated heterocyclic rings include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*,

imidazole, pyrrole, triazole, dihydropyrimidine, indole, pyridine, thiazole, tetrazole etc.). Typically these rings contain 0-1 oxygen or sulfur atoms, at least one and typically 2-3 carbon atoms, and up to four nitrogen atoms as ring members. Further contemplated heterocycles may be fused (*i.e.,* covalently bound with two atoms on the first heterocyclic ring) to one or two carbocyclic rings or heterocycles, and are thus termed "fused heterocycle" or "fused heterocyclic ring" or "fused heterocyclic moieties" as used herein. Where the ring is aromatic, these can be referred to herein as 'heteroaryl' or heteroaromatic groups.

[0033] Heterocyclic groups that are not aromatic can be substituted with groups suitable for alkyl group substituents, as set forth above.

[0034] Aryl and heteroaryl groups can be substituted where permitted. Suitable substituents include, but are not limited to, halo, $-OR^a$, $-NR^a_2$, $-SR^a$, $-SO_2R^a$, $-SO_2NR^a_2$, $-NR^aSO_2R^a$, $-NR^aCONR^a_2$, $-NR^aCOOR^a$, $-NR^aCOR^a$, -CN, $-COOR^a$, $-CONR^a_2$, $-OOCR^a$, $-COR^a$, and $-NO_2$, wherein each R^a is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C3-C8 heterocyclyl, C4-C10 heterocyclylalkyl, C1-C8 acyl, C2-C8 heteroacyl, C2-C8 alkenyl, C2-C8 heteroalkenyl, C2-C8 alkynyl, C2-C8 heteroalkynyl, C6-C10 aryl, or C5-C10 heteroaryl, and each R^a is optionally substituted with halo, =O, =N-CN, $=N-OR^b$, $=NR^b$, OR^b, NR^b_2, SR^b, SO_2R^b, $SO_2NR^b_2$, $NR^bSO_2R^b$, $NR^bCONR^b_2$, NR^bCOOR^b, NR^bCOR^b, CN, $COOR^b$, $CONR^b_2$, $OOCR^b$, COR^b, and NO_2, wherein each R^b is independently H, C1-C8 alkyl, C2-C8 heteroalkyl, C3-C8 heterocyclyl, C4-C10 heterocyclylalkyl, C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl. Alkyl, alkenyl and alkynyl groups can also be substituted by C1-C8 acyl, C2-C8 heteroacyl, C6-C10 aryl or C5-C10 heteroaryl, each of which can be substituted by the substituents that are appropriate for the particular group. Where a substituent group contains two R^a or R^b groups on the same or adjacent atoms (*e.g.*, $-NR^b2$, or $-NR^b-C(O)\ R^b$), the two R^a or R^b groups can optionally be taken together with the atoms in the substituent group to which are attached to form a ring having 5-8 ring members, which can be substituted as allowed for the R^a or R^b itself, and can contain an additional heteroatom (N, O or S) as a ring member.

[0035] As also used herein, the terms "imidazopyridine" or "imidazopyrimidine" or "thiazopyridine" or "thiazopyrimidine" herein refer to any compound in which the two designated heterocyclic rings are fused by any two adjacent atoms on the two heterocyclic rings.

[0036] The term "alkoxy" as used herein refers to a hydrocarbon group connected through an oxygen atom, *e.g.*, -O-Hc, wherein the hydrocarbon portion Hc may have any number of

carbon atoms, typically 1-10 carbon atoms, may further include a double or triple bond and may include one or two oxygen, sulfur or nitrogen atoms in the alkyl chains, and can be substituted with aryl, heteroaryl, cycloalkyl, and/or heterocyclyl groups. For example, suitable alkoxy groups include methoxy, ethoxy, propyloxy, isopropoxy, methoxyethoxy, benzyloxy, allyloxy, and the like. Similarly, the term "alkylthio" refers to alkylsulfides of the general formula –S-Hc, wherein the hydrocarbon portion Hc is as described for alkoxy groups. For example, contemplated alkylthio groups include methylthio, ethylthio, isopropylthio, methoxyethylthio, benzylthio, allylthio, and the like.

[0037] The term 'amino' as used herein refers to the group $–NH_2$. The term "alkylamino" refers to amino groups where one or both hydrogen atoms are replaced by a hydrocarbon group Hc as described above, wherein the amino nitrogen "N" can be substituted by one or two Hc groups as set forth for alkoxy groups described above. Exemplary alkylamino groups include methylamino, dimethylamino, ethylamino, diethylamino, etc. Also, the term "substituted amino" refers to amino groups where one or both hydrogen atoms are replaced by a hydrocarbon group Hc as described above, wherein the amino nitrogen "N" can be substituted by one or two Hc groups as set forth for alkoxy groups described above.

[0038] The term 'acyl' as used herein refers to a group of the formula –C(=O)-D, where D represents an alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, or heterocycle as described above. Typical examples are groups wherein D is a C1-C10 alkyl, C2-C10 alkenyl or alkynyl, or phenyl, each of which is optionally substituted. In some embodiments, D can be H, Me, Et, isopropyl, propyl, butyl, C1-C4 alkyl substituted with –OH, -OMe, or NH_2, phenyl, halophenyl, alkylphenyl, and the like.

[0039] The term "aryloxy" as used herein refers to an aryl group connecting to an oxygen atom, wherein the aryl group may be further substituted. For example suitable aryloxy groups include phenyloxy, etc. Similarly, the term "arylthio" as used herein refers to an aryl group connecting to a sulfur atom, wherein the aryl group may be further substituted. For example suitable arylthio groups include phenylthio, etc.

[0040] The hydrocarbon portion of each alkoxy, alkylthio, alkylamino, and aryloxy, etc. can be substituted as appropriate for the relevant hydrocarbon moiety.

[0041] The term "halogen" as used herein refers to fluorine, chlorine, bromine and iodine. Where present as a substituent group, halogen or halo typically refers to F or Cl or Br, more typically F or Cl.

[0042] The term "haloalkyl" refers to an alkyl group as described above, wherein one or more hydrogen atoms on the alkyl group have been substituted with a halo group. Examples of such groups include, without limitation, fluoroalkyl groups, such as fluoroethyl, trifluoromethyl, difluoromethyl, trifluoroethyl and the like.

[0043] The term "haloalkoxy" refers to the group alkyl-O- wherein one or more hydrogen atoms on the alkyl group have been substituted with a halo group and include, by way of examples, groups such as trifluoromethoxy, and the like.

[0044] The term "sulfonyl" refers to the group SO_2-alkyl, SO_2-substituted alkyl, SO_2-alkenyl, SO_2-substituted alkenyl, SO_2-cycloalkyl, SO_2-substituted cycloalkyl, SO_2-cycloalkenyl, SO_2-substituted cycloalkenyl, SO_2-aryl, SO_2-substituted aryl, SO_2-heteroaryl, SO_2-substituted heteroaryl, SO_2-heterocyclic, and SO_2-substituted heterocyclic, wherein each alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein. Sulfonyl includes, by way of example, methyl-SO_2-, phenyl-SO_2-, and 4-methylphenyl-SO_2-.

[0045] The term "sulfonylamino" refers to the group $-NR^{21}SO_2R^{22}$, wherein R^{21} and R^{22} independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{21} and R^{22} are optionally joined together with the atoms bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein

[0046] The term "aminosulfonyl" refers to the group $-SO_2NR^{21}R^{22}$, wherein R^{21} and R^{22} independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl,

heterocyclic, substituted heterocyclic and where R^{21} and R^{22} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group and alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0047] The term "acylamino" refers to the groups -$NR^{20}C(O)$alkyl, -$NR^{20}C(O)$substituted alkyl, -$NR^{20}C(O)$cycloalkyl, -$NR^{20}C(O)$substituted cycloalkyl, -$NR^{20}C(O)$cycloalkenyl, -$NR^{20}C(O)$substituted cycloalkenyl, -$NR^{20}C(O)$alkenyl, -$NR^{20}C(O)$substituted alkenyl, -$NR^{20}C(O)$alkynyl, -$NR^{20}C(O)$substituted alkynyl, -$NR^{20}C(O)$aryl, -$NR^{20}C(O)$substituted aryl, -$NR^{20}C(O)$heteroaryl, -$NR^{20}C(O)$substituted heteroaryl, -$NR^{20}C(O)$heterocyclic, and -NR20C(O)substituted heterocyclic, wherein R^{20} is hydrogen or alkyl and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic are as defined herein.

[0048] The term "alkoxycarbonylamino" refers to the group -NRC(O)OR where each R is independently hydrogen, alkyl, substituted alkyl, aryl, heteroaryl, or heterocyclyl wherein alkyl, substituted alkyl, aryl, heteroaryl, and heterocyclyl are as defined herein.

[0049] The term "aminocarbonylamino" refers to the group -$NR^{20}C(O)NR^{21}R^{22}$, wherein R^{20} is hydrogen or alkyl and R^{21} and R^{22} independently are selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic and where R^{21} and R^{22} are optionally joined together with the nitrogen bound thereto to form a heterocyclic or substituted heterocyclic group, and wherein alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic and substituted heterocyclic are as defined herein.

[0050] It should further be recognized that all of the above-defined groups may further be substituted with one or more substituents, which may in turn be substituted with hydroxy, amino, cyano, C1-C4 alkyl, halo, or C1-C4 haloalkyl. For example, a hydrogen atom in an alkyl or aryl can be replaced by an amino, halo or C1-4 haloalkyl or alkyl group.

[0051] The term "substituted" as used herein refers to a replacement of a hydrogen atom of the unsubstituted group with a functional group, and particularly contemplated functional groups include nucleophilic groups (*e.g.*, $-NH_2$, -OH, -SH, -CN, etc.), electrophilic groups (*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, heterocycle, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (*e.g.*, $-NH_3^+$), and halogens (*e.g.*, -F, -Cl), NHCOR, $NHCONH_2$, OCH_2COOH, OCH_2CONH_2, OCH_2CONHR, $NHCH_2COOH$, $NHCH_2CONH_2$, $NHSO_2R$, OCH_2-heterocycles, PO_3H, SO_3H, amino acids, and all chemically reasonable combinations thereof. Moreover, the term "substituted" also includes multiple degrees of substitution, and where multiple substituents are disclosed or claimed, the substituted compound can be independently substituted by one or more of the disclosed or claimed substituent moieties.

[0052] In addition to the disclosure herein, in a certain embodiment, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0053] It is understood that in all substituted groups defined above, compounds arrived at by defining substituents with further substituents to themselves (*e.g.*, substituted aryl having a substituted aryl group as a substituent which is itself substituted with a substituted aryl group, which is further substituted by a substituted aryl group, etc.) are not intended for inclusion herein. In such cases, the maximum number of such substitutions is three. For example, serial substitutions of substituted aryl groups specifically contemplated herein are limited to substituted aryl-(substituted aryl)-substituted aryl.

[0054] Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. For example, the substituent "arylalkyloxycarbonyl" refers to the group (aryl)-(alkyl)-O-C(O)-.

[0055] As to any of the groups disclosed herein which contain one or more substituents, it is understood, of course, that such groups do not contain any substitution or substitution patterns which are sterically impractical and/or synthetically non-feasible. In addition, the subject compounds include all stereochemical isomers arising from the substitution of these compounds.

[0056] The term "pharmaceutically acceptable salt" means a salt which is acceptable for administration to a patient, such as a mammal, such as human (salts with counterions having

acceptable mammalian safety for a given dosage regime). Such salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids. "Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts of a compound, which salts are derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, formate, tartrate, besylate, mesylate, acetate, maleate, oxalate, and the like.

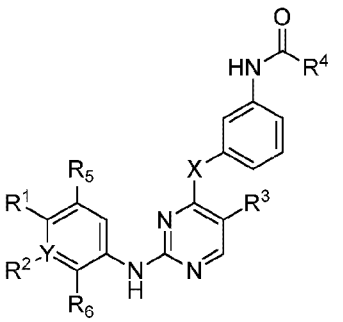
[0057] The term "salt thereof" means a compound formed when a proton of an acid is replaced by a cation, such as a metal cation or an organic cation and the like. Where applicable, the salt is a pharmaceutically acceptable salt, although this is not required for salts of intermediate compounds that are not intended for administration to a patient. By way of example, salts of the present compounds include those wherein the compound is protonated by an inorganic or organic acid to form a cation, with the conjugate base of the inorganic or organic acid as the anionic component of the salt.

[0058] The compounds and compositions described herein can be administered to a subject in need of treatment for a cell proliferation disorder such as cancer, particularly cancers selected from leukemia, lymphoma, lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, breast cancer, head and neck cancers, and pancreatic cancer. The subject is typically a mammal diagnosed as being in need of treatment for one or more of such proliferative disorders, and frequently the subject is a human. The methods comprise administering an effective amount of at least one compound of the invention; optionally the compound may be administered in combination with one or more additional therapeutic agents, particularly therapeutic agents known to be useful for treating the cancer or proliferative disorder afflicting the particular subject.

Exemplary Compounds

Formula I

[0059] In one aspect, the present disclosure provides for a compound of Formula (I):



(I)

wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo;

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and

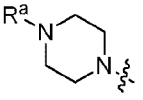
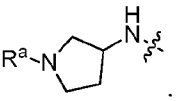
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,

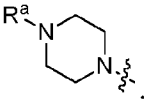
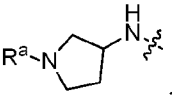
Y is CH optionally substituted with halo, or N,

wherein at least one of R^2, R^3, R^5 and R^6 is not H;
or a pharmaceutically acceptable salt thereof.

[0060] In some embodiments, R^1 is H, and R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring.

[0061] In some embodiments, R^1 is NR^cR^d and R^c is methyl. In other embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be a C_3 cyclic ring. R^d can be C_2 alkyl substituted with OZ, and Z is H or C_{1-4} alkyl, *e.g.*, methyl.

[0062] In some embodiments, R^1 is 3-7 member cyclic ring substituted with R^a. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, R^1 can be  or  .

[0063] In some embodiments, R^1 is  . R^a can be C_{1-4} alkyl optionally substituted with halo or C_{1-4} alkoxy. For example, R^a can be C_{1-4} alkyl substituted with fluoro or C_{1-8} alkyl substituted with fluoro. In other embodiments, R^1 is  . R^a can be C_{1-4} alkyl optionally substituted with halo or C_{1-4} alkoxy. For example, R^a can be C_{1-4} alkyl substituted with fluoro or C_{1-8} alkyl substituted with fluoro.

[0064] In some embodiments, R^2 can be H. In other embodiments, R^2 can be halo, *e.g.*, fluoro. In still other embodiments, R^2 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0065] In some embodiments, R^5 can be H. In other embodiments, R^5 can be halo, *e.g.*, fluoro. In still other embodiments, R^5 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0066] In some embodiments, R^6 can be H. In other embodiments, R^6 can be halo, *e.g.*, fluoro. In still other embodiments, R^6 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0067] In some embodiments, R^1 and R^5 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In other embodiments, R^1 and R^2 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In still other embodiments, R^2 and R^6 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be a 5 member cyclic ring. The 5 member cyclic ring can be heterocyclic ring, *e.g.*, a 5 member heterocyclic ring that comprises a N atom. The C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl. For example, Z can be methyl.

[0068] In some embodiments, R^3 can be H. In other embodiments, R^3 can be halo, *e.g.*, fluoro. In still other embodiments, R^3 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

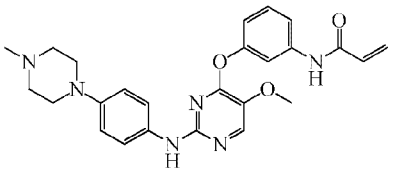
[0069] In some embodiments, R^2, R^5, or R^6 is H or halo and R^3 is halo, C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy.

[0070] In some embodiments, R^4 can be unsubstituted C_2 alkenyl. In other embodiments, R^4 can be C_2 alkenyl substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$.

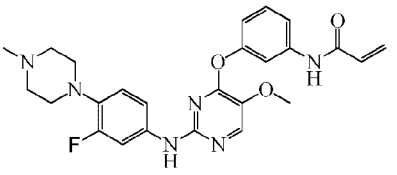
[0071] In some embodiments, X can be O. In other embodiments, X can be C_{1-4} alkyl optionally substituted with halo. For example, X can be unsubstituted C_{1-4} alkyl, *e.g.*, CH_2. In another example, X can be C_{1-4} alkyl substituted with halo, *e.g.*, CF_2. In still other embodiments, X can be NR^b, and R^b can be H, or C_{1-8} alkyl optionally substituted with halo. For example, R^b can be H. In another example, R^b can be C_{1-8} alkyl. In still another example, R^b is C_{1-4} alkyl, *e.g.*, C_1, C_2, C_3, or C_4 alkyl. The C_{1-4} alkyl or C_{1-8} alkyl can be substituted with halo, *e.g.*, fluoro.

[0072] In some embodiments, Y can be CH. In other embodiments, Y can be CF or N.

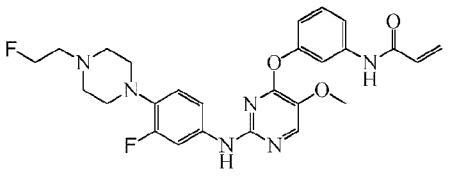
[0073] In some embodiments, the present disclosure provides for a compound selected from the group consisting of compound I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25 and I-41 having the Formula below.



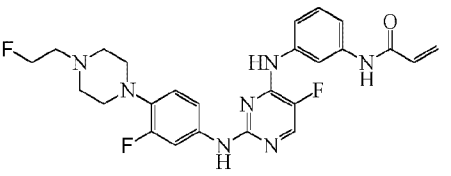
I-1



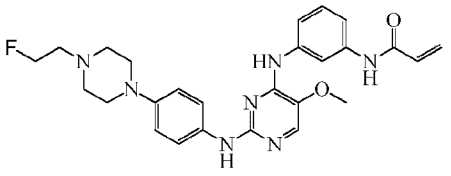
I-2



I-3



I-4



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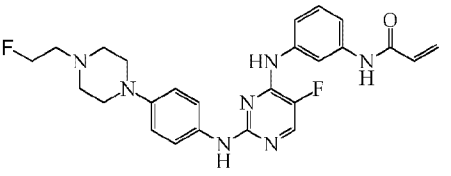
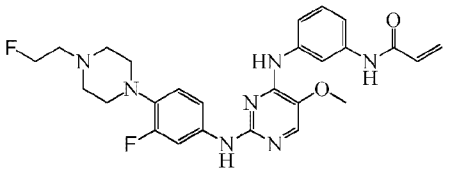
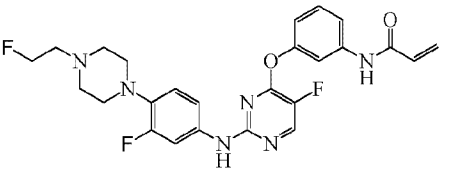


I-6



I-7



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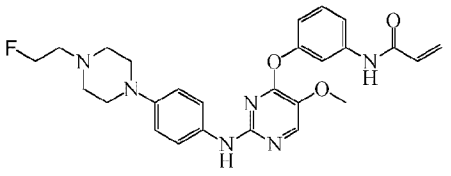
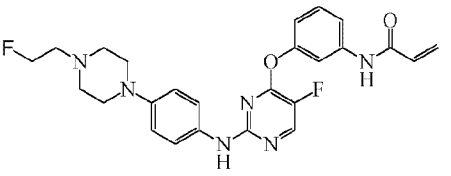
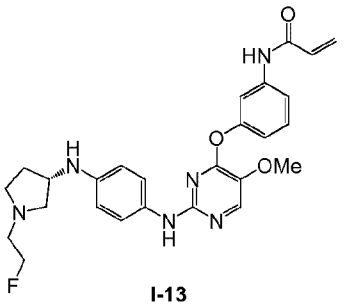


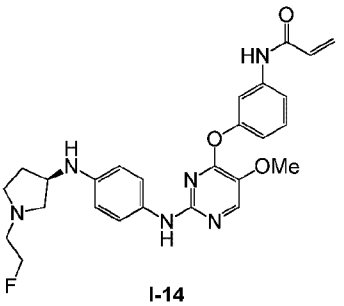
I-9



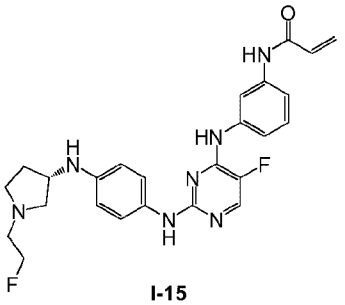
I-12



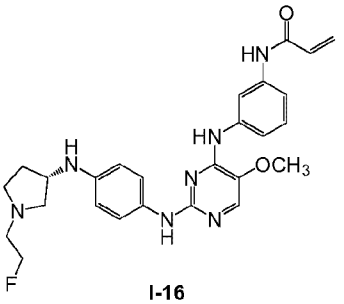
I-13



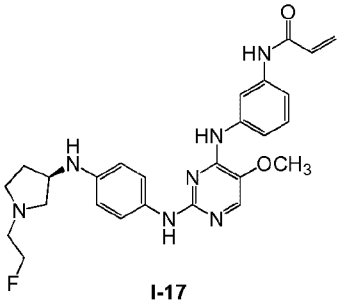
I-14



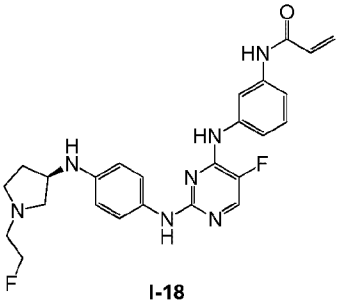
I-15



I-16



I-17



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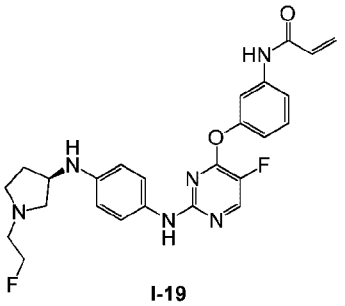
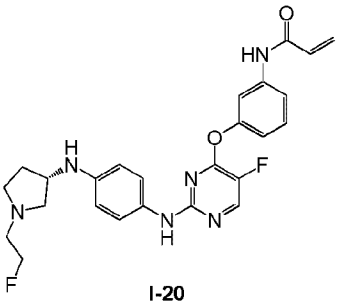
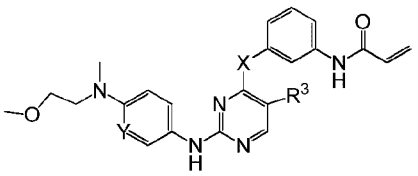


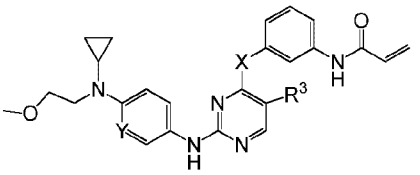
I-19



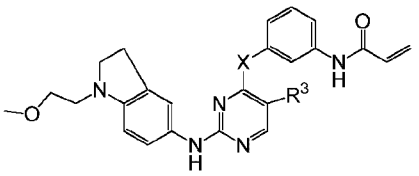
I-20



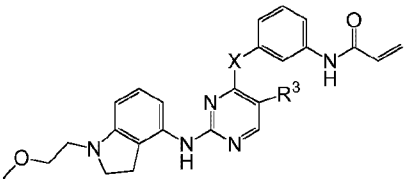
I-21 (X=O, NH, CH2, CF2; Y=CH, CF, N; R^3=OCH3, F)



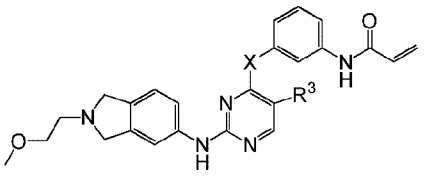
I-22 (X=O, NH, CH2, CF2; Y=CH, CF, N; R^3=OCH3, F)



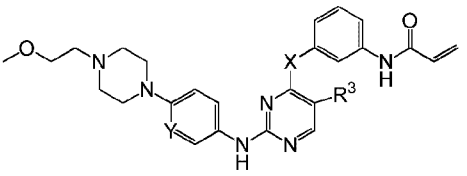
I-23 (X=O, NH, CH2, CF2; R^3=OCH3, F)



I-24 (X=O, NH, CH2, CF2; R^3=OCH3, F)



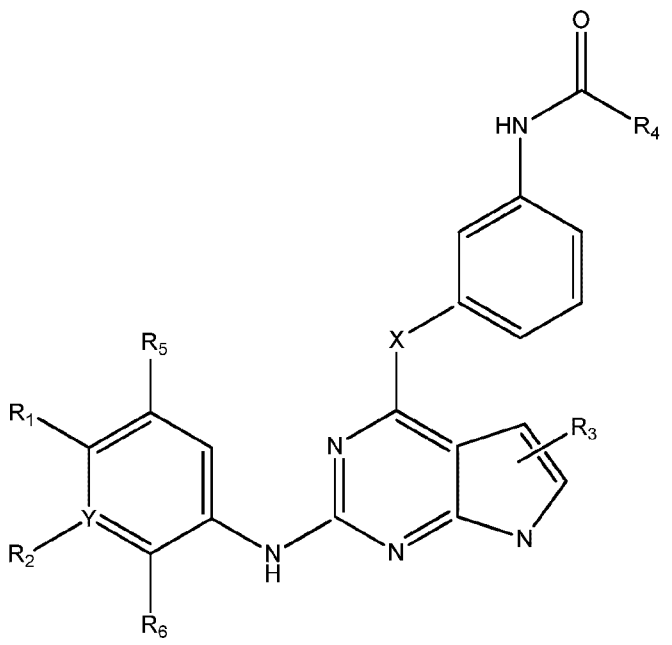
I-25 (X=O, NH, CH2, CF2; R^3=OCH3, F)



I-41 (X=O, NH, CH2, CF2; Y=CH, CF, N; R^3=OCH3, F)

Formula II

[0074] In another aspect, the present disclosure provides for a compound of Formula (II):



(II)

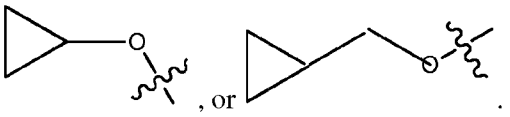
wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

NR^eR^f wherein R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo; or

OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,



.

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,

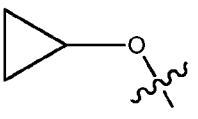
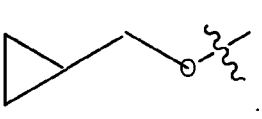
Y is CH optionally substituted with halo, or N,

or a pharmaceutically acceptable salt thereof.

[0075] In some embodiments, R^1 can be H, and R^2 and R^6 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring.

[0076] In some embodiments, R^1 can be NR^cR^d and R^c can be C_{1-4} alkyl, *e.g.*, methyl. In other embodiments, R^1 can be NR^cR^d and R^c can be 3-7 member cyclic ring. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be C_3 cyclic ring. R^d can be C_2 alkyl substituted with OZ, and Z can be C_{1-4} alkyl, *e.g.*, methyl.

[0077] In some embodiments, R^1 can be NR^eR^f, R^e can be C_{1-4} alkyl, and R^f can be 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be 5 member cyclic ring. In another example, the 5 member cyclic ring can be heterocyclic ring, *e.g.*, the 5 member heterocyclic ring that comprises a N atom. The 3-7 member cyclic ring can be substituted with FCH_2CH_2-. The C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl.

[0078] In some embodiments, R^1 is OR^g and R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,  , or  . The C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl, *e.g.*, C_2 alkyl.

[0079] In some embodiments, R^2 can be H. In other embodiments, R^2 can be halo, *e.g.*, fluoro. In still other embodiments, R^2 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0080] In some embodiments, R^5 can be H. In other embodiments, R^5 can be halo, *e.g.*, fluoro. In still other embodiments, R^5 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0081] In some embodiments, R^6 can be H. In other embodiments, R^6 can be halo, *e.g.*, fluoro. In still other embodiments, R^6 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0082] In some embodiments, R^1 and R^5 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In other embodiments, R^1 and R^2 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In still other embodiments, R^2 and R^6 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be a 5 member cyclic ring. The 5 member cyclic ring can be heterocyclic ring, *e.g.*, a 5 member heterocyclic ring that comprises a N atom. The C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl. For example, Z can be methyl.

[0083] In some embodiments, R^3 can be H. In other embodiments, R^3 can be halo, *e.g.*, fluoro. In still other embodiments, R^3 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

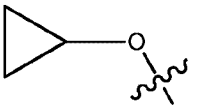
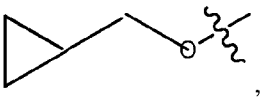
[0084] In some embodiments, R^2, R^5, or R^6 is H or halo and R^3 is halo, C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy.

[0085] In some embodiments, R^4 can be unsubstituted C_2 alkenyl. In other embodiments, R^4 can be C_2 alkenyl substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$.

[0086] In some embodiments, X can be O. In other embodiments, X can be C_{1-4} alkyl optionally substituted with halo. For example, X can be unsubstituted C_{1-4} alkyl, *e.g.*, CH_2. In another example, X can be C_{1-4} alkyl substituted with halo, *e.g.*, CF_2. In still other embodiments, X can be NR^b, and R^b can be H, or C_{1-8} alkyl optionally substituted with halo. For example, R^b

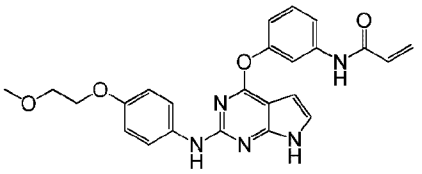
can be H. In another example, R^b can be C_{1-8} alkyl. In still another example, R^b is C_{1-4} alkyl, *e.g.*, C_1, C_2, C_3, or C_4 alkyl. The C_{1-4} alkyl or C_{1-8} alkyl can be substituted with halo, *e.g.*, fluoro.

[0087] In some embodiments, Y can be CH. In other embodiments, Y can be CF or N.

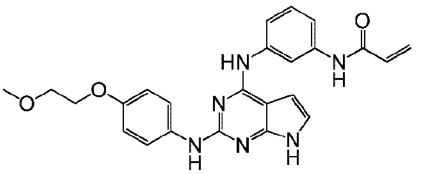
[0088] In some embodiments, R^1 is OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,  , or  , and R^2, R^3, R^5 and R^6 are H. In one example, R^g can be C_2 alkyl substituted with CH_3O-.

[0089] In some embodiments, at least one of R^1, R^2, R^3, R^5 and R^6 is not H. For example, one, two, three, four or five of R^1, R^2, R^3, R^5 and R^6 is or are not H.

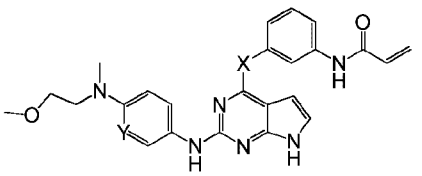
[0090] In some embodiments, the present disclosure provides for a compound selected from the group consisting of compound I-10, I-11, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, and I-40 having the Formula below.



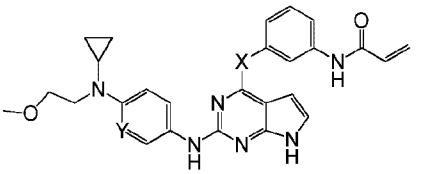
I-10



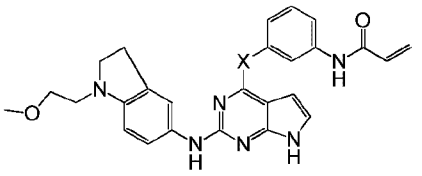
I-11



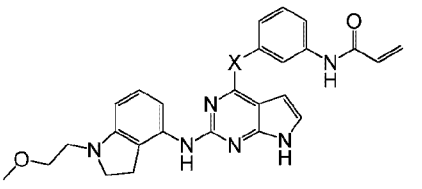
I-26 (X=O, NH, CH2, CF2; Y=CH, CF, N)



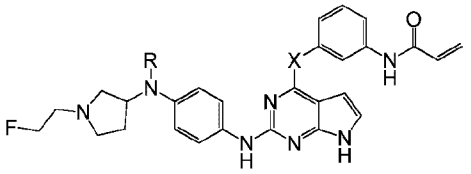
I-27 (X=O, NH, CH2, CF2; Y=CH, CF, N)



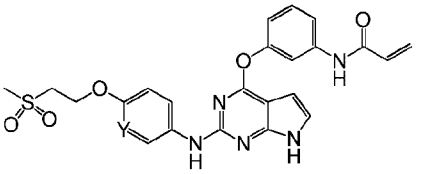
I-28 (X=O, NH, CH2, CF2)



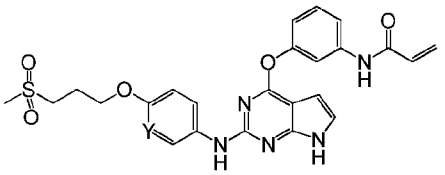
I-29 (X=O, NH, CH2, CF2)



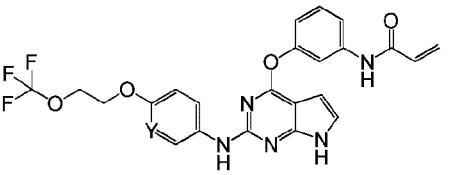
I-30 (X=O, NH, CH2, CF2; R=H, CH3)



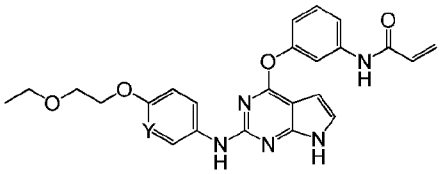
I-31 (Y = CH, CF, N)



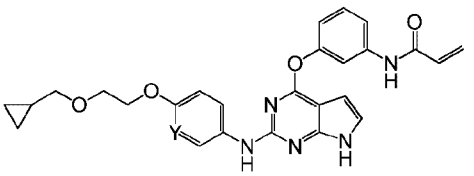
I-32 (Y = CH, CF, N)



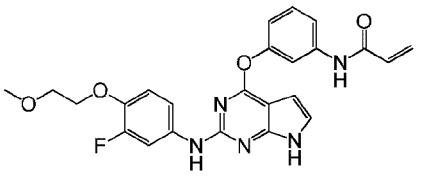
I-33 (Y = CH, CF, N)



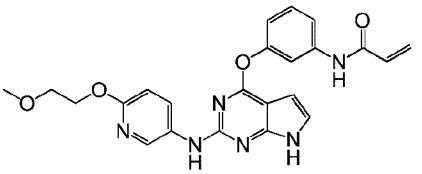
I-34 (Y = CH, CF, N)



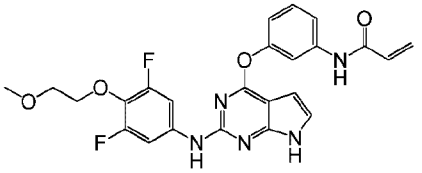
I-35 (Y = CH, CF, N)



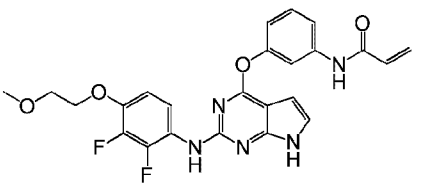
I-36



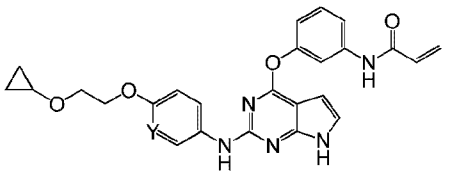
I-37



I-38



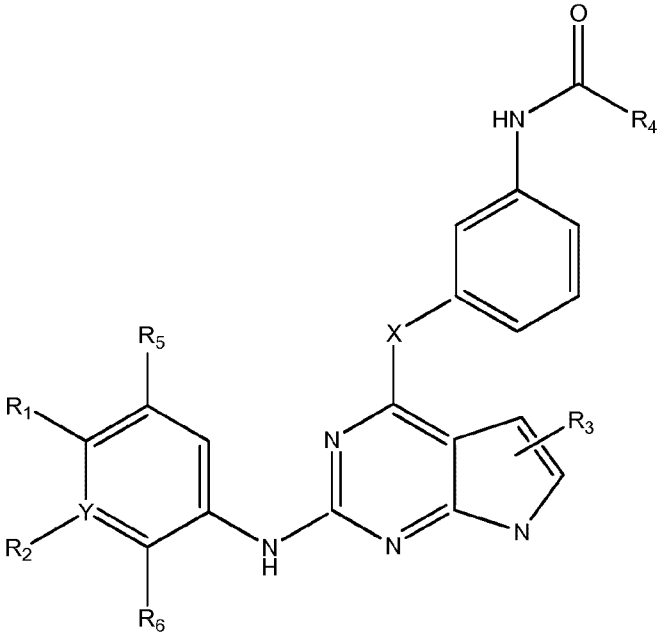
I-39



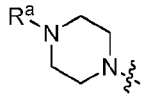
I-40 (Y = CH, CF, N)

Formula III

[0091] In another aspect, the present disclosure provides for a compound of Formula (III):



wherein

R^1 is  wherein R^a is CO-C_{1-4} alkyl-CONH-(C_{1-4} alkyl-O)$_m$-C_{1-4} alkyl-NH-(Detectable Label), m being an integer 1-4;

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;
R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or
R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or
R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or
R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl; or
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,
Y is CH optionally substituted with halo, or N,
or a pharmaceutically acceptable salt thereof.

[0092] In some embodiments, in R^a C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl.

[0093] In some embodiments, m can be 1, 2, 3 or 4.

[0094] Any suitable Detectable Label can be used. In some embodiments, the Detectable Label is biotin.

[0095] In some embodiments, R^2 can be H. In other embodiments, R^2 can be halo, *e.g.*, fluoro. In still other embodiments, R^2 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0096] In some embodiments, R^5 can be H. In other embodiments, R^5 can be halo, *e.g.*, fluoro. In still other embodiments, R^5 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0097] In some embodiments, R^6 can be H. In other embodiments, R^6 can be halo, *e.g.*, fluoro. In still other embodiments, R^6 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

[0098] In some embodiments, R^1 and R^5 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In other embodiments, R^1 and R^2 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. In still other embodiments, R^2 and R^6 can be part of 3-7 member cyclic ring, optionally substituted with C_{1-4}

alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl, *e.g.*, methyl. The 3-7 member cyclic ring can be a 3, 4, 5, 6, or 7 member cyclic ring. It can be carbon cyclic ring or hetero cyclic ring. For example, the 3-7 member cyclic ring can be a 5 member cyclic ring. The 5 member cyclic ring can be heterocyclic ring, *e.g.*, a 5 member heterocyclic ring that comprises a N atom. The C_{1-4} alkyl can be C_1, C_2, C_3, or C_4 alkyl. For example, Z can be methyl.

[0099] In some embodiments, R^3 can be H. In other embodiments, R^3 can be halo, *e.g.*, fluoro. In still other embodiments, R^3 can be C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy, *e.g.*, methoxy.

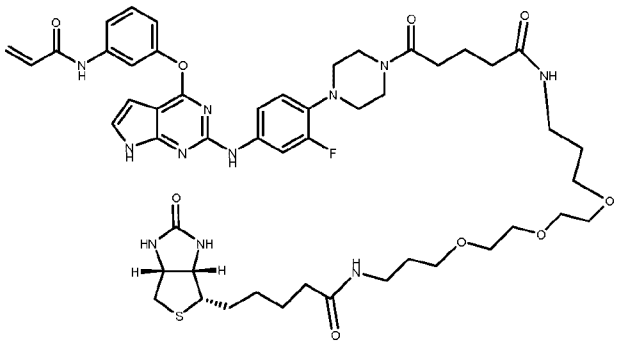
[00100] In some embodiments, R^2, R^5, or R^6 is H or halo and R^3 is halo, C_{1-4} alkyl, *e.g.*, methyl, or C_{1-4} alkoxy.

[00101] In some embodiments, R^4 can be unsubstituted C_2 alkenyl. In other embodiments, R^4 can be C_2 alkenyl substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$.

[00102] In some embodiments, X can be O. In other embodiments, X can be C_{1-4} alkyl optionally substituted with halo. For example, X can be unsubstituted C_{1-4} alkyl, *e.g.*, CH_2. In another example, X can be C_{1-4} alkyl substituted with halo, *e.g.*, CF_2. In still other embodiments, X can be NR^b, and R^b can be H, or C_{1-8} alkyl optionally substituted with halo. For example, R^b can be H. In another example, R^b can be C_{1-8} alkyl. In still another example, R^b is C_{1-4} alkyl, *e.g.*, C_1, C_2, C_3, or C_4 alkyl. The C_{1-4} alkyl or C_{1-8} alkyl can be substituted with halo, *e.g.*, fluoro.

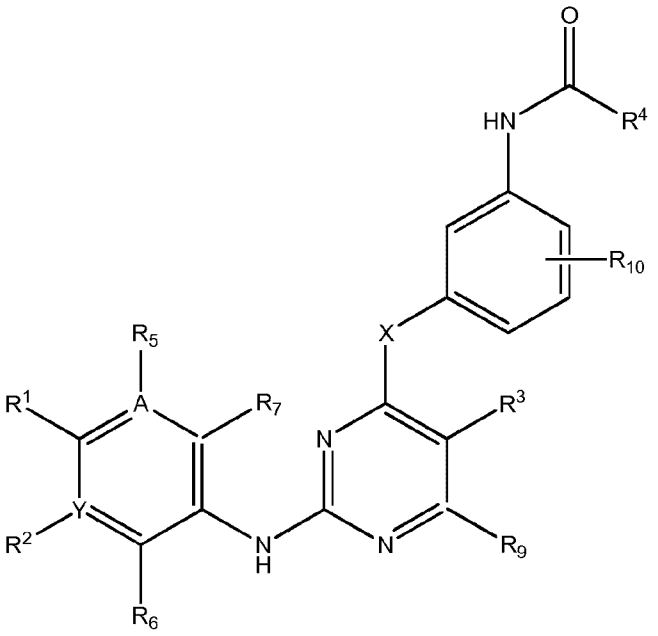
[00103] In some embodiments, Y can be CH. In other embodiments, Y can be CF or N.

[00104] In some embodiments, the present disclosure provides for a compound I-42 having the Formula below.



Formula Ia

[00105] In still another aspect, the present disclosure provides for a compound of Formula (Ia):



(Ia)

wherein

R^1 is H, or

NR^cR^d wherein

R^c is H, C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring, said C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, and

R^d is H, C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring, said C_{1-4} alkyl, C_{1-4} alkenyl or 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl; or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4; or

$O(CH_2)_mSO_2(CH_2)_nH$, wherein m is 1-4 and n is 1-4;

R^2 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^3 is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^5 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^6 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy; or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^7 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^9 is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^{10} is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl; or

R^1 and R^5 are part of 3-7 member cyclic ring, said 3-7 member cyclic being optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, or said 3-7 member cyclic being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl, said C_{1-4} alkyl further optionally substituted with halo, OZ, or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl, or one or more members of said 3-7 member cyclic ring is optionally part of a carbonyl group or a sulfonyl group; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$;
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo;
Y is C, CH optionally substituted with halo, or N;
A is C, CH optionally substituted with halo or N; and
wherein at least one of R^2, R^3, R^5 and R^6 is not H;
or a pharmaceutically acceptable salt thereof.

[00106] In some embodiments, R^1 is H, and R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00107] In some embodiments, R^1 is NR^cR^d and R^c is H.

[00108] In some embodiments, R^1 is NR^cR^d and R^c is C_{1-4} alkyl, *e.g.*, methyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

[00109] In some embodiments, R^1 is NR^cR^d and R^c is C_{1-4} alkenyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

[00110] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

[00111] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

[00112] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4.

[00113] In some embodiments, the 3-7 member cyclic ring is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, *e.g.*, q is 1.

[00114] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4. The 3-7 member cyclic ring can be a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with C_{1-4} alkyl that is further substituted with

$SO_2(CH_2)_qH$, wherein q is 1-4. The H linked to the N atom is substituted with C_2 alkyl that is further substituted with SO_2CH_3.

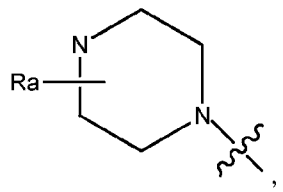
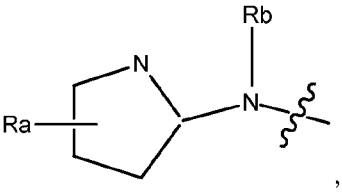
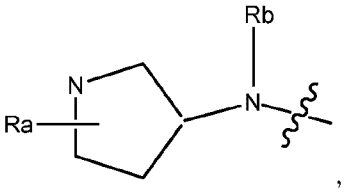
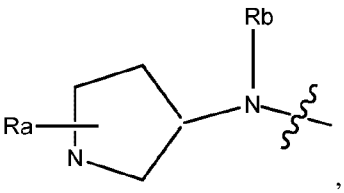
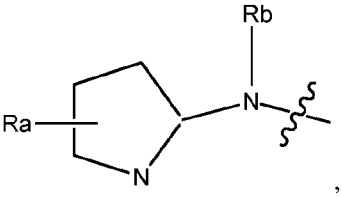
[00115] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl. R^1 can be NR^cR^d and R^c is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with R_8CO, wherein R_8 is C_{1-4} alkyl. The H linked to the N atom can be substituted with CH_3CO.

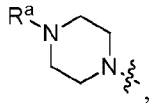
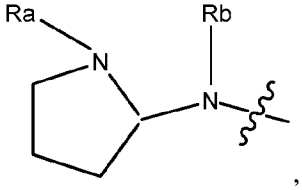
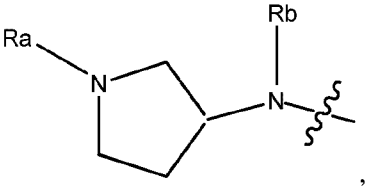
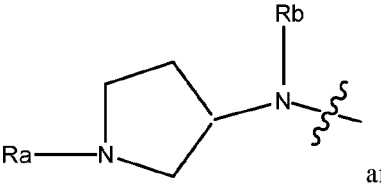
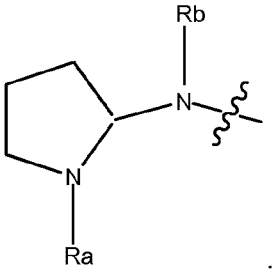
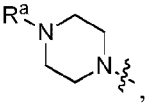
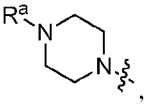
[00116] In some embodiments, R^d is H. In other embodiments, R^d is C_{1-4} alkyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl. In still other embodiments, R^d is C_{1-4} alkenyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl. In yet other embodiments, R^d is 3-7 member cyclic ring, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

[00117] In some embodiments, R^c is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with C_{1-4} alkyl that is further substituted with OZ, wherein Z is independently C_{1-4} alkyl, and R^d is 3-7 member cyclic ring, *e.g.*, C_3 cyclic ring.

[00118] In some embodiments, R^1 is 3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4. The 3-7 member cyclic ring can comprise a N atom. The H linked to the N atom can be substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4.

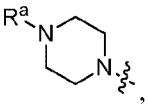
[00119] R^1 can be any suitable 3-7 member cyclic ring. In some embodiments, R^1 is selected from the group consisting of

[00120]  ,  ,  ,  , and  , R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4, and R^b is H or C_{1-8} alkyl

optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4. In other embodiments, R^1 is selected from the group consisting of  ,  ,  ,  , and  . In still other embodiments, R^1 is  , and R^a is C_2 alkyl further substituted with methoxy. In yet other embodiments, R^1 is  , and R^a is C_2 alkyl further substituted with SO_2CH_3.

[00121] In some embodiments, R^1 is $O(CH_2)_mSO_2(CH_2)_nH$, wherein m is 1-4 and n is 1-4. For example, R^1 can be $O(CH_2)_2SO_2CH_3$.

[00122] In some embodiments, R^2 is absent, H or halo. In other embodiments, R^2 is C_{1-4} alkyl or C_{1-4} alkoxy. In still other embodiments, R^2 is alkylamine ($NR_{11}R_{12}$), and R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00123] In some embodiments, R^3 is H. In other embodiments, R^3 is hydroxyl. In still other embodiments, R^3 is halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl. In yet other embodiments, R^1 is  , and R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4.

[00124] In some embodiments, R^5 is absent or H. In other embodiments, R^5 is halo. In still other embodiments, R^5 is C_{1-4} alkyl. In yet other embodiments, R^5 is C_{1-4} alkoxy. In yet other

embodiments, R^5 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00125] In some embodiments, R^6 is H. In other embodiments, R^6 is halo. In still other embodiments, R^6 is C_{1-4} alkyl. In yet other embodiments, R^6 is C_{1-4} alkoxy. In yet other embodiments, R^6 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00126] In some embodiments, R^7 is H. In other embodiments, R^7 is halo. In still other embodiments, R^7 is C_{1-4} alkyl. In yet other embodiments, R^7 is C_{1-4} alkoxy, *e.g.*, methoxy. In yet other embodiments, R^7 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00127] In some embodiments, R^9 is H. In other embodiments, R^9 is halo. In still other embodiments, R^9 is C_{1-4} alkyl. In yet other embodiments, R^9 is C_{1-4} alkoxy. In yet other embodiments, R^9 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00128] In some embodiments, R^{10} is H. In other embodiments, R^{10} is halo. In still other embodiments, R^{10} is C_{1-4} alkyl. In yet other embodiments, R^{10} is C_{1-4} alkoxy. In yet other embodiments, R^{10} is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00129] In some embodiments, R^1 and R^5 are part of 3-7 member cyclic ring, said 3-7 member cyclic being optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl. In other embodiments, R^1 and R^5 are part of 3-7 member cyclic ring, said 3-7 member cyclic being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl. For example, the 3-7 member cyclic ring is substituted with CH_3CO. In still other embodiments, R^1 and R^5 are part of 3-7 member cyclic ring, said 3-7 member cyclic being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4. For example, the 3-7 member cyclic is substituted with SO_2CH_3.

[00130] In some embodiments, R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl, said C_{1-4} alkyl further optionally substituted with halo, OZ, or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl. In other embodiments, R^1 and R^2 are part of 3-7 member cyclic ring, and one or more members of said 3-7 member cyclic

ring is optionally part of a carbonyl group or a sulfonyl group. The carbonyl group can be an amide or an ester group.

[00131] In some embodiments, R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted optionally with OZ or $NR_{11}R_{12}$ wherein Z, R_{11} and R_{12} are independently H or C_{1-4} alkyl.

[00132] In some embodiments, R^4 is unsubstituted C_2 alkenyl. In other embodiments, R^4 is C_2 alkenyl substituted with C_{1-4} alkyl. For example, R^4 can be C_2 alkenyl substituted with -CH_2OCH_3, or -$CH_2N(CH_3)_2$.

[00133] In some embodiments, X is O. In other embodiments, X is unsubstituted C_{1-4} alkyl, *e.g.*, CH_2, or C_{1-4} alkyl substituted with halo, *e.g.*, CF_2. In still other embodiments, X is NR^b, and R^b is H, or C_{1-8} alkyl optionally substituted with halo.

[00134] In some embodiments, Y is C. In other embodiments, Y is CH or CH substituted with halo, *e.g.*, CF_2. In still other embodiments, Y is N.

[00135] In some embodiments, A is C. In other embodiments, A is CH or CH substituted with halo, *e.g.*, CF_2. In still other embodiments, A is N.

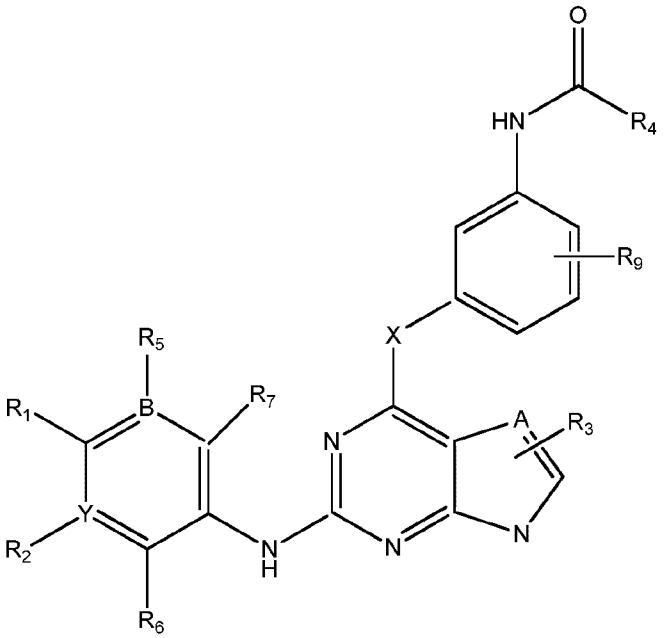
[00136] In some embodiments, the 3-7 member cyclic ring is a 3 member cyclic ring. In other embodiments, the 3-7 member cyclic ring is a 4 member cyclic ring. In still other embodiments, the 3-7 member cyclic ring is a 5 member cyclic ring. In yet embodiments, the 3-7 member cyclic ring is a 6 member cyclic ring. In yet embodiments, the 3-7 member cyclic ring is a 7 member cyclic ring.

[00137] In some embodiments, the 3-7 member cyclic ring is hydrocarbon 3-7 member cyclic ring. In other embodiments, the 3-7 member cyclic ring is a heterocyclic ring. For example, the heterocyclic ring can comprise one or more N atom.

[00138] In some embodiments, the present disclosure provides for a compound selected from the group consisting of compound I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-41, I-23a, I-25a, I-28a, I-29a, I-30a, I-31a, I-32a, I-33a, I-34a, I-35a, I-38a, I-39a, I-42a, I-43a, I-44a, I-45a, I-50a, I-51a, I-52a, I-53a, I-54a, I-55a, I-56a, I-57a, I-58a, I-59a, I-60a, I-66a, I-70a, and I-72a.

Formula IIa

[00139] In still another aspect, the present disclosure provides for a compound of Formula (IIa):



(IIa)

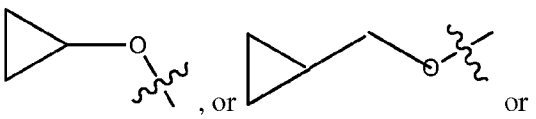
wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, said 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, or said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are H or C_{1-4} alkyl; or

NR^eR^f wherein R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo; or

OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,



, or

or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4, or said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl;

R^2 is absent, H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^3 is absent, H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^5 is absent, H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^7 is H, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^9 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy, or alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently are H or C_{1-4} alkyl,; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl;

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$;

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo;

Y is C, CH optionally substituted with halo, or N;

A is C, CH optionally substituted with halo, or N; and

B is C, CH optionally substituted with halo, or N,

or a pharmaceutically acceptable salt thereof.

[00140] In some embodiments, R^1 is H, and R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00141] In some embodiments, R^1 is NR^cR^d and R^c is H. In other embodiments, R^1 is NR^cR^d and R^c is C_{1-4} alkyl.

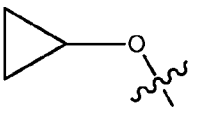
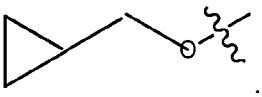
[00142] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring, said 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl. Said 3-7 member cyclic ring can be substituted with C_2 alkyl substituted with methoxy.

[00143] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring, said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl. Said 3-7 member cyclic ring can be substituted with CH_3CO.

[00144] In some embodiments, R^1 is NR^cR^d and R^c is 3-7 member cyclic ring, said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4. For example, said 3-7 member cyclic ring can be substituted with CH_3SO_2.

[00145] In some embodiments, R^d is H. In other embodiments, R^d is C_{1-4} alkyl, optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are H or C_{1-4} alkyl.

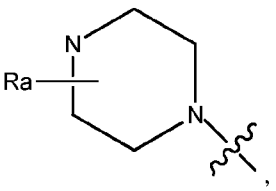
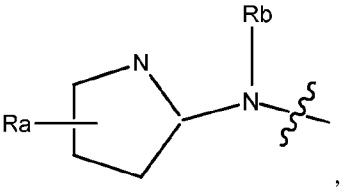
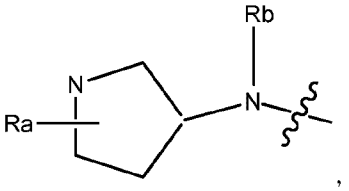
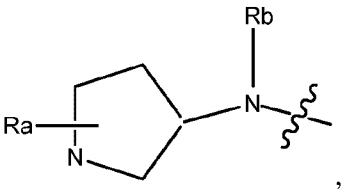
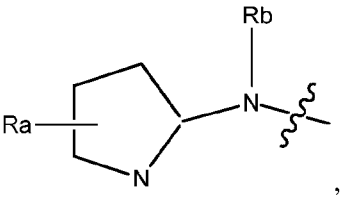
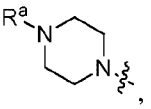
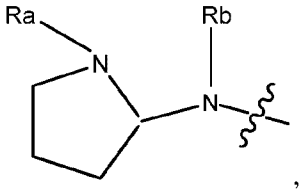
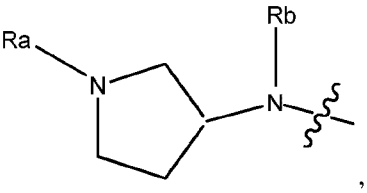
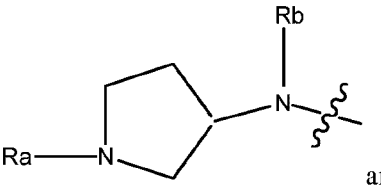
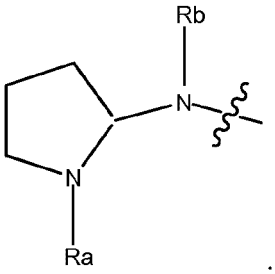
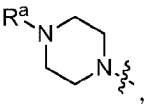
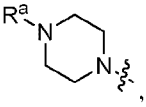
[00146] In some embodiments, R^1 is NR^eR^f and R^e is C_{1-4} alkyl. In other embodiments, R^1 is NR^eR^f and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo.

[00147] In some embodiments, R^1 is OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,  , or  .

[00148] In some embodiments, R^1 is 3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4. For example, R^a can be C_2 alkyl substituted with methoxy. In another example, R^a is $CH_3SO_2CH_2CH_2$.

[00149] In some embodiments, R^1 is 3-7 member cyclic ring, said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl. For example, said 3-7 member cyclic ring can be substituted with CH_3CO.

[0001] R^1 can be any suitable 3-7 member cyclic ring. In some embodiments, R^1 is selected from the group consisting of

[00150]  ,  ,  ,  , and  , R^a is C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4, and R^b is H or C_{1-8} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4. In other embodiments, R^1 is selected from the group consisting of  ,  ,  ,  , and  . In still other embodiments, R^1 is  , and R^a is C_2 alkyl further substituted with methoxy. In yet other embodiments, R^1 is  , and R^a is C_2 alkyl further substituted with SO_2CH_3.

[00151] In some embodiments, R^2 is absent or H. In other embodiments, R^2 is halo. In still other embodiments, R^2 is C_{1-4} alkyl or C_{1-4} alkoxy. In yet embodiments, R^2 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00152] In some embodiments, R^3 is absent. In other embodiments, R^3 is H. In still other embodiments, R^3 is halo. In yet embodiments, R^3 is C_{1-4} alkyl. In yet embodiments, R^3 is C_{1-4} alkoxy. In yet embodiments, R^3 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00153] In some embodiments, R^5 is absent. In other embodiments, R^5 is H. In still other embodiments, R^5 is halo. In yet embodiments, R^5 is C_{1-4} alkyl. In yet embodiments, R^5 is C_{1-4} alkoxy. In yet embodiments, R^5 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00154] In some embodiments, R^6 is H. In other embodiments, R^6 is halo. In still other embodiments, R^6 is C_{1-4} alkyl. In yet embodiments, R^6 is C_{1-4} alkoxy. In yet embodiments, R^6 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00155] In some embodiments, R^7 is H. In other embodiments, R^7 is halo. In still other embodiments, R^7 is C_{1-4} alkyl. In yet embodiments, R^7 is C_{1-4} alkoxy. In yet embodiments, R^7 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00156] In some embodiments, R^9 is H. In other embodiments, R^9 is halo. In still other embodiments, R^9 is C_{1-4} alkyl. In yet embodiments, R^9 is C_{1-4} alkoxy. In yet embodiments, R^9 is alkylamine ($NR_{10}R_{11}$), wherein R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00157] In some embodiments, R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or $NR_{10}R_{11}$ wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00158] In some embodiments, R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently are H or C_{1-4} alkyl.

[00159] In some embodiments, R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl optionally substituted with OZ or R_{10} and R_{11} wherein Z, R_{10} and R_{11} are independently H or C_{1-4} alkyl.

[00160] In some embodiments, X is O. In other embodiments, X is unsubstituted C_{1-4} alkyl, *e.g.*, CH_2, or C_{1-4} alkyl substituted with halo, *e.g.*, CF_2. In still other embodiments, X is NR^b, and R^b is H, or C_{1-8} alkyl optionally substituted with halo.

[00161] In some embodiments, Y is C. In other embodiments, Y is CH or CH substituted with halo, *e.g.*, CF. In still other embodiments, Y is N.

[00162] In some embodiments, A is C. In other embodiments, A is CH or CH substituted with halo, *e.g.*, CF. In still other embodiments, A is N.

[00163] In some embodiments, B is C. In other embodiments, B is CH or CH substituted with halo, *e.g.*, CF. In still other embodiments, B is N.

[00164] In some embodiments, the 3-7 member cyclic ring is a 3 member cyclic ring. In other embodiments, the 3-7 member cyclic ring is a 4 member cyclic ring. In still other embodiments, the 3-7 member cyclic ring is a 5 member cyclic ring. In yet embodiments, the 3-7 member cyclic ring is a 6 member cyclic ring. In yet embodiments, the 3-7 member cyclic ring is a 7 member cyclic ring.

[00165] In some embodiments, the 3-7 member cyclic ring is hydrocarbon 3-7 member cyclic ring. In other embodiments, the 3-7 member cyclic ring is a heterocyclic ring. For example, the heterocyclic ring can comprise one or more N atom.

[00166] In some embodiments, the present disclosure provides for a compound selected from the group consisting of compound I-10, I-11, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-24a, I-26a, I-27a, I-36a, I-37a, I-40a, I-41a, I-46a, I-47a, I-48a, I-49a, I-61a, I-62a, I-63a, I-64a, I-65a, I-67a, I-68a, I-69a, and I-71a.

Pharmaceutical compositions, combinations, and other related uses

[00167] In still another aspect, the present disclosure provides for a pharmaceutical composition comprising a compound described above admixed with at least one pharmaceutically acceptable carrier or excipient.

[00168] The above described compounds can be used for any suitable purpose. For example, the present compounds can be used in therapy and/or testing.

[00169] In yet another aspect, the present disclosure provides for a method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, or lupus, which comprises

administering to a subject in need thereof an effective amount of a compound described above or a pharmaceutical composition described above.

[00170] In yet another aspect, the present disclosure provides for a use of a compound described above for the manufacture of a medicament.

[00171] In yet another aspect, the present disclosure provides for a combination for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject, which combination comprises an effective amount of a compound described above, or a pharmaceutically acceptable salt thereof, and an effective amount of a second prophylactic or therapeutic agent for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject.

[00172] In yet another aspect, the present disclosure provides for a method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject, which methods comprises administering to a subject in need thereof an effective amount of the combination described above.

[00173] In yet another aspect, the present disclosure provides for a method for inhibiting an activity of a Bruton's tyrosine kinase (Btk or BTK) or a Janus kinase (JAK) EGFR (including HER), Alk, PDGFR, BLK, BMX/ETK, FLT3(D835Y), ITK, TEC, TXK, and the respective pathways, in a cell or subject, which methods comprises administering to a cell or subject in need thereof an effective amount of a compound described above, or a pharmaceutical composition described above, or a combination described above.

[00174] The present methods can be used to inhibit an activity of any suitable Btk, BTK or JAK. In some embodiments, the present methods can be used to inhibit an activity of JAK1, JAK2 or JAK3.

[00175] The present methods can be used for any suitable purpose. In some embodiments, the present methods can be used to treat and/or prevent a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in the subject. The present methods can be used to treat and/or prevent any suitable proliferation disorder. Exemplary proliferation disorders

include sarcoma, epidermoid cancer, fibrosarcoma, cervical cancer, gastric carcinoma, skin cancer, leukemia, lymphoma, lung cancer, non- small cell lung cancer, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, breast cancer, liver cancer, head and neck cancers, and pancreatic cancer.

[00176] In some embodiments, any of the compound selected from the group consisting of compound I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-41, I-23a, I-25a, I-28a, I-29a, I-30a, I-31a, I-32a, I-33a, I-34a, I-35a, I-38a, I-39a, I-42a, I-43a, I-44a, I-45a, I-50a, I-51a, I-52a, I-53a, I-54a, I-55a, I-56a, I-57a, I-58a, I-59a, I-60a, I-66a, I-70a, I-72a, I-10, I-11, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, I-24a, I-26a, I-27a, I-36a, I-37a, I-40a, I-41a, I-46a, I-47a, I-48a, I-49a, I-61a, I-62a, I-63a, I-64a, I-65a, I-67a, I-68a, I-69a, and I-71a can be used in the above pharmaceutical compositions, combinations and other related uses or methods.

Formulations

[00177] Any suitable formulation of the compounds described herein can be prepared. *See generally*, Remington's Pharmaceutical Sciences, (2000) Hoover, J. E. editor, 20 th edition, Lippincott Williams and Wilkins Publishing Company, Easton, Pa., pages 780-857. A formulation is selected to be suitable for an appropriate route of administration. In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids that form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts. Pharmaceutically acceptable salts are obtained using standard procedures well known in the art, for example, by a sufficiently basic compound such as an amine with a suitable acid, affording a physiologically acceptable anion. Alkali metal (*e.g.*, sodium, potassium or lithium) or alkaline earth metal (*e.g.*, calcium) salts of carboxylic acids also are made.

[00178] Where contemplated compounds are administered in a pharmacological composition, it is contemplated that the compounds can be formulated in admixture with a pharmaceutically acceptable excipient and/or carrier. For example, contemplated compounds can be administered

orally as neutral compounds or as pharmaceutically acceptable salts, or intravenously in a physiological saline solution. Conventional buffers such as phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated compounds may be modified to render them more soluble in water or other vehicle, which for example, may be easily accomplished with minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

[00179] The compounds having formula I-III as described herein are generally soluble in organic solvents such as chloroform, dichloromethane, ethyl acetate, ethanol, methanol, isopropanol, acetonitrile, glycerol, *N,N*-dimethylformamide, *N,N*-dimetheylaceatmide, dimethylsulfoxide, etc. In one embodiment, the present invention provides formulations prepared by mixing a compound having formula I-III with a pharmaceutically acceptable carrier. In one aspect, the formulation may be prepared using a method comprising: a) dissolving a described compound in a water-soluble organic solvent, a non-ionic solvent, a water-soluble lipid, a cyclodextrin, a vitamin such as tocopherol, a fatty acid, a fatty acid ester, a phospholipid, or a combination thereof, to provide a solution; and b) adding saline or a buffer containing 1-10% carbohydrate solution. In one example, the carbohydrate comprises dextrose. The pharmaceutical compositions obtained using the present methods are stable and useful for animal and clinical applications.

[00180] Illustrative examples of water soluble organic solvents for use in the present methods include and are not limited to polyethylene glycol (PEG), alcohols, acetonitrile, *N*-methyl-2-pyrrolidone, *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethyl sulfoxide, or a combination thereof. Examples of alcohols include but are not limited to methanol, ethanol, isopropanol, glycerol, or propylene glycol.

[00181] Illustrative examples of water soluble non-ionic surfactants for use in the present methods include and are not limited to CREMOPHOR® EL, polyethylene glycol modified CREMOPHOR® (polyoxyethyleneglyceroltriricinoleat 35), hydrogenated CREMOPHOR® RH40, hydrogenated CREMOPHOR® RH60, PEG-succinate, polysorbate 20, polysorbate 80,

SOLUTOL® HS (polyethylene glycol 660 12-hydroxystearate), sorbitan monooleate, poloxamer, LABRAFIL® (ethoxylated persic oil), LABRASOL® (capryl-caproyl macrogol-8-glyceride), GELUCIRE® (glycerol ester), SOFTIGEN® (PEG 6 caprylic glyceride), glycerin, glycol-polysorbate, or a combination thereof.

[00182] Illustrative examples of water soluble lipids for use in the present methods include but are not limited to vegetable oils, triglycerides, plant oils, or a combination thereof. Examples of lipid oils include but are not limited to castor oil, polyoxyl castor oil, corn oil, olive oil, cottonseed oil, peanut oil, peppermint oil, safflower oil, sesame oil, soybean oil, hydrogenated vegetable oil, hydrogenated soybean oil, a triglyceride of coconut oil, palm seed oil, and hydrogenated forms thereof, or a combination thereof.

[00183] Illustrative examples of fatty acids and fatty acid esters for use in the present methods include but are not limited to oleic acid, monoglycerides, diglycerides, a mono- or di-fatty acid ester of PEG, or a combination thereof.

[00184] Illustrative examples of cyclodextrins for use in the present methods include but are not limited to alpha-cyclodextrin, beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, or sulfobutyl ether-beta-cyclodextrin.

[00185] Illustrative examples of phospholipids for use in the present methods include but are not limited to soy phosphatidylcholine, or distearoyl phosphatidylglycerol, and hydrogenated forms thereof, or a combination thereof.

[00186] One of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, the compounds may be modified to render them more soluble in water or other vehicle. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

Drug combinations

[00187] The methods of the embodiments comprise administering an effective amount of at least one exemplary compound of the present disclosure; optionally the compound may be administered in combination with one or more additional therapeutic agents, particularly

therapeutic agents known to be useful for treating a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease afflicting the subject.

[00188] The additional active ingredients may be administered in a separate pharmaceutical composition from at least one exemplary compound of the present disclosure or may be included with at least one exemplary compound of the present disclosure in a single pharmaceutical composition. The additional active ingredients may be administered simultaneously with, prior to, or after administration of at least one exemplary compound of the present disclosure.

Methods of using the exemplary compounds and pharmaceutical compositions thereof

[00189] The present invention also provides pharmaceutical compositions for the treatment and/or prevention of a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, comprising any compound having formula I or II, or any of the compounds of I-1 to I-41.

[00190] To practice the method of the present invention, compounds having formula and pharmaceutical compositions thereof may be administered orally, parenterally, by inhalation, topically, rectally, nasally, buccally, vaginally, via an implanted reservoir, or other drug administration methods. The term "parenteral" as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

[00191] A sterile injectable composition, such as a sterile injectable aqueous or oleaginous suspension, may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Among the acceptable vehicles and solvents that may be employed include mannitol, water, Ringer's solution and isotonic sodium chloride solution. Suitable carriers and other pharmaceutical composition components are typically sterile.

[00192] In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (*e.g.*, synthetic mono- or diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives, are useful in the preparation of injectables, as are 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, or carboxymethyl cellulose or similar dispersing agents. Various emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purpose of formulation.

[00193] A composition for oral administration may be any orally acceptable dosage form including, but not limited to, tablets, capsules, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, commonly used carriers include lactose and corn starch. Lubricating agents, such as magnesium stearate, can also be added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If needed, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation compositions can be prepared according to techniques well-known in the art of pharmaceutical formulation and can be prepared as solutions in, for example saline, employing suitable preservatives (for example, benzyl alcohol), absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents known in the art.

[00194] In addition, the compounds having formula I or II, or any of the compounds of I-1 to I-41, may be administered alone or in combination with other therapeutic agents, *e.g.*, anticancer agents, for the treatment of various proliferation disorder, cancer, tumor, inflammatory disease, autoimmune disease, psoriasis, dry eye or immunologically related disease. Combination therapies according to the present invention comprise the administration of at least one exemplary compound of the present disclosure and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect.

Biological screening and anticancer activity:

[00195] Some exemplary assays and examples for assessing therapeutic efficacy, *e.g.*, anti-cancer effects, of exemplary compounds of the invention are described as below.

In vitro cell-based screening using real-time cell electronic sensing (RT-CES) system

[00196] Some of the exemplary heterocyclic compounds in the present invention are developed for the anticancer activities for cancer cells with certain molecular targets, *i.e.*, EGFR (epidermal growth factor receptor). The anticancer efficacy of these heterocyclic compounds and their analogues described above may be preliminarily screened *in vitro* using a penal of EGFR cancer cell lines by real time electronic cell sensing (RT-CES) system from ACEA Biosciences, Inc. (or xCELLigence system from Roche Applied Sciences/ACEA Biosciences Inc.), which provides dynamic cell response information after exposing to an anticancer agent.

[00197] The details of this cell electronic sensing technology, called real-time cell electronic sensing (RT-CES®) and associated devices, systems and methods of use are described in United States patent number 7,732,127; patent number 7,192,752; patent number 7,459,303; patent number 7,468,255; patent number 7,470,533; patent number 7,560,269; United States provisional application number 60/435,400, filed on December 20, 2002; United States Provisional application 60/469,572, filed on May 9, 2003, PCT application number PCT/US03/22557, filed on July 18, 2003; PCT application number PCT/US03/22537, filed on July 18, 2003; PCT application number PCT/US04/37696, filed on November 12, 2004; PCT application number PCT/US05/04481, filed on February 9, 2005; United States patent application number 10/705,447, filed on November 10, 2003; United States patent application number 10/705,615, filed on November 10, 2003; United States patent application number 10/987,732, filed on November 12, 2004; United States patent application number 11/055,639, filed on February 9, 2005. Additional details of RT-CES technology is further disclosed in United States provisional application number 60/519,567, filed on November 12, 2003, and United States provisional application number 60/542,927, filed on February 9, 2004, United States provisional application number 60/548,713, filed on February 27, 2004, United States provisional application number 60/598,608, filed on August 4, 2004; United States provisional application number 60/598,609, filed on August 4, 2004; United States provisional application number 60/613,749, filed on September 27, 2004; United States provisional application number 60/613,872, filed on September 27, 2004; United States provisional application number 60/614,601, filed on September 29, 2004; United States provisional application number 60/630,071, filed on

November 22, 2004; United States provisional application number 60/630,131, filed on November 22, 2004.

[00198] For measurement of cell-substrate or cell-electrode impedance using RT-CES technology, microelectrodes having appropriate geometries are fabricated onto the bottom surfaces of microtiter plate or similar device, facing into the wells. Cells are introduced into the wells of the devices, and make contact to and attach to the electrode surfaces. The presence, absence or change of properties of cells affects the electronic and ionic passage on the electrode sensor surfaces. Measuring the impedance between or among electrodes provides important information about biological status of cells present on the sensors. When there are changes to the biological status of the cells analogue, electronic readout signals are measured automatically and in real time, and are converted to digital signals for processing and analysis.

[00199] In a RT-CES system, a cell index is automatically derived and provided based on measured electrode impedance values. The cell index obtained for a given well reflects : 1) how many cells are attached to the electrode surfaces in this well; 2) how well cells are attached to the electrode surfaces in this well. Thus, the more the cells of same type in similar physiological conditions attach the electrode surfaces, the larger the cell index. And, the better the cells attach to the electrode surfaces (*e.g.*, the cells spread-out more to have larger contact areas, or the cells attach tighter to electrode surfaces), the larger the cell index. We have found that the cMet-addictive cell lines would produce a transient impedance response profile when treated with positive-control EGFR (epidermal growth factor receptor) inhibitors.

[00200] Through the use of the RT-CES system, the heterocyclic compounds described in the examples above have been shown to produce a similar cell response impedance profile on RT-CES system to that generated by positive control inhibitors. In addition, these compounds have been shown to inhibit EGFR (epidermal growth factor receptor)-induced cell migration in several cell lines. In addition, these compounds have shown no or negligible effects when they were used to treat non-cMet addictive cancer cell lines.

[00201] The RT-CES system (or xCELLigence RTCA system) comprises three components, an electronic sensor analyzer, a device station and 16X or 96X microtiter plate devices (i.e. E-Plate 16 or E-Plate 96). Microelectrode sensor array was fabricated on glass slides with lithographical microfabrication methods and the electrode-containing slides are assembled to

plastic trays to form electrode-containing wells. Each 16X (or 96X) microtiter plate device used in RT-CES system comprises up to 16 (or 96) such electrode-containing wells. The device station receives the 16X or 96X microtiter plate devices and is capable of electronically switching any one of the wells to the sensor analyzer for impedance measurement. In operation, the devices with cells cultured in the wells are placed into a device station (xCELLigence RTCA SP station or RT-CES SP station) that is located inside an incubator. Electrical cables connect the device station to the sensor analyzer (xCELLigence RTCA analyzer or RT-CES analyzer). Under the RT-CES or xCELLigence RTCA software control, the sensor analyzer can automatically select wells to be measured and continuously conduct impedance measurements. The impedance data from the analyzer is transferred to a computer, analyzed and processed by the integrated software.

[00202] Impedance measured between electrodes in an individual well depends on electrode geometry, ionic concentration in the well and whether there are cells attached to the electrodes. In the absence of the cells, electrode impedance is mainly determined by the ion environment both at the electrode/solution interface and in the bulk solution. In the presence of the cells, cells attached to the electrode sensor surfaces will alter the local ionic environment at the electrode/solution interface, leading to an increase in the impedance. The more cells there are on the electrodes, the larger the increase in cell-electrode impedance. Furthermore, the impedance change also depends on cell morphology and the extent to which cells attach to the electrodes.

[00203] To quantify cell status based on the measured cell-electrode impedance, a parameter termed Cell Index is derived, according to

$$CI = \max_{i=1,\ldots,N}\left(\frac{R_{cell}(f_i)}{R_b(f_i)} - 1\right)$$

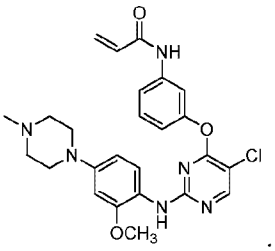
where $R_b(f)$ and $R_{cell}(f)$ are the frequency dependent electrode resistances (a component of impedance) without cells or with cell present, respectively. N is the number of the frequency points at which the impedance is measured. Thus, Cell Index is a quantitative measure of the status of the cells in an electrode-containing well. Under the same physiological conditions, more cells attached on to the electrodes leads to larger $R_{cell}(f)$ value, leading to a larger value for Cell Index. Furthermore, for the same number of cells present in the well, a change in the

cell status such as morphology will lead to a change in the Cell Index. For example, an increase in cell adhesion or cell spreading leads to larger cell-electrode contact area which will lead to an increase in $R_{cell}(f)$ and thus a larger value for Cell Index. The Cell Index may also be calculated using a formula different from the one described here. Other methods for calculating the Cell Index based on impedance measurement can be found in United States patent number 7,732,127; patent number 7,192,752; patent number 7,459,303; patent number 7,468,255; patent number 7,470,533; patent number 7,560,269; PCT application number PCT/US04/37696, fined on November 12, 2004, PCT application number PCT/US05/04481, filed on February 9, 2005, US patent application number 10/987,732, filed on November 12, 2004, and US patent application number 11/055,639, filed on February 9, 2005.

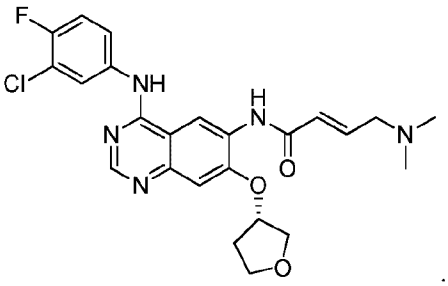
Control compounds for testing

[00204] The following compounds can be used as comparison compounds for testing the compounds in the present disclosure.

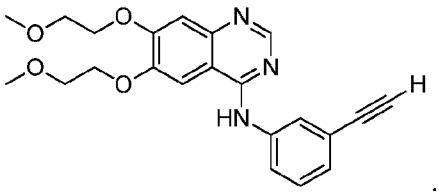
[00205] WZ4002 is an irreversible inhibitor against EGFR T790M. (Nature 2009 December 24;462(7276): 1070–1074) The structure of WZ4002 is shown below:



[00206] BIBW2992 (Afatinib) is an irreversible EGFR/HER2 inhibitor. (*Oncogene* 2008;27:4702–4711) The structure of BIBW2992 is shown below:



[00207] Erlotinib is a reversible tyrosine kinase inhibitor which acts on EGFR. (Drugs 2000, 60 Suppl 1: 15–23; discussion 41–2.) The structure of erlotinib is shown below:

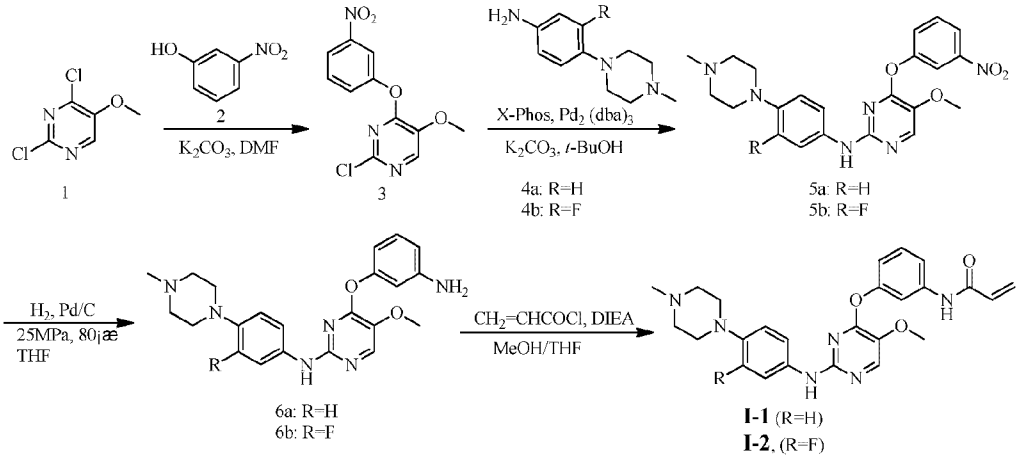


Examples

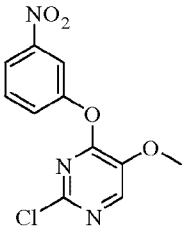
Example 1

Synthesis of *N*-(3-(5-methoxy-2-(4-(4-methylpiperazin-1-yl)phenylamino) pyrimidin-4-yloxy) phenyl)acrylamide (I-1) and N-(3-((2-((3-fluoro-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy) phenyl)acrylamide (I-2)

[00208] The synthetic scheme for compounds I-1 and I-2 are shown below:



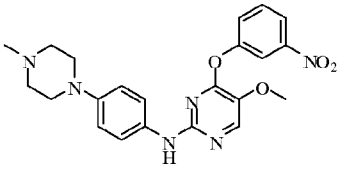
Step 1: Synthesis of 2-chloro-5-methoxy-4-(3-nitrophenoxy) pyrimidine (**3**)



3

[00209] A mixture of 2, 4-dichloro-5-methoxypyrimidine **1**(130.0 g, 726.3 mmol), 3-nitrophenol **2** (106.7 g, 767.0 mmol), and K_2CO_3 (193 g, 1.40mol) in DMF (625 mL) was stirred at 30°C for 24 h. Water (3.12 L) was then added into the reaction mixture. The mixture was stirred for ~10 min. The precipitation was collected, washed with water (200 mL×3), and dried overnight to afford compound **3** (196.0 g, $M+H^+$= 282.6) as white solid.

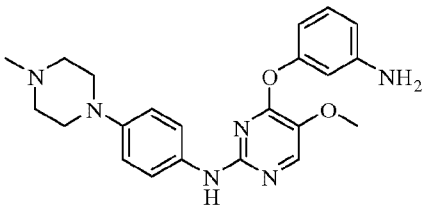
Step 2: Synthesis of 5-methoxy-N-(4-(4-methylpiperazin-1-yl)phenyl)-4-(3-nitrophenoxy)pyrimidin-2-amine (**5a**)



5a

[00210] A mixture of compound **3** (80.0 g, 284.0 mmol), 4-(4-methylpiperazin-1-yl)aniline **4** (54.3 g, 284.0 mmol), X-Phos(8.0 g, 56.8 mmol), $Pd_2(dba)_3$ (8.0 g, 28.4 mmol), K_2CO_3 (78.5 g, 568.1 mmol) in *t*-BuOH (1.0 L) was stirred at refluxing for 4 h. The mixture was allowed to cool down to room temperature and then filtered. The solvent was evaporated under reduced pressure. To the residue, water (400 mL) was added. The mixture was extracted with DCM (400 mL×3). The organic layers were combined, and treated with activated charcoal (for de-colorization), and then filtered. The filtrate was concentrated down under reduced pressure. The crude was further purified by crystallization from ethyl acetate to afford yellow crystals **6** (92.0 g, $M+H^+$= 437.5).

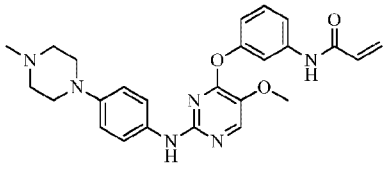
Step 3: Synthesis of 4-(3-aminophenoxy)-5-methoxy-*N*-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine (**6a**)



6a

[00211] A solution of **5a** (65.0g, 143.0 mmol) in THF (150 mL) and 10% Pd/C (3.4g, 5%) were stirred at 25 MPA hydrogen gas at 80 °C for 12h. The mixture was cooled and filtered, and the organic solvent was removed under reduced pressure. The crude was further purified by crystallization from ethyl acetate to afford **6a** (42.0g, $M+H^+$= 407.5).

Synthesis of N-(3-(5-methoxy-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-yloxy) phenyl)acrylamide (**I-1**)



I-1

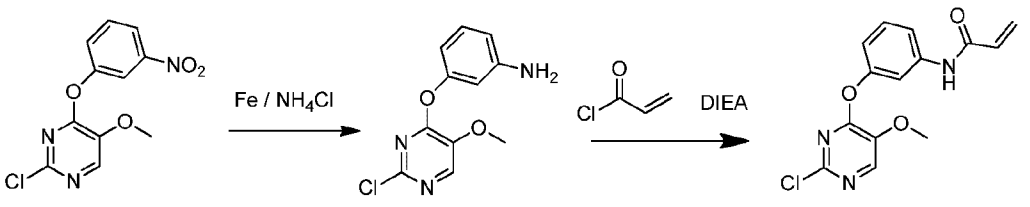
[00212] To a mixture of **6a** (42.0g, 103.3mmol), DIEA (22.4 g, 173.6 mmol) in MeOH (420 mL) and THF(150 mL) was added acryloyl chloride(15.7 g, 173.6 mmol) at 0 °C. The mixture was stirred for 1h. The organic solvent was removed under reduced pressure. The residue was re-dissolved in DCM (800 mL) and washed with saturated aqueous sodium bicarbonate(400ml). The organic layer was separated and the solvent was removed under reduced pressure. The crude was further purified by crystallization from THF/H_2O (3:10) to afford compound I-1 (25.0 g, $M+H^+$=461.5). ^1H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.01 (s, 1H), 8.17 (s, 1H), 7.64 – 7.59 (m, 2H), 7.43 (t, J = 8.4 Hz, 1H), 7.28 (d, J = 9.0 Hz, 2H), 6.95 (m, 1H), 6.64 (d, J = 9.1 Hz, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.35 – 6.19 (m, 1H), 5.78 (dd, J = 10.1, 1.9 Hz, 1H), 3.87 (s, 3H), 3.02 – 2.91 (m, 4H), 2.48 – 2.39 (m, 4H), 2.23 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.32 (s), 161.43 (s), 155.79 (s), 154.79 (s), 147.52 (s), 145.95 (s), 142.27 (s), 136.62 (s), 135.09 (s), 133.70 (s), 131.87 (s), 129.25 (s), 121.10 (s, 2C), 118.76 (s), 118.17 (s), 117.71 (s, 2C), 114.94 (s), 59.63 (s), 56.65 (s, 2C), 50.92 (s, 2C), 47.71 (s).

[00213] Compound (**I-2**) *N*-(3-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenyl amino)-5-methoxypyrimidin-4-yloxy)phenyl) acrylamide was synthesized using similar procedures as Compound **I-1** with similar yield. Compound (**I-2**): M+H$^+$=479.5. ^{1}H NMR (500 MHz, MeOD) δ 8.07 (s, 1H), 7.69 (t, J = 2.0 Hz, 1H), 7.57 (dd, J = 8.2, 1.0 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.30 (dd, J = 15.2, 2.5 Hz, 1H), 7.03 – 6.88 (m, 2H), 6.78 (t, J = 9.5 Hz, 1H), 6.45 (dd, J = 17.0, 9.9 Hz, 1H), 6.37 (dd, J = 17.0, 2.0 Hz, 1H), 5.78 (dd, J = 9.9, 2.0 Hz, 1H), 3.94 (s, 3H), 2.99 (br s, 4H), 2.62 (br s, 4H), 2.35 (s, J = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 166.29 (s), 162.07 (s), 158.04 (s), 156.11 (s), 155.29 (s), 154.60 (s), 144.75 (s), 141.44 (s), 138.09 (d, J = 11.1 Hz), 137.15 (s), 134.70 (d, J = 9.8 Hz), 132.55 (s), 131.07 (s), 128.26 (s), 120.31 (d, J = 4.1 Hz), 118.88 (s), 118.28 (s), 115.45 – 115.14 (m), 107.96 (d, J = 26.4 Hz), 58.81 (s), 56.19 (s, 2C), 51.83 (d, J = 2.6 Hz, 2C), 46.25 (s).

Example 2

Synthesis of key intermediates (I, II, III, IV and V)

[00214] Intermediate **I** (the synthetic scheme is shown below):



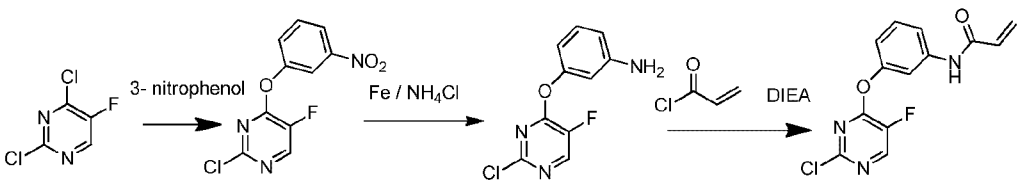
Step 1: Synthesis of 3-(2-chloro-5-methoxypyrimidin-4-yloxy) aniline

[00215] To a solution of compound 3 (35 g) in THF (200 mL), water (30 mL), NH4Cl (17 g) and Fe (15 g) were added. The reaction mixture was heated to reflux with stirring for 3h. The reaction mixture was cooled down and filtered, and the THF layer was concentrated under reduced pressure. The crude was re-dissolved in ethyl acetate (200 mL) and the pH was adjusted with aqueous sodium bicarbonate solution, and then washed with water (100 mL x3). The organic layer was separated and the solvent was removed under reduced pressure to obtain the title product (13 g, M+H$^+$ = 252.5).

Step 2: Synthesis of N-(3-(2-chloro-5-methoxypyrimidin-4-yloxy)phenyl) acryl amide (**I**)

[00216] To a solution of 3-(2-chloro-5-methoxypyrimidin-4-yloxy) aniline (7.5 g) and DIEA (6 g) in THF (150 mL), acryloyl chloride (2.7 g,) in THF (10 mL) was drop-wise added at 0°C with an ice-bath over 20 min. After the reaction mixture was stirred overnight, aqueous NaOH (1M, 40 mL) was added. The reaction mixture was stirred at room temperature for another 0.5h. The THF layer was separated, and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layer was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (200 mL), washed with water (100 mL x3). The organic layer was separated and the solvent was removed under reduced pressure to yield the crude, which was further purified by flash column chromatography to give the desired intermediate **I** (4 g, $M+H^+$= 306.5).

[00217] Intermediate **II** (the synthetic scheme is shown below):



Intermediate II

Step 1: the synthesis of 2-chloro-5-fluoro-4-(3-nitrophenoxy) pyrimidine

[00218] A mixture of 2,4-dichloro-5-fluoropyrimidine (10.20 g), 3-nitrophenol (8.6 g), and K_2CO_3 (15.30 g) in DMF (80 mL) was stirred overnight at room temperature. Water (300 mL) was added. The reaction mixture was stirred for 30 min and then filtered. The precipitate was collected, washed with water (100 mL ×2) and dried. The solid was re-dissolved in ethyl acetate (200 mL), washed with water (100 mL x3). The organic layer was separated and the solvent was removed under reduced pressure. The crude was further purified by crystallization from ethyl acetate/ petroleum ether (20 ml) to afford yellow crystals **3** (9.8 g, $M+H^+$= 270.6).

Step 2: the synthesis of 3-(2-chloro-5-fluoropyrimidin-4-yloxy) aniline

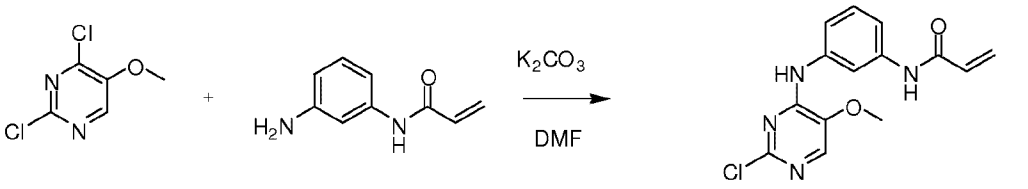
[00219] To a solution of 2-chloro-5-fluoro-4-(3-nitrophenoxy) pyrimidine (6.8 g) in THF (100 mL) water (20 mL), NH4Cl (6.5 g) and Fe (6.5 g) were added. The reaction mixture was stirred at refluxing for 5h, cooled to room temperature and then filtered. The filtrate was

concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (200 mL) and the PH was adjusted with aqueous sodium bicarbonate solution. The mixture was washed with water (100 mL x3). The organic layer was separated and the solvent was removed under reduced pressure to yield the desired product with, 66.2% yield (4 g, $M+H^+$= 240.5).

Step 3: the synthesis of N-(3-(2-chloro-5-fluoropyrimidin-4-yloxy)phenyl)acrylamide (**II**)

[00220] To a solution of 3-(2-chloro-5-fluoropyrimidin-4-yloxy) aniline (3.9 g) and DIEA (3 g) in THF (60 mL), acryloyl chloride (1.6 g) in THF (5 mL) was added drop-wise at 0°C (an ice-bath) over 15 min. After the reaction mixture was stirred for 4 h, aqueous sodium bicarbonate Aqueous (50 mL) was added drop-wise. The reaction mixture was stirred for another 0.5h. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (100 mL). The combined organic layers were concentrated down under reduced pressure. The residue was re-dissolved in ethyl acetate (200 mL), washed with water (100 mL x3). The organic layer was separated and the solvent was removed under reduced pressure. The crude was further purified by flash column chromatography to yield the desired intermediated **II** (4 g, $M+H^+$= 294.5).

[00221] Intermediate III (the synthetic scheme is shown below):



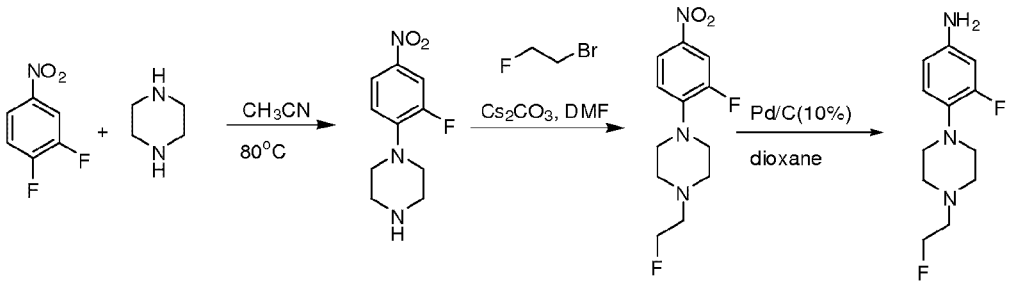
Intermediate III

Synthesis of N-(3-(2-chloro-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (III)

[00222] To a solution of 2,4-dichloro-5-methoxypyrimidine 1 (2.55 g) and N-(3-aminophenyl) acrylamide (2.32 g) in DMF (30mL), K_2CO_3(4.14 g) was added. The reaction mixture was stirred at 50°C for 16h. TLC (petroleum ether: ethyl acetate =1:1 as elution) indicated the completion of the reaction. Ethyl acetate (200 mL) was added, washed with water (200 mL x3). The organic layer was separated, and the solvent was removed under reduced

pressure. The crude was further purified by flash column chromatography to yield the desired product **III** (3.5g, M+H$^+$= 305.7).

[00223] Intermediate **IV** (the synthetic scheme is shown below):



Intermediate IV

Step 1: the synthesis of 1-(2-fluoro-4-nitrophenyl)piperazine

[00224] In a round-bottom flask, 1,2-difluoro-4-nitrobenzene (23 g, 144.57 mmol) was added to a solution of piperazine (21.66 g, 251.46 mmol) in MeCN (200 mL). The mixture was stirred at 80°C for 3h until the reaction was complete indicated by TLC (petroleum ether: ethyl acetate = 3:1). The mixture was concentrated followed by adding water (300 mL), extracted by ethyl acetate (200 mL×3). Organic layers were combined, dried over Na_2SO_4 and concentrated under reduced pressure to yield yellow crude product (30 g, M+H$^+$ = 226.5).

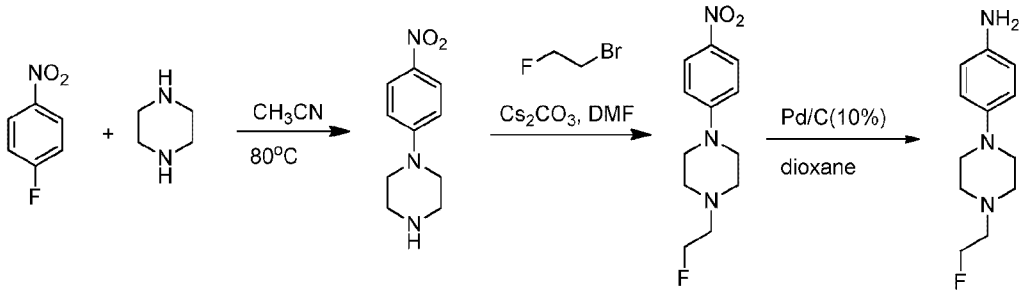
Step 2: the synthesis of 1-(2-fluoro-4-nitrophenyl)-4-(2-fluoroethyl)piperazine

[00225] 1-bromo-2-fluoroethane (5.4 g, 42.63 mmol), DMF (48 mL), 1-(2-fluoro-4-nitrophenyl)piperazine (8 g, 35.52 mmol) and Cs2CO3 (25.2 g,77.34 mmol) was sequentially added to the flask. The reaction mixture was stirred at 80 °C for 7h until the reaction was complete indicated by TLC (ethyl acetate: petroleum ether =1:3). After cooled to room temperature, the mixture was filtered. The filtrate was poured into water (700 mL) with stirring vigorously. The precipitate was collected, washed with water, and dried to yield the crude product (9 g, M+H$^+$ = 272.5).

Step 3: the synthesis of 3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (**IV**)

[00226] A solution of 1-(2-fluoro-4-nitrophenyl)-4-(2-fluoroethyl) piperazine (1.1g, 4.06 mmol) and Pd/C (10%) (0.2 g, 1. 87 mmol) in 1,4-dioxane (10 mL) was hydrogenated for 12h at room temperature until the reaction was complete indicated by TLC(MeOH: DCM= 1:4). The mixture was filtered through Celite-bed, and washed with 1, 4-dioxane (5 mL). The filtrate was concentrated under reduced pressure to give the crude product **IV** (1 g, $M+H^+$= 242.5), which was used for next step without further purification.

[00227] Intermediate V (the synthetic scheme is shown below):

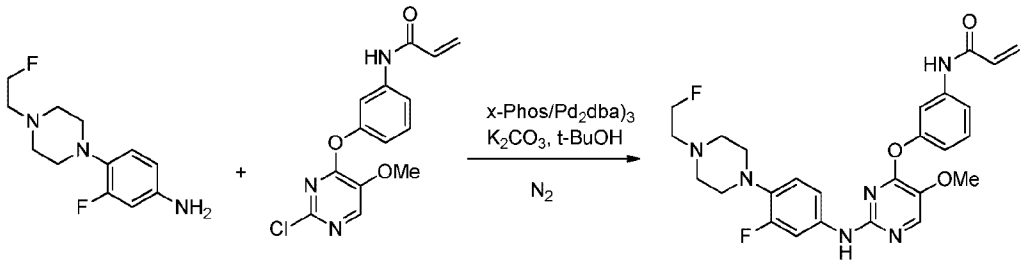


[00228] Using a similar chemistry as for intermediate **IV**, the intermediate (**V**) 4-(4-(2-fluoroethyl)piperazin-1-yl)aniline was synthesized.

Example 3

Synthesis of N-(3-(2-(3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-3)

[00229] The synthetic scheme for compound I-3 is shown below:



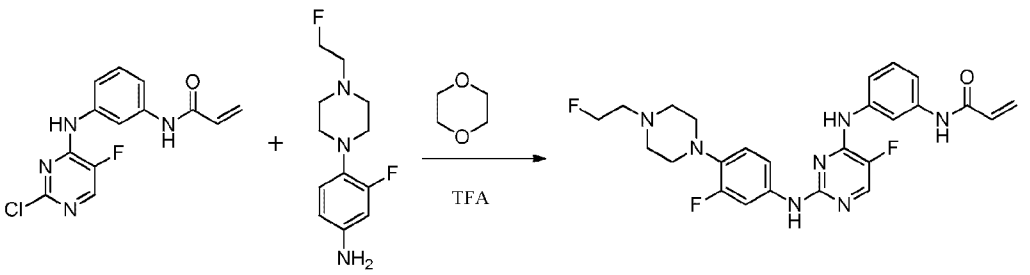
I-3

[00230] N-(2-(2-chloro-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (300 mg, 0.981 mmol), 3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (236.8 mg, 0.981 mmol), potassium carbonate (175 mg, 1.27 mmol), tris(dibenzylideneacetone)dipalladium (35 mg, 0.07 mmol) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (35 mg, 0.038 mmol) and *t*-BuOH (3 mL) were sequentially added to a 10mL round bottom flask with a magnetite. The flask was placed on an oil bath and stirred under N_2. The reaction mixture was heated to reflux for 5~7 h until reaction was complete indicated by TLC (ethyl acetate/ petroleum ether/ TEA = 1/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (10 mL) and activated charcoal (0.1 g). After stirred for 15min, the mixture was filtered through Celite®, and the filter cake was washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure. The crude was further purified by flash column chromatography (ethyl acetate / petroleum ether = 1/1 to 100% EtOAc as elution) to give the title compound **I-3** (120 mg, yield 26%, purity 97.35%, $M+H^+ = 511.5$) as white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.28 (s, 1H), 8.22 (s, 1H), 7.67 (t, J = 2.1 Hz, 1H), 7.56 (dd, J = 8.2, 1.0 Hz, 1H), 7.43 (t, J = 8.1 Hz, 1H), 7.35 (dd, J = 15.5, 1.9 Hz, 1H), 7.11 (dd, J = 8.7, 1.9 Hz, 1H), 6.97 (m, 1H), 6.79 – 6.71 (m, 1H), 6.43 (dd, J = 17.0, 10.2 Hz, 1H), 6.26 (dd, J = 17.0, 1.9 Hz, 1H), 5.77 (dd, J = 10.1, 1.9 Hz, 1H), 4.61 (t, J = 4.9 Hz, 1H), 4.51 (t, J = 4.9 Hz, 1H), 3.89 (s, 3H), 2.93 – 2.81 (m, 4H), 2.69 (t, J = 4.9 Hz, 1H), 2.63 (t, J = 4.9 Hz, 1H), 2.57 (br s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.32 (s), 161.39 (s), 157.66 (s), 155.73 (s), 154.92 (d, J = 65.0 Hz), 145.45 (s), 142.39 (s), 138.17 (d, J = 11.0 Hz), 137.16 (s), 135.13 (d, J = 9.3 Hz), 133.71 (s), 131.94 (s), 129.23 (s), 120.92 (s), 118.70 (s), 118.25 (s), 115.73 (s), 114.68 (s), 107.96 (d, J = 26.1 Hz), 83.84 (d, J = 164.5 Hz), 59.62 (s), 59.46 (s), 55.05 (s, 2C), 52.54 (s, 2C).

Example 4

Synthesis of N-(3-((5-fluoro-2-((3-fluoro-4-(4-(2-fluoroethyl)piperazin-1yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide (I-4)

[00231] The synthetic scheme for compound **I-4** is shown below:



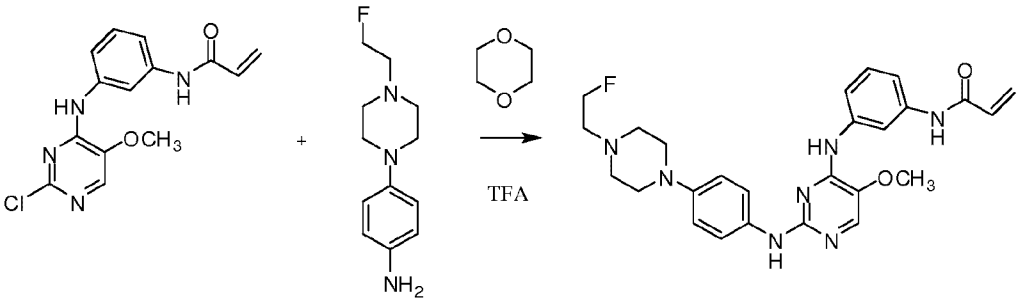
I-4

[00232] N-(3-(2-chloro-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide (878 mg), 1,4-dioxane (30 mL) , 3-fluoro-4-(4-(2-fluoroethyl)cyclohexyl)aniline (730 mg) and TFA (0.7 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing for 24 h. TLC (petroleum ether: ethyl acetate =2:1 as elution) indicated the completion of the reaction. The reaction mixture was concentrated under reduced pressure. The crude was re-dissolved in ethyl acetate (100 mL), adjusted the pH to 8 with aqueous solution of sodium bicarbonate, and washed by water (100 mL x3). The organic layer was separated, and the solvent was removed under reduced pressure. The crude was further purified by flash column chromatography to yield the title compound **I-4** (480 mg, $M+H^+$= 498.5 32% yield). ^1H NMR (500 MHz, MeOD) δ 8.08 (s, 1H), 7.93 (d, J = 3.8 Hz, 1H), 7.57 (dd, J = 15.1, 2.5 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.32 (t, J = 8.1 Hz, 1H), 7.23 – 7.13 (m, 1H), 6.90 (t, J = 9.2 Hz, 1H), 6.46 (dd, J = 17.0, 9.9 Hz, 1H), 6.38 (dd, J = 17.0, 1.9 Hz, 1H), 5.79 (dd, J = 9.9, 1.9 Hz, 1H), 4.68 (t, J = 4.5 Hz, 1H), 4.58 (t, J = 4.5 Hz, 1H), 3.11 – 3.03 (m, 4H), 2.81 (t, J = 4.5 Hz, 1H), 2.76 – 2.70(m, 5H). ^{13}C NMR (126 MHz, MeOD) δ 166.30 (s), 158.11 (s), 157.14 (s), 156.17 (s), 152.12 (d, J = 10.7 Hz), 143.43 (s), 141.61 – 140.82 (m), 140.37 (d, J = 35.4 Hz), 138.06 (d, J = 10.8 Hz), 135.17 (d, J = 9.7 Hz), 132.75 (s), 130.22 (s), 128.07 (s), 120.36 (d, J = 4.0 Hz), 119.38 (s), 117.04 (s), 116.11 (s), 115.41 (s), 108.84 (d, J = 25.9 Hz), 82.71 (d, J = 166.3 Hz), 59.44 (d, J = 19.8 Hz), 54.75 (s, 2C), 51.95 (d, J = 2.6 Hz, 2C).

Example 5

Synthesis of N-(3-(2-(4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-5)

[00233] The synthetic scheme for compound **I-5** is shown below:



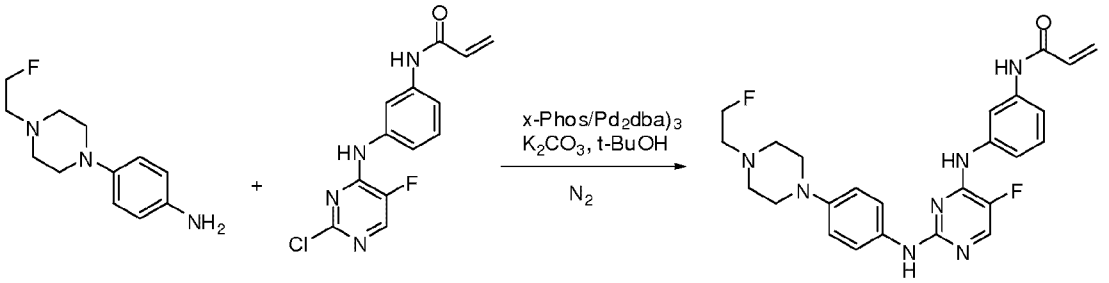
I-5

[00234] N-(3-(2-chloro-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (1.089 g,), 4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (0.800 g), potassium carbonate (1.231g), tris(dibenzylideneacetone) dipalladium (0.300 g) and dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (0.300 g) and *t*-BuOH (30 mL) were sequentially added to a 100mL round bottom flask with a magnetite. The flask was placed on an oil bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing for 5~7 h until reaction was complete indicated by TLC (ethyl acetate/ petroleum ether/ TEA = 1/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (50 mL) and activated charcoal (0.5 g). After stirred for 15min, the mixture was filtered through Celite®. The filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure and the crude was further purified by flash column chromatography (ethyl acetate / petroleum ether = 1/1 to 100% ethyl aceate as elution) to give the title compound **I-5** (750 mg, yield 42.65%, purity 95.8%, $M+H^+ = 492.5$) as white solid. ^1H NMR (500 MHz, DMSO-d_6) δ 10.09 (s, 1H), 8.69 (s, 1H), 8.58 (s, 1H), 7.98 (t, J = 1.8 Hz, 1H), 7.82 (s, 1H), 7.55 – 7.49 (m, 3H), 7.42 (d, J = 8.6 Hz, 1H), 7.26 (t, J = 8.1 Hz, 1H), 6.77 (d, J = 9.1 Hz, 2H), 6.47 (dd, J = 17.0, 10.2 Hz, 1H), 6.27 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz, 1H), 4.65 – 4.59 (m, 1H), 4.56 – 4.50 (m, 1H), 3.85 (s, 3H), 3.05 – 2.95 (m, 4H), 2.70 (t, J = 4.9 Hz, 1H), 2.64 (t, J = 4.9 Hz, 1H), 2.62 – 2.54 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.06 (s), 156.09 (s), 153.81 (s), 147.29 (s), 141.66 (s), 140.88 (s), 139.29 (s), 136.26 (s), 135.95 (s), 134.03 (s), 130.53 (s), 128.76 (s), 121.28 (s), 119.17 (s), 118.00 (s), 116.38 (s), 115.43 (s), 83.91 (d, J = 164.3 Hz), 59.58 (d, J = 19.5 Hz), 59.00 (s), 55.05 (s, 2C), 51.30 (s, 2C).

Example 6

Synthesis of N-(2-(5-fluoro-2-(4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide (I-6)

[00235] The synthetic scheme for compound **I-6** is shown below:



I-6

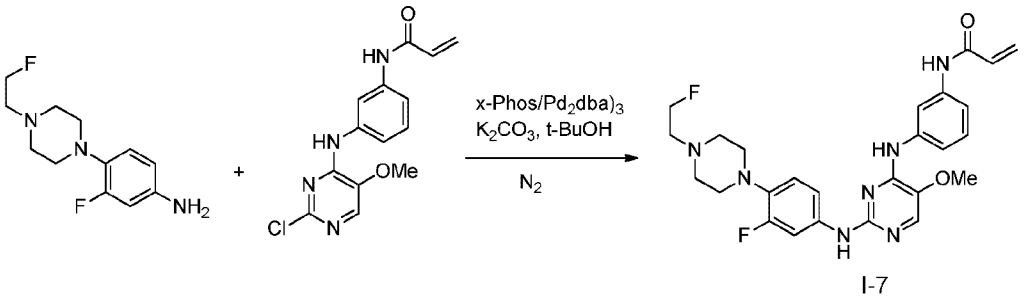
[00236] N-(2-(2-chloro-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide (2.010 g, 6.849 mmol), 4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (2.008 g, 8.969 mmol), potassium carbonate (1.880 g, 13.698 mmol), tris(dibenzylideneacetone)dipalladium (630 mg, 0.685 mmol) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (627 mg, 1.370 mmol) and *t*-BuOH (20mL) were sequentially added into a 100mL round bottom flask with a magnetite. The flask was placed on an oil bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing for 5~7 h until reaction was complete indicated by TLC (EtOAc/ petroleum ether/ TEA = 3/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (50 mL) and activated charcoal (0.5 g). After stirred for 15min, the mixture was filtered through Celite®. The filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure. The crude was further purified by flash column chromatography (EtOAc /petroleum ether = 3/1 to EtOAc as elution) to give the title compound **I-6** (1.85 g, yield 56.23%, purity 95%, $M+H^+ = 480.2$) as light yellow solid. ^1H NMR (500 MHz, MeOD) δ 8.07 (s, 1H), 7.88 (d, J = 3.7 Hz, 1H), 7.50 – 7.39 (m, 4H), 7.29 (t, J = 8.1 Hz, 1H), 6.92 – 6.85 (m, 2H), 6.46 (dd, J = 17.0, 9.8 Hz, 1H), 6.39 (dd, J = 17.0, 2.1 Hz, 1H), 5.80 (dd, J = 9.8, 2.1 Hz, 1H), 4.71 – 4.65 (m, 1H), 4.61 – 4.55 (m, 1H), 3.17 – 3.10 (m, 4H), 2.84 – 2.78 (m, 1H), 2.78 – 2.69 (m, 5H). ^{13}C NMR (126 MHz, MeOD) δ 166.25 (s),

157.72 (s), 152.10 (d, J = 10.7 Hz), 148.08 (s), 143.16 (s), 141.20 (s), 141.12 (s), 140.96 (s), 140.66 (s), 140.07 (s), 135.13 (s), 132.74 (s), 130.13 (s), 128.15 (s), 122.40 (s), 119.20 (s), 118.27 (s), 116.94 (s), 115.33 (s), 82.76 (d, J = 166.4 Hz), 59.42 (d, J = 19.7 Hz), 54.71 (s, 2C), 51.15 (s, 2C).

Example 7

Synthesis of N-(2-(2-(3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (I-7)

[00237] The synthetic scheme for compound **I-7** is shown below:



I-7

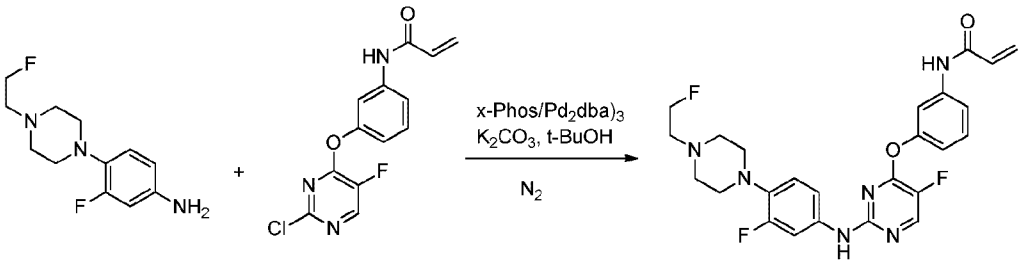
[00238] N-(2-(2-chloro-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (1.521 g, 5 mmol), 3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (1.210 g, 5 mmol), potassium carbonate (1.383 g, 10 mmol), tris(dibenzylideneacetone)dipalladium (460 mg, 0.5 mmol) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (475 mg, 1mmol) and *t*-BuOH (50 mL) were sequentially added into a 100mL round bottom flask with a magnetite. The flask was placed on an oil bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing for 5~7 h until the reaction was complete indicated by TLC (EtOAc/ petroleum ether/ TEA = 1/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (50 mL) and activated charcoal (0.5 g). After stirred for 15min, the mixture was filtered through Celite®, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated and the crude was further purified by flash column chromatography (EtOAc / petroleum ether = 1/1 to EtOAc as elution) to yield the title compound **I-7** (1.537 g, yield 60.2%,

purity 95.33%, M+H$^+$ = 510.3) as light yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.08 (s, 1H), 8.89 (s, 1H), 8.77 (s, 1H), 7.96 (t, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.67 (dd, *J* = 15.7, 2.4 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.7 Hz, 1H), 7.31 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.27 (t, *J* = 8.1 Hz, 1H), 6.84 (dd, *J* = 9.8, 9.1 Hz, 1H), 6.46 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.25 (dd, *J* = 17.0, 2.0 Hz, 1H), 5.75 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.61 (t, *J* = 4.9 Hz, 1H), 4.52 (t, *J* = 4.9 Hz, 1H), 3.87 (s, 3H), 2.97 – 2.86 (m, 4H), 2.70 (t, *J* = 4.9 Hz, 1H), 2.64 (t, *J* = 4.9 Hz, 1H), 2.59 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.07 (s), 157.89 (s), 155.97 (s), 155.49 (s), 153.84 (s), 141.51 (s), 141.07 (s), 139.06 (d, *J* = 11.0 Hz), 138.82 (s), 136.67 (s), 134.63 (d, *J* = 9.4 Hz), 134.06 (s), 130.60 (s), 128.67 (s), 121.06 (d, *J* = 4.0 Hz), 119.34 (s), 116.48 (s), 115.75 – 115.32 (m), 107.95 (d, *J* = 26.1 Hz), 83.85 (d, *J* = 164.4 Hz), 59.57 (d, *J* = 19.6 Hz), 58.89 (s), 55.11 (s, 2C), 52.65 (s, 2C).

Example 8

Synthesis of N-(2-(5-fluoro-2-(3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-8)

[00239] The synthetic scheme for compound **I-8** is shown below:



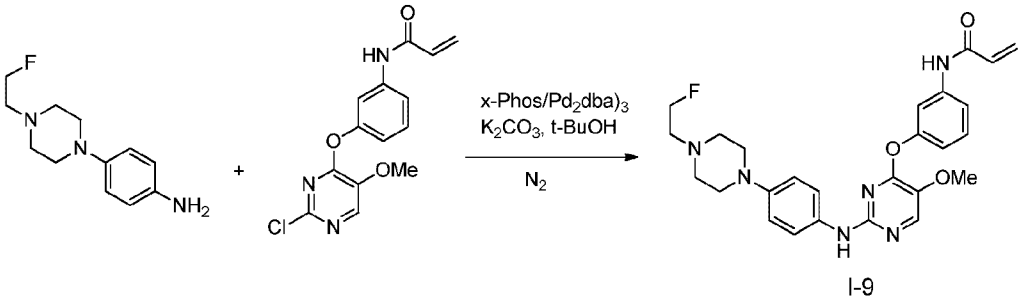
[00240] N-(2-(2-chloro-5-fluoropyrimidin-4-yloxy)phenyl)acrylamide (1.461 g, 5 mmol), 3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (1.210 g, 5 mmol), potassium carbonate (1.380 g, 10 mmol), tris(dibenzylideneacetone)dipalladium (460 mg, 0.5 mmol) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (475 mg, 1 mmol) and *t*-BuOH (50 mL) were sequentially added into a 100mL round bottom flask with a magnetite. The flask was placed on

an oil bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing for 5~7 h until reaction was complete indicated by TLC (EtOAc/ petroleum ether/ TEA = 1/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (50 mL) and activated charcoal (0.5 g). After stirred for 15min, the mixture was filtered through Celite®, and the filter cake was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure, and the crude was further purified by flash column chromatography (EtOAc /petroleum ether = 1/1 to EtOAc as elution) to give the title compound **I-8** (1.72 g, yield 69.1%, purity 98.67%, $M+H^+$ = 499.3) as light yellow solid. ^1H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.60 (s, 1H), 8.49 (d, *J* = 3.0 Hz, 1H), 7.74 (t, *J* = 2.0 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.46 (t, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 15.1 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.04 (m, 1H), 6.77 (t, *J* = 9.4 Hz, 1H), 6.44 (dd, *J* = 17.0, 10.2 Hz, 1H), 6.27 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.78 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.61 (t, *J* = 4.9 Hz, 1H), 4.51 (t, *J* = 4.9 Hz, 1H), 2.94 – 2.83 (m, 4H), 2.69 (t, *J* = 4.9 Hz, 1H), 2.63 (t, *J* = 4.9 Hz, 1H), 2.57 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.36 (s), 159.02 (d, *J* = 11.0 Hz), 157.52 (s), 156.87 (d, *J* = 3.4 Hz), 155.59 (s), 153.97 (s), 147.89 (d, *J* = 22.1 Hz), 142.88 (s), 142.47 (s), 140.90 (s), 137.36 (d, *J* = 10.9 Hz), 135.82 (d, *J* = 9.3 Hz), 133.67 (s), 132.04 (s), 129.30 (s), 120.86 (d, *J* = 3.9 Hz), 118.70 (s), 116.34 (s), 114.68 (s), 108.54 (d, *J* = 26.0 Hz), 83.83 (d, *J* = 164.4 Hz), 59.53 (d, *J* = 19.5 Hz), 55.01 (s, 2C), 52.46 (d, *J* = 2.4 Hz, 2C).

Example 9

Synthesis of N-(2-(2-(3-fluoro-4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-9)

[00241] The synthetic scheme for compound **I-9** is shown below:



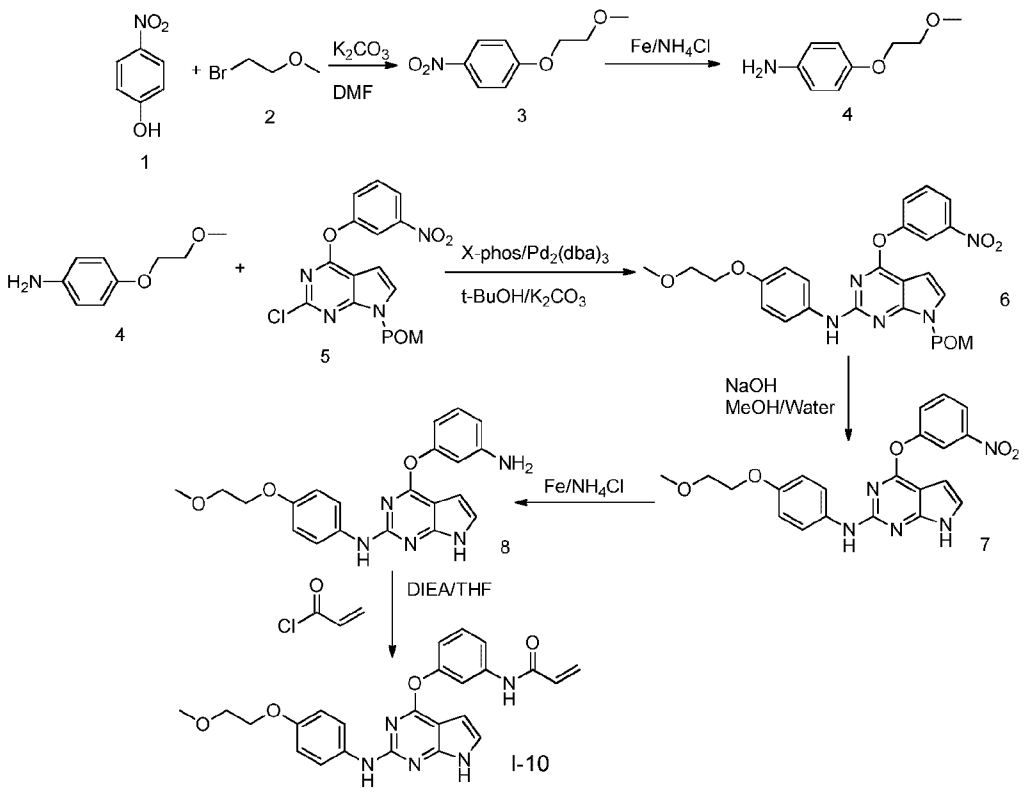
I-9

[00242] N-(2-(2-chloro-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (1.360 g, 4.48 mmol), 4-(4-(2-fluoroethyl)piperazin-1-yl)aniline **1** (1.002 g, 4.48 mmol), potassium carbonate (1.380 g, 10 mmol), tris(dibenzylideneacetone)dipalladium (460 mg, 0.5 mmol) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (475 mg, 1 mmol) and *t*-BuOH (50 mL) were sequentially added into a 100mL round bottom flask with a magnetite. The flask was placed on an oil bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing for 5~7 h until reaction was complete indicated by TLC (EtOAc/ petroleum ether/ TEA = 1/1/0.1 as elution). The mixture was concentrated under reduced pressure, followed by addition of EtOAc (50 mL) and activated charcoal (0.5 g). After stirred for 15min, the mixture was filtered through Celite®, and the filter cake was wash with EA (50 mL). The filtrate was concentrated and the crude was further purified by flash column chromatography (EtOAc /petroleum ether = 1/1 to EtOAc as elution) to yield the title compound **I-9** (840 mg, yield 38%, purity 96.93%, $M+H^+ = 493.5$) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1H), 9.00 (s, J = 24.8 Hz, 1H), 8.17 (s, 1H), 7.59 – 7.63 (m, 2H), 7.43 (t, J = 8.4 Hz, 1H), 7.29 (d, J = 9.0 Hz, 2H), 7.03 – 6.89 (m, 1H), 6.65 (d, J = 9.1 Hz, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.28 (dd, J = 17.0, 1.9 Hz, 1H), 5.78 (dd, J = 10.1, 1.9 Hz, 1H), 4.62 (t, J = 4.9 Hz, 1H), 4.52 (t, J = 4.9 Hz, 1H), 3.87 (s, J = 15.8 Hz, 3H), 3.05 – 2.89 (m, 4H), 2.69 (t, J = 4.9 Hz, 1H), 2.63 (t, J = 4.9 Hz, 1H), 2.61 – 2.53 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.32 (s), 161.44 (s), 155.80 (s), 154.79 (s), 147.56 (s), 145.97 (s), 142.27 (s), 136.63 (s), 135.12 (s), 133.70 (s), 131.88 (s), 129.26 (s), 121.13 (s, 2C), 118.76 (s), 118.16 (s), 117.74 (s, 2C), 114.95 (s), 83.90 (d, J = 164.3 Hz), 59.64 (s), 59.48 (s), 54.99 (s, 2C), 51.13 (s, 2C).

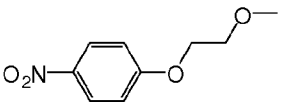
Example 10

Synthesis of N-(3-(2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-10)

[00243] The synthetic scheme for compound **I-10** is shown below:

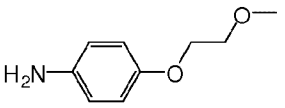


Step 1: Synthesis of 1-(2-methoxyethoxy)-4-nitrobenzene (**3**)



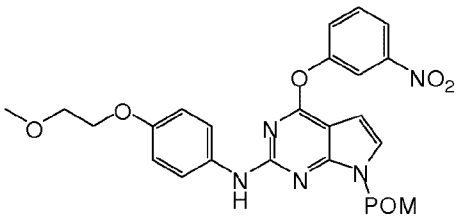
[00244] To a solution of 4-nitrophenol (18.2 g, 130 mmol) and 1-bromo-2-methoxyethane (20 g, 144 mmol) in DMF (60 ml), K_2CO_3 (36 g, 260 mmol) was added. The reaction mixture was stirred at 65~70°C for 4 h and then cooled to room temperature. Water (200 mL) was added and the mixture was extracted with ethyl acetate (200 mL x3). The combined organic layers were washed with water (200 ml x3), dried over Na_2SO_4. The solvent was removed under reduced pressure to yield the desired product (**3**) as white solid (25 g, 97.6% yield), which was used for the next step without further purification.

Step 2: Synthesis of 4-(2-methoxyethoxy)aniline (**4**)



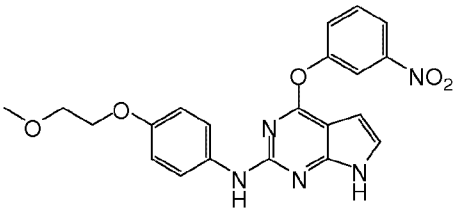
[00245] To a solution of compound **3** (25 g, 127 mmol) inTHF (180 mL), water (60 mL) was added. After stirred for ~ 5 min, NH_4Cl (28 g, 523 mmol) and Fe (36 g, 635 mmol) were sequentially added. The reaction mixture was heated to refluxing and stirred for 4h. After cooled to room temperature, the mixture was filtered through Celite® and washed with ethyl acetate (200 mL). The filtrate was concentrated under reduced pressure. The crude was re-dissolved in ethyl acetate (500 mL), washed with saturated $NaHCO_3$ (200 mL) and water (200 mL). The organic layer was concentrated under reduced pressure. The crude was further purified by flash column chromatography to yield the desired product **4** (12 g, 56.7% yield, $M+H^+$= 168.5).

Step 3: Synthesis of (2-(4-(2-methoxyethoxy)phenylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (**6**)



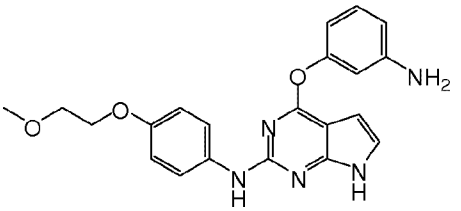
[00246] To a solution of (2-chloro-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (4 g,10 mmol), compound **4** (1.67 g, 10 mmol) int-BuOH (40 mL) , potassium carbonate (2.8 g, 20 mmol), tris(dibenzylideneacetone)dipalladium (500 mg) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (500 mg) were sequentially added. The reaction mixture was stirred under N_2 flow and heated to refluxing. After stirred for 3~4 , TLC (DCM/ MeOH = 10/1 as elution) indicated the completion of the reaction. The mixture was cooled to 40~50°C, filtered through Celite®. The filter cake was washed with t-BuOH. The filtrate was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (200 mL) washed with water, and concentrated under reduced pressure. The crude was further purified by flash column chromatography to yield the desired product **6** (5.9 g, $M+H^+$=536.5).

Step 4: Synthesis of N-(4-(2-methoxyethoxy)phenyl)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (**7**)



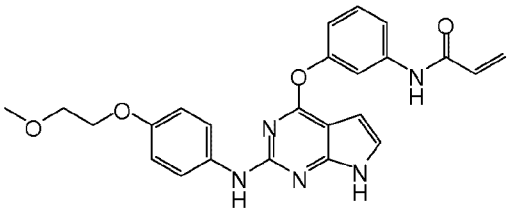
[00247] To a reactor (250mL) was charged with **6** (5.9 g, 0.01 mol) and MeOH (120 mL). When **6** was completely dissolved, the solution was cooled with ice-bath to ~10°C. NaOH solution (2.5 M, 8 mL) was then added over 45 min, maintaining the temperature under 16°C throughout the addition. When addition was complete, the reaction mixture was stirred for 4~5 h at ~ 16 °C. The completion of the reaction was monitored by TLC and LC-MS which indicated the consumption of **6** and low content (less than 8%) of an intermediate (MW: 493). Water (300mL) was added to the reaction over 90 min, maintaining the temperature below 20°C. The desired product **8** was precipitated during the addition of the water. The mixture was stirred for another 15 min after the addition of the water. The precipitate (crude) was collected and washed with water (200 mL). The crude was re-dissolved in ethyl acetate (200 mL) and washed with water (200 mLx3). The mixture was passed through Celite® to remove un-soluble solid. The solvent was removed under reduced pressure. The residue was further purified by re-crystallization from ethyl acetate/ petroleum ether (5:4) to yield the desired product **7** (3 g, 71.2% yield, $M+H^+$=422.5).

Step 5: Synthesis of 4-(3-aminophenoxy)-N-(4-(2-methoxyethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine(8)



[00248] To a solution of compound **7** (3 g, 7.1 mmol)in THF(40 mL),water (15 mL), NH4Cl (1.5 g, 28.4 mmol) and Fe (2 g, 35.5 mmol) were added. The reaction mixture was heated to refluxing for 4h and then cooled to room temperature. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (50 mL) and washed with saturated $NaHCO_3$ (30 mL) and water (50 mL x3). The organic solvent was removed under reduced pressure. The crude was further purified by re-crystallization from ethyl acetate/ PE (1:1) to yield the desired product **8** (2.4 g, 86.2% yield, $M+H^+$=392.5).

Step 6: Synthesis of N-(3-(2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (**I-10**)



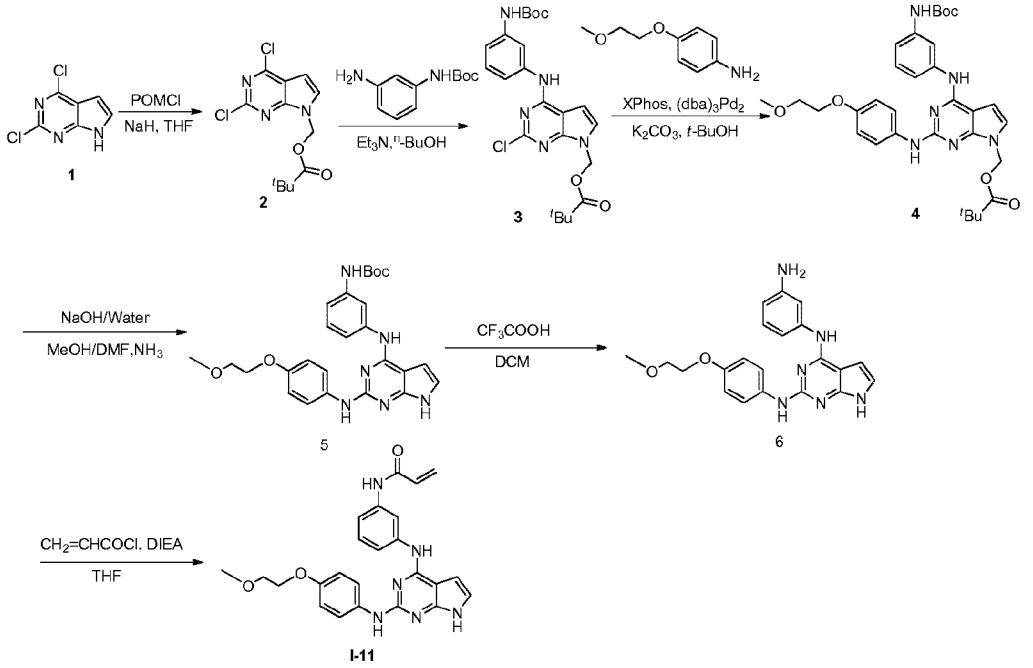
[00249] To a solution of compound **8** (328 mg, 0.83 mmol) and DIEA (112 mg, 0.87 mmol) in THF (5 mL) with ice-bath at -20°C, acryloyl chloride (79 mg, 0.87 mmol) was added over 5 min, maintaining the temperature around -10 °C throughout the addition. The reaction mixture was stirred for another 30min at the same temperature after the addition. After warmed up to room temperature, ethyl acetate (50 mL) was added. The mixture was washed with water (50 mL x3). The organic solvent was removed under reduced pressure. The crude was further purified by flash column chromatography to yield the desired product **I-10** (350 mg, 94.6% yield, $M+H^+$=446.5). ^1H NMR (500 MHz, DMSO-d_6) δ 11.51 (s, J = 26.7 Hz, 1H), 10.31 (s, 1H), 8.92 (s, J = 7.3 Hz, 1H), 7.66 (t, J = 2.1 Hz, 1H), 7.61 – 7.56 (m, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.43 (t, J = 8.1 Hz, 1H), 7.06 (dd, J = 3.5, 2.3 Hz, 1H), 7.00 (m, 1H), 6.70 (d, J = 9.0 Hz, 2H), 6.44 (dd, J = 17.0, 10.2 Hz, 1H), 6.30 – 6.23 (m, 2H), 5.77 (dd, J = 10.1, 1.9 Hz, 1H), 4.02 – 3.96 (m, 2H), 3.66 – 3.60 (m, 2H), 3.31 (s, J = 2.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.33 (s), 163.90 (s), 157.42 (s), 157.35 (s), 155.32 (s), 154.64 (s), 142.24 (s), 136.59 (s),

133.71 (s), 131.81 (s), 129.26 (s), 123.61 (s), 121.74 (s), 118.97 (s), 117.98 (s), 116.07 (s), 114.95 (s), 100.28 (s, 2C), 72.53 (s), 69.00 (s), 60.17 (s).

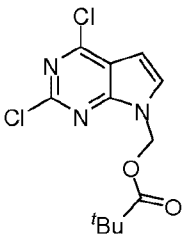
Example 11

Synthesis of N-(3-(2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acrylamide (I-11)

[00250] The synthetic scheme for compound **I-11** is shown below:

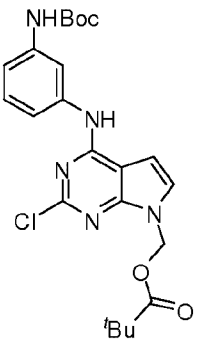


Step 1: Synthesis of (2, 4-dichloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (**2**)



[00251] NaH (80%, 3.54 g, 0.117 mol) was added slowly to a solution of 2, 4-dichloro-7H-pyrrolo[2,3-d]pyrimidine **1** (20.03 g, 0.106 mol) in THF (200 mL), and maintained the temperature between 0 ~ -5 °C. The mixture was stirred for another 15 min until the evolution of hydrogen ceased. A solution of POMCl (18.96 g, 0.12 mol) in THF (70 mL) was added over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 3~4 h. When HPLC indicated that **1** was consumed, the reaction mixture was filtered through Celite®, washed with ethyl acetate (100 mL). The combined organic layers were concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (300 mL), washed with water (100 mL x2) and brine (100 mL). The organic layer was separated and the solvent was removed under reduced pressure to afford the desired product **2** as yellow solid, which was used directly for the next step without further purification.

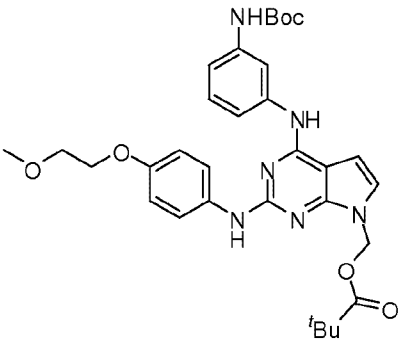
Step 2: Synthesis of (4-(3-(tertbutoxycarbonylamino)-2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yi)methyl pivalate (**3**)



[00252] To a mixture of pyrimidine **2** (6.1 g, 0.02 mol) and tert-butyl 3-aminophenylcarbamate (4.3 g, 0.019 mol) in n-BuOH (110 mL) was added TEA (7 mL). The reaction mixture was heated to refluxing and stirred for 12~18h. When HPLC indicated that compound **2** was consumed, the mixture was cooled to room temperature. Water (200 mL) and ethyl acetate (100 mL) were added into this mixture, which was agitated and separated layers. The organic layer was washed with 1N HCl (20mL), then 5% $NaHCO_3$ (50 mL), dried over sodium sulfate. The organic solvent was removed under reduced pressure to give a light oil, in

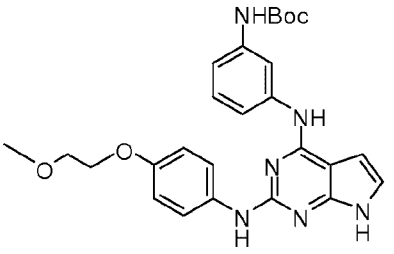
which hexane (60 mL) was added and stirred for 2~3 h. The precipitate was collected and dried to yield the desired product (3.92 g, $M+H^+$= 474.5) as white solid.

Step 3: Synthesis of (4-(3-(tert-butoxycarbonylamino)phenylamino)-2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (**4**)



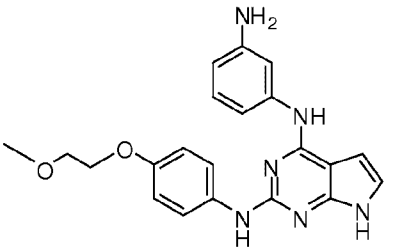
[00253] *t*-BuOH (80 mL) was added to a RBF (250mL) equipped with magic stirring. Compound **3** (3.92 g, 8.3 mmol) and 4-(2-methoxyethoxy)aniline (1.5 g, 9 mmol) were sequentially added and stirred for 5~10 min. Potassium carbonate (2.28 g, 16.5 mmol), tris(dibenzylideneacetone)dipalladium (750 mg, 0.9 mmol) and dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (750 mg, 18 mmol) were sequentially added and one more portion of *t*-BuOH (20 mL) was added. The flask was placed on an oil-bath and stirred under a N_2 flow. The reaction mixture was heated to refluxing. After stirred for 3~4 h, the reaction was complete indicated by TLC (DCM/MeOH = 10/1 as elution). The mixture was cooled to 40~50 °C and filtered through Celite®. The filter cake was washed with ethyl acetae (50 mL). The filtrate was concentrated under reduced pressure. The crude was then purified with Flash column chromatography (ethyl acetate: Hexane=1:10~1:3) to yield the desired product **4** (1.74 g, $M+H^+$= 605.5) as brown solid.

Step 4: tert-butyl 3-(2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenylcarbamate (**5**)



[00254] To a solution of compound 4 (1.74 g) in MeOH (25 mL) and THF (15 mL) in an ice-bath, NaOH solution (2.5 M, 2.3 mL) was added over 5 min(the temperature was kept around 6~10 °C throughout the addition). After the reaction mixture was stirred for 4~5 h at the same temperature, NH3 (gas) was bubbled into this reaction for 2~3 h. Once the reaction was complete indicated by TLC and LC-MS with the consumption of **4** and low content (less than 2%) of an intermediate (MW=521). Water (100 mL), and ethyl acetate (60 mL) were added. The mixture was agitated. Organic phase was separated and dried over sodium sulfate. The solvent was removed under reduced pressure to give the desired product **5** (1.35 g, $M+H^+$= 491.5) as brown oil, which was used directly for the next step without further purification.

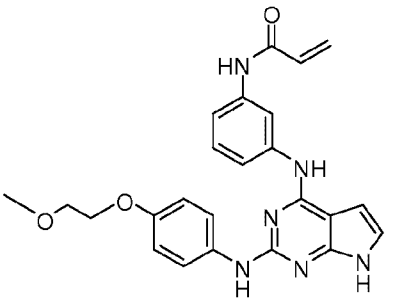
Step 5: Synthesis of N-(3-aminophenyl)-N-(4-(2-methoxyethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidine-2,4-diamine (**6**)



[00255] To a solution of **5** in DCM (49 mL) was added TFA (5.6 mL). The mixture was stirred at room temperature for 4 h. At this point the reaction was complete indicated by HPLC showing that compound **5** was consumed. The organic solvent was removed under reduced pressure. The crude was treated with cold (0°C) saturated sodium bicarbonate (30 mL) and ethyl acetate (60 mL). The mixture was agitated. Organic phase was separated and dried over sodium

sulfate. The organic solvent was removed under reduced pressure. The crude (brown oil) was further purified by flash column chromatography (Hexane: ethyl acetate = 1:5) to yield the desired product (918 mg, $M+H^+$= 391.5) as brown solid.

Step 6: Synthesis of N-(3-(2-(4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)phenyl)acrylamide (**I-11**)



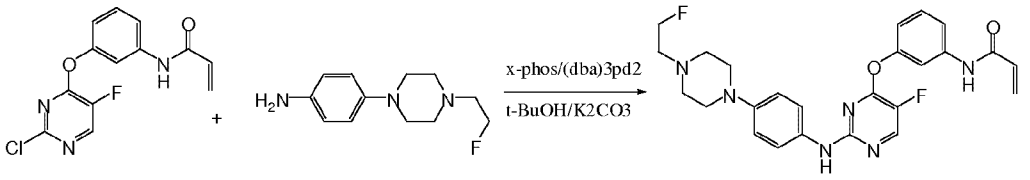
[00256] To a solution of **6** (918 mg, 2.35 mmol) and DIEA (320 mg, 2.48 mmol) in THF (20 mL) cooled with an ice bath (~--10 °C), acryloyl chloride (226 mg, 2.48 mmol) was added dropwise. The reaction mixture was stirred for 20 min. At this point, TLC (DCM/MeOH = 8/1 as elution) indicated the completion of the reaction. Saturated NaHCO3 solution (8 mL) was added to quench the reaction. THF was removed, and the residue was re-dissolved in ethyl acetate (50 mL) and water (20 mL). The mixture was agitated. The organic phase was separated and dried over sodium sulfate. The organic solvent was removed under reduced pressure. The crude (orange oil) was further purified by flash column chromatography (100% ethyl acetate) to yield the desired product I-11 (652 mg, $M+H^+$= 445.5) as white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.15 (s, 3H), 10.07 (s, 3H), 9.18 (s, 3H), 8.51 (s, 3H), 8.13 (s, 3H), 7.77 (d, *J* = 8.0 Hz, 3H), 7.73 – 7.66 (m, 6H), 7.33 (d, *J* = 8.5 Hz, 3H), 7.27 (t, *J* = 8.0 Hz, 3H), 6.88 (dd, *J* = 3.4, 2.2 Hz, 3H), 6.85 – 6.79 (m, 6H), 6.67 (dd, *J* = 3.5, 2.0 Hz, 3H), 6.48 (dd, *J* = 17.0, 10.2 Hz, 3H), 6.29 (dd, *J* = 17.0, 2.0 Hz, 3H), 5.77 (dd, *J* = 10.1, 2.0 Hz, 3H), 4.04 – 4.01 (m, 7H), 3.67 – 3.63 (m, 6H), 3.32 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.08 (s), 157.81 (s), 155.89 (s), 154.61 (s), 154.48 (s), 142.86 (s), 140.98 (s), 137.20 (s), 134.07 (s), 130.62 (s),

128.71 (s), 121.86 (s, 2C), 120.80 (s), 118.30 (s), 116.24 (s, 2C), 115.39 (s), 114.09 (s), 101.24 (s), 100.12 (s), 72.59 (s), 69.08 (s), 60.19 (s).

Example 12

Synthesis of N-(2-(5-fluoro-2-((4-(4-(2-fluoroethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-12)

[00257] The synthetic scheme for compound **I-12** is shown below:



I-12

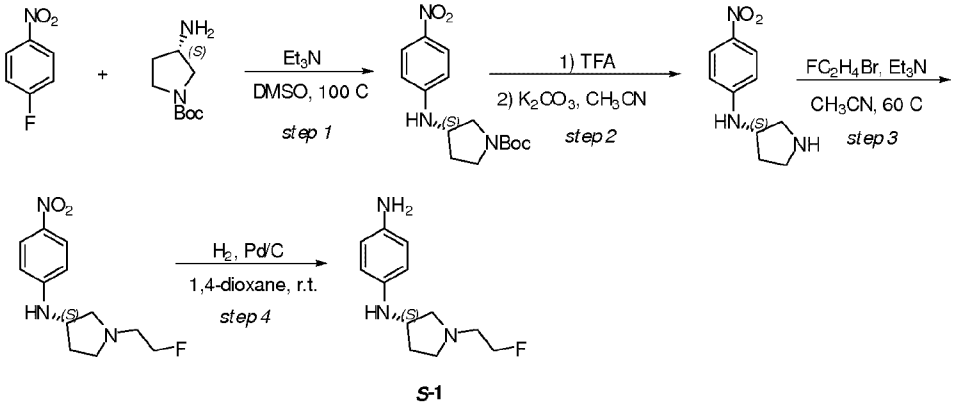
[00258] To a solution of N-(3-(2-chloro-5-fluoropyrimidin-4-yloxy)phenyl)acrylamide (1.3 g, 4.4 mmol), 4-(4-(2-fluoroethyl)piperazin-1-yl)aniline (1g, 4.4 mmol) in t-BuOH(15 mL), potassium carbonate (1.2 g, 8.8 mmol), tris(dibenzylideneacetone)dipalladium (400 mg) and dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (400 mg) were sequentially added. The reaction mixture was heated to refluxing and stirred under N_2 flow for 2 h. At this point, TLC (petroleum ether: ethyl acetate =1:1 as elution) indicated the completion of the reaction. The mixture was allowed to cool to 40~50°C, filtered through Celite®, and washed with t-BuOH. The filtrate was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (100 mL), washed with water. The organic solvent was removed under reduced pressure. The crude was further purified by flash column chromatography to yield the desired product **I-12** (1.2 g, 56.8% yield, $M+H^+$= 481.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.36 (s, 1H), 9.33 (s, 1H), 8.43 (d, *J* = 3.0 Hz, 1H), 7.68 (t, *J* = 2.1 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.45 (t, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.02 (m, 1H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.45 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.28 (dd, *J* = 17.0, 1.9 Hz, 1H), 5.79 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.66 – 4.58 (m, 1H), 4.56 – 4.49 (m, 1H), 3.04 – 2.93 (m, 4H), 2.69 (t, *J* = 4.9 Hz, 1H), 2.63 (t, *J* = 4.9 Hz, 1H), 2.60 – 2.54 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.37 (s), 158.94 (s),

158.86 (s), 157.34 (s), 157.31 (s), 154.09 (s), 148.11 (s), 142.33 (s), 134.28 (s), 133.65 (s), 131.99 (s), 129.34 (s), 121.74 (s), 118.76 (s), 118.63 (s), 117.59 (s), 114.94 (s), 83.90 (d, J = 164.4 Hz), 59.55 (d, J = 19.5 Hz), 54.96 (s, 2C), 50.96 (s, 2C).

Synthesis of intermediates (S-1 and R-1):

Intermediate **S-1**: (S)-N-(1-(2-fluoroethyl)pyrrolidin-3-yl)benzene-1,4-diamine

[00259] The synthetic scheme is shown below:



S-1

Step 1

[00260] A 3-neck round-bottom-flask (250 mL) equipped with a condenser was charged with 4-fluoro-1-nitrobenzene (7.3 g), (3S)-(-)-1-(t-Butoxycarbonyl)-3-aminopyrrolidine (11.2 g) and TEA (19 g) in dimethyl sulfoxide (58 mL). The reaction was heated at 100°C overnight. After completion of the reaction, the reaction mixture was poured into water. The mixture was extracted with ethyl acetate. Organic layer was washed with brine and dried over sodium sulfate. Organic solvent was removed under reduce pressure. The resulting crude product (22.75 g) was used directly for the next step reaction without further purification.

Step 2

[00261] To the crude product from step 1 (22.7 g) in a 3-neck round-bottom-flask (250 mL) was added TFA (74 mL) at room temperature. The reaction mixture was stirred for 2 h at room

temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to remove un-reacted TFA. The residue was re-dissolved in MeOH and then basified using K_2CO_3 under 0°C. The crude product (29.95 g) was obtained after removal of un-reacted K_2CO_3 and solvent.

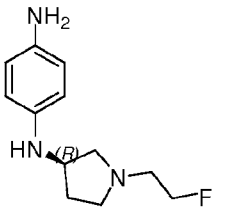
Step 3

[00262] To the crude from step 2 (27 g) in MeCN (170 mL) was added TEA (35 mL) and 1,2-bromofluoroethane (12 g). The reaction mixture was heated at 60 °C for 25 hours. After completion of the reaction, the reaction mixture was poured into water. The mixture was extracted with ethyl acetate. The organic layer was separated, washed with brine, and dried over sodium sulfate. The organic solvent was removed under reduce pressure. The resulted crude was purified by flash chromatography to afford the desired product (11.3 g, 86% yield over 3 steps) as yellow solid.

Step 4

[00263] A solution of above product from step 3 (2.183 g) and Pd/C (0.798 g) in 1,4-dioxane (43 mL) was hydrogenated for 22 hours at room temperature. After completion of the reaction, the reaction mixture was filtered through Celite-bed. The Celite bed was washed with 1,4-dioxane. The filtrate was concentrated to provide the desired amine (2.022 g) as dark oil which was used directly for the next step reaction without further purification.

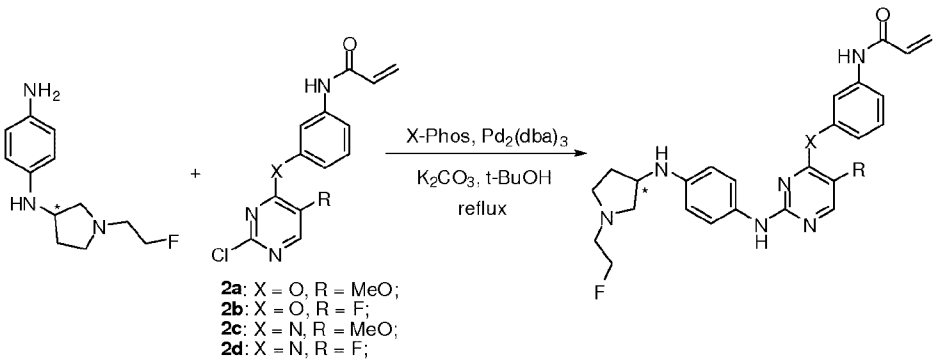
(R)-N-(1-(2-fluoroethyl)pyrrolidin-3-yl)benzene-1,4-diamine (*R*-1)



***R*-1**

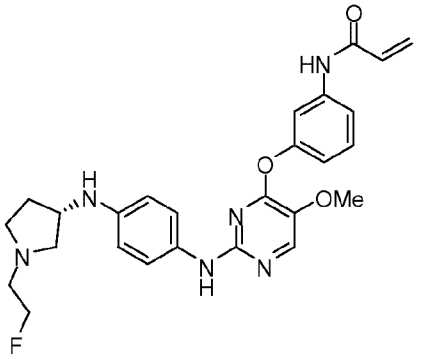
[00264] The title compound was synthesized using similar chemistry and procedures described above with starting from (3R)-(+)-1-(t-Butoxycarbonyl)-3-aminopyrrolidine.

[00265] The synthetic scheme for Example **XIII** to **XX** is shown below:



Example 13

Synthesis of (S)-N-(3-(2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-13)



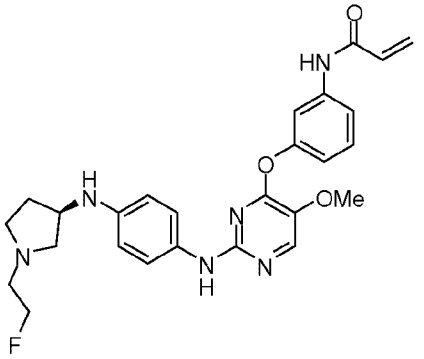
I-13

[00266] A mixture of above **2a** (828 mg, 2.71 mmol), ***S*-1** (630 mg, 2.82 mmol), tris(dibenzylideneacetone)dipalladium (79 mg, 0.086 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (84 mg, 0.176 mmol) and potassium carbonate (758 mg, 5.48 mmol) in tert-butanol (26 mL) was stirred under argon at refluxing temperature for 3.5 h. After cooling to RT, the reaction mixture was filtered through Celite. The Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (DCM/MeOH = 50/1) to give the title compound (1.07 g, yield 81%, $M+H^+ = 493.5$). ^1H NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.80 (s,

1H), 8.13 (s, 1H), 7.65 – 7.53 (m, 2H), 7.41 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.94 (m, 1H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.35 – 6.20 (m, 3H), 5.78 (dd, J = 10.1, 1.9 Hz, 1H), 5.23 (d, J = 7.0 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.46 (t, J = 5.0 Hz, 1H), 3.85 (s, 3H), 3.79 – 3.71 (m, 1H), 2.82 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 – 2.60 (m, 3H), 2.55 – 2.47 (m, 2H), 2.36 (dd, J = 9.3, 4.6 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.57 – 1.43 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.30 (s), 161.44 (s), 156.14 (s), 154.83 (s), 146.15 (s), 145.00 (s), 142.28 (s), 136.28 (s), 133.69 (s), 132.06 (s), 131.79 (s), 129.28 (s), 122.07 (s), 118.79 (s), 117.96 (s), 114.70 (s), 114.33 (s), 84.85 (d, J = 164.4 Hz), 62.73 (s), 59.70 (s), 57.21 (d, J = 19.5 Hz), 55.14 (s), 53.86 (s), 33.88 (s).

Example 14

Synthesis of (R)-N-(3-(2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-14)

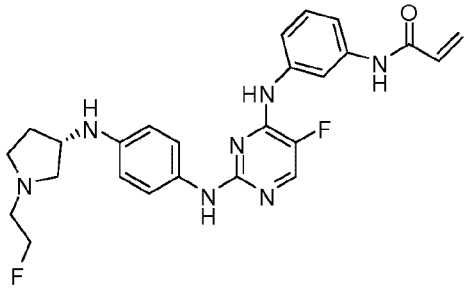


I-14

[00267] A mixture of above **2a** (1.5g, 4.91mmol), ***R*-1** (1.1g, 4.91mmol), tris(dibenzylideneacetone)dipalladium (400 mg, 0.437 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (400 mg, 5.87 mmol) and potassium carbonate (1.36g , 9.84 mmol) in tert-butanol (100 mL) was stirred under argon at reflux temperature for 5 h. After cooling to RT, the reaction mixture was filtered through Celite. The Celite was washed with ethyl acetate, and the combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (EA/PE = 10/1) to give the title compound (0.94 g, 40%, M+H$^+$ = 493.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1H), 8.80 (s, 1H), 8.13 (s, 1H), 7.65 – 7.53 (m, 2H), 7.41 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 2H), 6.94 (m, 1H), 6.44

(dd, J = 17.0, 10.1 Hz, 1H), 6.35 – 6.20 (m, 3H), 5.78 (dd, J = 10.1, 1.9 Hz, 1H), 5.23 (d, J = 7.0 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.46 (t, J = 5.0 Hz, 1H), 3.85 (s, 3H), 3.79 – 3.71 (m, 1H), 2.82 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 – 2.60 (m, 3H), 2.55 – 2.47 (m, 2H), 2.36 (dd, J = 9.3, 4.6 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.57 – 1.43 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.30 (s), 161.44 (s), 156.14 (s), 154.83 (s), 146.15 (s), 145.00 (s), 142.28 (s), 136.28 (s), 133.69 (s), 132.06 (s), 131.79 (s), 129.28 (s), 122.07 (s), 118.79 (s), 117.96 (s), 114.70 (s), 114.33 (s), 84.85 (d, J = 164.4 Hz), 62.73 (s), 59.70 (s), 57.21 (d, J = 19.5 Hz), 55.14 (s), 53.86 (s), 33.88 (s).

Example 15
Synthesis of (S)-N-(3-(5-fluoro-2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide (I-15)



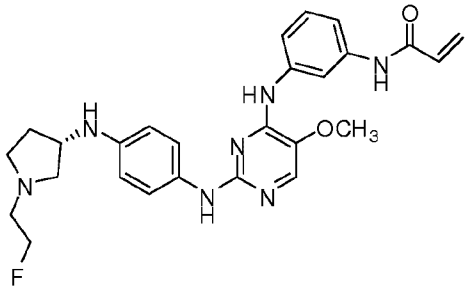
I-15

[00268] A mixture of above **2d** (812 mg), ***S*-1** (627 mg), tris(dibenzylideneacetone)dipalladium (262 mg), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (271mg,) and potassium carbonate (818 mg,) in tert-butanol (20 mL) was stirred under argon at refluxing temperature for 3.5 h. After cooling to RT, the reaction mixture was filtered through Celite and the Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ EtOH = 10/1) to give the title compound (100 mg, yield 7.4%, M+H$^+$ = 480.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.12 (s, J = 14.4 Hz, 1H), 9.30 (s, 1H), 8.67 (s, 1H), 8.02 (d, J = 3.7 Hz, 1H), 7.94 (s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.24 (t, J = 8.1 Hz, 1H), 6.53 – 6.39 (m, 3H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.84 – 5.69 (m, 1H), 5.30 (d, J = 7.1 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.47 (t, J = 5.0 Hz, 1H), 3.87 –

3.74 (m, 1H), 2.84 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.62 (m, 2H), 2.57 – 2.48 (m, 2H), 2.40 (dd, J = 9.3, 4.5 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.61 – 1.48 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.53 (s), 156.57 (s), 150.06 (d, J = 10.5 Hz), 143.84 (s), 141.73 – 141.13 (m), 139.74 (s), 139.55 (s), 139.48 (s), 132.41 (s), 130.46 (s), 129.00 (s), 127.25 (s), 121.71 (s), 117.51 (s), 114.88 (s), 113.42 (s), 112.86 (s), 83.31 (d, J = 164.4 Hz), 61.21 (s), 55.66 (d, J = 19.5 Hz), 53.60 (s), 52.33 (s), 32.35 (s).

Example 16

Synthesis of (*S*)-*N*-(3-(2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (I-16)



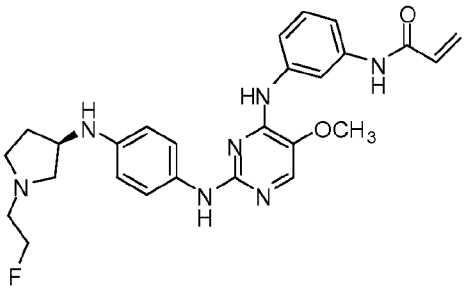
I-16

[00269] A mixture of above **2c** (873 mg, 2.87 mmol), ***S*-1** (640 mg, 2.87 mmol), tris(dibenzylideneacetone)dipalladium (250 mg, 0.272 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (250 mg, 0.544 mmol) and potassium carbonate (795 mg, 5.84 mmol) in tert-butanol (20 mL) was stirred under argon at reflux temperature for 3.5 h. After cooling to RT, the reaction mixtures was filtered through Celite and the Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (DCM/MeOH = 50/1) to give the title compound (407 mg, yield 28.89%, M+H$^+$ = 492.6). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.63 (s, 1H), 8.32 (s, 1H), 7.97 (s, 1H), 7.78 (s, J = 5.0 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.9 Hz, 2H), 7.23 (t, J = 8.1 Hz, 1H), 6.53 – 6.38 (m, 3H), 6.27 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz, 1H), 5.21 (d, J = 6.2 Hz, 1H), 4.57 (t, J = 5.0 Hz, 1H), 4.47 (t, J = 5.0 Hz, 1H), 3.83 (s, 3H), 3.81 (br s, 1H), 2.84 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 –

2.71 (m, 1H), 2.71 – 2.62 (m, 2H), 2.56 – 2.47 (m, 2H), 2.40 (dd, J = 9.3, 4.6 Hz, 1H), 2.16 (qd, J = 13.4, 7.9 Hz, 1H), 1.55 (dq, J = 7.7, 6.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.06 (s), 156.50 (s), 153.76 (s), 144.87 (s), 141.82 (s), 140.91 (s), 139.47 (s), 136.04 (s), 134.03 (s), 132.85 (s), 130.46 (s), 128.74 (s), 122.60 (s, 2C), 118.91 (s), 116.05 (s), 114.92 (s), 114.56 (s, 2C), 84.88 (d, J = 164.4 Hz), 62.81 (s), 59.08 (s), 57.24 (d, J = 19.5 Hz), 55.16 (s), 53.98 (s), 33.94 (s).

Example 17

Synthesis of (R)-N-(3-(2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)-5-methoxypyrimidin-4-ylamino)phenyl)acrylamide (I-17)



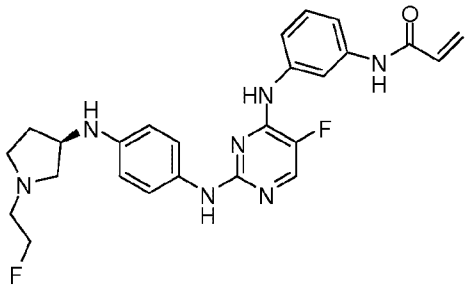
I-17

[00270] A mixture of above **2c** (1412 mg), ***R*-1** (1048 mg), tris(dibenzylideneacetone)dipalladium (312 mg), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (324mg,) and potassium carbonate (1246 mg,) in tert-butanol (40 mL) was stirred under argon at reflux temperature for 3.5 h. After cooling to RT, the reaction mixture was filtered through Celite, and the Celite was washed with EA. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ EtOH = 10/1) to give the title compound (800 mg, yield 34.6%, M+H$^+$ = 492.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.63 (s, 1H), 8.32 (s, 1H), 7.97 (s, 1H), 7.78 (s, J = 5.0 Hz, 1H), 7.59 (d, J = 8.1 Hz, 1H), 7.40 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 8.9 Hz, 2H), 7.23 (t, J = 8.1 Hz, 1H), 6.53 – 6.38 (m, 3H), 6.27 (dd, J = 17.0, 2.0 Hz, 1H), 5.76 (dd, J = 10.1, 2.0 Hz, 1H), 5.21 (d, J = 6.2 Hz, 1H), 4.57 (t, J = 5.0 Hz, 1H), 4.47 (t, J = 5.0 Hz, 1H), 3.83 (s, 3H), 3.81 (br s, 1H), 2.84 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.62 (m, 2H), 2.56 – 2.47 (m, 2H), 2.40 (dd, J = 9.3, 4.6 Hz, 1H), 2.16 (qd, J = 13.4, 7.9 Hz, 1H), 1.55 (dq, J = 7.7,

6.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.06 (s), 156.50 (s), 153.76 (s), 144.87 (s), 141.82 (s), 140.91 (s), 139.47 (s), 136.04 (s), 134.03 (s), 132.85 (s), 130.46 (s), 128.74 (s), 122.60 (s, 2C), 118.91 (s), 116.05 (s), 114.92 (s), 114.56 (s, 2C), 84.88 (d, J = 164.4 Hz), 62.81 (s), 59.08 (s), 57.24 (d, J = 19.5 Hz), 55.16 (s), 53.98 (s), 33.94 (s).

Example 18

Synthesis of (R)-N-(3-(5-fluoro-2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-18)



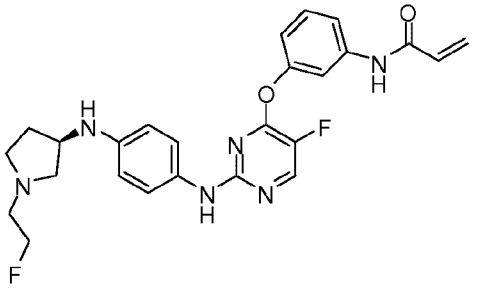
I-18

[00271] A mixture of above **2d** (870mg, 2.97mmol), ***R*-1** (660mg, 2.96mmol) tris(dibenzylideneacetone)dipalladium (172 mg, 0.188 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (172 mg, 0.360 mmol) and potassium carbonate (800 mg, 5.79 mmol) in tert-butanol (50 mL) was stirred under argon at reflux temperature for 5 h. After cooling to RT, the reaction mixture was filtered through Celite, and the Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ petroleum ether = 10/1) to give the title compound (0.58 g, yield 41%, M+H$^+$ = 480.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.12 (s, J = 14.4 Hz, 1H), 9.30 (s, 1H), 8.67 (s, 1H), 8.02 (d, J = 3.7 Hz, 1H), 7.94 (s, 1H), 7.55 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.24 (t, J = 8.1 Hz, 1H), 6.53 – 6.39 (m, 3H), 6.28 (dd, J = 17.0, 2.0 Hz, 1H), 5.84 – 5.69 (m, 1H), 5.30 (d, J = 7.1 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.47 (t, J = 5.0 Hz, 1H), 3.87 – 3.74 (m, 1H), 2.84 (dd, J = 9.2, 6.9 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.62 (m, 2H), 2.57 – 2.48 (m, 2H), 2.40 (dd, J = 9.3, 4.5 Hz, 1H), 2.22 – 2.11 (m, 1H), 1.61 – 1.48 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.53 (s), 156.57 (s),

150.06 (d, J = 10.5 Hz), 143.84 (s), 141.73 – 141.13 (m), 139.74 (s), 139.55 (s), 139.48 (s), 132.41 (s), 130.46 (s), 129.00 (s), 127.25 (s), 121.71 (s), 117.51 (s), 114.88 (s), 113.42 (s), 112.86 (s), 83.31 (d, J = 164.4 Hz), 61.21 (s), 55.66 (d, J = 19.5 Hz), 53.60 (s), 52.33 (s), 32.35 (s).

Example 19

Synthesis of (R)-N-(3-(5-fluoro-2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-19)



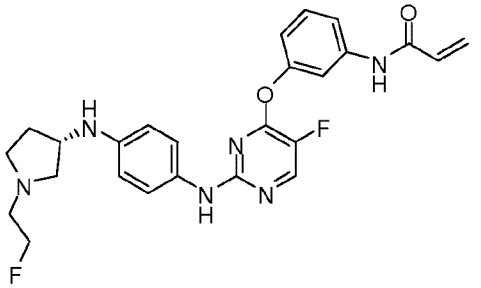
I-19

[00272] A mixture of above **2b** (1408 mg), ***R*-1** (1062 mg), tris(dibenzylideneacetone)dipalladium (353 mg), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (359mg,) and potassium carbonate (1260mg,) in tert-butanol (35mL) was stirred under argon at reflux temperature for 4.5 h. After cooling to RT, the reaction mixture was filtered through Celite, and the Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ EtOH = 10/1) to give the title compound (987 mg, yield 42.9%, $M+H^+$ = 481.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.13 (s, 1H), 8.38 (d, J = 3.0 Hz, 1H), 7.67 (t, J = 1.9 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.02 (m, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.35 – 6.24 (m, 3H), 5.79 (dd, J = 10.1, 1.9 Hz, 1H), 5.32 (d, J = 6.8 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.46 (t, J = 5.0 Hz, 1H), 3.83 – 3.69 (m, 1H), 2.82 (dd, J = 9.1, 7.0 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.60 (m, 2H), 2.55 – 2.47 (m, 2H), 2.37 (dd, J = 9.2, 4.5 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.59 – 1.45 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.35 (s), 158.84 (d, J = 11.0 Hz), 157.58 (d, J = 2.8 Hz), 154.14 (s), 147.88 (d, J = 21.9 Hz), 145.58 (s), 142.35 (s), 140.31 (s), 133.66 (s), 131.90 (s), 131.24 (s), 129.34 (s),

122.68 (s), 118.78 (s), 118.43 (s), 114.69 (s), 114.23 (s), 84.84 (d, J = 164.5 Hz), 62.69 (s), 57.19 (d, J = 19.5 Hz), 55.13 (s), 53.80 (s), 33.85 (s).

Example 20

Synthesis of (S)-N-(3-(5-fluoro-2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-20)

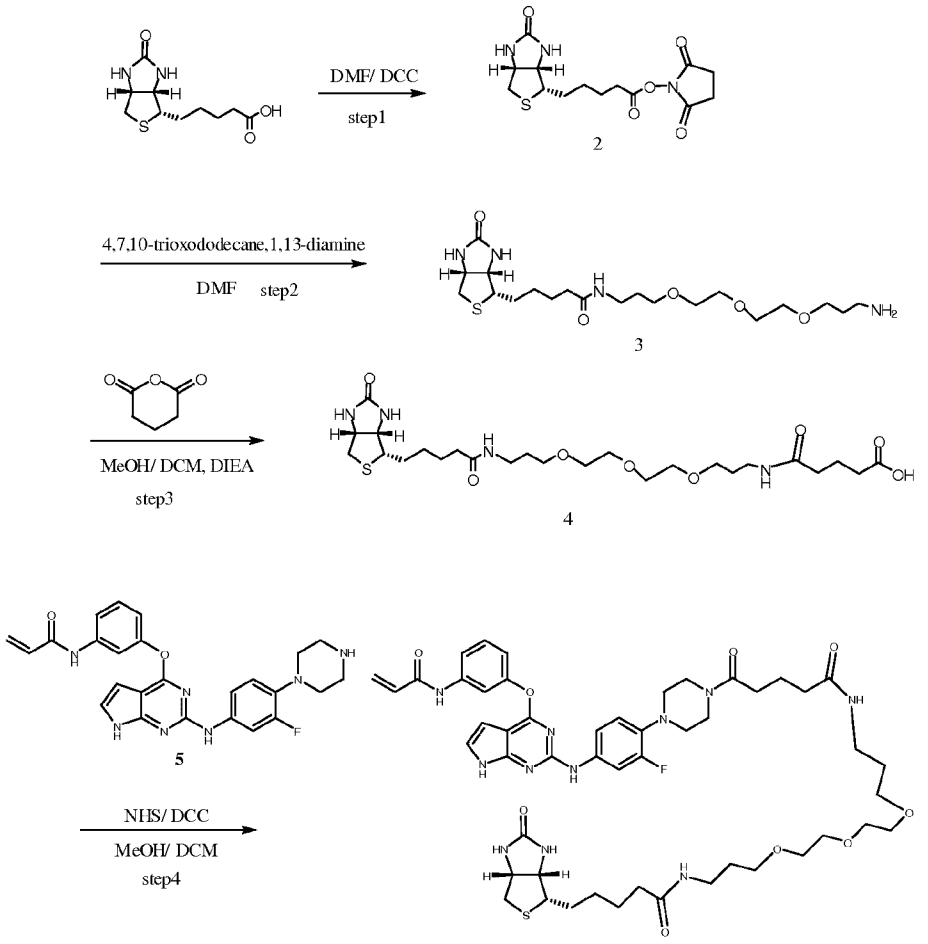


I-20

[00273] A mixture of above **2b** (791 mg), ***S*-1** (607mg), tris(dibenzylideneacetone)dipalladium (193mg), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (200mg,) and potassium carbonate (758mg,) in tert-butanol (30mL) was stirred under argon at reflux temperature for 7 h. After cooling to RT, the reaction mixture was filtered through Celite, and the Celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/ EtOH = 10/1) to give the title compound (441 mg, yield 34.1%, $M+H^+$ = 481.5). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.35 (s, 1H), 9.13 (s, 1H), 8.38 (d, J = 3.0 Hz, 1H), 7.67 (t, J = 1.9 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.43 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 7.8 Hz, 2H), 7.02 (m, 1H), 6.45 (dd, J = 17.0, 10.1 Hz, 1H), 6.35 – 6.24 (m, 3H), 5.79 (dd, J = 10.1, 1.9 Hz, 1H), 5.32 (d, J = 6.8 Hz, 1H), 4.56 (t, J = 5.0 Hz, 1H), 4.46 (t, J = 5.0 Hz, 1H), 3.83 – 3.69 (m, 1H), 2.82 (dd, J = 9.1, 7.0 Hz, 1H), 2.77 – 2.71 (m, 1H), 2.71 – 2.60 (m, 2H), 2.55 – 2.47 (m, 2H), 2.37 (dd, J = 9.2, 4.5 Hz, 1H), 2.19 – 2.10 (m, 1H), 1.59 – 1.45 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.35 (s), 158.84 (d, J = 11.0 Hz), 157.58 (d, J = 2.8 Hz), 154.14 (s), 147.88 (d, J = 21.9 Hz), 145.58 (s), 142.35 (s), 140.31 (s), 133.66 (s), 131.90 (s), 131.24 (s), 129.34 (s), 122.68 (s), 118.78 (s), 118.43 (s), 114.69 (s), 114.23 (s), 84.84 (d, J = 164.5 Hz), 62.69 (s), 57.19 (d, J = 19.5 Hz), 55.13 (s), 53.80 (s), 33.85 (s).

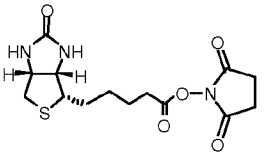
Example 21

Synthesis of biotin substituted Compound (I-42)



I-42

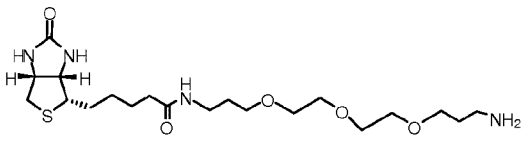
Step1:



[00274] To a round bottom flask with a stirring bar, biotin (2.0 g, 8.2 mmol) and DMF (60 mL) were added. After the solid was dissolved with heat, N-hydroxysuccinimide (0.944 g, 8.2 mmol) and DCC (2.2 g, 10.7 mmol) were added. The reaction mixture was stirred at room

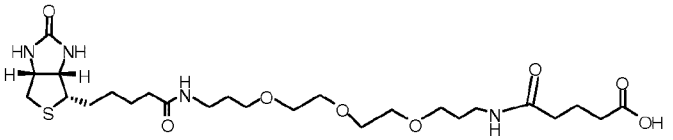
temperature overnight. The white solid was filtered, and the DMF was evaporated under reduced pressure. The resulting residue was further purified by re-crystallization from isopropanol to give the desired product **2** (2.7 g, $M+H^+ = 342.5$) as white crystals.

Step2:



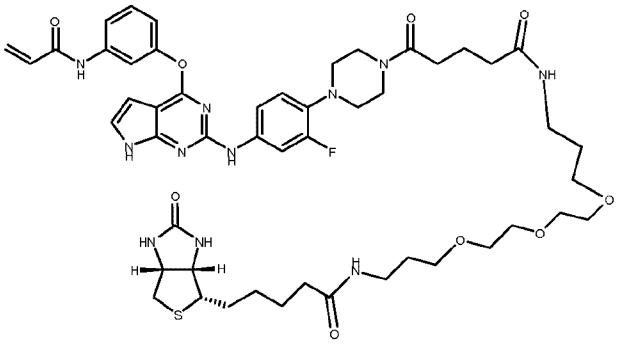
[00275] To a solution of 4,7,10-trioxododecane1,13-diamine (6.7 g, 30.4 mmol) in anhydrous DMF(100 mL) was drop-wise added a solution of **2** (2.0 g, 5.86 mmol) in dry DMF (50 mL) over a period of 30 min under N_2. The resulting thick white suspension was stirred for 30 min. The precipitate was filtered and washed with DMF. The combined filtrate was concentrated and diethyl ester was added. The precipitate (sticky solid) was collected and purified by flash chromatography (DCM/ MeOH = 5/1) to give desired compound **3** (2.44 g, yield 93%, $M+H^+ =$ 448.5).

Step3:



[00276] To a solution of **3** (2.44 g, 5.44 mmol) in dry methanol/ DCM (1:1, 60 mL) were added glutaric anhydride (0.61 g, 5.35 mmol) and anhydrous diisopropyl ethylamine (2.5 g, 19 mmol). The reaction mixture was stirred at room temperature for 3 h, and then solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (DCM/ MeOH = 5/1) to give desired compound **4** (1.3 g, yield 43%, $M+H^+ =$ 561.5).

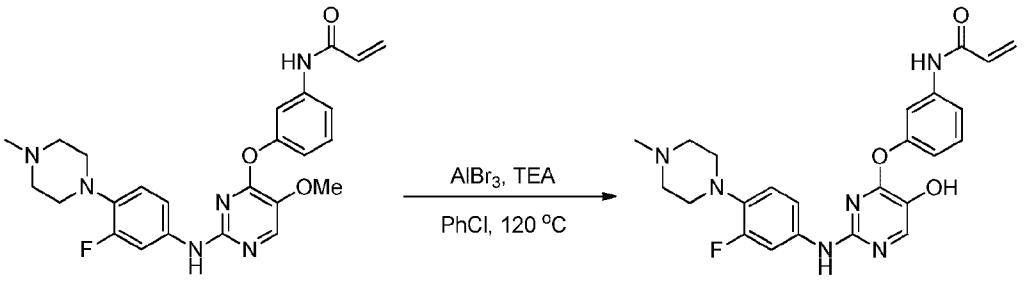
Step4:



[00277] To a solution of **4** (290 mg, 0.516 mmol) in dry methanol/ DCM (3:5, 16 mL) were added N-hydroxysuccinimide (89 mg, 0.775 mmol) and DCC (160 mg, 0.775 mmol). The mixture was stirred at room temperature for 3h, and then a solution of 5 (synthesized separated) in dry methanol/ DCM (1:1, 6 mL) was added. The reaction mixture was stirred overnight, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (DCM/ MeOH = from 50/1 to 15/1) to give the desired product **I-42** (174mg, yield 44%, $M+H^+ = 1017.6$).

Example 22

Synthesis of N-(3-(2-(3-fluoro-4-(4-methylpiperazin-1-yl)phenylamino)-5-hydroxypyrimidin-4-yloxy)phenyl)acrylamide (I-23a)



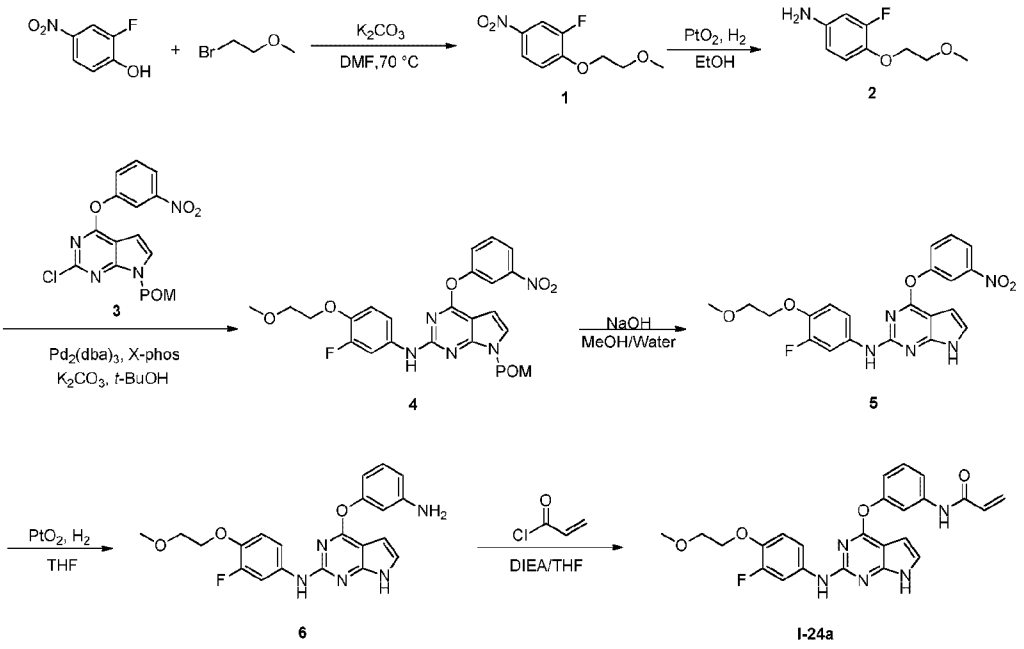
I-2 I-23a

[00278] To a solution of $AlBr_3$ (2.733 g) in chlorobenzene (20 mL) was drop-wise added TEA (0.434 g, 4.8 mmol). Compound **I-2** (0.518 g) was then added. The reaction mixture was stirred at 120℃ for 4.5 h. MeOH (10 mL) was then added in to quench the reaction. Water was

added in, and the mixture was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The crude was purified by column chromatography (DCM/MeOH = 15/1 as mobile phase) to give desired product **I-23a** (0.07 g, 13.88%, M+H+=465.5).

Example 23

Synthesis of N-(3-(2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-24a)



Synthesis of 2-fluoro-1-(2-methoxyethoxy)-4-nitrobenzene (1)

[00279] A mixture of 2-fluoro-4-nitrophenol (7.940 g, 50.57 mmol), 1-bromo-2-methoxyethane (7.656 g, 55.09 mmol), K_2CO_3 (13.880 g, 100.57 mmol) in DMF (50 mL) was stirred at 70-75 for 3 h until TLC (DCM/MeOH = 50/1 as mobile phase) indicated the completion of the reaction. The mixture was allowed to cool down to room temperature and then poured onto ice water (180 mL). The yellow precipitate was collected, washed with water (100

mL) and dried under vacuum for 5 hours to afford 2-fluoro-1-(2-methoxyethoxy)-4-nitrobenzene **1** (10.33 g, 95.81%).

Synthesis of 3-fluoro-4-(2-methoxyethoxy)aniline (2)

[00280] A mixture of **1** (5.15 g, 23.93 mmol) and PtO_2 (0.143 g, 0.63 mmol) in EtOH (100 mL) was stirred at room temperature with hydrogen balloon overnight. After completion of the reaction, the reaction mixture was filtered through Celite®. The Celite layer was washed with EtOH. The combined filtrate was concentrated under reduced pressure to afford **2** (4 g, 91%, $M+H^+=186.5$) without further purification.

Synthesis of (2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (4)

[00281] Compound **2** (4.432 g, 23.95 mmol), compound **3** (9.752 g, 24 mmol), K_2CO_3 (6.659 g, 48.25 mmol), tris(dibenzylideneacetone)dipalladium (1.027 g, 1.12 mol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (1.121 g, 2.36 mmol) and *t*-BuOH (50 mL) were sequentially added to a round-bottom flask. The reaction mixture was stirred at refluxing under N_2 flow. After reaction for 3~4 h, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and then filtered through Celite®. The celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (Ethyl acetate: Petroleum ether = from 50% to 100% as mobile phase) to give **4** (9.61 g, 72.39%, $M+H^+ = 554.5$) as a slight yellow solid.

Synthesis of N-(3-fluoro-4-(2-methoxyethoxy)phenyl)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (5)

[00282] To a round-bottom flask (250 mL) was charged with compound **4** (9.608 g, 17.36 mmol) and MeOH (60 mL). After compound **4** was completely dissolved, the solution was cooled down to ~10 °C with an ice-bath. NaOH aqu solution (2.5 M, 20 mL) was slowly added into the flask with maintaining of the temperature around 16 °C during the addition. The mixture was continued to stir for another 2 h at this temperature. Water (150 mL) was added slowly to

the flask over 45 min with maintaining of the temperature below 20°C during the addition of water. The precipitate was collected, washed with water (50 mL) and dried under vacuum to afford the desired product **5** (4.232 g, 55%, $M+H^+ = 440.6$), which was used for next step without further purification.

Synthesis of 4-(3-aminophenoxy)-N-(3-fluoro-4-(2-methoxyethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (6)

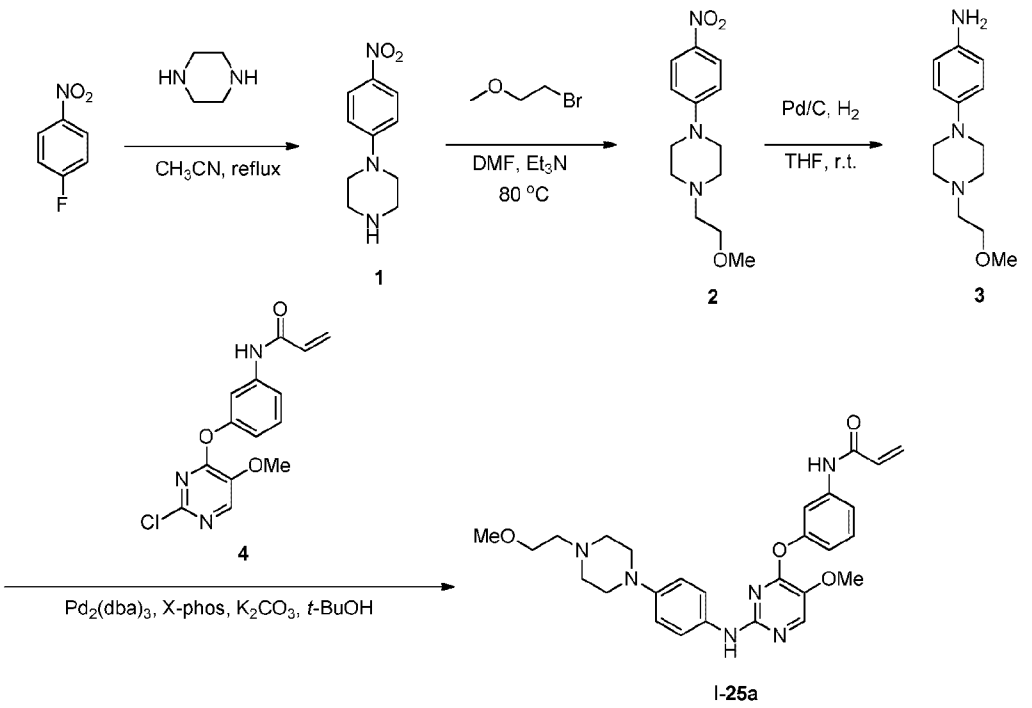
[00283] A mixture of **5** (4.232 g, 9.6mmol) and PtO_2 (0.101 g, 0.45 mmol) in THF (40 mL) was stirred at room temperature with hydrogen balloon overnight. After completion of the reaction, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford the desired product **6** (3.35 g, 85%, $M+H^+ = 410.5$) as a white solid.

Synthesis of N-(3-(2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-24a)

[00284] To a solution of compound **6** (2.05 g, 4 mmol) and DIEA (1.341 g, 10.4 mmol) in THF (50 mL) at 0°C, acryloyl chloride (0.434 g, 4.8 mmol) was dropwise added over 5 min. The reaction mixture was stirred for 1 h at 0°C. At this point, TLC indicated the reaction to be complete. NaOH aq. solution (1 M, 4 mL) and water (20 mL) were added to quench the reaction. The resulting mixture was continued to stir for another 10 min. The upper THF phase was separated and the solvent was removed under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate: Petroleum ether from 50% to 100% as mobile phase) to give **I-24a** (1.420 g, 76.67%, $M+H^+ = 464.6$) as a white solid.

Example 24

Synthesis of N-(3-(5-methoxy-2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-25a)



Synthesis of 1-(4-nitrophenyl)piperazine (1)

[00285] A mixture of 4-nitrofluorobenzene (70.7 g), piperazine (49.8 g) and acetonitrile (400 mL) was stirred at refluxing overnight. The reaction was monitored by TLC. After the reaction was complete, the reaction mixture was allowed to cool down to room temperature, basified with saturated K_2CO_3 solution (500 mL), and then extracted with ethyl acetate. The combined organic layers was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to afforded 1-(4-nitrophenyl)piperazine **2** (88.4 g, 85.1%, $M+H^+$= 208.5) as a yellow solid.

Synthesis of 1-(2-methoxyethyl)-4-(4-nitrophenyl)piperazine (2)

[00286] To a solution of 1-bromo-2-methoxyethane (60.5 g) and **1** (78.5 g) in DMF (400 mL) at room temperature was added Et_3N (65.6 g). The mixture was then heated up at 80 °C and stirred for 4.5 h. At this point, TLC indicated the reaction to be complete. The reaction mixture was poured onto ice-water (1 L). The yellow precipitate was collected and dissolved with ethyl acetate. The solution was washed with water, brine and dried over Na_2SO_4. The organic solvent was removed under reduced pressure. The crude residue was re-dissolved with ethyl acetate

(300 mL), and petroleum ether (250 mL) was then added. The resulting precipitate was removed (undesired product). The filtrate was concentrated under reduced pressure to afforded desired product **2** (65.4 g, 65.1%, $M+H^+$= 266.6) as a yellow solid.

Synthesis of 4-(4-(2-methoxyethyl)piperazin-1-yl)aniline (3)

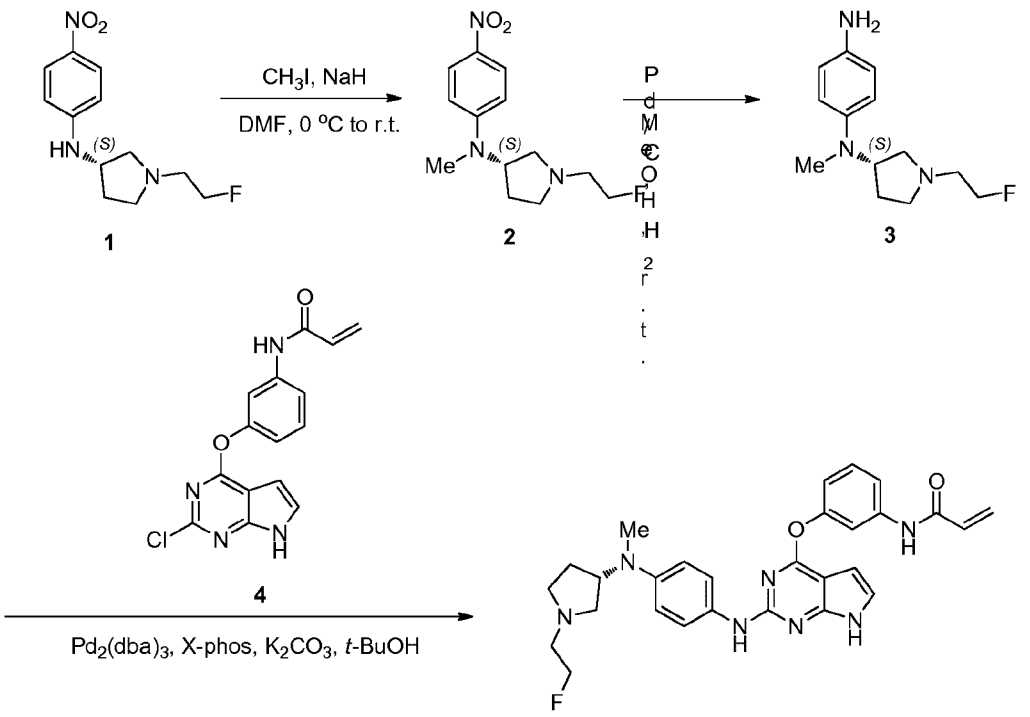
[00287] A solution of **2** (63.4 g) and Pd/C (4.634 g, 10% activated on carbon) in THF (500 mL) was stirred at room temperature with hydrogen balloon overnight. After completion of the reaction, the reaction mixture was filtered through Celite®. The celite was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford the crude compound **3** (54.0 g, 96.0%, $M+H^+$= 236.6) without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-25a)

[00288] Compound **3** (0.835 g), compound **4** (1.1 g), K_2CO_3 (0.964 g), tris(dibenzylideneacetone)dipalladium (0.164 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.157 g) and *t*-BuOH (20 mL) were sequentially added to a round-bottom flask. The reaction mixture was stirred at refluxing under N_2 flow. After reaction for 3~4 h, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and was filtered through Celite®. The celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure. The crude was further purified by column chromatography (EtOAc: EtOH = 20:1 as mobile phase) to give **I-25a** (0.923 g, 98.37%, $M+H^+$= 505.6) as a white solid.

Example 25

Synthesis of (*S*)-N-(3-(2-(4-((1-(2-fluoroethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-26a)



I-26a

Synthesis of (*S*)-1-(2-fluoroethyl)-N-methyl-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00289] To a solution of 1 (see the previous section of intermediate *S*-1, 2.572 g) in DMF (28 mL) at 0°C was sequentially added NaH (0.35 g, 80% dispersion in mineral oil) and CH_3I (1.65 g). The resulting mixture was allowed to warm up to room temperature and stirred for 1 h. At this point, TLC indicated the reaction to be complete. The reaction mixture was then quenched with water and extracted with ethyl acetate. The combined organic layers was washed with water and dried over Na_2SO_4. The organic solvent was removed under reduced pressure to afford crude product**2** (2.501 g, 91.1%, $M+H^+$= 268.5), which was used directly in next step without further purification.

Synthesis of (*S*)-N^1-(1-(2-fluoroethyl)pyrrolidin-3-yl)-N^1-methylbenzene-1,4-diamine (3)

[00290] A mixture of **2** (2.501 g) and Pd/C (0.495 g, 10% activated on carbon) in MeOH (39 mL) was stirred at room temperature with hydrogen balloon for 4.5 h. At this point, TLC showed the reaction to be complete. The reaction mixture was filtered through Celite®. The

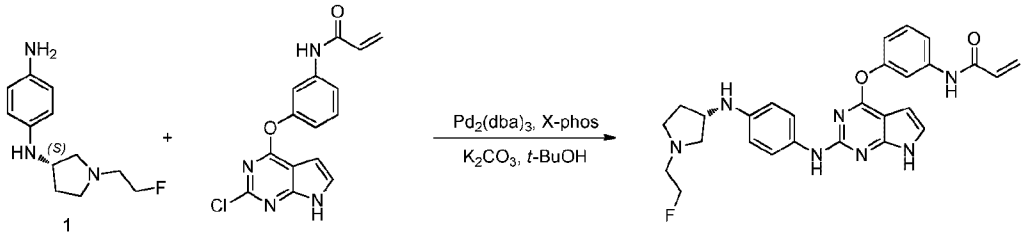
celite layer was washed with MeOH. The combined filtrate was concentrated under reduced pressure to afford dark oil. The oil residue was re-dissolved in ethyl acetate. The resulting mixture was washed with water and dried over Na_2SO_4. The organic solvent was removed under reduced pressure to afford the crude compound **3** (1.4g, 63.1%, $M+H^+$= 238.5), which was used in next step without further purification.

Synthesis of (*S*)-N-(3-(2-(4-((1-(2-fluoroethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-26a)

[00291] Compound **3** (1.401 g), compound **4** (1.985 g), K_2CO_3 (1.460 g), tris(dibenzylideneacetone)dipalladium (0.65 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.65 g) and *t*-BuOH (32 mL) were sequentially added into a round-bottom flask. The reaction mixture was stirred at refluxing under N_2 flow for 3-4 h. At this point, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The mixture was allowed to cool down to 40~50°C and then filtered through Celite®. The celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure to give crude product, which was further purified by column chromatography to afford **I-26a** (415 mg, 13.16%, $M+H^+$= 516.6).

Example 26

Synthesis of (*S*)-N-(3-(2-(4-(1-(2-fluoroethyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-27a)

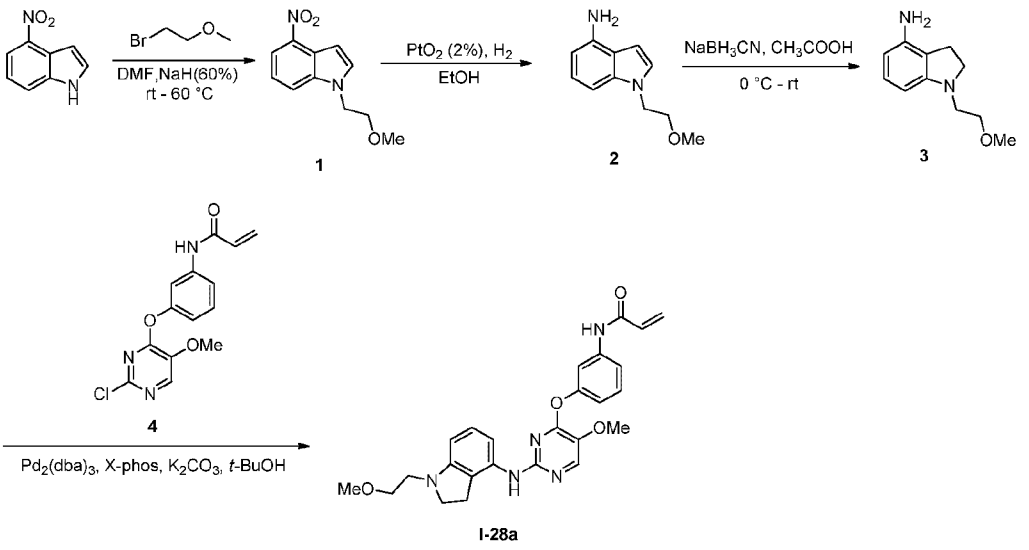


[00292] Compound **1** (see the previous section of intermediate *S*-1, 1.010 g), compound **2** (1.415 g), K_2CO_3 (1.30 g), tris(dibenzylideneacetone)dipalladium (0.602 g), dicyclohexyl

(2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.601 g) and *t*-BuOH (28 mL) were sequentially added to a round-bottom flask. The reaction mixture was stirred at refluxing under N_2 flow for 3~4 h. At this point,, TLC (DCM/ MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure to give a crude product, which was further purified by column chromatography to afford **I-27a** (400 mg, 17.81%, $M+H^+$= 502.6) as a gray solid.

Example 27

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)indolin-4-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-28a)



Synthesis of 1-(2-methoxyethyl)-4-nitro-1H-indole (1)

[00293] To a solution of 4-nitro-1H-indole (5.1 g, 30.77 mmol), 1-bromo-2-methoxyethane (5.134 g, 37 mmol) in DMF (30 mL), NaH (1.610 g, 80% dispersion in mineral oil, 40 mmol) was added potion-wise at room temperature. The mixture was stirred at 60°C for 3 h until TLC (petroleum ether: ethyl acetate = 6:1 as mobile phase) indicated the completion of the reaction. The mixture was allowed to cool down to room temperature, and then poured onto water (60 mL) and extracted with ethyl acetate (50 mL ×4). The combined organic layers was washed with

water and brine, dried and concentrated. The residue was purified by column chromatography (ethyl acetate/ petroleum ether from 1/10 to 1/3 as mobile phase) to give compound **1** (4.778 g, 21.5 mmol, 69%) as a yellow solid.

Synthesis of 1-(2-methoxyethyl)-1H-indol-4-amine (2)

[00294] A mixture of 1-(2-methoxyethyl)-4-nitro-1H-indole **1** (4.778 g, 21 mmol) and PtO_2 (0.091 g, 0.40 mmol) in EtOH (40 mL) was stirred at room temperature with hydrogen balloon overnight. TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with EtOH. The combined filtrate was concentrated under reduced pressure to afford compound **2** (3.67 g, 91%, $M+H^+$=191.2), which was used for next step reaction without further purification.

Synthesis of 1-(2-methoxyethyl)indolin-4-amine (3)

[00295] To a solution of 1-(2-methoxyethyl)-1H-indol-4-amine **2** (1.590 g, 7.16 mmol) in CH_3COOH (10 mL) at 0 °C was added $NaBH_3CN$ (1.286 g, 20.74 mmol) portion-wise. The mixture was stirred for 3 h until TLC (petroleum ether/ ethyl acetate = 1/2 as mobile phase) indicated the reaction to be complete. After the solvent was removed, the residue was basified with saturated $NaHCO_3$ (50 mL) and then extracted with ethyl acetate (30 mL ×4). The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude was purified by column chromatography (ethyl acetate / petroleum ether from 1/3 to 3/1 as mobile phase) to give compound **3** (0.96 g, 4.37 mmol, 61%, $M+H^+$=193.5) as a yellow solid.

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)indolin-4-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-28a)

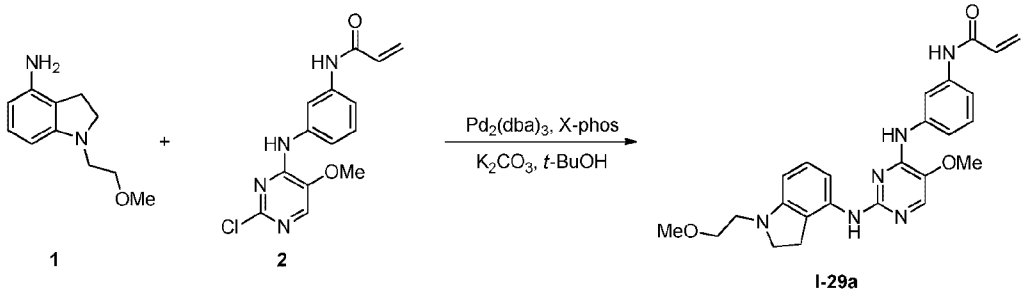
[00296] Compound **3** (0.430 g, 2.24 mmol), compound **4** (0.936 g, 3.063 mmol), K_2CO_3 (0.660 g, 4.783 mmol), tris(dibenzylideneacetone)dipalladium (0.270 g, 0.295 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.243 mg, 0.512 mmol) and *t*-BuOH (30 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5~7 h, TLC (Ethyl acetate: Petroleum ether: TEA = 1:1:0.1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50 °C and filtered through Celite®. The Celite layer was washed with ethyl acetate

(50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (Ethyl acetate: Petroleum ether from 50% to 100% as mobile phase) to give **I-28a** (773 mg, 79.89%, M+H$^+$ = 462.5) as a white solid.

[00297] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.92 (s, 1H), 7.54 (s, 1H), 7.48 (d, *J* = 7.9 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 14.6 Hz, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.57 (s, 1H), 6.42 (d, *J* = 16.8 Hz, 1H), 6.23 (dd, *J* = 16.8, 10.2 Hz, 1H), 6.16 (d, *J* = 7.8 Hz, 1H), 5.74 (d, *J* = 10.8 Hz, 1H), 3.94 (s, 3H), 3.60 (t, *J* = 5.7 Hz, 2H), 3.42 (s, 3H), 3.36 (t, *J* = 8.3 Hz, 2H), 3.23 (t, *J* = 5.7 Hz, 2H), 2.74 (t, *J* = 8.3 Hz, 2H).

Example 28

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)indolin-4-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide (I-29a)

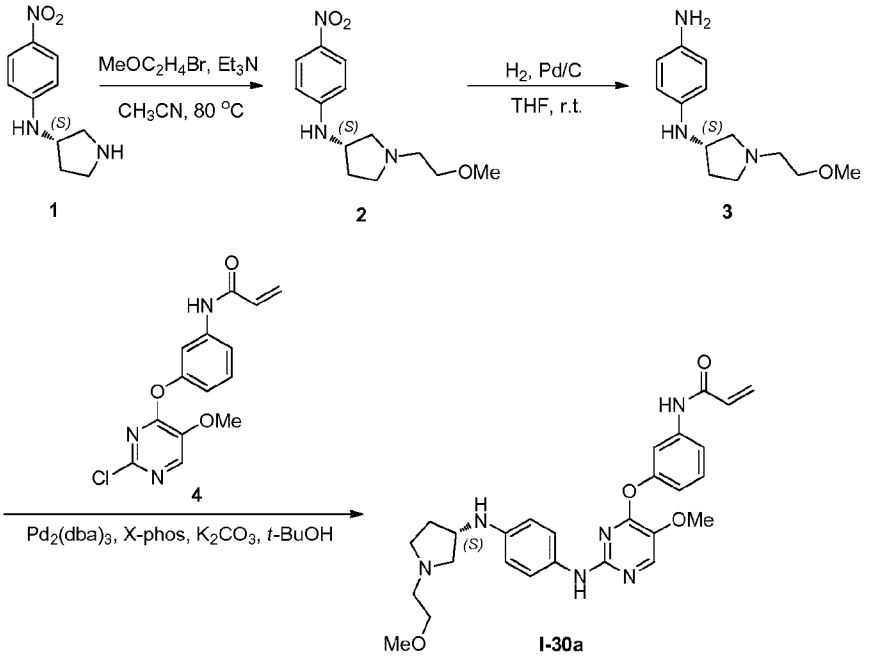


[00298] Compound **1** (0.403 g, 2.099 mmol), compound **2** (0.880 g, 2.890 mmol), K_2CO_3 (0.643 g, 4.659 mmol), tris(dibenzylideneacetone)dipalladium (0.233 g, 0.255 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.243 mg, 0.512 mmol) and *t*-BuOH (30 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5~7 h, TLC (Ethyl acetate: Petroleum ether: TEA = 1:1:0.1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50 °C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL). The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (Ethyl acetate: Petroleum ether from 50% to 100% as mobile phase) to give **I-29a** (646 mg, 62.7%, M+H$^+$ = 461.5) as a white solid.

[00299] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.68 (s, 1H), 7.58 (s, 1H), 7.57 (d, *J* = 7.0 Hz, H), 7.26 (dt, *J* = 10.6, 4.1 Hz, 3H), 7.13 (d, *J* = 6.8 Hz, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.45 (d, *J* = 16.9 Hz, 1H), 6.32 – 6.19 (m, 2H), 5.78 (d, *J* = 10.3 Hz, 1H), 3.89 (s, 3H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.45 (t, *J* = 8.3 Hz, 2H), 3.41 (s, 3H), 3.30 (t, *J* = 5.7 Hz, 2H), 2.95 (t, *J* = 8.3 Hz, 2H).

Example 29

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-30a)



Synthesis of (*S*)-1-(2-methoxyethyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00300] To compound 1 (10 g) in MeCN (70 mL) was added Et_3N (6.5 g) and 2-bromoethyl methyl ether (6.5 g). The reaction was stirred at 80 °C for 28 h. Once the reaction was complete, organic solvent was removed under reduced pressure. The residue was re-dissolved in ethyl acetate, and a small amount of saturated K_2CO_3 aqueous solution was added. After stirred for a

few minutes, the organic layer was separated, washed with brine and dried over Na_2SO_4. The solution was concentrated under reduced pressure. The resulting crude was purified by flash chromatography to afford the desired product **2** (6.213 g, 48%, $M+H^+ = 266.5$) as a yellow solid.

Synthesis of (*S*)-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)benzene-1,4-diamine (3)

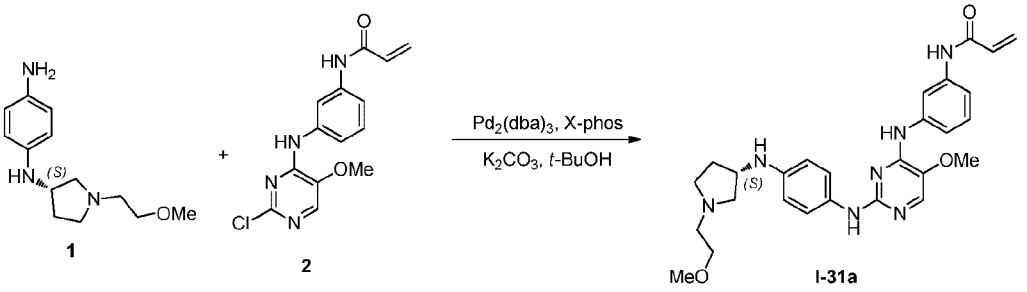
[00301] A solution of **2** (6.213 g) and Pd/C (0.584 g, 10% activated on carbon) in THF (50 mL) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC was indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with MeOH. The combined layers was concentrated under reduced pressure to afford the desired product **3** (4.8 g, 87.3%, M+H+= 236.5) without further purification.

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-30a)

[00302] Compound **3** (0.786 g), compound **4** (1.083 g), K_2CO_3 (1.154 g), tris(dibenzylideneacetone)dipalladium (0.117 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.120 g) and *t*-BuOH (20 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 6 h, TLC (DCM: MeOH = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure. The crude was purified by column chromatography (Ethyl acetate: MeOH = 9:1 as mobile phase) to give **I-30a** (1.2 g, 72.56%, $M+H^+ = 505.6$).

Example 30

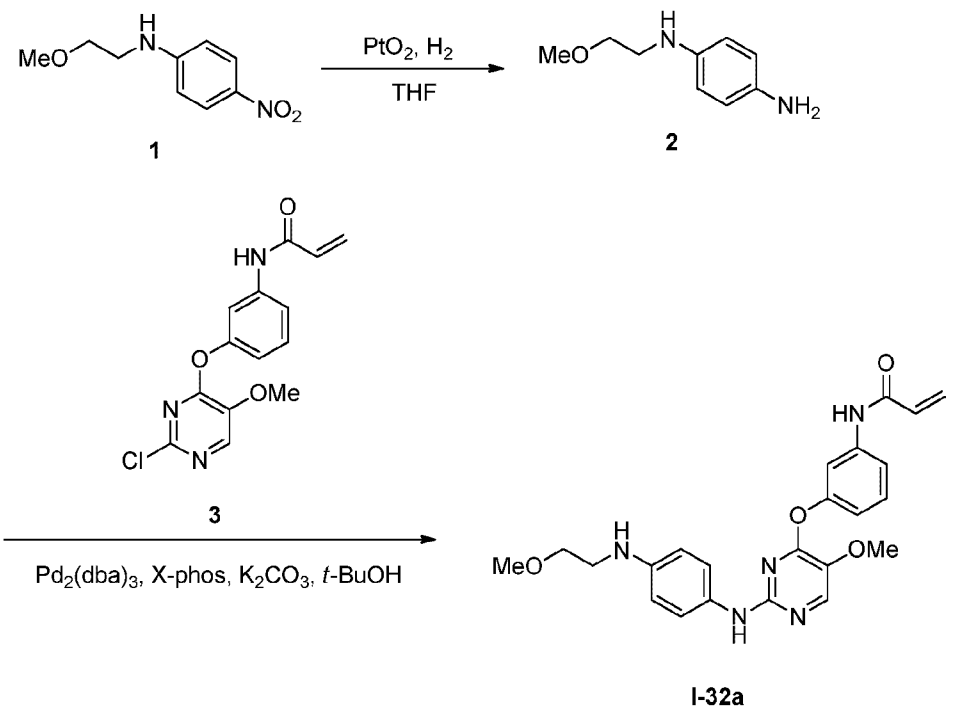
Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide (I-31a)



[00303] Compound **1** (0.789 g), compound **2** (1.041 g), K_2CO_3 (0.686 g), tris(dibenzylideneacetone)dipalladium (0.148 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.156 g) and *t*-BuOH (30 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 18 h, TLC (DCM: MeOH = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (30 mL). The filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate: MeOH = 10:1 as mobile phase) to give **I-31a** (0.2 g, 12%, $M+H^+$ = 504.6).

Example 31

Synthesis of N-(3-(5-methoxy-2-(4-(2-methoxyethylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-32a)



I-32a

Synthesis of N^1-(2-methoxyethyl)benzene-1,4-diamine (2)

[00304] A mixture of compound **1** (1.496 g) and PtO_2 (0.060 g) in THF (15 mL) was hydrogenated at room temperature overnight. At this point, TLC was indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with ethyl acetate. The combined layers were concentrated under reduced pressure to afford the desired product **2** (1.201 g, 94.43%, M+H+= 236.5) without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-(2-methoxyethylamino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-32a)

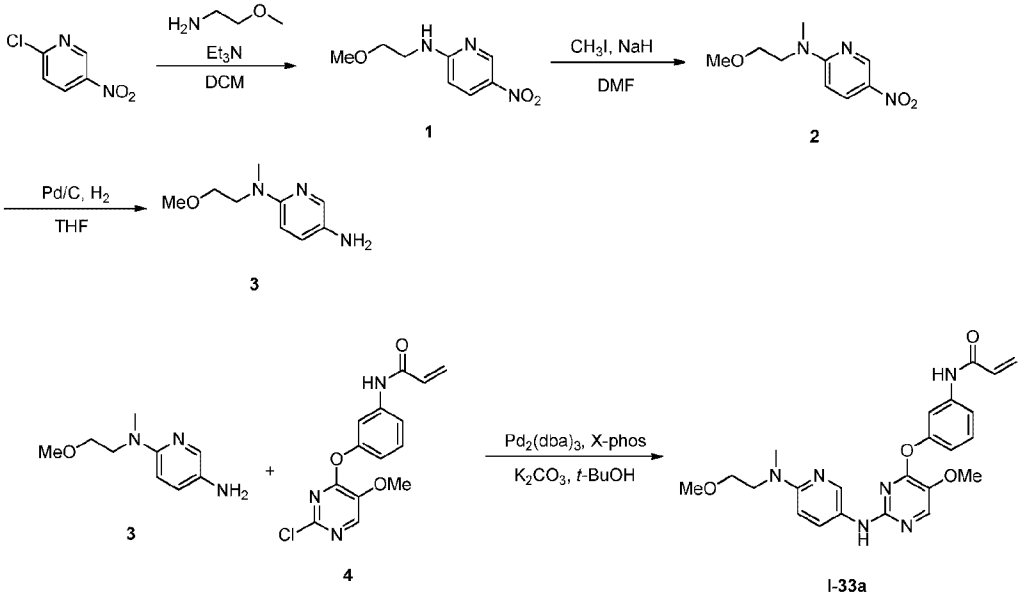
[00305] Compound **2** (0.532 g), compound **3** (0.925 g), K_2CO_3 (0.931 g), tris(dibenzylideneacetone)dipalladium (0.145 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.150 g) and *t*-BuOH (10 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 2 h, TLC (DCM: MeOH = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL).

The filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate: MeOH = 10:1 as mobile phase) to give **I-32a** (0.672 g, 48.2%, $M+H^+$ = 436.2).

[00306] ^1H NMR (500 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.79 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 7.0 Hz, 1H), 6.78 (s, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 6.43 (dd, *J* = 16.9, 1.0 Hz, 1H), 6.23 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.75 (dd, *J* = 10.3, 1.0 Hz, 1H), 3.92 (s, 3H), 3.58 (t, *J* = 5.2 Hz, 2H), 3.39 (s, 3H), 3.22 (t, *J* = 5.2 Hz, 2H).

Example 32

Synthesis of N-(3-(5-methoxy-2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-33a)



Synthesis of N-(2-methoxyethyl)-5-nitropyridin-2-amine (1)

[00307] A mixture of 2-chloro-5-nitropyridine (1.578 g), 2-methoxyethylamine (1.522 g) and Et_3N (2.070 g) in DCM (10 mL) was stirred at room temperature for 6 h. Then the mixture was heated up and stirred at refluxing for another 2 h. CH_3CN (5 mL) was added in, and refluxed

overnight. At this point, TLC indicated the reaction to be complete. The reaction was quenched with water, and then extracted with ethyl acetate. Organic layers was combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give desired compound **1** (1.868 g, 95%, $M+H^+$ = 198.2).

Synthesis of N-(2-methoxyethyl)-N-methyl-5-nitropyridin-2-amine (2)

[00308] To a solution of **1** (1.648 g) in DMF (15 mL) with ice-water bath was sequentially added NaH (0.302 g, 80% dispersion in mineral oil) and CH_3I (1.418 g). The resulting mixture was then stirred at 0°C for 10 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude product **2** (2.0 g, $M+H^+$= 212.2) was used directly in next step without further purification.

Synthesis of N^2-(2-methoxyethyl)-N^2-methylpyridine-2,5-diamine (3)

[00309] A solution of **2** (2.0 g) and Pd/C (0.300 g, 10% activated on carbon) in THF (20 mL) was hydrogenated at 40°C overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with MeOH. The combined filtrate was concentrated under reduced pressure to afford desired product **3** (1.687 g, 98%, $M+H^+$=182.3) without further purification.

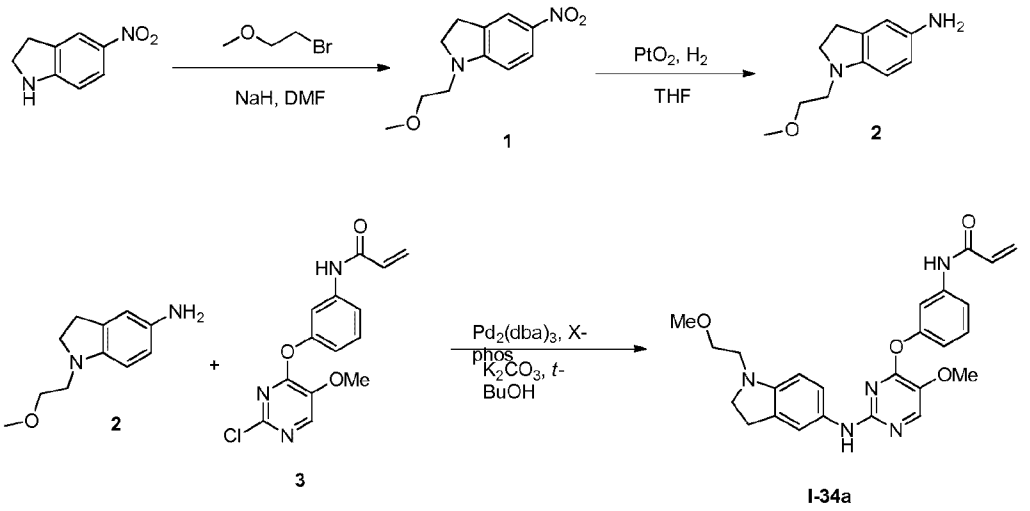
Synthesis of N-(3-(5-methoxy-2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-33a)

[00310] Compound **3** (1.687 g), compound **4** (2.827 g), K_2CO_3 (2.570 g), tris(dibenzylideneacetone)dipalladium (0.6 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.6 g) and *t*-BuOH (60 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3 h, TLC (Ethyl acetate: EtOH = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was

purified by column chromatography (Ethyl acetate as mobile phase) to give **I-33a** (2.591 g, 62.4%, $M+H^+ = 451.5$).

Example 33

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)indolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-34a)



Synthesis of 1-(2-methoxyethyl)-5-nitroindoline (1)

[00311] To a solution of 5-nitroindoline (5.718 g) in DMF (60 mL) at 0°C was sequentially added NaH (1.348 g, 60% dispersion in mineral oil) and 1-bromo-2-methoxyethane (5.368 g). The mixture was stirred at 0°C for 2 h, and then was allowed to warm up to room temperature and stirred for another 3 h. At this point, TLC indicated the reaction to be complete. The reaction mixture was poured onto ice-water. The precipitate was collected, and re-dissolved in ethyl acetate. The organic layer was washed with water, brine and concentrated under reduced pressure to afford the desired product **1** (7.292 g, 94%, $M+H^+ = 223.3$) as a yellow solid.

Synthesis of 1-(2-methoxyethyl)indolin-5-amine (2)

[00312] A solution of **1** (7.272 g) and PtO_2 (0.202 g) in THF (100 mL) was hydrogenated at room temperature overnight. At this point, TLC indicated the reaction to be complete. The

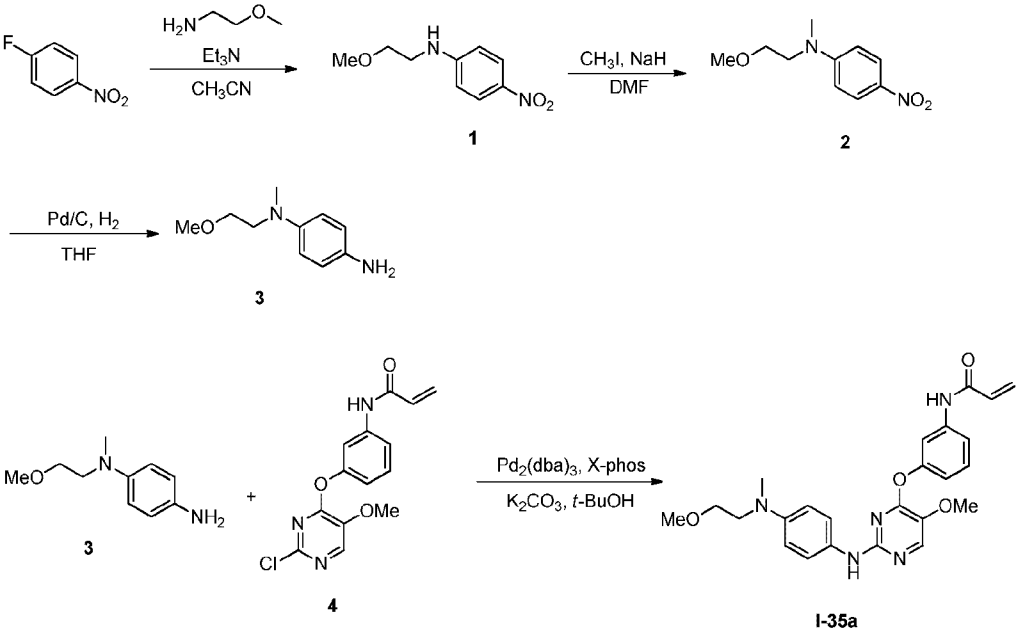
reaction mixture was filtered through Celite®. The celite layer was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford desired product **2** (6.247 g, 99.3%, $M+H^+$= 193.5) which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)indolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-34a)

[00313] Compound **2** (1.059 g), compound **3** (1.813 g), K_2CO_3 (1.037 g), tris(dibenzylideneacetone)dipalladium (0.146 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.152 g) and *t*-BuOH (50 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (Ethyl acetate: petroleum ether = 1:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate: petroleum ether = 1:3 as mobile phase) to give desired product **I-34a** (1.368 g, 53.9%, $M+H^+$ = 462.6).

Example 34

Synthesis of N-(3-(5-methoxy-2-(4-((2-methoxyethyl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-35a)



Synthesis of N-(2-methoxyethyl)-4-nitroaniline (1)

[00314] A mixture of 1-fluoro-4-nitrobenzene (2.820 g), 2-methoxyethylamine (3.00 g) and Et_3N (4.04 g) in CH_3CN (20 mL) was stirred at 50°C overnight. The reaction was quenched with water, then extracted with ethyl acetate. Organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and then concentrated under reduced pressure to give desired compound **1** (3.9 g, 99%, $M+H^+$= 197.3), which was used for next step without further purification.

Synthesis of N-(2-methoxyethyl)-N-methyl-4-nitroaniline (2)

[00315] To a solution of **1** (1.047 g) in DMF (15 mL) with ice-water bath was sequentially added NaH (0.200 g) and CH_3I (0.906 g). The resulting mixture was then stirred at 0°C 10 min. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude **2** (1.0 g, 89%, $M+H^+$ = 211.3) was used directly in next step without further purification.

Synthesis of N^1-(2-methoxyethyl)-N^1-methylbenzene-1,4-diamine (3)

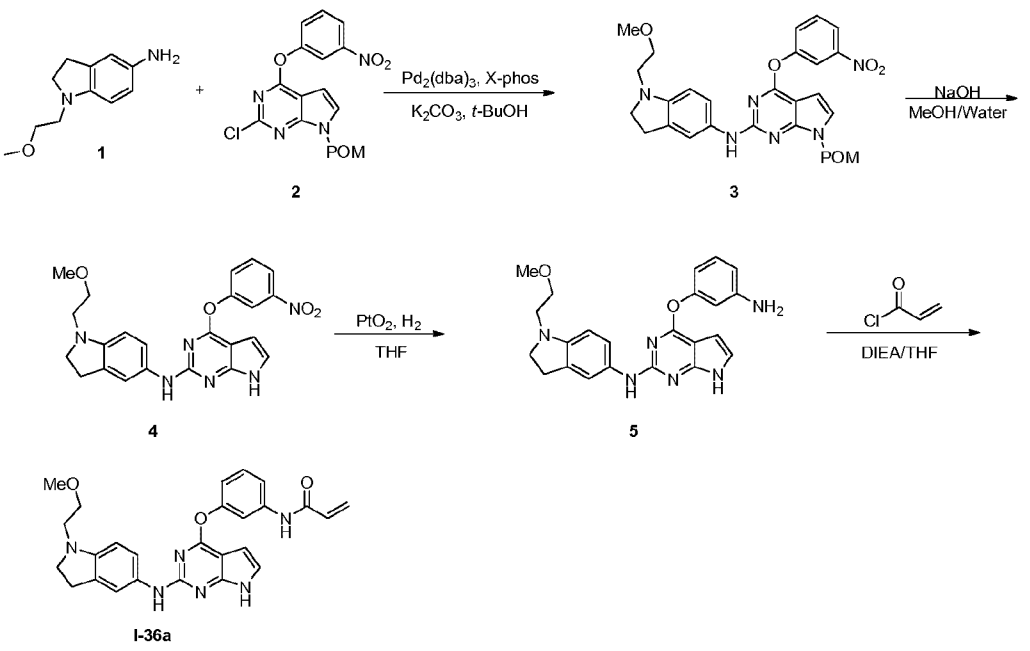
[00316] A mixture of **1** (1.0 g) and Pd/C (0.100 g, 10% activated on carbon) in THF (20 mL) was hydrogenated at 40°C overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford desired product **3** (1.058 g, $M+H^+$= 181.3) without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-((2-methoxyethyl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-35a)

[00317] Compound **3** (1.058 g), compound **80** (4 g), K_2CO_3 (1.630 g), tris(dibenzylideneacetone)dipalladium (0.3 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.3 g) and *t*-BuOH (50 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (Ethyl acetate: Ethanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate as mobile phase) to give desired product **I-35a** (1.8 g, 68.7%, $M+H^+$ = 450.6).

Example 35

Synthesis of N-(3-(2-(1-(2-methoxyethyl)indolin-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-36a)



Synthesis of (2-(1-(2-methoxyethyl)indolin-5-ylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

[00318] Compound **1** (0.7 g), compound **2** (1.780 g), K_2CO_3 (1.01 g), tris(dibenzylideneacetone)dipalladium (0.4 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.401 g) and *t*-BuOH (16 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3.5 h, TLC (Ethyl acetate: Ethanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography to give compound **3** (0.7 g, 34.2%).

Synthesis of N-(1-(2-methoxyethyl)indolin-5-yl)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (4)

[00319] To a round-bottom flask (250 mL) was charged with compound **3** (700 mg), MeOH (6 mL) and THF (1 mL). When compound **3** was completely dissolved, the reaction mixture was cooled down to ~10°C with an ice-bath. NaOH solution (2.5 M, 2 mL) was then added into the

flask slowly, maintaining the temperature ~16 °C throughout the addition. The mixture was stirred for 2 h at this temperature and then water (20 mL) was added. The mixture was extracted with ethyl acetate. The organic layers were combined and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford compound **4** (320 mg, 57.4%, $M+H^+$= 447.6).

Synthesis of 4-(3-aminophenoxy)-N-(1-(2-methoxyethyl)indolin-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (5)

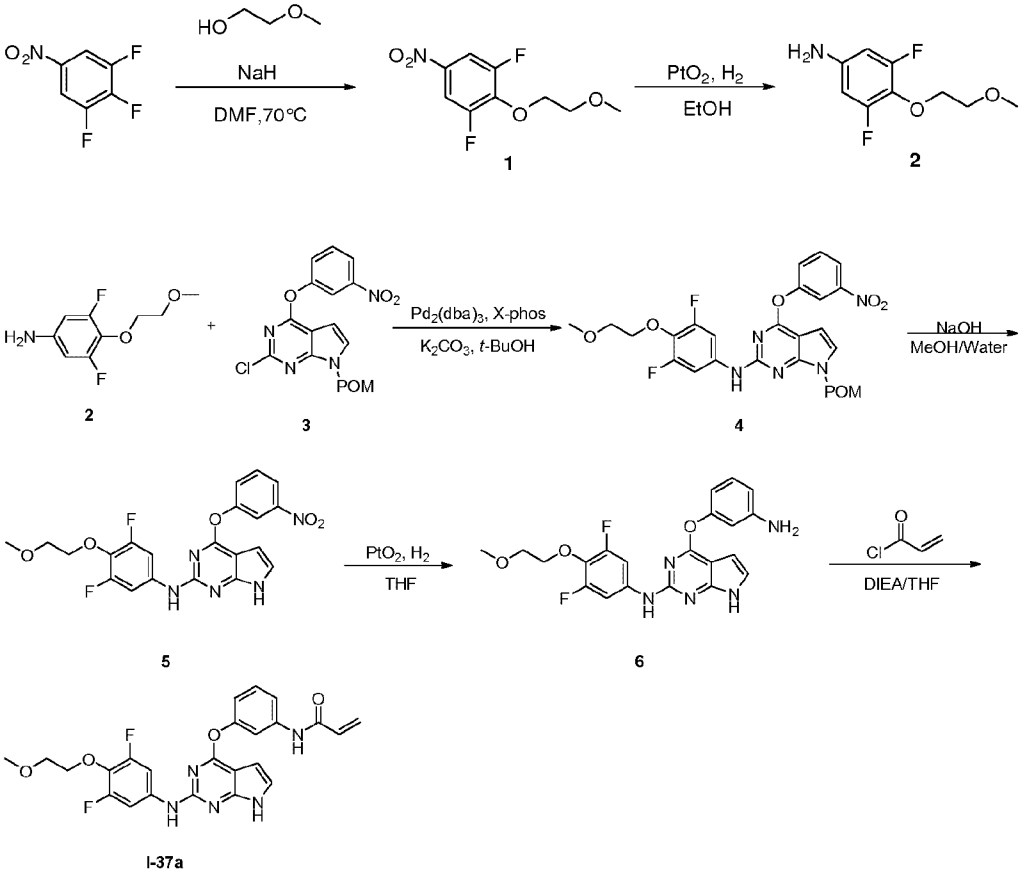
[00320] A mixture of **4** (320 mg) and PtO_2 (8 mg) in THF (5 ml) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The celite layer was washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford desired compound **5** (0.25 g, 83.75%).

Synthesis of N-(3-(2-(1-(2-methoxyethyl)indolin-5-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-36a)

[00321] To a mixture of compound **5** (0.25 g) and DIEA (125 mg) in THF (4 mL) at 0°C was dropwise added acryloyl chloride (82 mg) over 5 min. The mixture was stirred for 2 h at this temperature. NaOH solution (1M, 2 mL) was added to quench the reaction. The mixture was stirred for 30 min, and then diluted with water (30 mL) before being extracted with ethyl acetate (30 mL). The organic layer was separated and concentrated under reduced pressure. The resulting crude was purified by column chromatography to give **I-36a** (186 mg, 65.85%, M+H+=471.6).

Example 36

Synthesis of N-(3-(2-(3,5-difluoro-4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-37a)



Synthesis of 1, 3-difluoro-2-(2-methoxyethoxy)-5-nitrobenzene (1)

[00322] To a solution of 1, 2, 3-trifluoro-5-nitrobenzene (2.625 g, 14 mmol) and 2-methoxyethanol (1.3 g, 17 mmol) in DMF (20 mL) was added NaH (0.815 g, 80% dispersion in mineral oil). The mixture was stirred at room temperature for 3 h until TLC (Petroleum: Ethyl acetate = 1:6 as mobile phase) indicated the reaction to be complete. The mixture was poured into water (60 mL) and extracted with EA (40 mL ×4). The organic layer was combined, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was purified by column chromatography (EtOAc/ Petroleum ether from 1/7 to 1/3 as mobile phase) to give **1** (2.609 g, 80%) as a dark yellow solid.

Synthesis of 3, 5-difluoro-4-(2-methoxyethoxy)aniline (2)

[00323] A mixture of **1** (3.88 g) and PtO_2 (0.089 g) in EtOH (30 mL) was hydrogenated at room temperature overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite® and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford the desired product **2** (2.7 g, 95%) without further purification.

Synthesis of (2-(3,5-difluoro-4-(2-methoxyethoxy)phenylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (4)

[00324] Compound **2** (2.7g, 13.3mmol), compound **3** (6.075 g, 15 mmol), K_2CO_3 (4.140 g, 30 mmol), tris(dibenzylideneacetone)dipalladium (0.064 g, 0.07 mol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (0.065 g, 0.14 mmol) and *t*-BuOH (50 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3-4 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The Celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (EtOAc/ Petroleum ether from 50% to 100%) to give compound **4** (4.932 g, 65%) as a slight yellow solid.

Synthesis of N-(3,5-difluoro-4-(2-methoxyethoxy)phenyl)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (5)

[00325] To a round-bottom flask (250 mL) was charged with compound **4** (4.932 g, 8.64 mmol) and MeOH (40 mL). When compound **4** was completely dissolved, the solution was cooled down to ~10°C with an ice-bath. NaOH solution (2.5 M, 10 mL) was then added into the flask slowly, maintaining the temperature ~16°C during the addition. The mixture was stirred for 2 h at this temperature. Water (100 mL) was added to the flask over 15 min, maintaining the temperature below 20°C. The mixture was continuously stirred for another 15 min. The precipitate was collected, washed with water (50 mL) and dried under vacuum to afford compound **5** (1.579 g, 40%).

Synthesis of 4-(3-aminophenoxy)-N-(3,5-difluoro-4-(2-methoxyethoxy)phenyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (6)

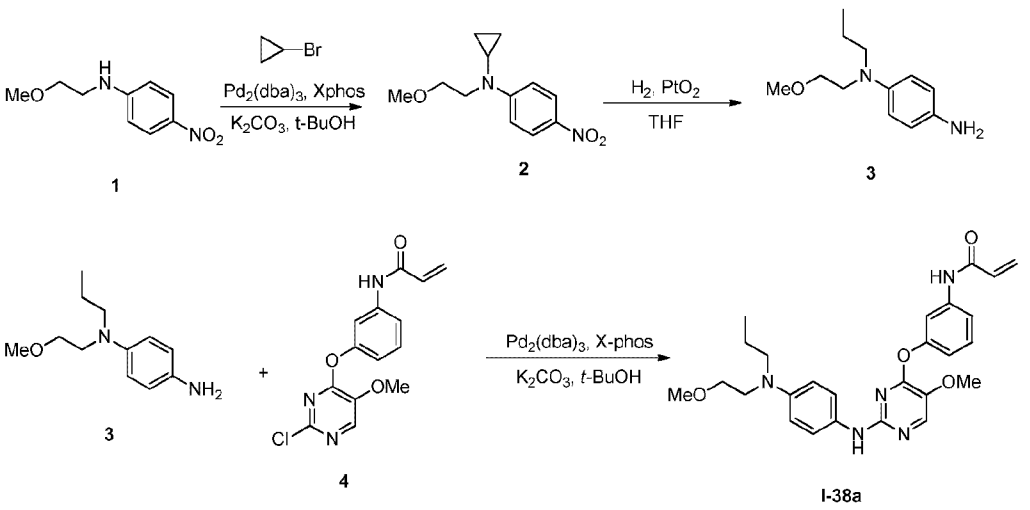
[00326] A mixture of **5** (1.579 g, 3.456 mmol) and PtO_2 (16 mg, 0.07 mmol) in THF (30 mL) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite® and washed ethyl acetate. The combined filtrate was concentrated to afford the desired compound **6** (1.401 g, 95%) as a white solid.

Synthesis of N-(3-(2-(3,5-difluoro-4-(2-methoxyethoxy)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-37a)

[00327] To a solution of compound **6** (1.401g, 3.28mmol) and DIEA (0.464 g, 3.6 mmol) in THF (50 mL) at 0 °C was dropwise added acryloyl chloride (0.307 g, 3.4 mmol) over 5 min. The mixture was stirred for 1 h at this temperature. NaOH solution (1M, 3 mL) and water (20 mL) were added to quench the reaction. The mixture was stirred for additional 10 min, and the upper THF phase was separated and evaporated to under reduced pressure. The resulting crude was purified by column chromatography (EtOAc / Petroleum ether from 50% to 100% as mobile phase) to give **I-37a** (1.090 g, 63%, $M+H^+ = 482.2$) as a white solid.

Example 37

Synthesis of N-(3-(5-methoxy-2-(4-((2-methoxyethyl)(propyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-38a)



1 2 3 3 4 I-38a

Synthesis of N-cyclopropyl-N-(2-methoxyethyl)-4-nitroaniline (2)

[00328] A mixture of compound **1** (1.001 g), cyclopropyl bromide (2.300 g), $Pd_2(dba)_3$ (0.132 g), X-Phos (0.100 g) and potassium carbonate (1.070 g) in *t*-butanol (20 mL) was stirred under argon at refluxing overnight. TLC indicated the reaction to be complete. After cooling to room temperature, the reaction mixture was filtered through Celite®, and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by flash column chromatography to afford the desired compound **2** (700 mg, 58.13%).

Synthesis of N^1-(2-methoxyethyl)-N^1-propylbenzene-1,4-diamine (3)

[00329] A mixture of **2** (0.556 g) and PtO_2 (0.060 g) in THF (15 mL) was hydrogenated at room temperature overnight. TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®, and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure afford to the crude product **3** (0.55 g), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-((2-methoxyethyl)(propyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-38a)

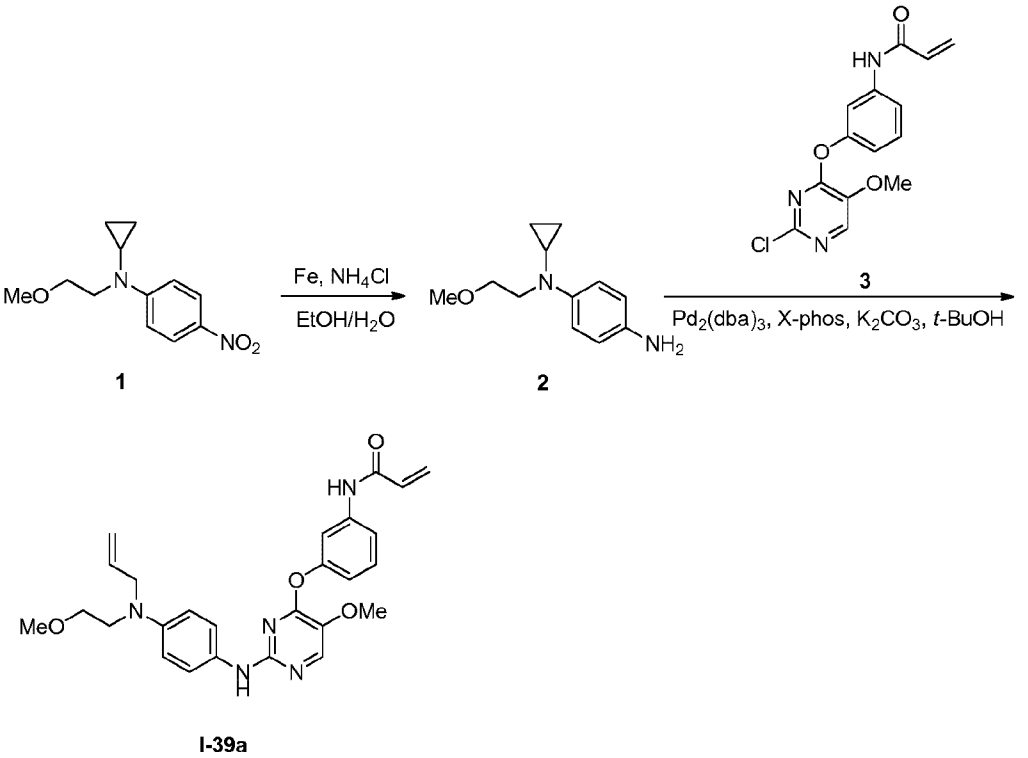
[00330] Compound **3** (0.550 g), compound **4** (0.571 g), K_2CO_3 (0.075 g), tris(dibenzylideneacetone)dipalladium (0.075 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.071 g) and *t*-BuOH (15 mL) were sequentially added to the flask. The reaction

mixture was stirred at refluxing under N_2 flow. After 3 h, TLC (Ethyl acetate: Ethanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C and filtered through Celite®. The celite layer was washed with ethyl acetate (10 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography (EtOAc/ Petroleum ether from 50% to 100%) to give compound **I-38a** (0.182 g, 21.2%, $M+H^+$=478.6).

[00331] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.65 (s, 1H), 7.54 – 7.46 (m, 2H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 8.9 Hz, 2H), 6.96 ((dd, *J* = 7.9, 1.0 Hz, 1H), 6.61 (s, 1H), 6.50 (d, *J* = 8.9 Hz, 2H), 6.42 (dd, *J* = 16.8, 1.2 Hz, 1H), 6.22 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.75 (dd, *J* = 10.2, 1.1 Hz, 1H), 3.90 (s, 3H), 3.48 (t, *J* = 5.8 Hz, 2H), 3.42 (t, *J* = 6.0 Hz, 2H), 3.35 (s, 3H), 3.19 (t, *J* = 6.0 Hz, 2H), 1.58 – 1.49 (m, 2H), 0.88 (t, *J* = 7.4 Hz, 3H).

Example 38

Synthesis of N-(3-(2-(4-(cyclopropyl(2-methoxyethyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-39a)



1 2 I-39a

Synthesis of N^1-cyclopropyl-N^1-(2-methoxyethyl)benzene-1,4-diamine (2)

[00332] Compound **1** (0.580 g) in EtOH/H_2O (24 mL, 17:7) was treated with iron (0.62 g) followed by ammonium chloride (2.092 g). The mixture was stirred at refluxing for 2 h. The reaction mixture was filtered through Celite®. The filtrate was basified with $NaHCO_3$ (*aq,* 30 mL) and extracted with ethyl acetate (30 mL ×4). The organic layer was combined, dried and concentrated to provide the crude compound **2** (0.545 g which was used in next step without further purification.

Synthesis of N-(3-(2-(4-(cyclopropyl(2-methoxyethyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-39a)

[00333] Compound **2** (0.5 g), compound **3** (0.745 g), K_2CO_3 (0.890 g), tris(dibenzylideneacetone)dipalladium (0.232 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.240 g) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 4 h, TLC (Ethyl acetate: Ethanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool

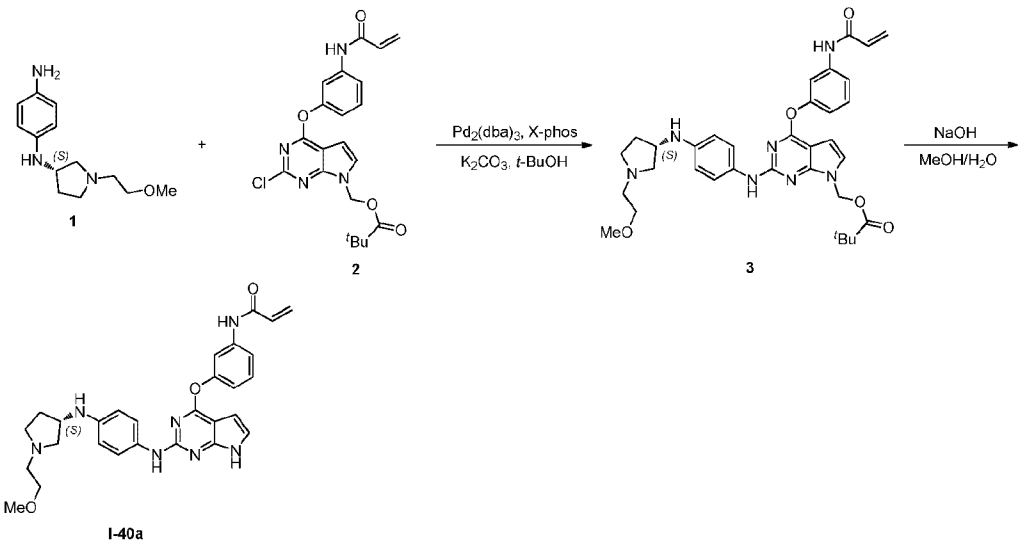
down to 40~50°C and filtered through Celite®. The celite layer was washed with ethyl acetate (10 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography to give compound **I-39a** (0.228 g, 17.4%, $M+H^+$=476.6).

[00334] ^{1}H NMR (500 MHz, DMSO) δ 10.33 (s, 1H), 8.86 (s, 1H), 8.13 (s, 1H), 7.60 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 26.8, 18.9 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.44 (dd, *J* = 19.2, 9.1 Hz, 3H), 6.27 (d, *J* = 17.0 Hz, 1H), 5.76 (dd, *J* = 17.6, 7.7 Hz, 2H), 5.09 (d, *J* = 13.0 Hz, 2H), 3.85 (s, 3H), 3.89-3.80 (m, 2H), 3.47 – 3.32 (m, 4H), 3.25 (s, 3H).

[00335] ^{13}C NMR (126 MHz, DMSO) δ 165.31 (s), 161.44 (s), 156.04 (s), 154.80 (s), 146.07 (s), 144.92 (s), 142.28 (s), 136.95 (s), 136.35 (s), 133.67 (s), 132.17 (s), 131.82 (s), 129.29 (s), 121.98 (s), 118.79 (s), 118.01 (s), 117.82 (s), 114.78 (s), 114.05 (s), 71.98 (s), 60.24 (s), 59.67 (s), 55.20 (s), 51.87 (s).

Example 39

Synthesis of (*S*)-N-(3-(2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-40a)



Synthesis of (*S*)-(4-(3-acrylamidophenoxy)-2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

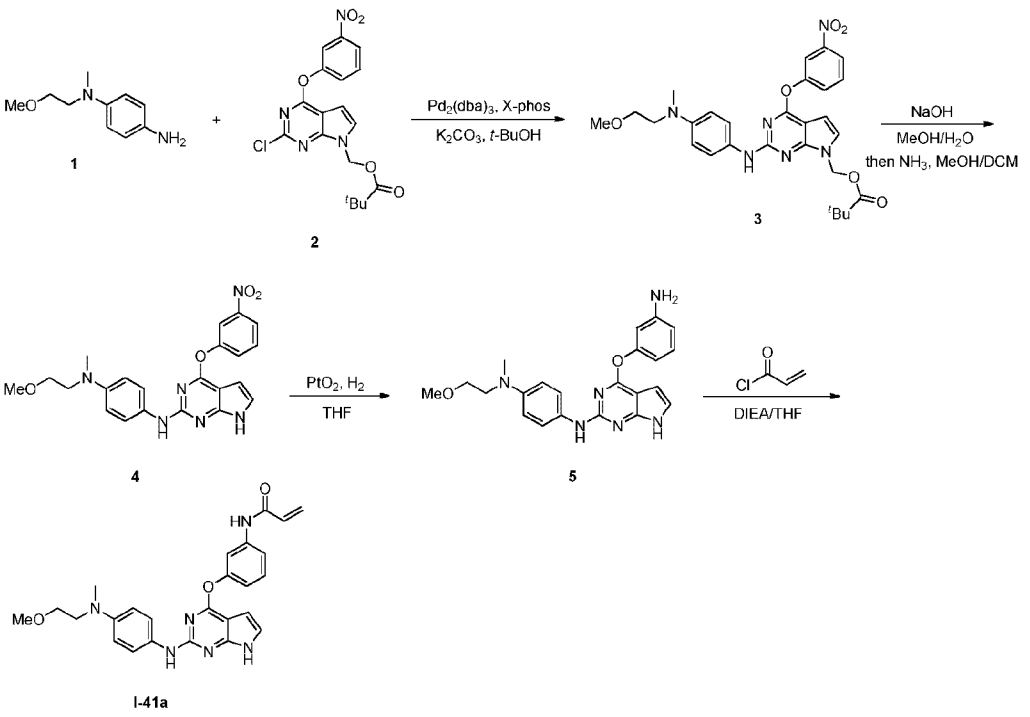
[00336] Compound **1** (1.008 g, 4.289 mmol), compound **2** (2.143 g, 5.007 mmol), K_2CO_3 (1.455 g, 10.543 mmol), tris(dibenzylideneacetone)dipalladium (0.432 g, 0.472 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.434 g, 0.992 mmol) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5-7 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, concentrated under reduced pressure, and followed by addition of ethyl acetate (50 mL) and activated charcoal (0.5 g). The mixture was stirred for 15 min and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure to afford crude **3** (1.723 g, 64%) as a white solid, which was used for next step without further purification.

Synthesis of (*S*)-N-(3-(2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-40a)

[00337] To a round-bottom flask (250 mL) was charged with compound **3** (0.550 g, 0.877 mmol) and MeOH (20 mL). After compound **3** was completely dissolved, the mixture was cooled down to ~10 °C with an ice-bath. NaOH solution (2.5 M, 2 mL) was then added into the flask slowly, keeping the temperature below 16°C during the addition. The mixture was stirred for 1 h at this temperature. Water (100 mL) was then added slowly to the flask over 15 min (maintaining the temperature below 20°C). The mixture was extracted with ethyl acetate (30 mL ×4). The combined organic layers were concentrated under reduced pressure. The resulting crude was purified by column chromatography (Ethyl acetate /Petroleum ether = from 10% to 100% as mobile phase) to give **I-40a** (0.17 g, 29%, $M+H^+$ =514.5) as a yellow solid.

Example 40

Synthesis of N-(3-(2-(4-((2-methoxyethyl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-41a)



Synthesis of (2-(4-((2-methoxyethyl)(methyl)amino)phenylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

[00338] Compound **1** (3.0 g), compound **2** (7.1 g), K_2CO_3 (4.78 g), tris(dibenzylideneacetone)dipalladium (1.2 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (1.2 g) and *t*-BuOH (100 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **3** (6.010 g, 65.8%).

Synthesis of N^1-(2-methoxyethyl)-N^1-methyl-N^4-(4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)benzene-1,4-diamine (4)

[00339] To a round-bottom flask (250 mL) was charged with compound **3** (6.01 g) and MeOH (50 mL). When compound **3** was completely dissolved, the solution was cooled down to

~10°C with an ice-bath. NaOH solution (2.5 M, 10 mL) was then added slowly into the flask with the temperature remained below 16°C during the addition. The mixture was stirred for 2.5 h at this temperature. Water (150 mL) was slowly added into the flask over 15 min with the temperature remained below 20°C during the addition. The mixture was extracted with ethyl acetate (100 mL ×2). The organic layers were combined, and concentrated under reduced pressure. The resulting crude was re-dissolved in MeOH/DCM (1:1, 50 mL) and the resulting solution was bubbled with NH_3(g) at room temperature. After 7 hr, LC-MS indicated the reaction to be complete. The organic solvent was removed under reduced pressure to afford **4** (4.5 g, 94.7%), which was used in next step without further purification.

Synthesis of N^1-(4-(3-aminophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-N^4-(2-methoxyethyl)-N^4-methylbenzene-1,4-diamine (5)

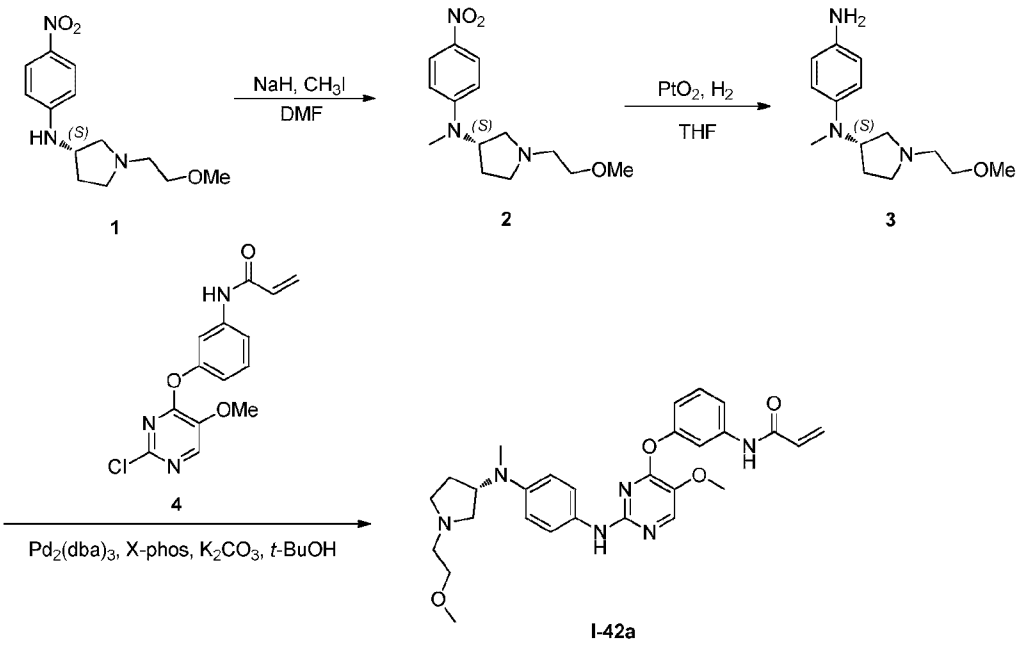
[00340] A mixture of **4** (4.5 g) and PtO_2 (50 mg) in THF (52 mL) was hydrogenated with hydrogen balloon at room temperature for 44 h. TLC and LC-MS indicated the incompletion of the reaction because of the slow conversion from hydroxylamine to amine. The reaction mixture was filtered through Celite®. The filtrate was concentrated. The residue was treated with iron/NH_4Cl aq/EtOH system for 24 h. The crude was purified by column chromatography to afford the desired compound **5** (2.1 g, 50 %) as a white solid.

Synthesis of N-(3-(2-(4-((2-methoxyethyl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-41a)

[00341] To a solution of compound **5** (2.1 g) and DIEA (1.01 g) in THF (30 mL) at 0°C was added acryloyl chloride (0.810 g) drop-wise over 5 min. The mixture was stirred for 3 h at this temperature. NaOH solution (1M, 3 mL) and water (50 mL) were added to quench the reaction. The resulting mixture was stirred for another 10 min, and then extracted with ethyl acetate. The organic layers were combined and concentrated under reduced pressure. The resulting crude was purified by column chromatography (DCM/MeOH = 20/1 as mobile phase) to give compound **I-41a** (0.605 g, 95.9%, $M+H^+$=459.5).

Example 41

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-42a)



Synthesis of (*S*)-1-(2-methoxyethyl)-N-methyl-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00342] To a solution of **1** (2.7 g) in DMF (15 mL) at 0°C was sequentially added NaH (0.611 g, 80% dispersion in mineral oil) and CH_3I (1.5 g). The resulting mixture was stirred for 3 h at this temperature. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude **2** (2.3 g) was used directly in next step without further purification.

Synthesis of (*S*)-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)-N^1-methylbenzene-1,4-diamine (3)

[00343] A mixture of **2** (2.3 g) and PtO_2 (0.057 g) in THF (40 mL) was hydrogenated with hydrogen balloon at room temperature for 41 h. TLC showed the reaction to be complete. The reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford the crude compound **3** (1.7 g) without further purification.

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-42a)

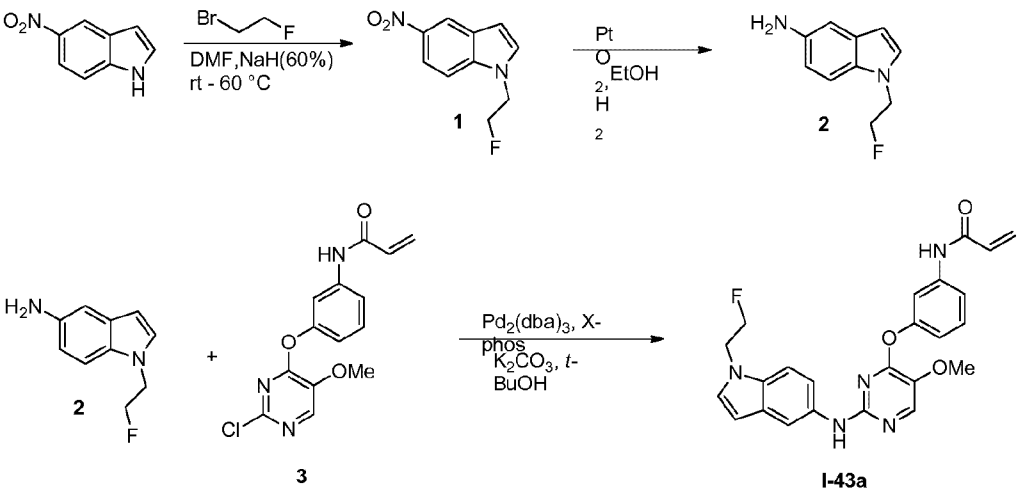
[00344] Compound **3** (0.7 g), compound **4** (0.905 g), K_2CO_3 (0.838 g), tris(dibenzylideneacetone)dipalladium (0.275 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.271 g) and *t*-BuOH (15 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-42a** (0.66 g, 45.4%, $M+H^+$=519.6).

[00345] ^{1}H NMR (500 MHz, DMSO) δ 10.36 (s, 1H), 8.94 (s, 1H), 8.15 (s, 1H), 7.74 – 7.53 (m, 2H), 7.42 (t, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 2H), 7.09 – 6.85 (m, 1H), 6.55 (d, *J* = 9.0 Hz, 2H), 6.45 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.28 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.78 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.24 – 4.08 (m, 1H), 3.86 (s, 3H), 3.47 – 3.37 (m, 2H), 3.24 (s, 3H), 2.71 (td, *J* = 8.5, 4.3 Hz, 1H), 2.65 (s, 3H), 2.58 (dt, *J* = 8.1, 6.0 Hz, 2H), 2.55 – 2.45 (m, 2H), 2.33 (q, *J* = 7.7 Hz, 1H), 2.05 – 1.90 (m, 1H), 1.57 (td, *J* = 13.4, 7.8 Hz, 1H).

[00346] ^{13}C NMR (126 MHz, DMSO) δ 165.32 (s), 161.43 (s), 155.90 (s), 154.78 (s), 147.40 (s), 145.98 (s), 142.28 (s), 136.44 (s), 133.57 (d, *J* = 18.4 Hz), 131.87 (s), 129.30 (s), 121.49 (s), 118.77 (s), 118.09 (s), 116.72 (s), 114.93 (s), 72.92 (s), 60.02 (s), 59.79 (s), 59.62 (s), 59.30 (s), 56.79 (s), 55.89 (s), 35.77 (s), 29.76 (s).

Example 42

Synthesis of N-(3-(2-(1-(2-fluoroethyl)-*1H*-indol-5-ylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-43a)



Synthesis of 1-(2-fluoroethyl)-5-nitro-1H-indole (1)

[00347] To a solution of 5-nitro-1H-indole (1.618 g, 10 mmol) in DMF (10 ml) at 0 °C was sequentially added NaH (0.805 g, 60% dispersion in mineral oil) and 1-bromo-2-methoxyethane (1.32 g). The mixture was stirred at 60°C for 3 h until TLC (Petroleum ether: Ethyl acetate = 5:1 as mobile phase) indicated the reaction to be complete. The mixture was allowed to cool down to room temperature, poured onto water (60 mL) and then extracted with ethyl acetate (50 mL ×4). The organic layers were combined and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (EtOAc /Petroleum ether from 1/10 to 1/3 as mobile phase) to give **1** (1.767 g, 8.5 mmol, 85%) as a yellow solid.

Synthesis of 1-(2-fluoroethyl)-1H-indol-5-amine (2)

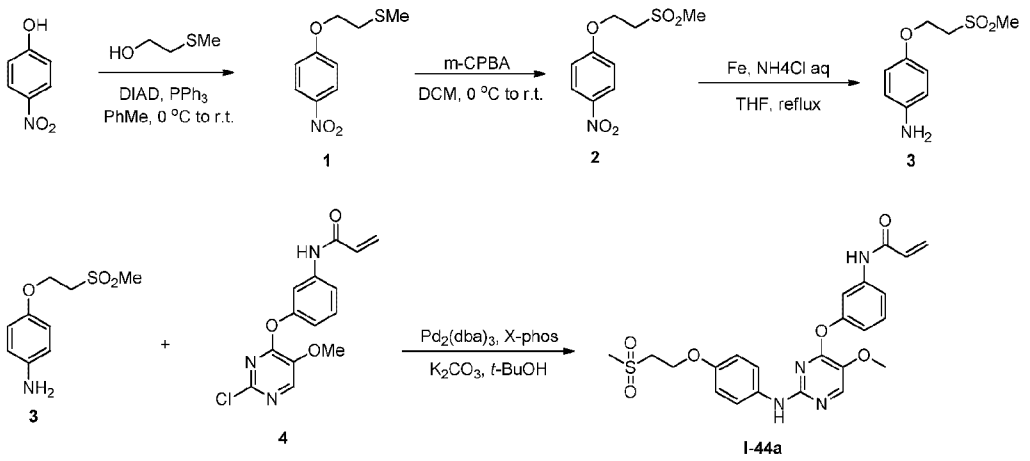
[00348] A mixture of **1** (1.767 g, 8.5 mmol) and PtO_2 (0.046 g, 0.20 mmol) in EtOH (40 mL) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite® and washed with small amount of ethanol. The combined filtrates was concentrated under reduced pressure to afford **2** (1.347 g, 89%), which was used in next step without further purification.

Synthesis of N-(3-(2-(1-(2-fluoroethyl)-1H-indol-5-ylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-43a)

[00349] Compound **2** (0.877 g, 4.867 mmol), compound **3** (1.902 g, 6.327 mmol), K_2CO_3 (1.347 g, 9.743 mmol), tris(dibenzylideneacetone)dipalladium (0.455 g, 0.487 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.471 g, 0.974 mmol) and *t*-BuOH (30 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (EtOAc/Petroleum ether/TEA = 1:1:0.1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-43a** (1.66 g, 74%, $M+H^+$=448.6) as a light yellow solid.

Example 43

Synthesis of N-(3-(5-methoxy-2-(4-(2-(methylsulfonyl)ethoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-44a)



Synthesis of methyl(2-(4-nitrophenoxy)ethyl)sulfane (1)

[00350] To a solution of 4-nitrophenol (1.413 g), 2-(methylthio)ethanol (0.948 g) and PPh_3 (3.216 g) in toluene (30 mL) at 0 °C was slowly added DIAD (4 mL). The mixture was allowed to warm to room temperature and stirred overnight. Solvent was evaporated under reduced

pressure. The residue was purified by column chromatography (EtOAc /Petroleum ether from 1:20 to 1:10 as mobile phase) to afford compound **1** (1.879 g, 86.7%) as a yellow oil.

Synthesis of 1-(2-(methylsulfonyl)ethoxy)-4-nitrobenzene (2)

[00351] A solution of **1** (1.490 g) in DCM (10 mL) at 0°C was treated with 3-chloroperbenzoic acid (2.511 g). The resulting mixture was stirred at ambient temperature overnight. The reaction was quenched with saturated aqueous $NaHCO_3$solution, and then extracted with DCM. The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield crude compound **2** (4.542 g), which was used directly in next step without further purification.

Synthesis of 4-(2-(methylsulfonyl)ethoxy)aniline (3)

[00352] A solution of **2** (4.542 g) in THF (50 mL) was treated with iron (5.823 g) and saturated aqueous ammonium chloride (5 mL). The mixture was stirred at refluxing for 2.5 h. After cooling to room temperature, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to yield crude product **3** (2.785 g), which was used for next reaction without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-(2-(methylsulfonyl)ethoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-44a)

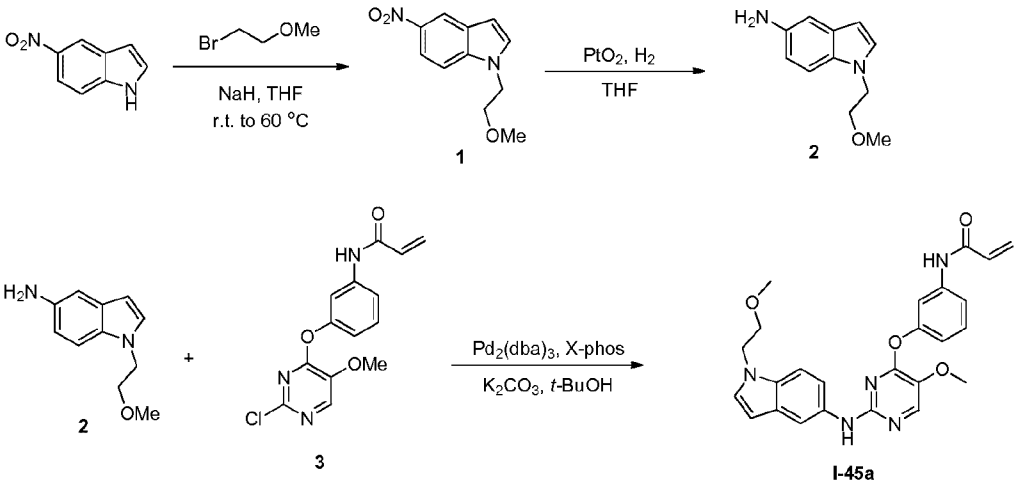
[00353] Compound **3** (2.304 g), compound **4** (2.270 g), K_2CO_3 (3.270 g), tris(dibenzylideneacetone)dipalladium (0.517 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.512 g) and *t*-BuOH (60 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3.5 h, TLC (EtOAc/ Petroleum ether /TEA = 1:1:0.1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-44a** (1.8 g, 29.1%, $M+H^+$=485.5) as a light yellow solid.

[00354] ^1H NMR (500 MHz, DMSO) δ 10.37 (s, 1H), 9.14 (s, 1H), 8.19 (s, 1H), 7.63 (t, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 9.1 Hz, 1H), 7.44 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 6.96

(ddd, J = 8.1, 2.3, 0.8 Hz, 1H), 6.69 (d, J = 9.1 Hz, 2H), 6.44 (dd, J = 17.0, 10.1 Hz, 1H), 6.27 (dd, J = 17.0, 1.9 Hz, 1H), 5.78 (dd, J = 10.1, 1.9 Hz, 1H), 4.23 (t, J = 5.6 Hz, 2H), 3.87 (s, 3H), 3.57 (t, J = 5.6 Hz, 2H), 3.05 (s, 3H).

Example 44

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)-1H-indol-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-45a)



1-(2-methoxyethyl)-5-nitro-1H-indole (1)

[00355] To a solution of 5-nitro-1*H*-indole (1.620 g) and 1-bromo-2-methoxyethane (1.412 g) in THF (15 mL) at room temperature was added NaH (0.420 g, 80% dispersion in mineral oil). The mixture was stirred at 60°C for 6 h. Another portion of 1-bromo-2-methoxyethane (0.301 g) was added, and the mixture was continuously stirred at 60 °C overnight. The reaction mixture was cooled and poured onto ice-water. The precipitates was filtered, washed with water, and dried to afford **1** (2.10 g, 95.45%) as a yellow solid.

Synthesis of 1-(2-methoxyethyl)-1H-indol-5-amine (2)

[00356] A solution of **1** (2.052 g) and PtO_2 (0.062 g) in THF (20 mL) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC indicated the reaction to be

complete. The reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford **2** (1.600 g), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)-1H-indol-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-45a)

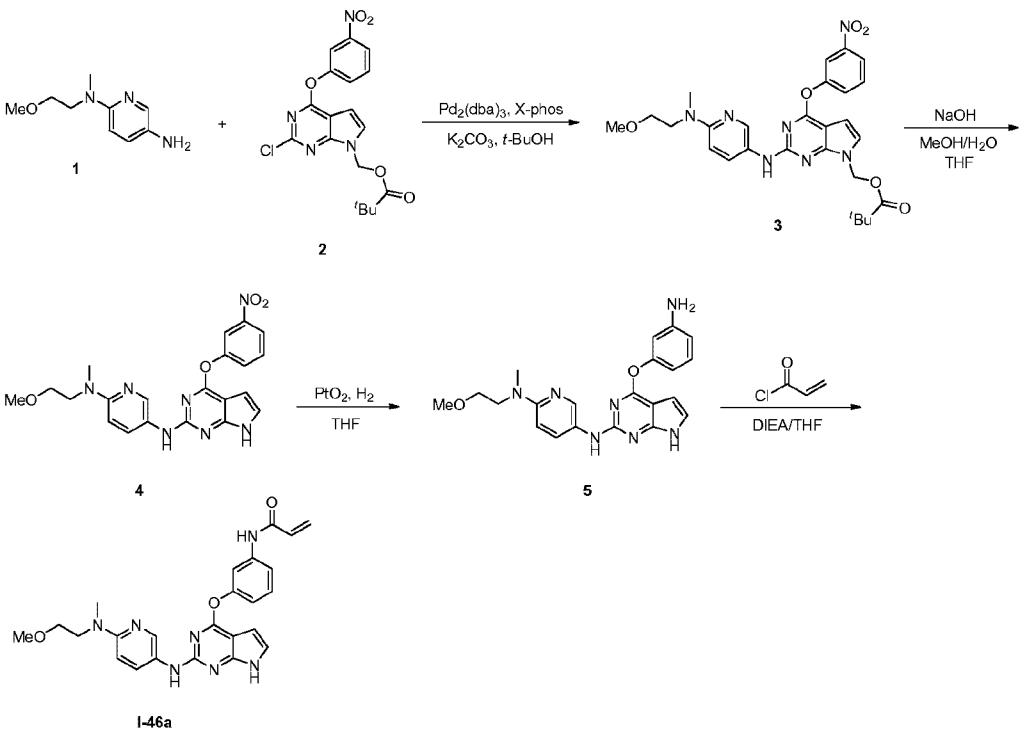
[00357] Compound **2** (1.001 g), compound **3** (1.624 g), K_2CO_3 (1.495 g), tris(dibenzylideneacetone)dipalladium (0.456g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.480 g) and *t*-BuOH (15 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 6 h, TLC (EtOAc/ Petroleum ether /TEA = 1:1:0.1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-45a** (1.5 g, 62.5%, $M+H^+$=460.5) as a white solid.

[00358] ^1H NMR (500 MHz, DMSO) δ 10.37 (s, 1H), 9.06 (s, 1H), 8.20 (s, 1H), 7.70 – 7.66 (m, 2H), 7.64 (d, *J* = 8.2 Hz, 1H), 7.51 – 7.36 (m, 1H), 7.22 – 7.16 (m, 2H), 7.10 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.99 (ddd, *J* = 8.1, 2.3, 0.7 Hz, 1H), 6.44 (dd, *J* = 17.0, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 1.9 Hz, 1H), 6.11 (d, *J* = 2.9 Hz, 1H), 5.77 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.21 (t, *J* = 5.3 Hz, 2H), 3.88 (s, 3H), 3.59 (t, *J* = 5.4 Hz, 2H), 3.19 (s, 3H).

[00359] ^{13}C NMR (126 MHz, DMSO) δ 165.36 (s), 161.45 (s), 156.17 (s), 154.90 (s), 146.13 (s), 142.38 (s), 136.38 (s), 134.91 (s), 133.62 (d, *J* = 14.8 Hz), 131.92 (s), 130.87 (s), 129.95 (s), 129.31 (s), 118.93 (s), 118.06 (s), 116.55 (s), 114.68 (s), 111.23 (s), 111.10 (d, *J* = 27.6 Hz), 102.25 (s), 73.05 (s), 60.05 (s), 59.67 (s), 47.31 (s).

Example 45

Synthesis of N-(3-(2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-46a)



Synthesis of (2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

[00360] Compound **1** (3.1 g), compound **2** (10.0 g), K_2CO_3 (5.2 g), tris(dibenzylideneacetone)dipalladium (1.2 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (1.2 g) and *t*-BuOH (100 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow.. After 3.5 h, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **3** (6.875 g, 62.5).

Synthesis of N^2-(2-methoxyethyl)-N^2-methyl-N^5-(4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)pyridine-2,5-diamine (4)

[00361] To a round-bottom flask (250 mL) was charged with compound **3** (6.857 g) and MeOH (120 mL). When compound **3** was completely dissolved, the solution was cooled with

ice-bath to around 10 °C. NaOH solution (2.5 M, 10 ml) was then added into the flask slowly, maintaining the temperature below 16 °C during the addition. The mixture was stirred for 1 h at this temperature followed by addition of THF (50 mL). After 1.5 h, water (100 mL) was added to the flask over 15 min, maintaining the temperature below 20 °C. The mixture was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure. Solvents (50 mL, ethyl acetate/ petroleum ether = 1:4) were added into this crude product, and stirred for 2 h. The resulting solid was filtered and dried to afford **4** (5.13 g), which was used for next step without further purification.

Synthesis of N^5-(4-(3-aminophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-N^2-(2-methoxyethyl)-N^2-methylpyridine-2,5-diamine (5)

[00362] A mixture of **4** (5.13 g) and PtO_2 (117 mg) in THF (50 mL) was hydrogenated with hydrogen balloon at 40°C overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite® and washed with ethyl acetate. The combined filtrate was concentrated under reduced pressure to afford the crude compound **5** (4.69 g), which was used for next step without further purification.

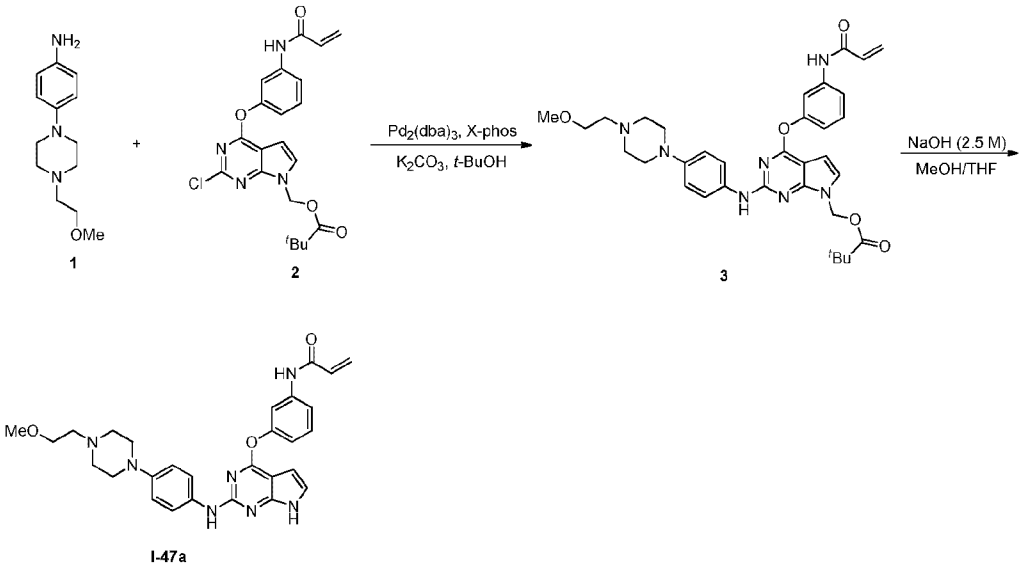
Synthesis of N-(3-(2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-46a)

[00363] To a solution of compound **5** (3.734 g) and DIEA (1.480 g) in THF (30 mL) at 0°C was drop-wise added acryloyl chloride (1.133 g) over 5 min. The mixture was stirred for 1 at this temperature. Saturated $NaHCO_3$ aqueous (10 mL) was added in to quench the reaction. The resulting mixture was stirred for 10 min, and then extracted with ethyl acetate. Organic layers were combined and concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford compound **I-46a** (1.2 g, 28.4%, $M+H^+$=460.5).

[00364] ^1H NMR (500 MHz, DMSO) δ 11.48 (s, 1H), 10.31 (s, 1H), 8.73 (s, 1H), 8.28 (s, 1H), 7.72 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.63 (t, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.03 (dd, *J* = 3.4, 2.3 Hz, 1H), 6.99 (dd, *J* = 8.1, 1.5 Hz, 1H), 6.43 (dd, *J* = 16.9, 10.1 Hz, 2H), 6.27 (dd, *J* = 17.0, 1.9 Hz, 1H), 6.22 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.82 – 5.75 (m, 1H), 3.62 (t, *J* = 5.8 Hz, 2H), 3.46 (t, *J* = 5.8 Hz, 2H), 3.24 (s, 3H), 2.95 (s, 3H).

Example 46

Synthesis of N-(3-(2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-47a)



Synthesis of (4-(3-acrylamidophenoxy)-2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

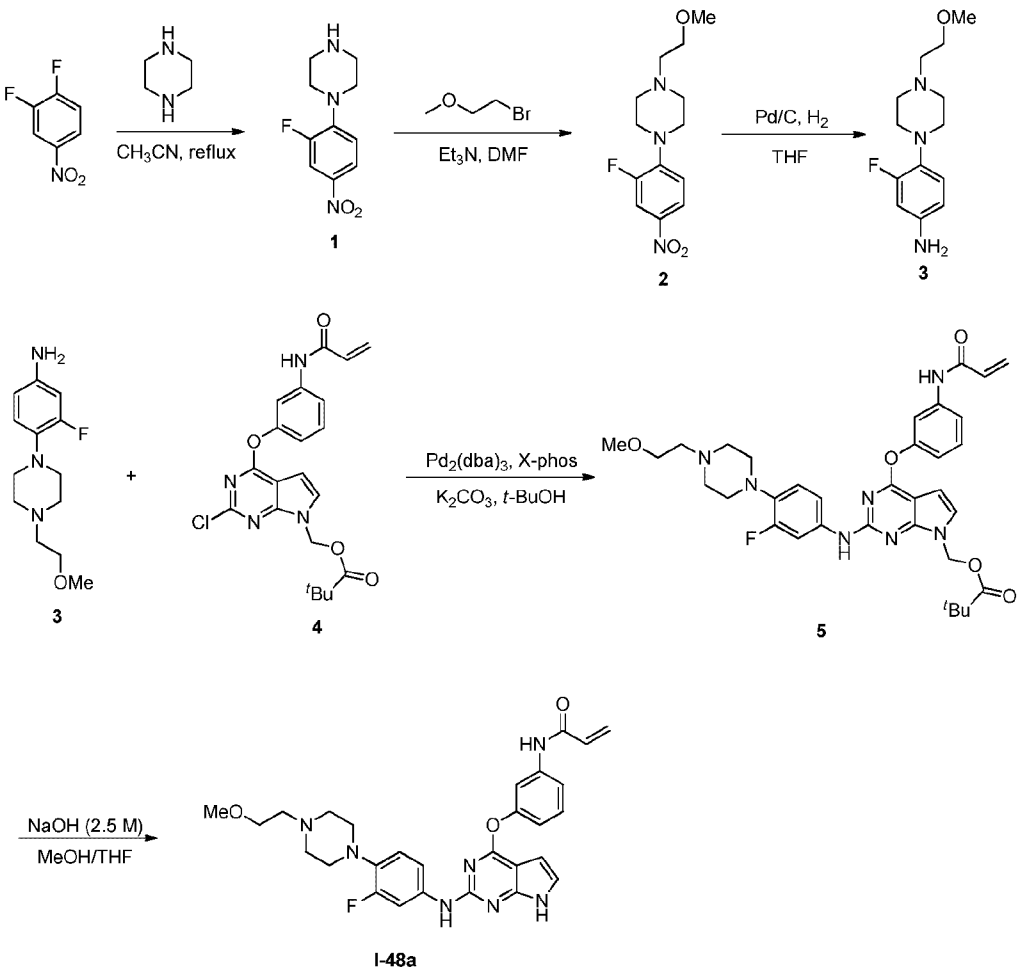
[00365] Compound **1** (2.445 g), compound **2** (4.325 g), K_2CO_3 (2.801 g), tris(dibenzylideneacetone)dipalladium (0.416 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.404 g) and *t*-BuOH (60 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **3** (4.6 g, 72.7%).

Synthesis of N-(3-(2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-47a)

[00366] To a round-bottom flask (250 mL) was charged with compound **3** (4.5 g), MeOH (30 mL) and THF (30 mL). When compound **3** was completely dissolved, the solution was cooled down to around 10 °C with ice-bath. NaOH solution (2.5 M, 6 mL) was then added into the flask slowly, maintaining the temperature below 16°C throughout the addition. The mixture was stirred for 1.5 h at this temperature. Then water (200 mL) was added to the flask over 15 min, maintaining the temperature below 20°C. The mixture was extracted with ethyl acetate (500 mL). the combined organic layers were separated, dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography (EtOAc as mobile phase) to give **I-47a** (2.96 g, 80.4%, $M+H^+$=514.6) as a white solid.

Example 47

Synthesis of N-(3-(2-(3-fluoro-4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-48a)



Synthesis of 1-(2-fluoro-4-nitrophenyl)piperazine (1)

[00367] A mixture of 1, 2-difluoro-4-nitrobenzene (15.9 g), piperazine (10.39 g) and acetonitrile (100 mL) was stirred at refluxing for 7 h. TLC showed the reaction to be complete. After cooling, the mixture was basified with saturated K_2CO_3 aqueous solution (100 mL), and extracted with ethyl acetate. The combined organic layers was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Solvents (40 mL, petroleum ether/ ethyl acetate = 1:1) were added in the clued and stirred overnight. The resulting precipitates was collected and dried to afford the desired product 1, (13.5 g) as a yellow solid.

Synthesis of 1-(2-fluoro-4-nitrophenyl)-4-(2-methoxyethyl)piperazine (2)

[00368] To a solution of 1-bromo-2-methoxyethane (8.7 g) and **1** (11.4 g) in DMF (100 mL) at room temperature was added Et_3N (8.2 g). The mixture was stirred at 54 °C overnight. The reaction mixture was poured onto ice-water (300 mL). The precipitate was collected and re-dissolved in ethyl acetate (200 mL). The organic layer was washed with brine and concentrated under reduced pressure to afford the desired compound **2** (14.0 g, 98%), which was used for next step without further purification.

Synthesis of 3-fluoro-4-(4-(2-methoxyethyl)piperazin-1-yl)aniline (3)

[00369] A mixture of **2** (7.0 g) and Pd/C (0.586 g, 10% activated on carbon) in THF (100 mL) was hydrogenated with hydrogen balloon at room temperature overnight. At this point, TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford **3** (6.3 g), which was used for next step without further purification.

Synthesis of (4-(3-acrylamidophenoxy)-2-(3-fluoro-4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (5)

[00370] Compound **3** (1.051 g), compound **4** (1.806 g), K_2CO_3 (0.936 g), tris(dibenzylideneacetone)dipalladium (0.166 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.195 g) and *t*-BuOH (60 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 6 h, TLC (DCM/MeOH = 10/1 as mobile phase) indicated the reaction to be complete. The mixture was allowed to cool down to 40~50°C, filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was purified by column chromatography to afford compound **5** (2.316 g, 90.9%).

Synthesis of N-(3-(2-(3-fluoro-4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-48a)

[00371] To a round-bottom flask (250 mL) was charged with compound **5** (2.3 g), MeOH (10 mL) and THF (10 mL). When compound **5** was completely dissolved, the solution was cooled down to around 10 °C with ice-bath. NaOH solution (2.5 M, 3.5 mL) was then added into the

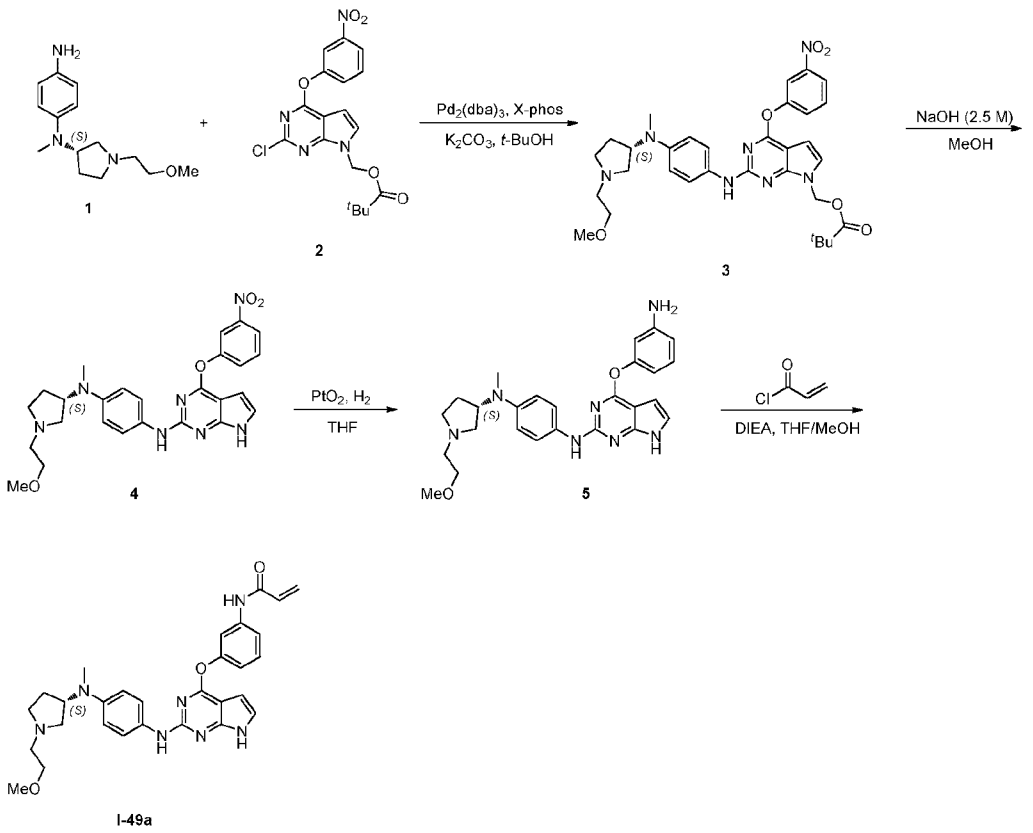
flask slowly, maintaining the temperature below 16 °C throughout the addition. The mixture was continuously stirred for another h at this temperature. Then water (40 mL) was added to the flask over 15 min, maintaining the temperature below 20°C. The mixture was extracted with ethyl acetate (500 mL). The combined organic layers were separated, dried over Na_2SO4 and concentrated under reduced pressure. The resulting crude was purified by column chromatography to give **I-48a** (0.814 g, 42.5%, $M+H^+$=532.6).

[00372] ^1H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 8.06 (s, 1H), 7.64 (s, 1H), 7.51 – 7.37 (m, 2H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.26 (s, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.71 (t, *J* = 9.1 Hz, 1H), 6.67 (s, 1H), 6.40 (d, *J* = 16.8 Hz, 1H), 6.29 – 6.17 (m, 2H), 5.70 (d, *J* = 10.2 Hz, 1H), 3.56 (dd, *J* = 15.9, 11.0 Hz, 2H), 3.38 (s, 3H), 3.00 (s, 4H), 2.66 (d, *J* = 4.7 Hz, 6H).

[00373] ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.28 (s), 163.75 (s), 162.68 (s), 156.59 (s), 155.11 (d, *J* = 9.0 Hz), 154.65 (s), 153.45 (s), 138.98 (s), 135.62 (d, *J* = 11.0 Hz), 134.26 (d, *J* = 9.3 Hz), 130.98 (s), 129.75 (s), 128.04 (s), 120.68 (s), 119.07 (s), 117.96 (s), 116.88 (s), 114.53 (s), 114.08 (s), 107.60 (d, *J* = 26.0 Hz), 99.56 (s), 99.39 (s), 69.91 (s), 58.91 (s), 57.96 (s), 53.63 (s), 50.69 (s).

Example 48

Synthesis of (*S*)-N-(3-(2-(4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-49a)



Synthesis of (*S*)-(2-(4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)-4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (3)

[00374] Compound **1** (1.010 g), compound **2** (1.642 g), K_2CO_3 (1.262 g), tris(dibenzylideneacetone)dipalladium (0.371 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.367 g) and *t*-BuOH (15 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 22.5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (30 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (Ethyl acetate/ MeOH = 20:1 as mobile phase) to afford compound **3** (1.74 g, 70.24%) as a brown oil.

Synthesis of (*S*)-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)-N^1-methyl-N^4-(4-(3-nitrophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)benzene-1,4-diamine (4)

[00375] To a round-bottom flask (250 mL) was charged with compound **3** (1.74 g), THF (10 mL) and MeOH (20 mL). After compound **3** was completely dissolved, the solution was cooled to ~10°C with ice-bath. NaOH solution (2.5 M, 3 mL) was then added into the flask slowly, maintaining the temperature below 16°C during the addition. The mixture was stirred for 5.5 h at this temperature. Water (50 mL) was added slowly to the flask over 15 min, maintaining the temperature below 20°C during the addition. The mixture was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure to afford compound **4** (1.2 g).

Synthesis of (*S*)-N^1-(4-(3-aminophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-2-yl)-N^4-(1-(2-methoxyethyl)pyrrolidin-3-yl)-N^4-methylbenzene-1,4-diamine (5)

[00376] A mixture of **4** (1.2 g) and PtO_2 (33 mg) in THF (15 mL) was hydrogenated with hydrogen balloon at 50°C for 40 h. TLC and LC-MS indicated that the reaction was not complete. The reaction mixture was filtered through Celite® and the filtrate was concentrated under reduced pressure. The resulting residue was treated with iron/NH_4Cl aq/EtOH system for 4 h. At this point, TLC and LC/MS indicated the reaction to be complete. The mixture was extracted with ethyl acetate. The combined organic layers were concentrated under reduced pressure to afford crude product **5** (1.1 g), which was used for next step without further purification.

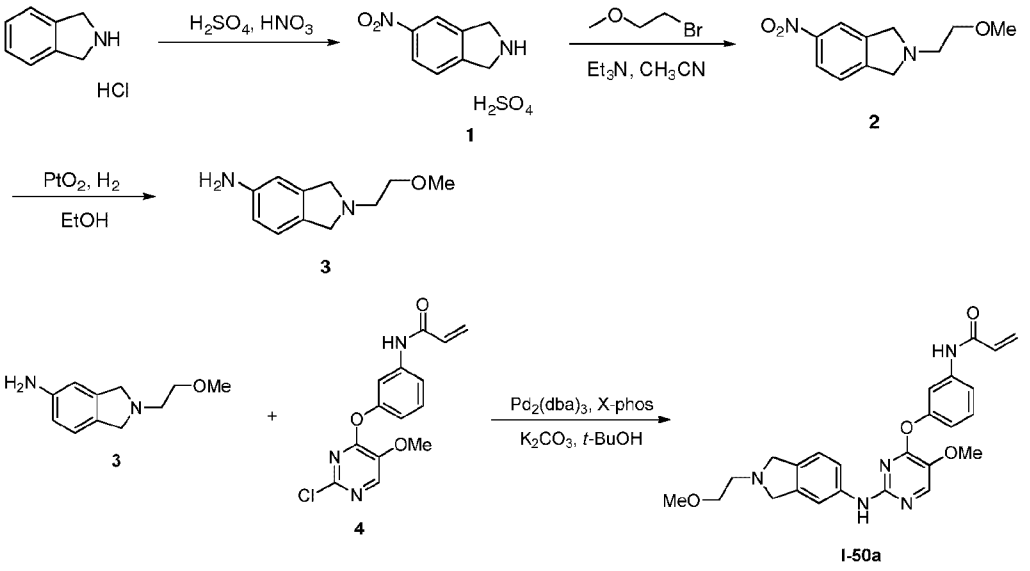
Synthesis of (*S*)-N-(3-(2-(4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-49a)

[00377] To a solution of compound **5** (1.1 g) and DIEA (1.001 g) in THF/MeOH (4:1, 25 mL) at 0°C was drop-wise added acryloyl chloride (0.462 g) over 5 min. The mixture was stirred for 1 h at this temperature. At this point, TLC and LC/MS indicated the reaction to be complete. Saturated Na_2CO_3 aqueous solution (50 mL) was added to quench the reaction. The resulting mixture was stirred for 10 min, and extracted with ethyl acetate. The combined organic layers

were combined and concentrated under reduced pressure. The resulting crude was further purified by column chromatography to give compound **I-49a** (0.7 g, 57.1%, M+H$^+$=528.6).

Example 49

Synthesis of N-(3-(5-methoxy-2-(2-(2-methoxyethyl)isoindolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-50a)



Synthesis of 5-nitroisoindoline (1)

[00378] To concentrated sulphuric acid (3 mL) at -10°C was added isoindoline hydrochloride (1.569 g). The mixture was stirred at -10°C for 15 min. Fuming nitric acid (3 mL) was added drop-wise. The resulting mixture was stirred for 35 min at room temperature and then heated up and stirred at 50 °C for 35 min. After cooling to room temperature, the mixture was diluted with ethyl acetate (5 mL) and poured onto ice-water. The resulting precipitate was collected, washed with small amount of ethyl acetate and dried to afford 5-nitroisoindoline hydrosulfate **1** (1.644 g, 62.7%).

Synthesis of 2-(2-methoxyethyl)-5-nitroisoindoline (2)

[00379] To a solution of 1-bromo-2-methoxyethane (0.5 g) and **1** (0.5 g) in CH_3CN (15 mL) was added Et_3N (0.8 g). The mixture was then heated at 80°C and stirred for 7 h. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. The organic layer was washed with brine and concentrated under reduced pressure to afford the desired compound **2** (650 mg, 96%), which was used for next step without further purification.

Synthesis of 2-(2-methoxyethyl)isoindolin-5-amine (3)

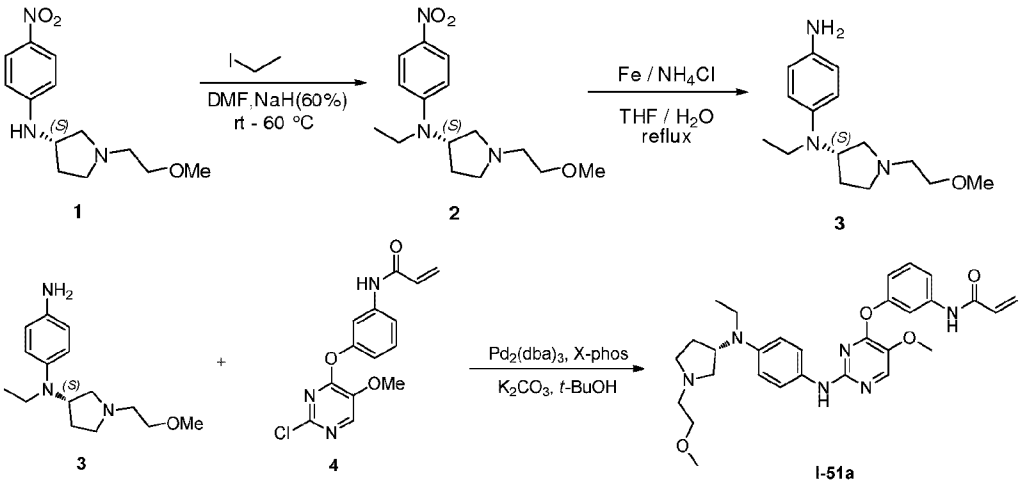
[00380] A mixture of **2** (650 mg) and PtO_2 (0.025 g) in THF (10 mL) was hydrogenated with hydrogen balloon at room temperature overnight. TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite® and washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure to afford the desired product **3** (0.50 g), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(2-(2-methoxyethyl)isoindolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-50a)

[00381] Compound **3** (0.5 g), compound **4** (0.8 g), K_2CO_3 (0.787 g), tris(dibenzylideneacetone)dipalladium (0.116 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.126 g) and *t*-BuOH (20 mL) were sequentially added to a flask. The reaction mixture was stirred at refluxing under N_2 flow. After 19 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-50a** (0.512 g, 42.7%, $M+H^+$=462.5).

Example 50

Synthesis of (*S*)-N-(3-(2-(4-(ethyl(1-(2-methoxyethyl)pyrrolidin-3-yl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-51a)



Synthesis of (*S*)-N-ethyl-1-(2-methoxyethyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00382] To a solution of **1** (1.969 g, 7.428 mmol) in DMF (10 ml) at 0°C was sequentially added NaH (0.318 g, 80% dispersion in mineral oil, 13.25 mmol) and C_2H_5I (1.330 g, 8.52 mmol). The mixture was stirred at 60 °C for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude was further purified by column chromatography (ethyl acetate/ petroleum ether from 33.3% to 100% as mobile phase) to give **2** (0.280 g, 0.9 mmol, 13%) as a yellow oil.

Synthesis of (*S*)-N^1-ethyl-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)benzene-1,4-diamine (3)

[00383] To compound **2** (0.280 g, 0.9 mmol) in THF/H_2O (20 mL/3 mL) was added iron (0.280 g, 5 mmol) and NH_4Cl (0.535 g, 10 mmol). The mixture was stirred at refluxing for 2 h. At this point, TLC indicated the reaction to be complete. The mixture was filtered. The filtrate was diluted with ethyl acetate and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford desired compound **3** (0.191 g, 81%), which was used for next step without further purification.

Synthesis of (*S*)-N-(3-(2-(4-(ethyl(1-(2-methoxyethyl)pyrrolidin-3-yl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-51a)

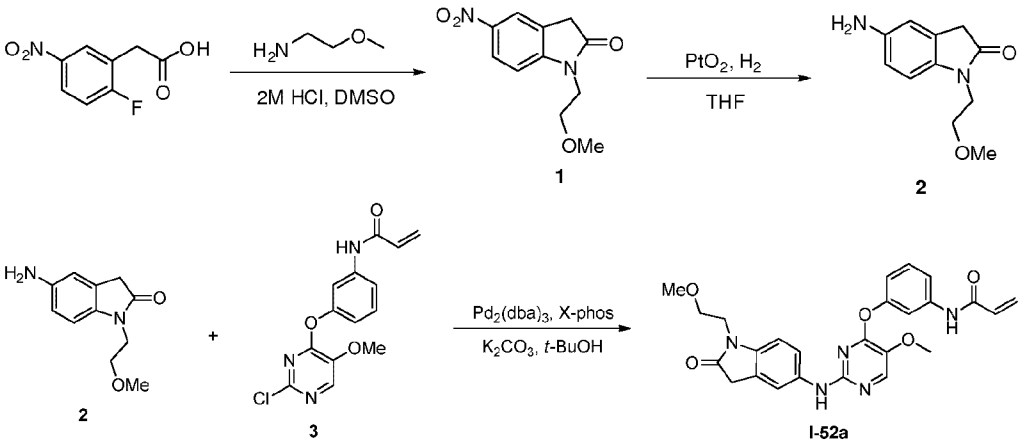
[00384] Compound **3** (0.191g, 0.73 mmol), compound **4** (0.315g, 1 mmol), K_2CO_3 (0.330 g, 2.5 mmol), tris(dibenzylideneacetone)dipalladium (0.096 g, 0.1 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (0.094 g, 0.2 mmol) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-51a** (0.150 g, 32%, $M+H^+$=433.6).

[00385] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.96 (s, 1H), 7.66 (s, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 2H), 7.01 – 6.91 (m, 2H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.41 (d, *J* = 16.7 Hz, 1H), 6.28 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.71 (d, *J* = 10.4 Hz, 1H), 4.21 – 4.00 (m, 1H), 3.93 (d, *J* = 16.2 Hz, 3H), 3.51 (t, *J* = 5.6 Hz, 2H), 3.37 (s, 3H), 3.20 – 3.11 (m, 2H), 2.85 (d, *J* = 10.0 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.67 – 2.52 (m, 2H), 2.43 (dd, *J* = 9.0, 7.3 Hz, 1H), 2.17 – 2.01 (m, 1H), 1.80 – 1.63 (m, 1H), 0.99 (t, *J* = 7.0 Hz, 3H).

[00386] ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.73 (s), 160.38 (s), 154.20 (s), 152.97 (s), 144.59 (s), 142.94 (s), 139.24 (s), 135.36 (s), 131.91 (s), 131.07 (s), 129.61 (s), 127.97 (s), 120.12 (s), 118.43 (s), 117.96 (s), 116.76 (s), 114.05 (s), 71.14 (s), 58.87 (s), 58.60 (s), 58.53 (s), 58.06 (s), 55.76 (s), 53.89 (s), 44.13 (s), 29.32 (s), 13.36 (s).

Example 51

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)-2-oxoindolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-52a)



Synthesis of 1-(2-methoxyethyl)-5-nitroindolin-2-one (1)

[00387] A solution of 2-(2-fluoro-5-nitrophenyl) acetic acid (1.001 g) and 2-methoxyethanamine (1.892 g) in DMSO (5 mL) was stirred at 45°C overnight. Excess 2-methoxyethanamine was removed under reduced pressure before HCl (2M, 3 mL) was added to the mixture. The mixture was stirred at 45°C for 1 h. The reaction was quenched with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (DCM/petru = 5/1 with drops of AcOH as mobile phase) to give **1** (0.720 g, yield 60.7%) as a yellow solid.

Synthesis of 5-amino-1-(2-methoxyethyl)indolin-2-one (2)

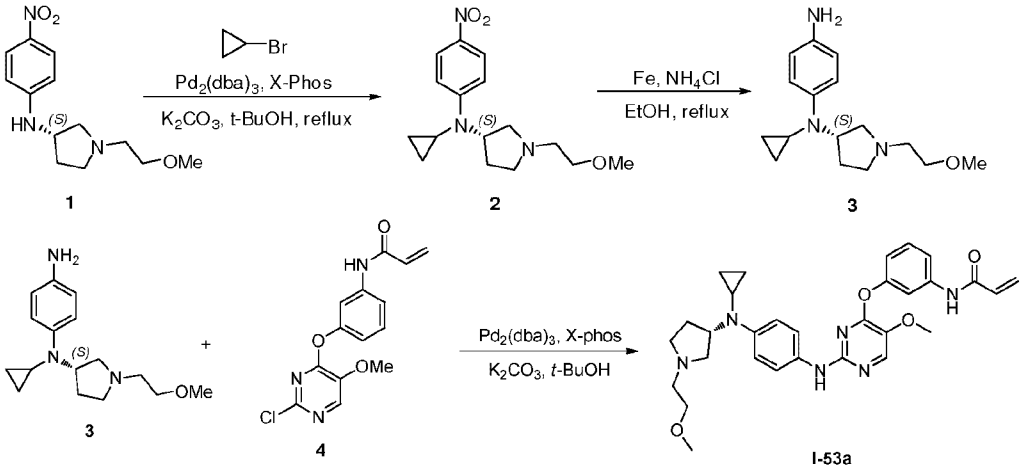
[00388] A mixture of **1** (0.401 g) and PtO_2 (0.019 g) in THF (15 mL) was hydrogenated with hydrogen balloon at room temperature overnight. After completion of the reaction, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure and the residue was re-dissolved with ethyl acetate. The solution was washed with water. The aqueous layer was separated and extracted with ethyl acetate (50 mL×3). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product **2** (0.345 g), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(1-(2-methoxyethyl)-2-oxoindolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-52a)

[00389] Compound **2** (0.360 g), compound **3** (0.650 g), K_2CO_3 (0.610 g), tris(dibenzylideneacetone)dipalladium (0.05 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.11 g) and *t*-BuOH (13 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 6 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-52a** (0.47 g, 56.6%, $M+H^+$=476.5).

Example 52

Synthesis of (*S*)-N-(3-(2-(4-(cyclopropyl(1-(2-methoxyethyl)pyrrolidin-3-yl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-53a)



Synthesis of (S)-N-cyclopropyl-1-(2-methoxyethyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00390] A mixture of compound **1** (1.090 g), cyclopropyl bromide (1.825 g), $Pd_2(dba)_3$ (0.200 g), X-Phos (0.201 g) and potassium carbonate (2.032 g) in *t*-butanol (15 mL) was stirred under argon at refluxing overnight. After cooling to room temperature, the reaction mixture was filtered through Celite®, and washed with ethyl acetate. The combined filtrates were concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired compound **2** (260 mg, 21.85%).

Synthesis of (*S*)-N^1-cyclopropyl-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)benzene-1,4-diamine (3)

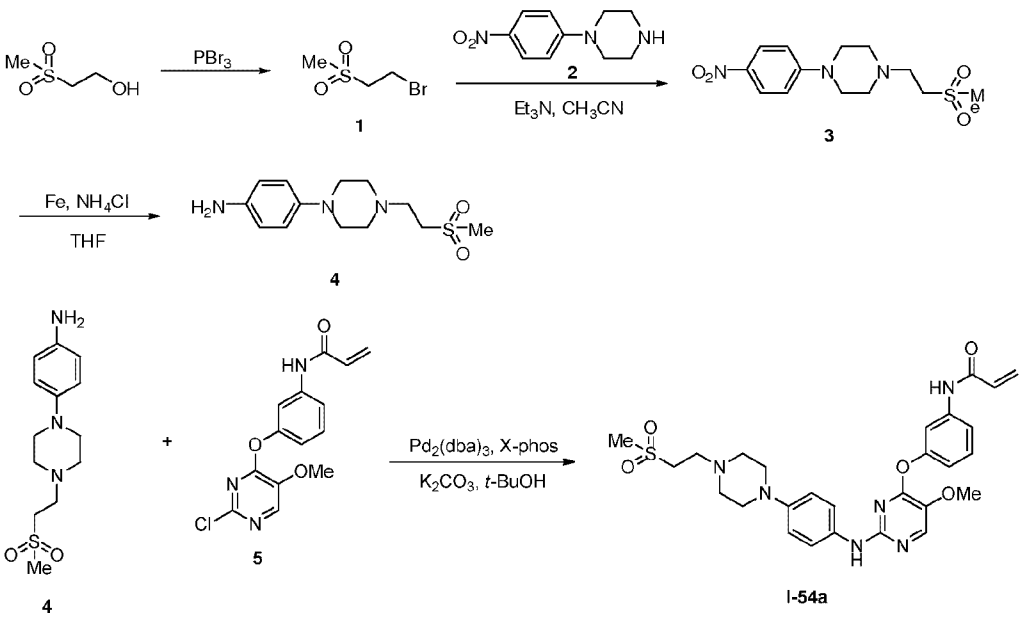
[00391] To compound **2** (260 mg) in EtOH/H_2O (5:2, 14 mL) was added iron (201 mg) and NH_4Cl (800 mg). The mixture was stirred at refluxing for 2 h. The reaction was filtered. The filtrate was diluted with ethyl acetate and washed with saturated $NaHCO_3$ aqueous solution. The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to afford desired compound **3** (200 mg, 85.47%), which was used for next step without further purification.

Synthesis of (*S*)-N-(3-(2-(4-(cyclopropyl(1-(2-methoxyethyl)pyrrolidin-3-yl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-53a)

[00392] Compound **3** (0.188 g), compound **4** (0.235 g), K_2CO_3 (0.250 g), tris(dibenzylideneacetone)dipalladium (0.076 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.085 g) and *t*-BuOH (10 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-53a** (70 mg, 18.8%, $M+H^+$=545.6).

Example 53

Synthesis of N-(3-(5-methoxy-2-(4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-54a)



Synthesis of 1-bromo-2-(methylsulfonyl)ethane (1)

[00393] A solution of 2-(methylsulfonyl)ethanol (2.5 g) and pyridine (0.1 mL) in DCM (30 mL) at 0°C was added PBr_3 (6.3 g). The mixture was warmed up and stirred at room temperature for 4 h. At this point, TLC indicated the reaction to be complete. The mixture was cooled to 0°C and water was added to quench the reaction. The organic layer was separated, washed with saturated$NaHCO_3$ aqueous solution, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude product **1** (0.841 g, 22%), which was used for next step without further purification.

Synthesis of 1-(2-(methylsulfonyl)ethyl)-4-(4-nitrophenyl)piperazine (3)

[00394] To a solution of 1-bromo-2-(methylsulfonyl)ethane **1** (0.841 g) and **2** (1.212 g) in CH_3CN (20 mL) at room temperature was added Et_3N (1 mL). The mixture was then heated up and stirred at 70°C overnight. Organic solvent was removed under reduced pressure. The residue was washed with ethyl acetate, THF and water. The resulting solid was collected and dried to afford the crude compound **3** (1.2 g, 85%), which was used for next step without further purification.

Synthesis of 4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)aniline (4)

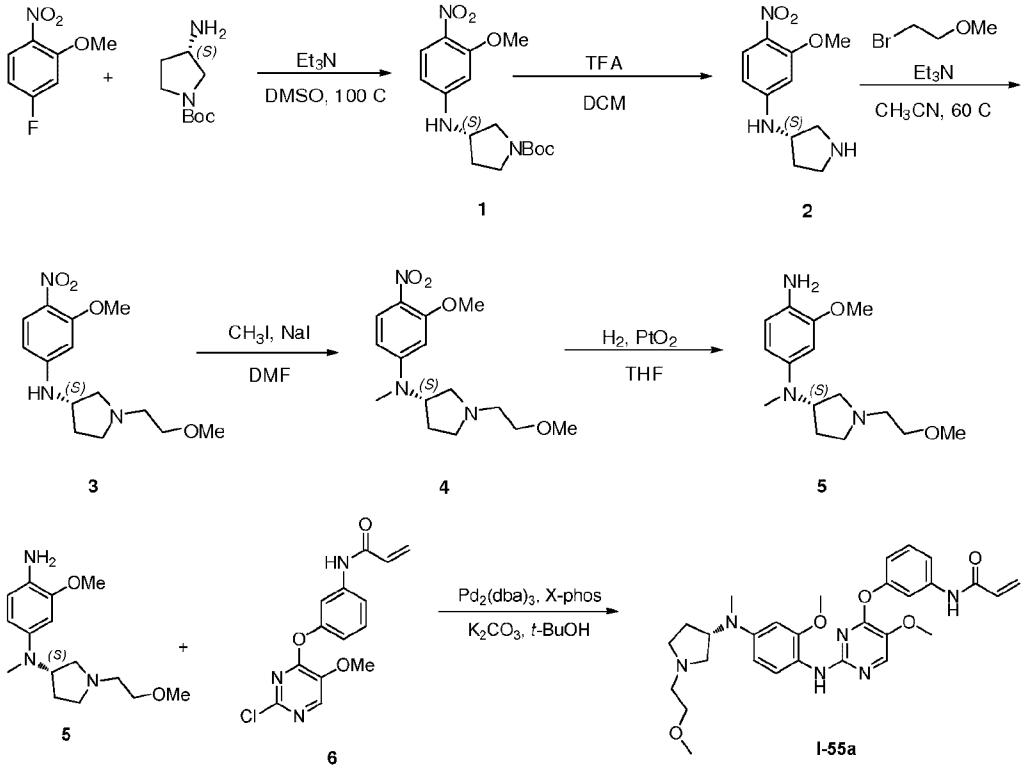
[00395] A solution of **3** (1.2 g) in THF/H_2O (30 ml/5 ml) was treated with iron (2.1 g) and ammonium chloride (1.0 g). The mixture was stirred at refluxing for 2 h. The mixture was filtered through Celite® and washed with ethyl acetate (100 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ solution and water and then dried over Na_2SO_4 and concentrated under reduced pressure to afford crude product **4** (0.380 g, 35%), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-54a)

[00396] Compound **4** (0.38 g), compound **5** (0.463 g), K_2CO_3 (0.440 g), tris(dibenzylideneacetone)dipalladium (0.913 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.860 g) and *t*-BuOH (10 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-54a** (0.564 g, 74.1%, $M+H^+$=553.6).

Example 54

Synthesis of (S)-N-(3-(5-methoxy-2-(2-methoxy-4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-55a)



Synthesis of (S)-tert-butyl 3-(3-methoxy-4-nitrophenylamino)pyrrolidine-1-carboxylate (1)

[00397] Into a 3-Neck round-bottom flask (250 mL) equipped with a refluxing condenser was charged 4-fluoro-2-methoxy-1-nitrobenzene (4.594 g) and (3*S*)-(-)-1-(t-Butoxycarbonyl)-3-aminopyrrolidine (5.0 g), TEA (3.030 g) in DMSO (50 mL). The reaction was heated up and stirred at 80 °C overnight. After TLC indicated the reaction to be complete, the reaction mixture was quenched with water and stirred for 0.5 h at room temperature. The resulting precipitation was filtered and dried to afford the crude compound **1** (10.0 g) which was used for next step without further purification.

Synthesis of (S)-N-(3-methoxy-4-nitrophenyl)pyrrolidin-3-amine (2)

[00398] To the crude compound **1** (10.0 g) in DCM (25 mL) was added TFA (10 mL). The reaction mixture was stirred at room temperature overnight. After TLC indicated that the reaction to be complete, the reaction mixture was concentrated under reduced pressure (to remove most of TFA). The residue was diluted with ethyl acetate and basified by addition of

saturated $NaHCO_3$ (*aq*) at 0°C. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude compound **2** (12 g), which was used for next step without further purification.

Synthesis of (*S*)-N-(3-methoxy-4-nitrophenyl)-1-(2-methoxyethyl)pyrrolidin-3-amine (3)

[00399] To a solution of 2-bromoethyl methyl ether (4.500 g) and **2** (3.512 g) in CH_3CN (100 mL) at room temperature was added Et_3N (6.0 g). The mixture was heated up and stirred at refluxing for 2.5 h. The reaction mixture was concentrated under reduced pressure. The residue was re-dissolved in ethyl acetate (200 mL) and the resulting solution was washed with water, The aqueous layer was separated and extracted with ethyl acetate. The organic layers were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material was washed with solvents (petroleum ether/ethyl acetate = 2:1) to afford the desired compound **3** (8.59 g, 57.5%).

(*S*)-N-(3-methoxy-4-nitrophenyl)-1-(2-methoxyethyl)-N-methylpyrrolidin-3-amine (4)

[00400] To a solution of compound **3** (8.590 g) in DMF (5 mL) at 0°C was sequentially added NaH (1.1 g, 80% dispersion in mineral oil) and CH_3I (5.55 g). The resulting mixture was then stirred for 0.5 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude material **4** (3.80 g, 42.2%) was used directly in next step without further purification.

Synthesis of (*S*)-3-methoxy-N^1-(1-(2-methoxyethyl)pyrrolidin-3-yl)-N^1-methylbenzene-1,4-diamine (5)

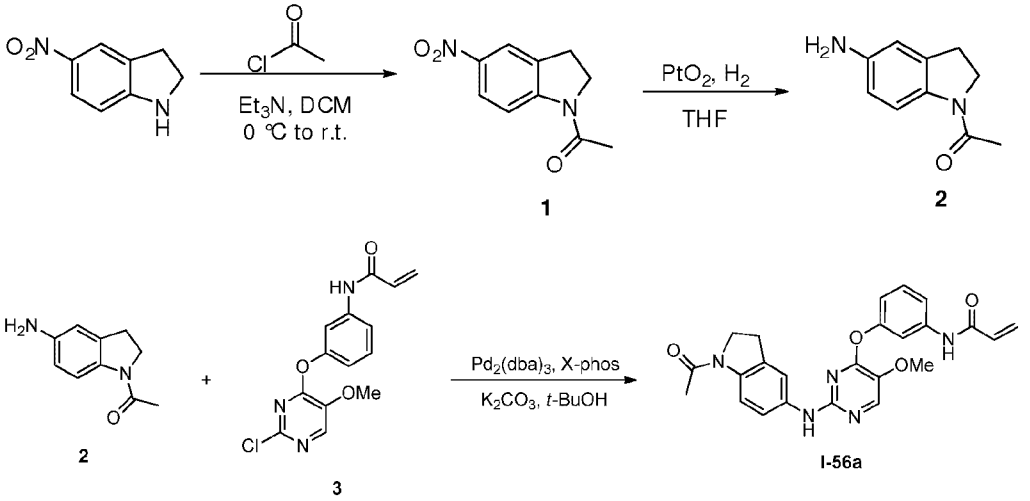
[00401] A mixture of **4** (3.8 g) and PtO_2 (0.130 g) in THF (30 mL) was hydrogenated with hydrogen balloon at room temperature overnight. Once the reaction was complete by TLC, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate/EtOH = 8/2, with 0.5% TEA as mobile phase) to afford the desired compound **5** (2.323 g, 67.7%).

Synthesis of (S)-N-(3-(5-methoxy-2-(2-methoxy-4-((1-(2-methoxyethyl)pyrrolidin-3-yl)(methyl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-55a)

[00402] Compound **5** (2.323 g), compound **6** (3.036 g), K_2CO_3 (2.289 g), tris(dibenzylideneacetone)dipalladium (0.380 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.380 g) and *t*-BuOH (40 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-55a** (2.845 g, 62.4%, $M+H^+$=549.6).

Example 55

Synthesis of N-(3-(2-(1-acetylindolin-5-ylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-56a)



Synthesis of 1-(5-nitroindolin-1-yl)ethanone (1)

[00403] A solution of 5-nitroindoline (1.010 g, 6.159 mmol), TEA (0.810 g, 8.020 mmol) in DCM (30 mL) at 0°C was slowly added acetyl chloride (0.610 g, 7.82 mmol). The mixture was

warmed up and stirred at room temperature for 0.5 h. The reaction was quenched with water (30 mL) and extracted with DCM (25 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to afford crude **1** (1.015 g, 4.927 mmol, 85%), which was used foe next step without further purification.

Synthesis of 1-(5-aminoindolin-1-yl)ethanone (2)

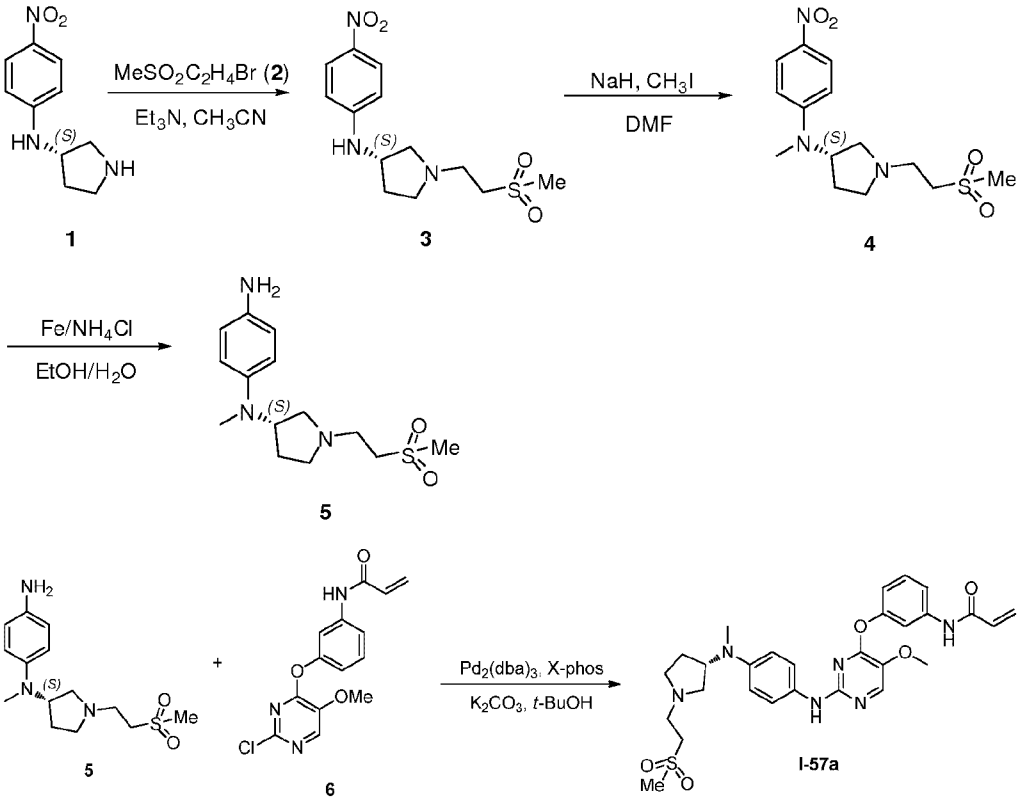
[00404] A mixture of **1** (1.015 g, 4.927 mmol) and PtO_2 (0.028 g, 0.14 mmol) in THF (30 mL) was hydrogenated with hydrogen balloon at room temperature overnight. Once the reaction was complete indicated by TLC, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford the desired product **2** (0.798 g, 92%), which was used for next step without further purification.

Synthesis of N-(3-(2-(1-acetylindolin-5-ylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-56a)

[00405] Compound **2** (0.798 g, 4.531 mmol), compound **3** (1.956 g, 6.774 mmol), K_2CO_3 (1.553 g, 11 mmol), tris(dibenzylideneacetone)dipalladium (0.313 g, 0.34 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.360 g, 0.68 mmol) and *t*-BuOH (40 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-56a** (1.71 g, 84.8%, $M+H^+$=446.6).

Example 56

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(methyl(1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-57a)



Synthesis of (*S*)-1-(2-(methylsulfonyl)ethyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (3)

[00406] To a solution of 1-bromo-2-(methylsulfonyl)ethane (**2**, 3.824 g) and **1** (3.512 g) in CH_3CN (40 mL) at room temperature was added Et_3N (3.490 g). The mixture was heated up and stirred at refluxing for 5 h. The reaction mixture was then poured onto ice-water (150 mL). The resulting precipitate was collected, washed and dried to afford the desired compound **3** (3.484, 65.83%) as a yellow solid, which was used for next step without further purification.

(*S*)-N-methyl-1-(2-(methylsulfonyl)ethyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (4)

[00407] To a solution of **3** (1.5 g) in DMF (10 mL) at 0°C was sequentially added NaH (0.399 g, 80% dispersion in mineral oil) and CH_3I (0.924 g). The resulting mixture was then stirred for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material **4** (1.664 g) was used directly in the next step without further purification.

Synthesis of (*S*)-N^1-methyl-N^1-(1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)benzene-1,4-diamine (5)

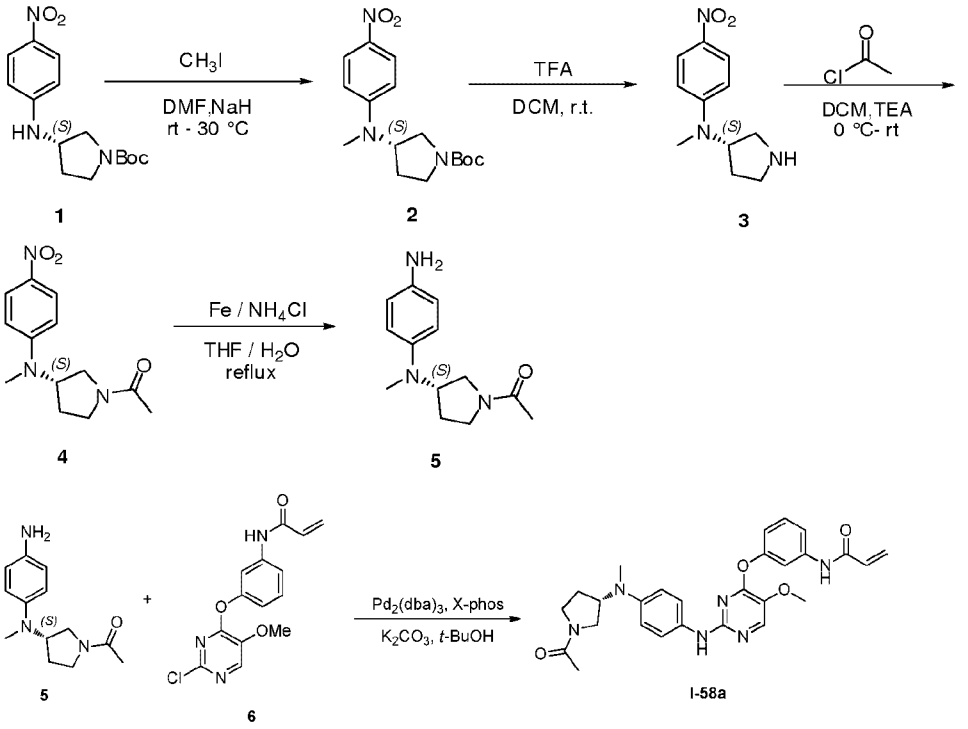
[00408] A solution of **4** (1.664 g) in EtOH/H_2O (30 mL/1 mL) was treated with iron (1.143 g) and ammonium chloride (4.512 g). The mixture was stirred at refluxing for 2 h. The reaction was cooled to room temperature, and filtered through Celite®. The filtrate was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous K_2CO_3 solution, and concentrated under reduced pressure to afford crude product **5** (0.758 g, 50%), which was used for next step without further purification.

(*S*)-N-(3-(5-methoxy-2-(4-(methyl(1-(2-(methylsulfonyl)ethyl)pyrrolidin-3-yl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-57a)

[00409] Compound **5** (0.654 g), compound **6** (0721 g), K_2CO_3 (0.702 g), tris(dibenzylideneacetone)dipalladium (0.182 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.191 g) and *t*-BuOH (30 ml) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 4.5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-57a** (662 mg, 53.13%, $M+H^+$=567.6).

Example 57

Synthesis of (S)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-58a)



Synthesis of (*S*)-tert-butyl 3-(methyl(4-nitrophenyl)amino)pyrrolidine-1-carboxylate (2)

[00410] To a solution of (*S*)-tert-butyl 3-(4-nitrophenylamino)pyrrolidine-1-carboxylate (1, 0.995 g, 3.257 mmol) in DMF (5 mL) at 0°C was sequentially added NaH (0.165 g, 80% dispersion in mineral oil) and CH_3I (0.705 g, 4.88 mmol). The resulting mixture was stirred for 0.5 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude material **2** (0.894 g, 2.931 mmol, 90%) was collected, washed, dried, and used directly in next step without further purification.

Synthesis of (*S*)-N-methyl-N-(4-nitrophenyl)pyrrolidin-3-amine (3)

[00411] To crude compound **2** (0.894 g, 2.931 mmol) in DCM (10 mL) was added TFA (2 mL). The reaction mixture was stirred at room temperature until TLC (petroleum ether/ ethyl acetate=1/3 as mobile phase) indicated the reaction to be complete. The reaction mixture was concentrated under reduced pressure to remove most of TFA. The residue was basified with $NaHCO_3$ (*aq*, 30 mL) and extract with ethyl acetate (30 mL ×4). The organic layers were

combined, dried and concentrated under reduced pressure to afford crude **3** (0.504g, 2.28 mmol, 78%), which was used in next step without further purification.

Synthesis of (*S*)-1-(3-(methyl(4-nitrophenyl)amino)pyrrolidin-1-yl)ethanone (4)

[00412] A solution of **3** (0.504 g, 2.28 mmol), TEA (0.303 g, 3 mmol) in DCM (20 mL) at 0°C was slowly added acetyl chloride (0.610 g, 7.82 mmol). The mixture was warmed up and stirred at room temperature for 0.5 h. The reaction was quenched with water (30 mL) and extracted with DCM (25 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to afford crude **4** (0.492 g, 1.87 mmol, 82%), which was used for next step without further purification.

Synthesis of (*S*)-1-(3-((4-aminophenyl)(methyl)amino)pyrrolidin-1-yl)ethanone (5)

[00413] A solution of **4** (0.320 g, 1.217 mmol) in THF/H_2O (20 mL/3 mL) was treated with iron (0.280 g, 5 mmol) and ammonium chloride (0.535 g, 10 mmol). The mixture was stirred at refluxing for 2 h. The reaction was filtered through Celite®. The filtrate was basified with $NaHCO_3$ (*aq,* 30 mL) and extracted with ethyl acetate (30 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to afford crude product **5** (0.230 g, 1 mmol, 82%), which was used for next step without further purification.

Synthesis of (S)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-58a)

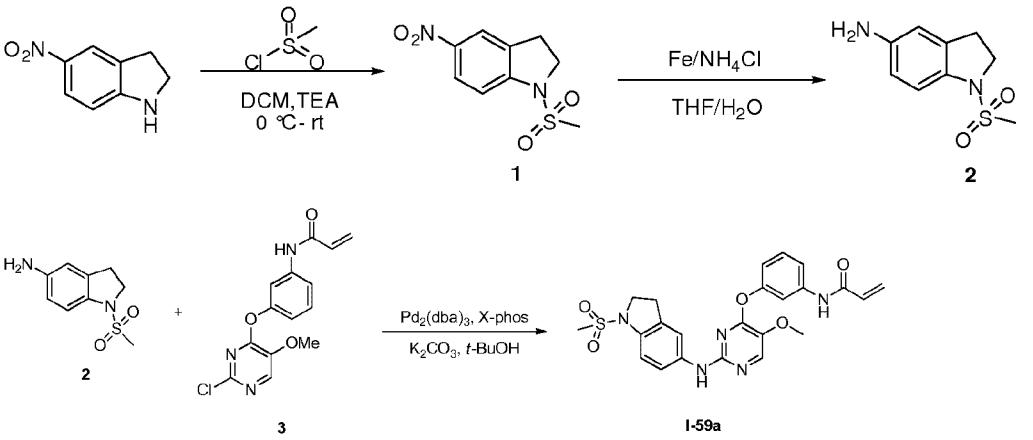
[00414] Compound **5** (0.230 g, 1 mmol), compound **6** (0.368 g, 1.217 mmol), K_2CO_3 (0.376 g, 2.5 mmol), tris(dibenzylideneacetone)dipalladium (0.058 g, 0.06 mmol), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.060 g, 0.12 mmol) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 4.5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-58a** (0.15 g, 30%, $M+H^+$=503.6).

[00415] ^{1}H NMR (500 MHz, DMSO) δ 10.35 (s, 1H), 8.99 (d, *J* = 4.3 Hz, 1H), 8.16 (s, 1H), 7.67 – 7.56 (m, 2H), 7.49 – 7.37 (m, 1H), 7.28 (dd, *J* = 9.0, 2.1 Hz, 2H), 6.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.65 (dd, *J* = 9.1, 3.4 Hz, 2H), 6.44 (dd, *J* = 16.9, 10.1 Hz, 1H), 6.27 (dd, *J* = 17.0, 1.2 Hz, 1H), 5.77 (dd, *J* = 10.1, 1.9 Hz, 1H), 4.24 – 3.99 (m, 1H), 3.87 (s, 3H), 3.63 – 3.46 (m, 2H), 3.33 – 3.07 (m, 2H), 2.63 (d, *J* = 15.0 Hz, 3H), 1.93 (d, *J* = 1.6 Hz, 3H), 2.06 – 1.80 (m, 2H).

[00416] ^{13}C NMR (126 MHz, DMSO) δ 168.77 (d, *J* = 6.8 Hz), 163.80 (s), 159.89 (s), 154.25 (d, *J* = 1.6 Hz), 153.24 (s), 145.45 (d, *J* = 7.3 Hz), 144.39 (s), 140.70 (s), 135.05 (d, *J* = 2.5 Hz), 133.41 (s), 133.13 (s), 132.07 (s), 130.33 (s), 127.75 (s), 119.79 (d, *J* = 4.9 Hz), 117.23 (s), 116.62 (d, *J* = 5.8 Hz), 113.41 (s), 59.72 (s), 58.58 (s), 58.07 (s), 48.76 (s), 47.70 (s), 45.94 (s), 44.16 (s), 35.59 (s), 34.90 (s), 29.04 (s), 27.37 (s), 22.73 (s), 22.19 (s).

Example 58

Synthesis of N-(3-(5-methoxy-2-(1-(methylsulfonyl)indolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-59a)



Synthesis of 1-(methylsulfonyl)-5-nitroindoline (1)

[00417] A solution of 5-nitroindoline (1.033 g, 6.30 mmol), TEA (0.827g, 8.19 mmol) in DCM (30 mL) at 0°C was slowly added methylsufonyl chloride (0.868 g, 7.56 mmol). The mixture was warmed up and stirred at room temperature for 0.5 h. The reaction was quenched with water (30 mL) and extracted with DCM (25 mL ×4). The organic layers were combined,

dried and concentrated under reduced pressure to afford crude **1** (1.427 g, 5.9 mmol, yield 95%), which was used for next step without further purification.

Synthesis of 1-(methylsulfonyl)indolin-5-amine (2)

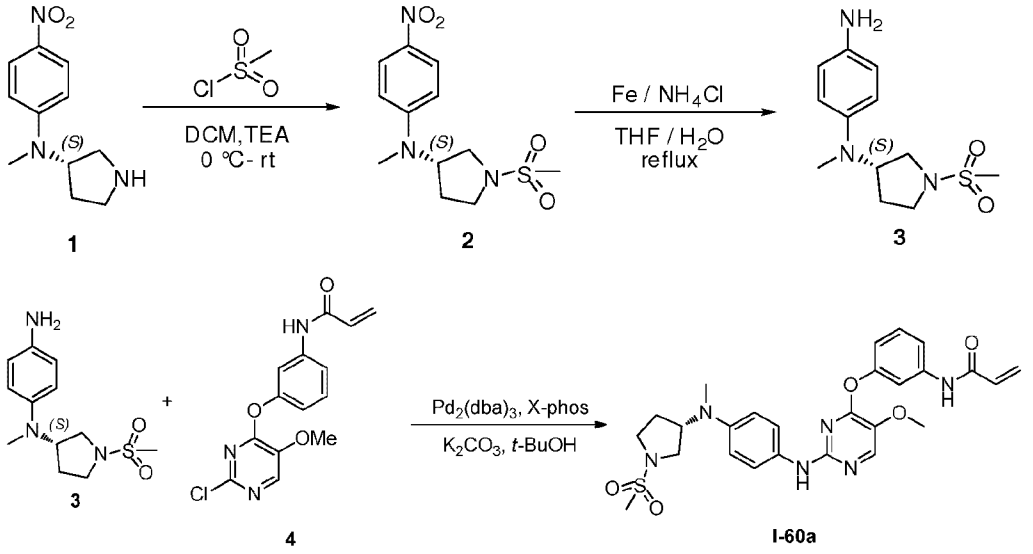
[00418] A solution of **1** (1.427 g, 5.9 mmol) in THF/H_2O (20 mL/3 mL) was treated with iron (1.372 g, 24.5 mmol) and ammonium chloride (2.621 g, 49 mmol). The mixture was stirred at refluxing for 2 h. The reaction was filtered through Celite®. The filtrate was basified with $NaHCO_3$ (*aq*, 30 mL) and extracted with ethyl acetate (30 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to provide crude product **2** (0.742 g, 3.5 mmol, 59.3%), which was used for next step without further purification.

Synthesis of N-(3-(5-methoxy-2-(1-(methylsulfonyl)indolin-5-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-59a)

[00419] Compound **2** (0.420 g, 2 mmol), compound **3** (0.660 g, 2.3 mmol), K_2CO_3 (0.494 g, 3 mmol), tris(dibenzylideneacetone)dipalladium (0.093 g, 0.1 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (0.115 g, 0.22 mmol) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-59a** (0.24 g, 25%, $M+H^+$=482.5).

Example 59

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-60a)



Synthesis of (*S*)-N-methyl-1-(methylsulfonyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00420] A solution of **1** (0.504 g, 3 mmol), TEA (0.404 g, 4 mmol) in DCM (20 mL) at 0°C was slowly added methylsufonyl chloride (0.402 g, 3.5 mmol). The mixture was warmed up and stirred at room temperature for 0.5 h. The reaction was quenched with water (30 mL) and extracted with DCM (25 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to afford crude **2** (0.762 g, 2.55 mmol, yield 85%), which was used for next step without further purification.

(*S*)-N^1-methyl-N^1-(1-(methylsulfonyl)pyrrolidin-3-yl)benzene-1,4-diamine (3)

[00421] A solution of **2** (0.762 g, 2.55 mmol) in THF/H_2O (20 mL/3 mL) was treated with iron (0.560 g, 10 mmol) and ammonium chloride (1.070 g, 20 mmol). The mixture was stirred at refluxing for 2 h. The reaction mixture was filtered through Celite®. The filtrate was basified with $NaHCO_3$ (*aq*, 30 mL) and extracted with ethyl acetate (30 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to provide crude product **3** (0.511 g, 1.9 mmol, 75%), which was used for next step without further purification.

Synthesis of (*S*)-N-(3-(5-methoxy-2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide (I-60a)

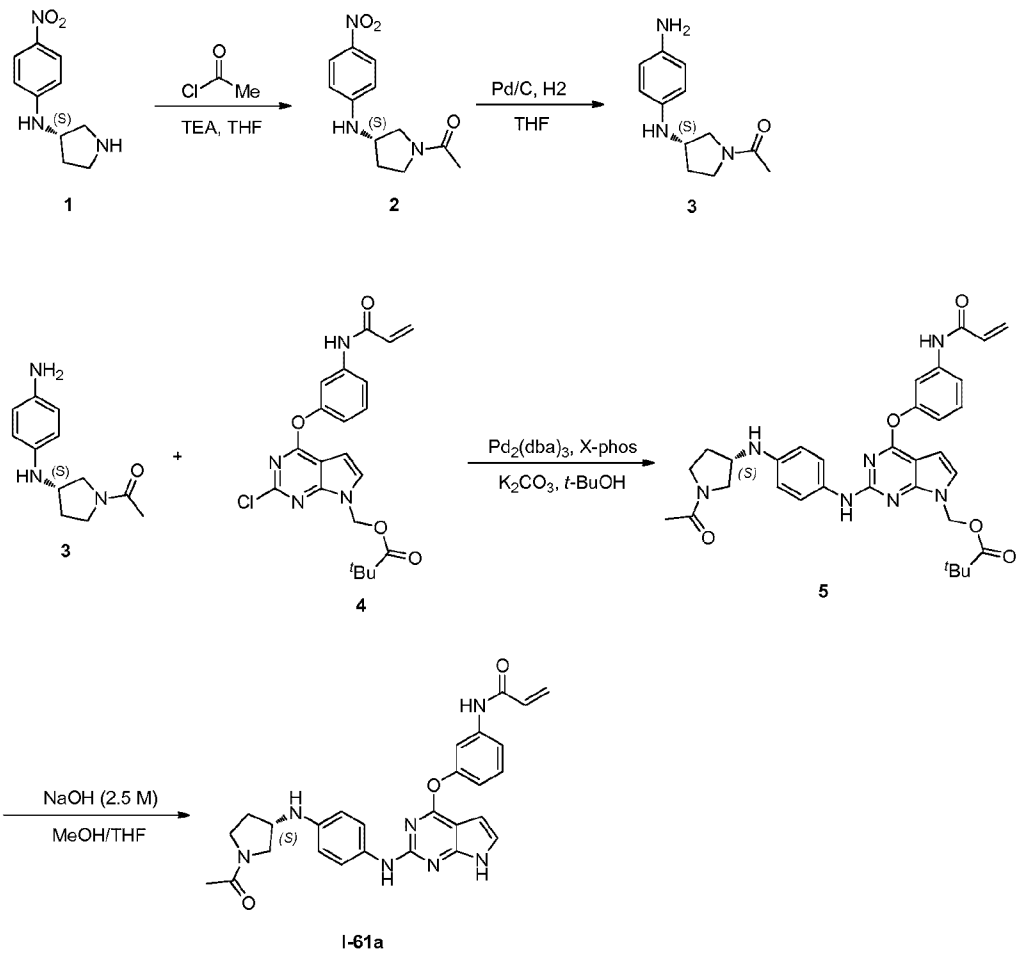
[00422] Compound **3** (0.340 g, 1.5 mmol), compound **4** (0.550 g, 1.8 mmol), K_2CO_3 (0.414 g, 3 mmol), tris(dibenzylideneacetone)dipalladium (0.137 g, 0.15 mmol), dicyclohexyl (2',4',6'-triisopropylbiphenyl-2-yl) phosphine (0.143 g, 0.3 mmol) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **I-60a** (0.33 g, 41%, $M+H^+$=539.6).

[00423] ^1H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.94 (s, 1H), 7.67 (s, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 8.1 Hz, 1H), 7.22 (s, *J* = 14.5 Hz, 1H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 7.1 Hz, 1H), 6.68 (d, *J* = 8.8 Hz, 2H), 6.38 (dd, *J* = 16.8, 1.3 Hz, 1H), 6.29 (dd, *J* = 16.9, 10.0 Hz, 1H), 5.68 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.07 – 3.97 (m, 1H), 3.89 (s, 3H), 3.51 – 3.41 (m, 2H), 3.37 – 3.26 (m, 1H), 3.17 (dd, *J* = 10.2, 6.7 Hz, 1H), 2.84 (s, 3H), 2.70 (s, 3H), 2.14 – 2.05 (m, 1H), 2.03 – 1.94 (m, 1H).

[00424] ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.90 (s), 160.47 (s), 153.91 (s), 152.97 (s), 145.41 (s), 142.83 (s), 139.37 (s), 135.46 (s), 133.38 (s), 131.13 (s), 129.61 (s), 127.92 (s), 119.96 (s, ×2), 118.61 (s, ×2), 117.87 (s), 116.88 (s), 114.16 (s), 60.56 (s), 58.04 (s), 49.98 (s), 46.60 (s), 37.28 (s), 34.79 (s), 29.24 (s).

Example 60

Synthesis of (*S*)-N-(3-(2-(4-(1-acetylpyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-61a)



Synthesis of (*S*)-1-(3-(4-nitrophenylamino)pyrrolidin-1-yl)ethanone (2)

[00425] A solution of compound **1** (2.139 g), TEA (1.568 g) in THF (40 mL) at -10 °C was slowly added acetyl chloride (0.806 g, dissolved in 4 mL THF). The mixture was stirred at this temperature for 4 h. The reaction was quenched with water and extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure to afford crude **2** (1.88 g, 73.2%), which was used for next step without further purification.

Synthesis of (*S*)-1-(3-(4-aminophenylamino)pyrrolidin-1-yl)ethanone (3)

[00426] A mixture of **2** (1.88 g) and Pd/C (0.198 g, 10% activated on carbon) in THF (30 mL) was hydrogenated with hydrogen balloon at room temperature overnight. Once the reaction

was complete indicated by TLC, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford **3** (1.65 g), which was used for next step) without further purification.

Synthesis of (*S*)-(2-(4-(1-acetylpyrrolidin-3-ylamino)phenylamino)-4-(3-acrylamidophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (5)

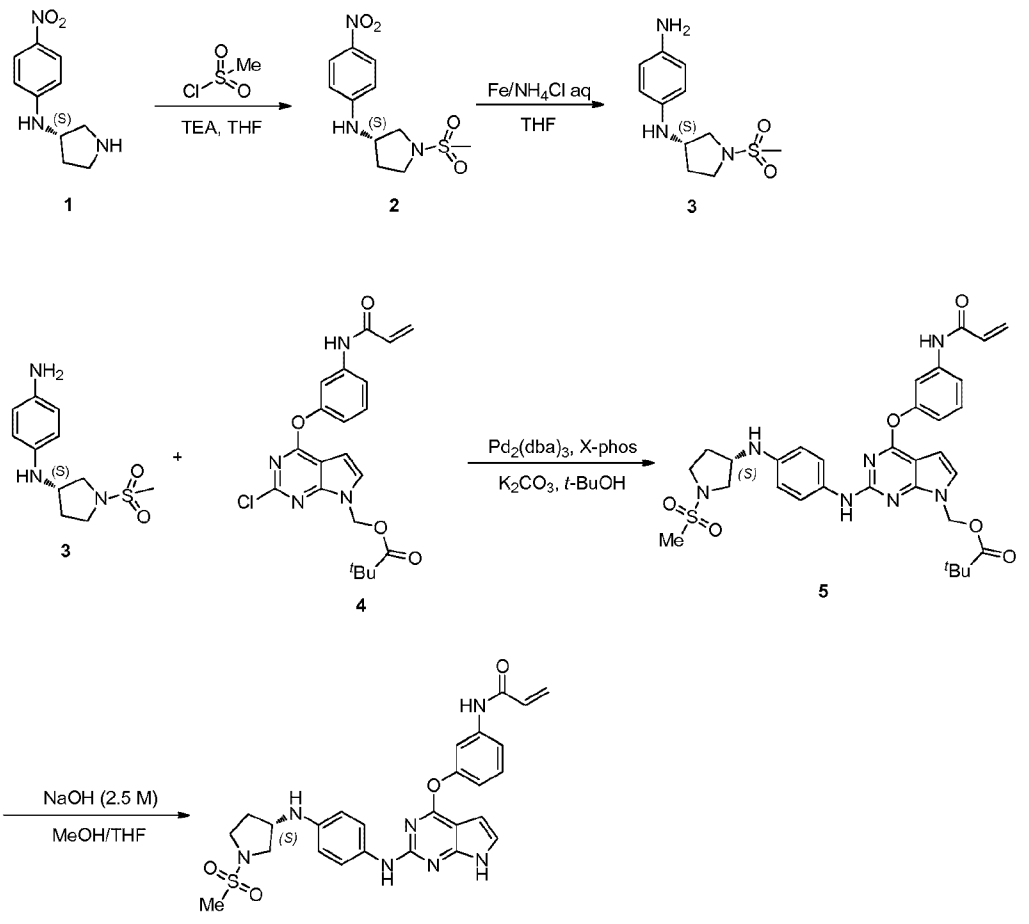
[00427] Compound **3** (1.6 g), compound **4** (3.1 g), K_2CO_3 (2.0 g), tris(dibenzylideneacetone)dipalladium (0.3 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.3 g) and *t*-BuOH (50 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **5** (2.4 g, 54.2%).

Synthesis of (*S*)-N-(3-(2-(4-(1-acetylpyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-61a)

[00428] To a round-bottom flask (250 mL) was charged with compound **5** (2.4 g), MeOH (15 mL) and THF (15 mL). After compound **5** was completely dissolved, the solution was cooled down to -5 °C. NaOH aqueous solution (2.5 M, 3.1 mL) was then added into the flask slowly. The mixture was stirred for 2 h at this temperature. Water (80 mL) was then added in to quench the reaction. The mixture was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The resulting crude was further purified by column chromatography to give **I-61a** (1.4 g, 71.8%, $M+H^+$=498.6).

Example 61

(*S*)-N-(3-(2-(4-(1-(methylsulfonyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-62a)



Synthesis of (*S*)-1-(methylsulfonyl)-N-(4-nitrophenyl)pyrrolidin-3-amine (2)

[00429] A solution of compound **1** (4.158 g), TEA (3.026 g) in THF (50 mL) at -10 °C was slowly added methylsufonyl chloride (2.3 g, dissolved in 5 mL THF). The mixture was stirred at this temperature for 3 h. The reaction was quenched with water (100 mL) and extracted with ethyl acetate (150 mL). The organic layers were combined, dried and concentrated under reduced pressure to afford crude **2** (4.3 g, 75.2%), which was used for next step without further purification.

Synthesis of (*S*)-N^1-(1-(methylsulfonyl)pyrrolidin-3-yl)benzene-1,4-diamine (3)

[00430] A solution of **2** (4.3 g) in THF/H_2O (90 mL/30 mL) was treated with iron (3.3 g) followed by ammonium chloride (4.8 g). The mixture was stirred at refluxing for 4.5 h. After

cooling down to room temperature, the reaction mixture was filtered through Celite®. The filtrate was basified with $NaHCO_3$ (*aq,* 30 mL) and extracted with ethyl acetate (30 mL ×4). The organic layer were combined, dried and concentrated under reduced pressure to provide crude compound **3** (3.1g, 80.7%), which was used for next step without further purification.

Synthesis of (*S*)-(4-(3-acrylamidophenoxy)-2-(4-(1-(methylsulfonyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl pivalate (5)

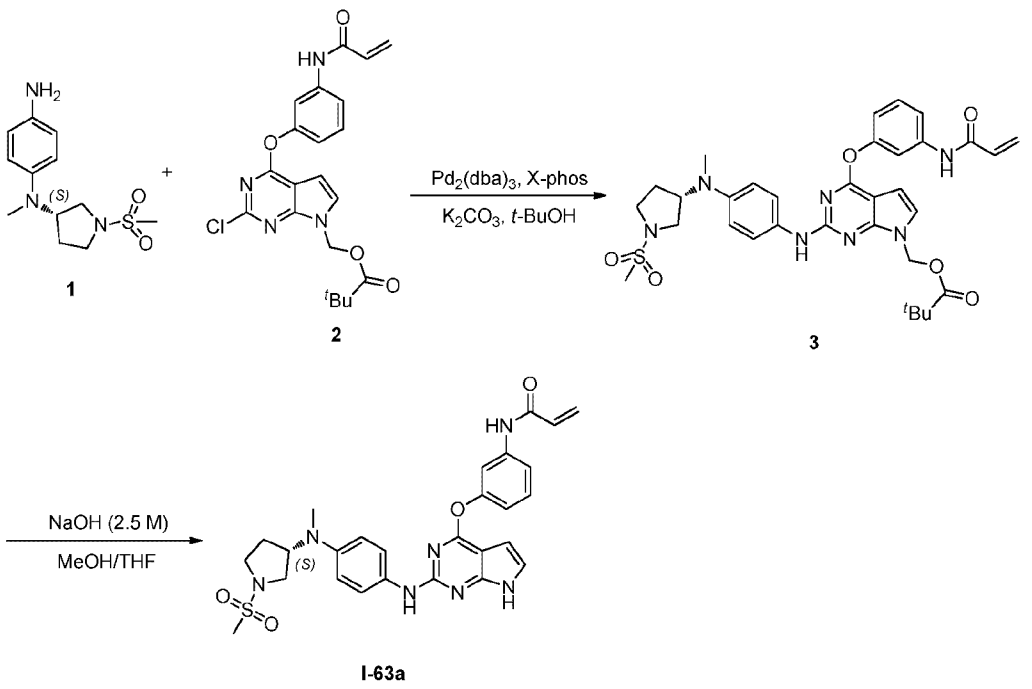
[00431] Compound **3** (3.1 g), compound **4** (5.2 g), K_2CO_3 (2.5 g), tris(dibenzylideneacetone)dipalladium (0.6 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.6 g) and *t*-BuOH (80 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 4 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **5** (4.1 g, 52.2%).

Synthesis of (*S*)-N-(3-(2-(4-(1-(methylsulfonyl)pyrrolidin-3-ylamino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-62a)

[00432] To a round-bottom flask (250 mL) was charged with compound **5** (2.1 g), MeOH (12 mL) and THF (12 mL). After compound **5** was completely dissolved, the solution was cooled down to -5 °C. NaOH solution (2.5 M, 3 mL) was then added into the flask slowly. The mixture was stirred for 1 h at this temperature. Water (40 mL) was then added in to quench the reaction. The mixture was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The resulting crude was purified by column chromatography to give **I-62a** (1.0 g, 57.8%, $M+H^+$=498.6).

Example 62

(*S*)-N-(3-(2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-63a)



Synthesis of (*S*)-(4-(3-acrylamidophenoxy)-2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl tert-butyl carbonate (3)

[00433] Compound **1** (0.5 g), compound **2** (0.876 g), K_2CO_3 (0.512 g), tris(dibenzylideneacetone)dipalladium (0.102 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.104 g) and *t*-BuOH (30 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 3.5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **3** (0.8 g, 59.3%).

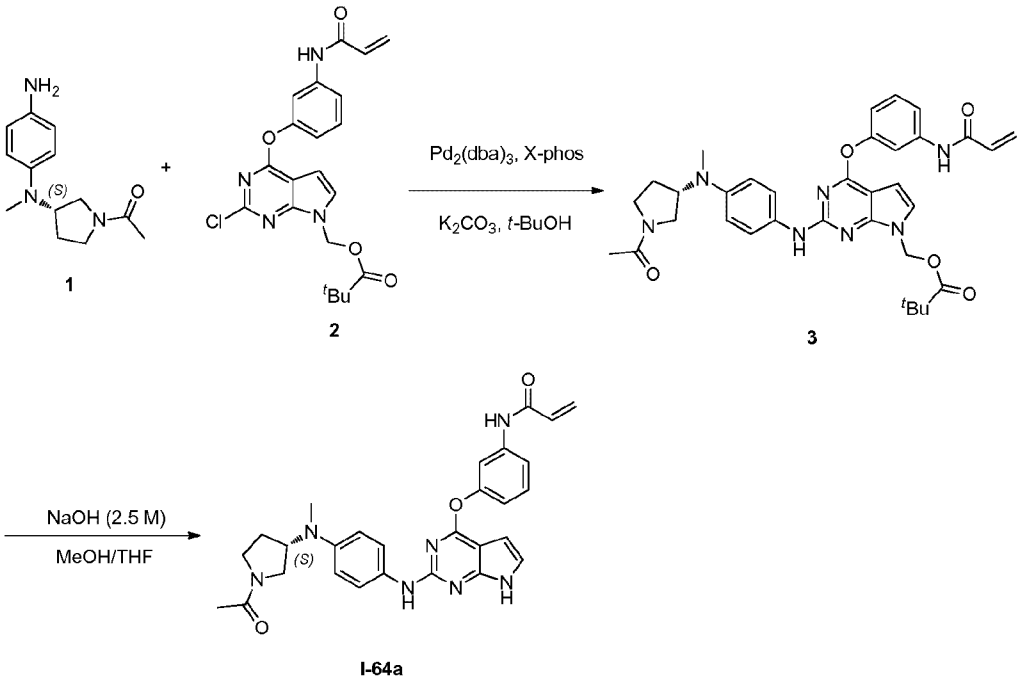
Synthesis of (*S*)-N-(3-(2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-63a)

[00434] To a round-bottom flask (250 mL) was charged with compound **3** (0.8 g), MeOH (20 mL) and THF (2 mL). After compound **3** was completely dissolved, the solution was cooled down to -5 °C. NaOH solution (2.5 M, 1.5 mL) was then added into the flask slowly. The

mixture was stirred for 2 h at this temperature. Water (40 mL) was added in to quench the reaction. The mixture was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced. The resulting crude was purified by column chromatography to give **I-63a** (0.25 g, 37.8%, $M+H^+$=548.6).

Example 63

Synthesis of (S)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-64a)



Synthesis of (S)-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-4-(3-acrylamidophenoxy)-7H-pyrrolo[2,3-d]pyrimidin-7-yl)methyl tert-butyl carbonate (3)

[00435] Compound **1** (0.9 g), compound **2** (1.65 g), K_2CO_3 (1.07 g), tris(dibenzylideneacetone)dipalladium (0.35 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.35 g) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 4 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl

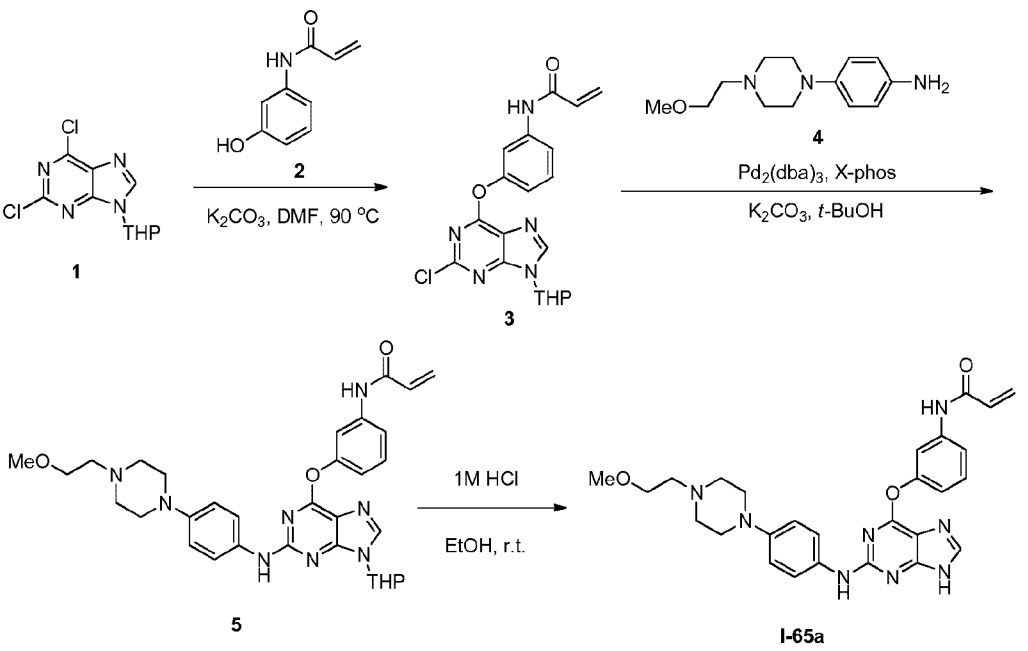
acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography to afford compound **3** (1.24 g, 51.7%).

Synthesis of (S)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-7H-pyrrolo[2,3-d]pyrimidin-4-yloxy)phenyl)acrylamide (I-64a)

[00436] To a round-bottom flask (250 mL) was charged with compound **3** (1.24 g), MeOH (10 mL) and THF (5 mL). When compound **3** was completely dissolved, the solution was cooled down to -5°C. NaOH solution (2.5 M, 1.6 mL) was then added into the flask slowly. The mixture was stirred for 1 h at this temperature. Water (40 mL) was added in to quench the reaction. The mixture was extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure. The resulting crude was further purified by column chromatography to give **I-64a** (0.265 g, 26.2%, $M+H^+$=512.6).

Example 64

Synthesis of N-(3-(2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-65a)



Synthesis of N-(3-(2-chloro-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (3)

[00437] To a mixture of purine **1** (2.7 g) and phenol **2** (1.6 g) in DMF (40 mL) was added K_2CO_3 (2.2 g). The reaction mixture was stirred at 90℃ for 4 h. Once TLC indicated the reaction to be complete, the mixture was poured onto water (150 mL). The resulting precipitate was collected, washed with water (100 ml), and dried under vacuum to afford desired compound **3** (3.2 g, 80%) as a white solid.

Synthesis of N-(3-(2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (5)

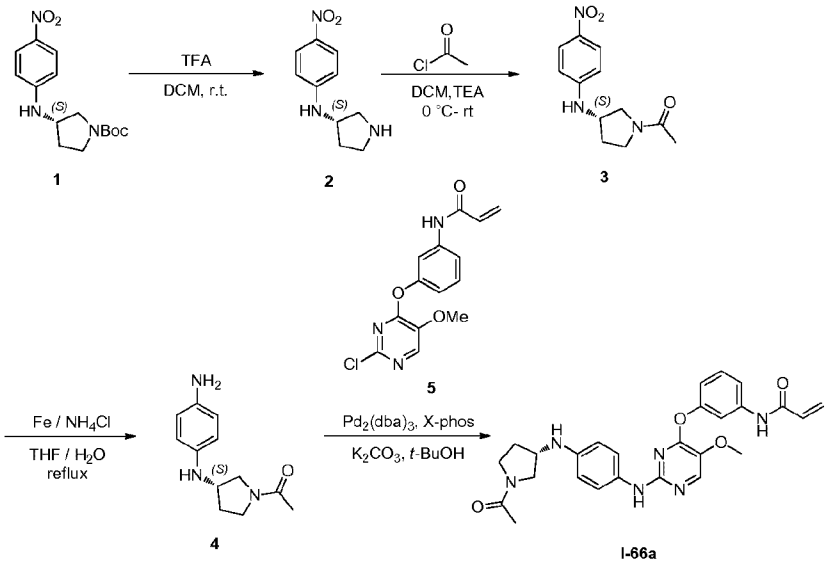
[00438] Compound **3** (1.6 g), compound **4** (0.8 g), K_2CO_3 (0.97 g), tris(dibenzylideneacetone)dipalladium (0.115 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.126 g) and *t*-BuOH (20 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 23 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool

down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (EtOAc/ MeOH = 15:1 as mobile phase) to afford compound **5** (1.1 g, 54.2%, $M+H^+$= 599) as a slight yellow solid.

[00439] Synthesis of N-(3-(2-(4-(4-(2-methoxyethyl)piperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-65a) To a solution of compound **5** (0.6 g) in EtOH (10 mL) was HCl *aq.* (2 mL, 1N). The mixture was stirred at room temperature for 3 h. another portion of HCl *aq.* (0.5 mL, ~ 12 M) was then added in and the reaction was stirred for another 3.5 h before being quenched and basified with K_2CO_3 (1.3 g in 10 mL water). The mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. To this crude material (600 mg) was added ethyl acetate (30 mL) and stirred for 1.5 h. The solution was concentrated till the volume was down to 10 mL. The resulting precipitate was collected, washed and dried to afford the desired compound **I-65a** (250 mg, 48.5%, $M+H^+$=515.6)

Example 65

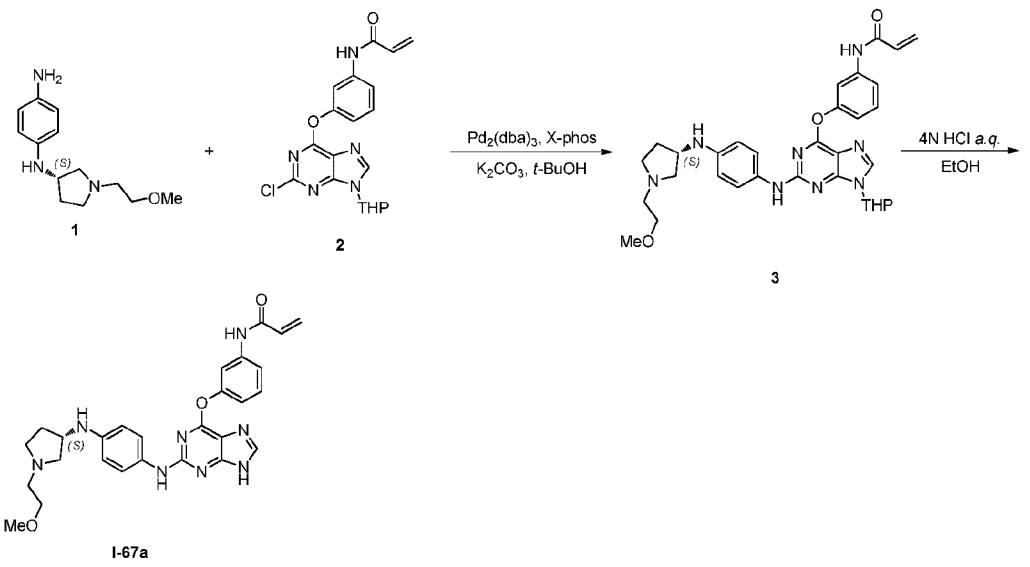
Synthesis of (S)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-66a)



[00440] I-66 can be synthesized using above synthetic scheme. We isolated I-66a as a byproduct (un-methylated) from the synthesis of **I-58a**.

Example 66

Synthesis of (*S*)-N-(3-(2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-67a)



Synthesis of N-(3-(2-(4-((S)-1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (3)

[00441] Compound **1** (0.99 g), compound **2** (1.53 g), K_2CO_3 (1.90 g), tris(dibenzylideneacetone)dipalladium (0.21 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.23 g) and *t*-BuOH (25 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 20 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (EtOAc/ EtOH = 10:1 as mobile phase) to afford compound **3** (1.0 g, 43.7%) as a slight yellow solid.

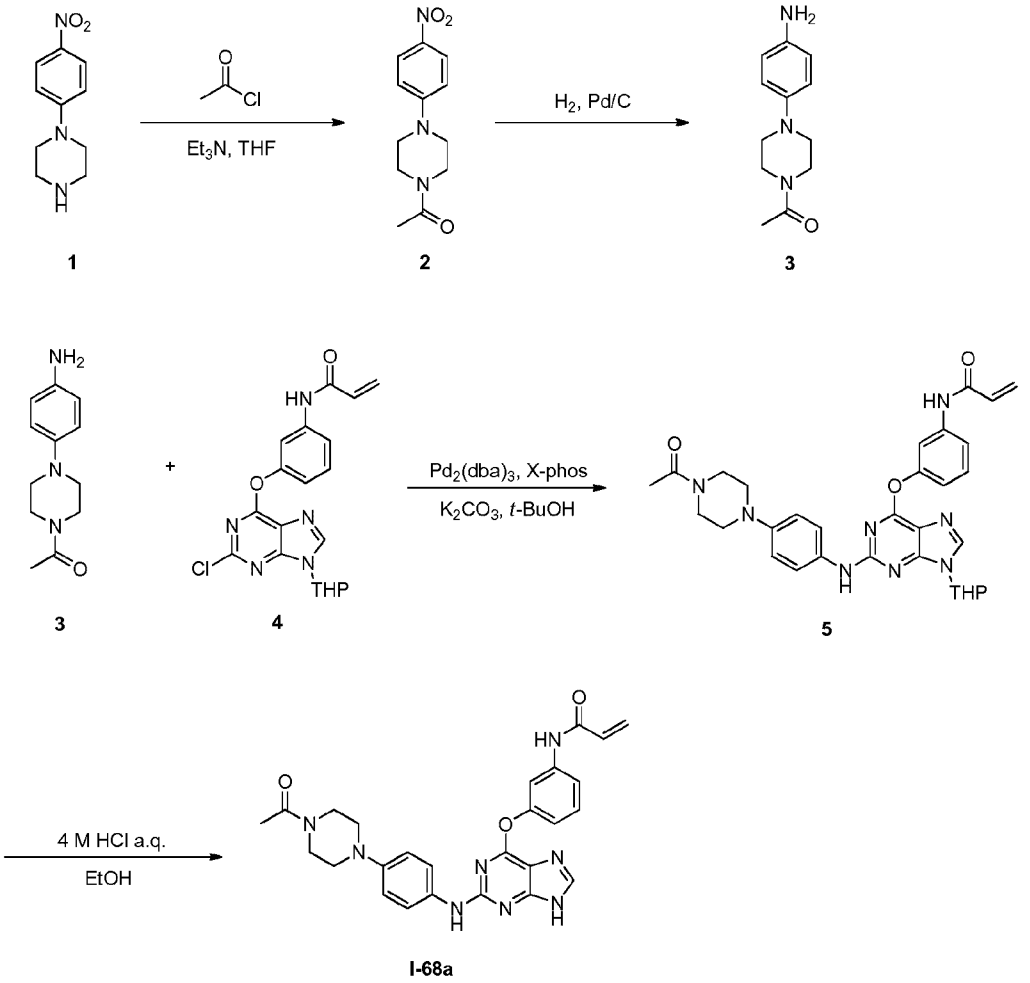
Synthesis of (*S*)-N-(3-(2-(4-(1-(2-methoxyethyl)pyrrolidin-3-ylamino)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-67a)

[00442] To a solution of compound **3** (1.0 g) in EtOH (10 mL) was HCl *aq.* (3 mL, 4N). The mixture was stirred at room temperature overnight. The reaction was quenched and basified with $NaHCO_3$ aqueous solution. The mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The

crude was purified by column chromatography (EtOAc /EtOH = 10/1 as mobile phase) to give compound **I-67a** (0.41 g, 47.7%, $M+H^+$=515.6).

Example 67

Synthesis of N-(3-(2-(4-(4-acetylpiperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-68a)



Synthesis of 1-(4-(4-nitrophenyl)piperazin-1-yl)ethanone (2)

[00443] A solution of compound **1** (10 g), TEA (5.891 g) in THF (50 mL) at 0 °C was slowly added acetyl chloride (4.605 g). The mixture was stirred at this temperature for 1.5 h. Solvent was removed. The resulting residue was diluted with water (30 mL), basified with K_2CO_3 aqueous solution (saturated, 20 mL) and then extracted with ethyl acetate. The organic layers were combined, dried and concentrated under reduced pressure to afford crude compound **2** (10.2 g), which was used for next step without further purification.

Synthesis of 1-(4-(4-aminophenyl)piperazin-1-yl)ethanone (3)

[00444] A solution of **2** (9.0 g) and Pd/C (0.700 g, 10% activated on carbon) in THF (30 mL) and 1, 4-dioxane (30 mL) was hydrogenated with hydrogen balloon at room temperature overnight. Once TLC indicated the reaction was to be complete, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford compound **3** (9.7 g), which was used for next step without further purification.

N-(3-(2-(4-(4-acetylpiperazin-1-yl)phenylamino)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (5)

[00445] Compound **3** (0.798 g), compound **4** (1.605 g), K_2CO_3 (1.32 g), tris(dibenzylideneacetone)dipalladium (0.167 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.172 g) and *t*-BuOH (30 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5.5 h, TLC (DCM: Methanol = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (EtOAc/ EtOH = 25:1 as mobile phase) to afford compound **5** (1.4 g, 66.0%) as a brown solid.

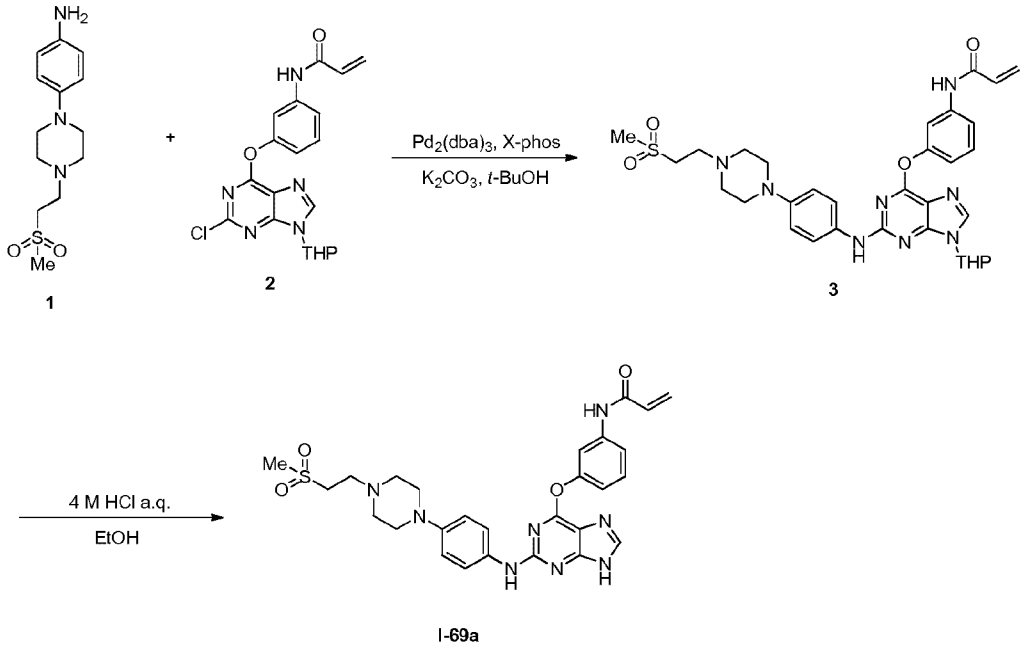
Synthesis of N-(3-(2-(4-(4-acetylpiperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-68a)

[00446] To a solution of compound **5** (1.4 g) in EtOH (10 mL), HCl *aq.* (4.6 mL, 4N) was added. The mixture was stirred at room temperature for 5 h. Additional HCl *aq.* (1 mL, ~ 12 M) was added and the reaction was stirred for another 18 h. TLC indicated the reaction to be

complete. The reaction was quenched and basified with K_2CO_3 *aq.*. The mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting crude was further purified by column chromatography (EtOAc /EtOH = 15/1 as mobile phase) to give compound **I-68a** (0.254 g, 21.2%, M+H+=499.6).

Example 68

Synthesis of N-(3-(2-(4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-69a)



1 2 3 I-69a

Synthesis of N-(3-(2-(4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)phenylamino)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (3)

[00447] Compound **1** (1.033 g), compound **2** (1.616 g), K_2CO_3 (0.97 g), tris(dibenzylideneacetone)dipalladium (0.170 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.185 g) and *t*-BuOH (30 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 6 h, TLC (EtOAc: EtOH = 5:1 as mobile

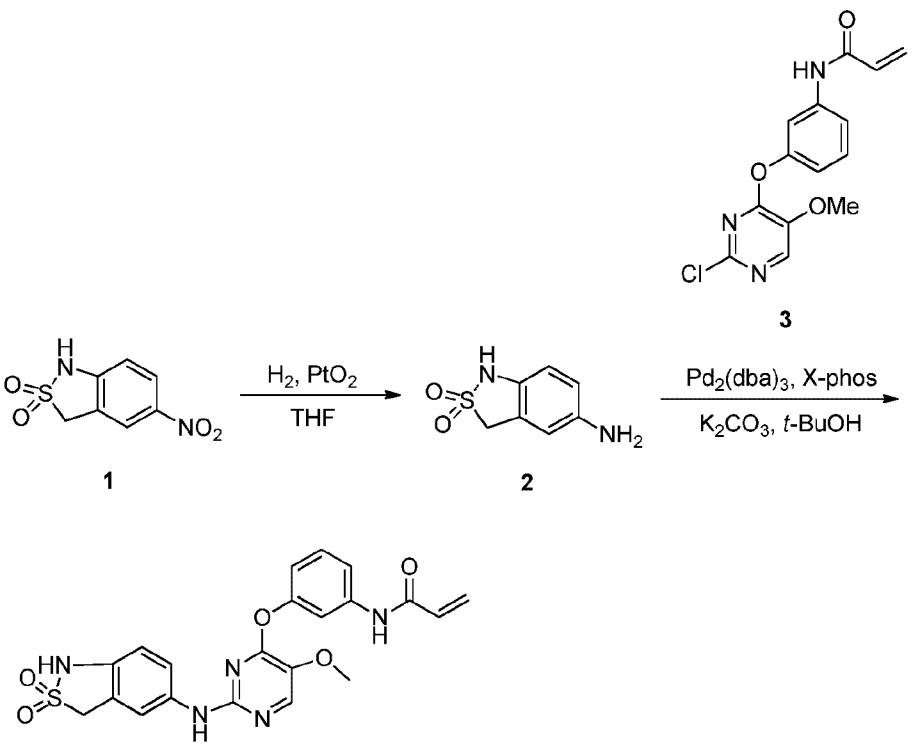
phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (EtOAc/ EtOH = 15:1 as mobile phase) to afford compound **5** (1.4 g, 59.3%, $M+H^+$=647) as a slight yellow solid.

Synthesis of N-(3-(2-(4-(4-(2-(methylsulfonyl)ethyl)piperazin-1-yl)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-69a)

[00448] To a solution of compound **3** (1.4 g) in EtOH (50 mL) was HCl *aq.* (4.5 mL, 4N). The mixture was stirred at room temperature for 5 h. Additional HCl *aq.* (1 mL, ~ 12M) was added and the reaction was stirred for another 60 h. TLC indicated the reaction to be complete. The reaction was quenched and basified with K_2CO_3 *aq.*. The reaction mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting crude was purified by column chromatography (EtOAc /EtOH = 20/1 as mobile phase) to give compound **I-69a** (0.22 g, 18%, $M+H^+$ = 563.5).

Example 69

Synthesis of N-(3-((2-((2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-5-yl)amino)-5-methoxypyrimidin-4-yl)oxy)phenyl)acrylamide (I-70a)



Synthesis of 5-amino-1,3-dihydrobenzo[c]isothiazole 2,2-dioxide (2):

[00449] A mixture of **1** (180 mg, **synthesized according to WO2005/12295)** and PtO_2 (10 mg) in THF (4 mL) was hydrogenated with hydrogen balloon at room temperature overnight. TLC indicated the reaction to be complete. The reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford **2** (0.11 g), which was used for the next step without further purification.

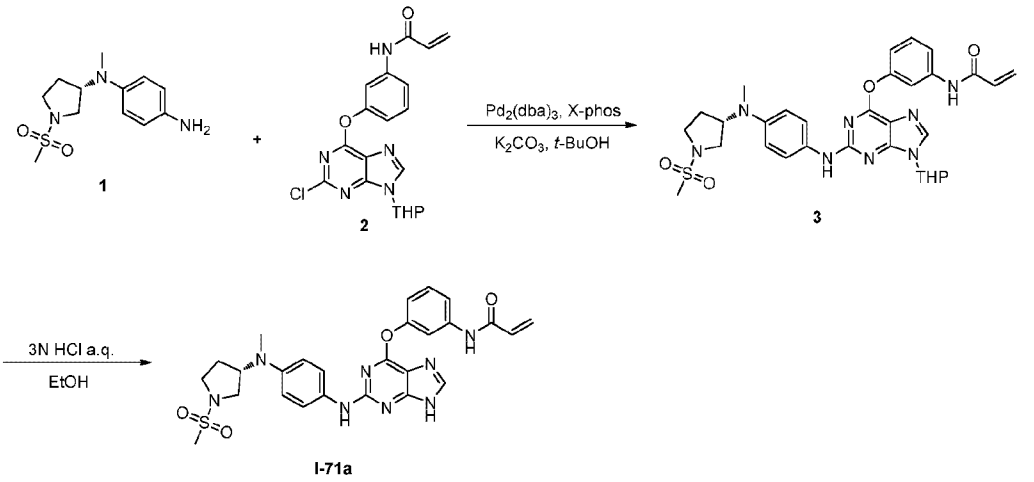
Synthesis of N-(3-((2-((2,2-dioxido-1,3-dihydrobenzo[c]isothiazol-5-yl)amino)-5-methoxypyrimidin-4-yl)oxy)phenyl)acrylamide (I-70a)

[00450] Compound **2** (0.11 g), compound **3** (0.219 g), K_2CO_3 (0.22 g), tris(dibenzylideneacetone)dipalladium (0.02 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.04 g) and *t*-BuOH (3 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 7.5 h, TLC (DCM: MeOH = 10:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool

down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (DCM/ MeOH = 50:1 as mobile phase) to afford compound **I-70a** (26 mg, 11.1%, $M+H^+$=454.5) as a slight yellow solid.

Example 70

Synthesis of (*S*)-N-(3-(2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-71a)



N-(3-(2-(4-(methyl((S)-1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-9-(tetrahydro-2H-pyran-2-yl)-9H-purin-6-yloxy)phenyl)acrylamide (3)

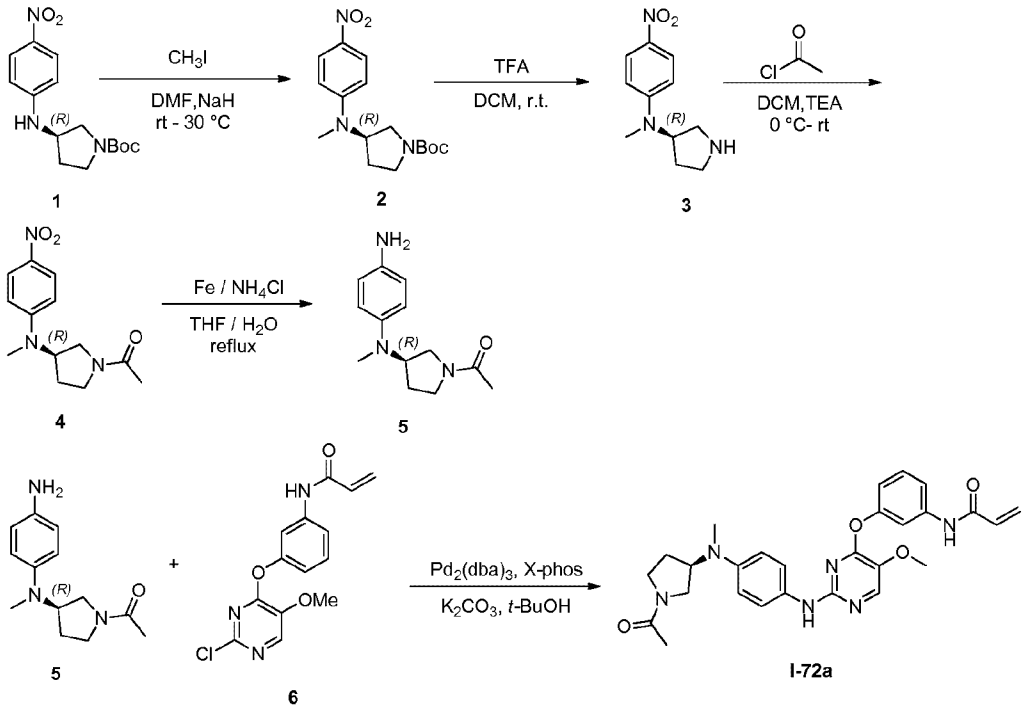
[00451] Compound **1** (0.35 g), compound **2** (0.532 g), K_2CO_3 (0.362 g), tris(dibenzylideneacetone)dipalladium (0.064 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.063 g) and *t*-BuOH (10 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 5 h, TLC (DCM: MeOH = 25:1 as mobile phase) indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure to afford compound 3 (664 mg), which was used for next step without further purification.

Synthesis of (*S*)-N-(3-(2-(4-(methyl(1-(methylsulfonyl)pyrrolidin-3-yl)amino)phenylamino)-9H-purin-6-yloxy)phenyl)acrylamide (I-71a)

[00452] To a solution of compound **3** (1.4 g) in EtOH (20 mL) was HCl *aq.* (6 mL, 3N). The mixture was stirred at room temperature for 16 h. TLC indicated the reaction to be complete. The reaction was quenched and basified with K_2CO_3 *aq.*. The mixture was extracted with ethyl acetate. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting crude was further purified by column chromatography (DCM/MeOH = 20/1 as mobile phase) to give compound **I-71a** (0.31 g, 53.88%, $M+H^+$ = 549.6).

Example 71

Synthesis of (*R*)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-72a)



Synthesis of (*R*)-tert-butyl 3-(methyl(4-nitrophenyl)amino)pyrrolidine-1-carboxylate (2)

[00453] To a solution of (*R*)-tert-butyl 3-(4-nitrophenylamino)pyrrolidine-1-carboxylate (**1**, 5.1 g) in DMF (50 mL) at 0°C was sequentially added NaH (0.6 g, 80% dispersion in mineral oil) and CH_3I (2.7 g). The resulting mixture was then stirred for 3 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting crude **2** (5.38 g) was used directly in next step without further purification.

Synthesis of (*R*)-N-methyl-N-(4-nitrophenyl)pyrrolidin-3-amine (3)

[00454] To the crude **2** (5.3 g) in DCM (15 mL) was added TFA (6.8 mL). The reaction mixture was stirred at room temperature until TLC (petroleum ether/ ethyl acetate =1:3 as mobile phase) indicated the reaction to be complete. The reaction mixture was concentrated under reduced pressure to remove most of TFA. The resulting residue was basified with $NaHCO_3$ (*aq*, 30 mL) and extracted with EA (30 mL ×4). The organic layers were combined, dried and concentrated under reduced pressure to afford crude **3** (4.54 g), which was used for next step without further purification.

(*R*)-1-(3-(methyl(4-nitrophenyl)amino)pyrrolidin-1-yl)ethanone (4)

[00455] A solution of **3** (4.0 g), TEA (2.31 g) in MeOH (60 ml) at 0°C was slowly added acetyl chloride (1.84 g). The mixture was warmed up and stirred at room temperature for 0.5 h. The reaction was quenched with water (30 mL) and extracted with DCM (25 mL ×4). The organic layers were combined, dried and concentrated to afford crude **4** (3.72 g), which was used for next step without further purification.

Synthesis of (*R*)-1-(3-((4-aminophenyl)(methyl)amino)pyrrolidin-1-yl)ethanone (5)

[00456] A mixture of **4** (3.56 g) and Pd/C (310 mg, 10% activated on carbon) in THF (60 mL) was hydrogenated with hydrogen balloon at room temperature overnight. After the reaction was complete indicated by TLC, the reaction mixture was filtered through Celite®. The filtrate was concentrated under reduced pressure to afford **5** (3.21 g), which was used for next step without further purification.

Synthesis of (*R*)-N-(3-(2-(4-((1-acetylpyrrolidin-3-yl)(methyl)amino)phenylamino)-5-methoxypyrimidin-4-yloxy)phenyl)acrylamide (I-72a)

[00457] Compound **5** (3.21 g), compound **6** (4.26 g), K_2CO_3 (2.87 g), tris(dibenzylideneacetone)dipalladium (0.64 g), dicyclohexyl (2',4',6'- triisopropylbiphenyl-2-yl) phosphine (0.65 g) and *t*-BuOH (80 mL) were sequentially added to the flask. The reaction mixture was stirred at refluxing under N_2 flow. After 17 h, TLC indicated the reaction to be complete. The reaction mixture was allowed to cool down to 40~50°C, and then filtered through Celite®. The celite layer was washed with ethyl acetate (50 mL). The combined filtrate was concentrated under reduced pressure. The resulting crude was further purified by column chromatography (ethyl acetate/ EtOH = 20:1 as mobile phase) to afford compound **I-72a** (1.5 g, 22%, $M+H^+$=503.6).

Example 72

Btk Tyr223 phosphorylation inhibition assays

Material and Methods

Cell culture and reagents

[00458] Ramos cell line was obtained from the American Type Culture Collection and was maintained at 37°C with 5% CO2, in media supplemented with 10% fetal bovine serum, penicillin (100 units/mL) and streptomycin (100 µg/mL). Goat F(ab')2 Anti-Human IgM-UNLB was obtained from SouthernBiotech.

Western blotting assay

[00459] Ramos cells were treated with compounds at indicated doses for 45min at room temperature, followed by stimulation of 12 µg/mL of IgM for 30min, and then lysed. Western blots were performed on the cell lysate using Phospho-Btk (Tyr223), Phospho-Btk (Tyr551), Btk, Phospho-PLCγ2 (Tyr1217), PLCγ2, Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) and p44/42 MAPK (Erk1/2) antibodies (Cell Signaling Technology). The density of blotting band was acquired using ImageJ software, and the IC_{50} of Btk (Tyr223) phosphorylation was fitted using a non-linear regression model by GraphPad Prism version 4.0.

Pulse chase western blotting assay for irreversibility assessment of compound

[00460] Ramos cells were treated with Compound I-1 at 100 nM for 45min. Cells were then re-suspended in compound free media and stimulated with 6 μg/ml IgM at 0, 4, 6 or 8 hours after compound removal. Cells were then lysed after 30 min IgM stimulation. West blotting analysis were then performed.

Btk Target Site Occupancy ELISA assay

[00461] Ramos cells were treated with Compound **I-1** at indicated concentrations for 1 h, followed by stimulation with 6 μg/mL of IgM for 30 min, and then lysed. Lysates were incubated with Compound **I-21** (biotin labeled) at a final concentration of 1μM in a PBS, 0.05% Tween-20, 1% BSA solution while shaking for 1h at room temperature. Samples were transferred to a streptavidin-coated 96-well ELISA plate and mixed while shaking for 1h at room temperature. The Btk antibody (BD 611116, 1:1000 dilution in PBS + 0.05% Tween-20 + 0.5% BSA) was then applied and incubated for 1 h at room temperature. After wash, goat anti-mouse-HRP (Pierce 31432, 1:1000 dilution in PBS + 0.05% Tween-20 + 0.5% BSA) was added and incubated for 1 h at room temperature. The ELISA was developed with addition of tetramethyl benzidine (TMB) followed by Stop Solution and read at OD 450 nM.

Results

Compounds significantly reduced the Btk Tyr223 phosphorylation in Ramos cells

[00462] The results from this assay were shown in Table 1 below. Compounds having an activity designated as "A" provided an $IC_{50} \leq 10$ nM; compounds having an activity designated as "B" provided an IC_{50} 10- 100 nM; compounds having an activity designated as "C" provided an $IC_{50} > 100$ nM.

Table 1

Compound #	BTK Inhibition

I-1	**A**
I-2	**A**
I-3	**A**
I-4	**A**
I-5	**A**
I-6	**A**
I-7	**B**
I-8	**A**
I-9	**A**
I-10	**A**
I-11	**B**
I-12	**B**
I-13	**A**
I-14	**B**
I-15	**A**
I-16	**A**
I-17	**A**
I-18	**A**

[00463] Ramos cells were treated with compounds at indicated concentrations for 45 mins, and the phosphorylations of BTK and potential downstream effectors PLCγ2 and Erk were

monitored. Most compounds dose-dependently inhibited the phosphorylation of BTK protein, Compound **I-1** achieving the inhibition IC_{50} at 1.1 nM and Compound **I-2** achieving the inhibition IC_{50} at 5.0 nM.

Compounds I-1 and I-2 irreversibly inhibited the BTK phosphorylation in Ramos cells

[00464] Ramos cells were treated Compound **I-1** and Compound **I-2** at 100 nM for 45 mins, and inhibition of BTK phosphorylation was monitored 4, 6 and 8 hrs post Compound **I-1** and Compound **I-2** removal. BTK remains inhibited up to 8 hrs after treatment with the covalent-bonded Compound **I-1** and Compound **I-2**, indicating that Compound **I-1** and Compound **I-2** are strong irreversible inhibitors of BTK protein.

Compounds I-1 and I-2 irreversibly inhibited the phosphorylation of the BTK in Ramos cells

[00465] The BTK target site occupancy ELISA was used to detect free BTK protein from Romas cells treated with increasing concentrations of Compounds I-1. As shown in Table 2 and Figure 3, compound I-1 dose-dependent occupancy of the BTK proteins correlates with its inhibitory activity of BTK kinase, achieving IC_{50} at 0.5 nM.

Table 2

Compound I-1 (nM)	OD 450 (average)	free Btk (pg)
3000	-0.0487	-689
750	-0.0456	-646
188	-0.0207	-290
47	0.0114	168
12	-0.0161	-224
3	0.1219	1747
0.7	0.1811	2592
0.2	0.1686	2414
0	0.3888	5560

Example 73

Material and Methods

Cell culture and reagents

[00466] All cell lines were obtained from the American Type Culture Collection and were maintained at 37°C with 5% CO2. Ramos cell line was maintained in media supplemented with 10% fetal bovine serum, penicillin (100 units/mL) and streptomycin (100 µg/mL). NK-92 cell line was maintained in media supplemented with 10% fetal bovine serum and 10% horse serum, penicillin (100 units/mL) and streptomycin (100 µg/mL), IL-2 10ng/mL. Goat F(ab')2 Anti-Human IgM-UNLB was obtained from SouthernBiotech. IL-2 was obtained from Peprotech.

Western blotting assay for Btk

[00467] Ramos cells were treated with compounds at indicated doses for 45min at room temperature, followed by stimulation of 6 µg/mL of anti-IgM for 30min, and then lysed. Western blots were performed on the cell lysate using Phospho-Btk (Tyr223), Phospho-Btk (Tyr551), Btk, Phospho-PLCγ2 (Tyr1217), PLCγ2, Phospho-p44/42 MAPK (Erk1/2) (Thr202/Tyr204) and p44/42 MAPK (Erk1/2) antibodies (Cell Signaling Technology). The density of blotting band was acquired using ImageJ software, and the IC_{50} of Btk (Tyr223) phosphorylation was fitted using a non-linear regression model by GraphPad Prism.

Western blotting assay for Jak3 and Stat5

[00468] NK-92 cells were treated with compounds at the dosed indicated for 1 hour in incubator, followed by the IL-2 stimulation for 15 minutes. Cells were then collected and lysed to prepare the cellular extraction. Western blots were performed on cell lysate using Phospho-Jak3, Jak3, Phospho-Stat5, Stat5 antibodies (Cell Signaling Technology). The intensity of blotting band was acquired using Image Lab (Bio-Rad) software, and the IC_{50} of target was generated with GraphPad Prism.

Pulse chase western blotting assay to assess the binding property of compound

[00469] Ramos cells were treated with Compounds at 100 nM for 45min. Cells were then re-suspended in compound free media and stimulated with 6 µg/ml anti-IgM at 0, 4, 6 or 8 hours after compound removal. Cells were then lysed after 30 min anti-IgM stimulation. Western blotting analysis was then performed.

Btk Target Site Occupancy ELISA assay

[00470] Ramos cells were treated with Compounds at indicated concentrations for 1 h, followed by stimulation with 6 μg/mL of anti-IgM for 30 min, and then lysed. Lysates were incubated with Compound **I-21** (biotin labeled) at a final concentration of 1μM in a PBS, 0.05% Tween-20, 1% BSA solution while shaking for 1h at room temperature. Samples were transferred to a streptavidin-coated 96-well ELISA plate and mixed while shaking for 1h at room temperature. The Btk antibody (BD 611116, 1:1000 diluted in PBS + 0.05% Tween-20 + 0.5% BSA) was then applied and incubated for 1 h at room temperature. After wash, goat anti-mouse-HRP (Pierce 31432, 1:1000 diluted in PBS + 0.05% Tween-20 + 0.5% BSA) was added and incubated for 1 h at room temperature. The ELISA was developed with addition of tetramethylbenzidine (TMB) followed by Stop Solution and read at OD 450nM.

Results

1. Compounds significantly reduced the Btk Tyr223 phosphorylation in Ramos cells

[00471] The results from western blotting assay for Btk were shown in Table 3 below. Compounds having an activity designated as "A" provided an $IC_{50} \leq 10$ nM; compounds having an activity designated as "B" provided an IC_{50} 10- 100nM; compounds having an activity designated as "C" provided an $IC_{50} \geq 100$ nM. "N/A" means the compound has not been tested. PCI-327265 was used as the positive control.

Table 3

Compound #	Btk Inhibition
	A: ≤10 nM **B: 10~100 nM** **C: ≥ 100nM**
I-1	**A**
I-2	**A**
I-3	**A**
I-4	**A**
I-5	**A**
I-6	**A**

I-7	B
I-8	N/A
I-9	A
I-10	A
I-11	B
I-12	B
I-13	A
I-14	B
I-15	A
I-16	A
I-17	A
I-18	A
I-19	A
I-20	A
I-21	N/A
I-22	C
I-23a	B
I-24a	B
I-25a	A
I-26a	B
I-27a	A
I-28a	B
I-29a	C
I-30a	A
I-31a	A
I-32a	A
I-33a	B
I-34a	A
I-35a	A
I-36a	B
I-37a	B
I-38a	B
I-39a	B
I-40a	A
I-41a	B
I-42a	A
I-43a	A
I-44a	A
I-45a	B

I-46a	**B**
I-47a	**A**
I-48a	**A**
I-49a	**A**
I-50a	**B**
I-51a	**A**
I-52a	**A**
I-53a	**A**
I-54a	**A**
I-55a	**C**
I-56a	**A**
I-57a	**A**
I-58a	**A**
I-59a	**A**
I-60a	**A**
I-61a	**A**
I-62a	**A**
I-63a	**A**
I-64a	**A**
I-65a	**A**
I-66a	**A**
I-67a	**B**
I-68a	**B**
I-69a	**B**
I-70a	**B**
I-71a	**A**
I-72a	**A**

[00472] Exemplary western blotting image from several of the above compounds are listed below left panel in Figure 4, while PCI-32765 served as positive Btk inhibitor. IC_{50} curves are displayed in the right panel in Figure 4.

2. Compounds reduced the Jak3 phosphorylation in NK-92 cells

[00473] The results from western blotting assay for Jak3 were shown in Table 4 below. Compounds having an activity designated as "A" provided an IC_{50} ≤200 nM; compounds having

an activity designated as "B" provided an IC_{50} 200~400 nM; compounds having an activity designated as "C" provided an IC_{50}≥400 nM.

Table 4

Compound #	Jak3 inhibition
	A: ≤ 200 nM **B: 200~400 nM** **C: ≥ 400 nM**
I-1	**A**
I-2	**B**
I-25a	**C**

3. Compounds reduced the Stat5 phosphorylation in NK-92 cells

[00474] The results from western blotting assay for Stat5 were shown in Table 5 below. Compounds having an activity designated as "A" provided an IC_{50} ≤200 nM; compounds having an activity designated as "B" provided an IC_{50} 200~400 nM; compounds having an activity designated as "C" provided an IC_{50}≥400 nM.

Table 5

Compound #	Stat5 inhibition
	A: ≤200 nM **B: 200~400 nM** **C: ≥ 400 nM**
I-1	**C**
I-2	**B**
I-3	**B**
I-4	**B**
I-5	**B**
I-6	**B**
I-7	**C**

I-9	B
I-10	B
I-11	C
I-12	B
I-13	C
I-14	C
I-15	C
I-16	C
I-17	C
I-18	B
I-23a	C
I-25a	C
I-30a	A
I-31a	C
I-32a	C
I-33a	C
I-34a	C
I-35a	B
I-36a	B
I-37a	C
I-38a	C
I-39a	C
I-40a	C
I-41a	B
I-42a	C
I-43a	B
I-44a	B
I-45a	B
I-46a	C

I-47a	**B**
I-48a	**B**
I-49a	**C**
I-50a	**C**
I-51a	**C**
I-52a	**C**
I-53a	**C**
I-54a	**C**
I-56a	**B**
I-57a	**B**
I-58a	**C**

4. Pulse chase western blotting assay to assess the binding property of compounds

[00475] As shown in Figures 5A and 5B, the result after compound I-1 and I-2 treated and removal, long term effect of the inhibition was observed after compounds removal up to 8 hours. This strong binding of the compound to the target enzyme indicates the strong binding of the compound I-1 and I-2, which was chemically designed to covalently bind Btk protein at the specific position.

[00476] As shown in Figures 5A and 5B, compounds I-1 and I-2 inhibited the Btk phosphorylation in Ramos cells after 8 hours of removal. Ramos cells were treated with Compound I-1and Compound I-2 at 100nM for 45mins, and inhibition of Btk phosphorylation was monitored 4, 6 and 8hrs post Compound I-1 and Compound I-2 removal. Btk remains inhibited up to 8hrs after treatment with the covalent-bonded Compound I-1 and Compound I-2, indicating that Compound I-1 and Compound I-2 are strong irreversible inhibitors of Btk protein.

5. Btk Target Site Occupancy ELISA assay

[00477] The Btk target site occupancy ELISA was used to detect free Btk protein from Romas cells treated with increasing concentrations of several compounds. Compounds dose-

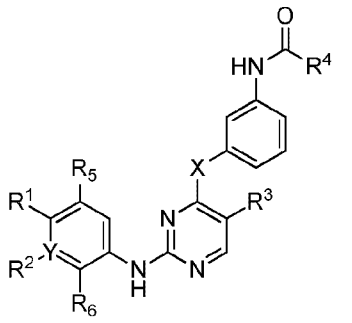
dependent occupancy of the Btk proteins correlates with their inhibitory activity of Btk kinase as shown in Table 6 below and in Figures 6A-6L.

Table 6

Compound #	Btk Occupancy Assay (IC_{50})
	A: ≤ 10 nM B: 10~100 nM C: ≥ 100nM
I-1	A
I-10	B
I-13	A
I-20	A
I-25a	A
I-58a	A

[00478] The present invention is further illustrated by the following exemplary embodiments:

1. A compound of Formula (I):



(I)

wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

3-7 member cyclic ring substituted with R^a wherein R^a is C_{1-8} alkyl optionally substituted with halo;

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or

R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,

Y is CH optionally substituted with halo, or N,

wherein at least one of R^2, R^3, R^5 and R^6 is not H;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein R^1 is H, and R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl.

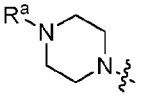
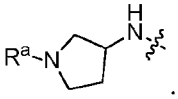
3. The compound of embodiment 1, wherein R^1 is NR^cR^d and R^c is methyl.

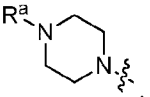
4. The compound of embodiment 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring.

5. The compound of embodiment 4, wherein the 3-7 member cyclic ring is C_3 cyclic ring.

6. The compound of any of embodiments 3-5, wherein R^d is C_2 alkyl substituted with OZ, and Z is methyl.

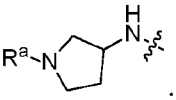
7. The compound of embodiment 1, wherein R^1 is 3-7 member cyclic ring substituted with R^a.

8. The compound of embodiment 7, wherein R^1 is  or  .

9. The compound of embodiment 8, wherein R^1 is  .

10. The compound of embodiment 9, wherein R^a is C_{1-4} alkyl optionally substituted with halo or C_{1-4} alkoxy.

11. The compound of embodiment 9 or 10, wherein R^a is C_{1-4} alkyl substituted with fluoro or C_{1-8} alkyl substituted with fluoro.

12. The compound of embodiment 8, wherein R^1 is  .

13. The compound of embodiment 12, wherein R^a is C_{1-4} alkyl optionally substituted with halo or C_{1-4} alkoxy.

14. The compound of embodiment 12 or 13, wherein R^a is C_{1-4} alkyl substituted with fluoro or C_{1-8} alkyl substituted with fluoro.

15. The compound of any of embodiments 1-14, wherein R^2 is H.

16. The compound of any of embodiments 1-14, wherein R^2 is halo.

17. The compound of any of embodiments 1-14, wherein R^2 is C_{1-4} alkyl or C_{1-4} alkoxy.

18. The compound of any of embodiments 1-14, wherein R^5 is H.

19. The compound of any of embodiments 1-14, wherein R^5 is halo.

20. The compound of any of claims 1-14, wherein R^5 is C_{1-4} alkyl or C_{1-4} alkoxy.

21. The compound of any of embodiments 1-14, wherein R^6 is H.

22. The compound of any of embodiments 1-14, wherein R^6 is halo.

23. The compound of any of embodiments 1-14, wherein R^6 is C_{1-4} alkyl or C_{1-4} alkoxy.

24. The compound of embodiment 1, wherein R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

25. The compound of embodiment 1, wherein R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

26. The compound of embodiment 1, wherein R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

27. The compound of any of embodiments 24-26, wherein the 3-7 member cyclic ring is a 5 member cyclic ring.

28. The compound of embodiment 27, wherein the 5 member cyclic ring is heterocyclic ring.

29. The compound of embodiment 28, wherein the 5 member heterocyclic ring comprises a N atom.

30. The compound of any of embodiments 24-29, wherein the C_{1-4} alkyl is C_2 alkyl.

31. The compound of embodiment 30, wherein Z is methyl.

32. The compound of any of embodiments 1-31, wherein R^3 is H.

33. The compound of any of embodiments 1-31, wherein R^3 is halo.

34. The compound of any of embodiments 1-31, wherein R^3 is C_{1-4} alkyl or C_{1-4} alkoxy.

35. The compound of any of embodiments 1-34, wherein R^2, R^5, or R^6 is H or halo and R^3 is halo, C_{1-4} alkyl or C_{1-4} alkoxy.

36. The compound of any of embodiments 1-35, wherein R^4 is unsubstituted C_2 alkenyl.

37. The compound of any of embodiments 1-35, wherein R^4 is C_2 alkenyl substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$.

38. The compound of any of embodiments 1-37, wherein X is O.

39. The compound of any of embodiments 1-37, wherein X is C_{1-4} alkyl optionally substituted with halo.

40. The compound of embodiment 39, wherein X is unsubstituted C_{1-4} alkyl.

41. The compound of embodiment 40, wherein X is CH_2.

42. The compound of embodiment 39, wherein X is C_{1-4} alkyl substituted with halo.

43. The compound of embodiment 42, wherein X is CF_2.

44. The compound of any of embodiments 1-37, wherein X is NR^b, and R^b is H, or C_{1-8} alkyl optionally substituted with halo.

45. The compound of embodiment 44, wherein R^b is H.

46. The compound of embodiment 44, wherein R^b is C_{1-8} alkyl.

47. The compound of embodiment 46, wherein R^b is C_{1-4} alkyl.

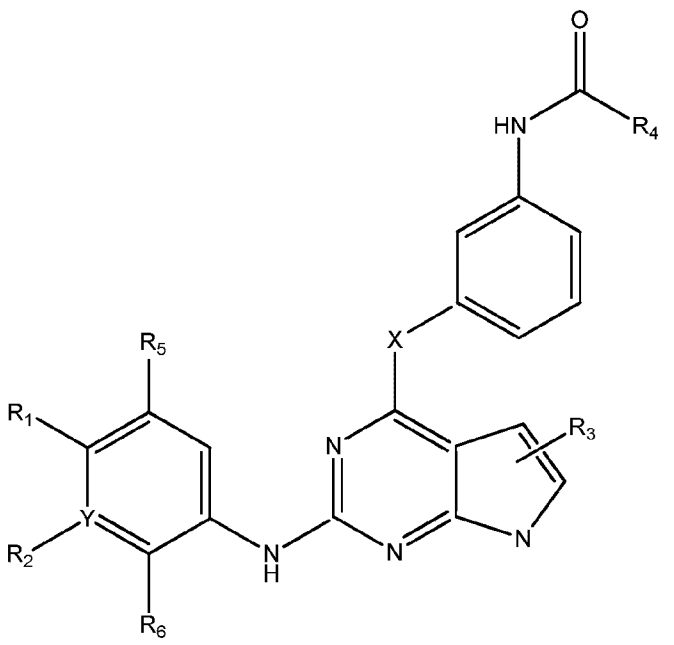
48. The compound of embodiment 46 or 47, wherein C_{1-4} alkyl or C_{1-8} alkyl is substituted with halo.

49. The compound of any of embodiments 1-48, wherein Y is CH.

50. The compound of any of embodiments 1-48, wherein Y is CF or N.

51. The compound of embodiment 1, which is selected from the group consisting of compound I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25 and I-41.

52. A compound of Formula (II):



(II)

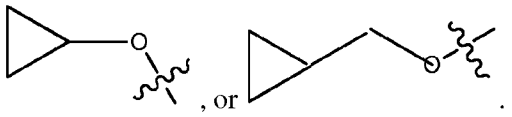
wherein

R^1 is H, or

NR^cR^d wherein R^c is H, C_{1-4} alkyl or 3-7 member cyclic ring, and R^d is H, C_{1-4} alkyl, optionally substituted with OZ, wherein Z is H or C_{1-4} alkyl; or

NR^eR^f wherein R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo; or

OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,



R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or

R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or

R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,
Y is CH optionally substituted with halo, or N,
or a pharmaceutically acceptable salt thereof.

53. The compound of embodiment 52, wherein R^1 is H, and R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or methyl.

54. The compound of embodiment 52, wherein R^1 is NR^cR^d and R^c is methyl.

55. The compound of embodiment 52, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring.

56. The compound of embodiment 55, wherein the 3-7 member cyclic ring is C_3 cyclic ring.

57. The compound of any of embodiments 54-56, wherein R^d is C_2 alkyl substituted with OZ, and Z is methyl.

58. The compound of embodiment 52, wherein R^1 is NR^eR^f, R^e is C_{1-4} alkyl, and R^f is 3-7 member cyclic ring optionally substituted with C_{1-4} alkyl optionally substituted with halo.

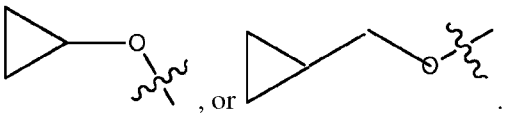
59. The compound of embodiment 58, wherein the 3-7 member cyclic ring is 5 member cyclic ring.

60. The compound of embodiment 59, wherein the 5 member cyclic ring is heterocyclic ring.

61. The compound of embodiment 60, wherein the 5 member heterocyclic ring comprises a N atom.

62. The compound of any of embodiments 58-61, wherein the 3-7 member cyclic ring is substituted with FCH_2CH_2-.

63. The compound of embodiment 52, wherein R^1 is OR^g and R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,


, or .

64. The compound of embodiment 63, wherein the C_{1-4} alkyl is C_2 alkyl.

65. The compound of any of embodiments 52-64, wherein R^2 is H.

66. The compound of any of embodiments 52-64, wherein R^2 is halo.

67. The compound of any of embodiments 52-64, wherein R^2 is C_{1-4} alkyl or C_{1-4} alkoxy.

68. The compound of any of embodiments 52-64, wherein R^5 is H.

69. The compound of any of embodiments 52-64, wherein R^5 is halo.

70. The compound of any of embodiments 52-64, wherein R^5 is C_{1-4} alkyl or C_{1-4} alkoxy.

71. The compound of any of embodiments 52-64, wherein R^6 is H.

72. The compound of any of embodiments 52-64, wherein R^6 is halo.

73. The compound of any of embodiments 52-64, wherein R^6 is C_{1-4} alkyl or C_{1-4} alkoxy.

74. The compound of embodiment 52, wherein R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

75. The compound of embodiment 52, wherein R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

76. The compound of embodiment 52, wherein R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl.

77. The compound of any of embodiments 74-76, wherein the 3-7 member cyclic ring is a 5 member cyclic ring.

78. The compound of embodiment 77, wherein the 5 member cyclic ring is heterocyclic ring.

79. The compound of embodiment 78, wherein the 5 member heterocyclic ring comprises a N atom.

80. The compound of any of embodiments 74-79, wherein the C_{1-4} alkyl is C_2 alkyl.

81. The compound of embodiment 80, wherein Z is methyl.

82. The compound of any of embodiments 52-81, wherein R^3 is H.

83. The compound of any of embodiments 52-81, wherein R^3 is halo.

84. The compound of any of embodiments 52-81, wherein R^3 is C_{1-4} alkyl or C_{1-4} alkoxy.

85. The compound of any of embodiments 52-84, wherein R^2, R^5, or R^6 is H or halo and R^3 is halo, C_{1-4} alkyl or C_{1-4} alkoxy.

86. The compound of any of embodiments 52-85, wherein R^4 is unsubstituted C_2 alkenyl.

87. The compound of any of embodiments 52-85, wherein R^4 is C_2 alkenyl substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$.

88. The compound of any of embodiments 52-87, wherein X is O.

89. The compound of any of embodiments 52-87, wherein X is C_{1-4} alkyl optionally substituted with halo.

90. The compound of embodiment 89, wherein X is unsubstituted C_{1-4} alkyl.

91. The compound of embodiment 90, wherein X is CH_2.

92. The compound of embodiment 89, wherein X is C_{1-4} alkyl substituted with halo.

93. The compound of embodiment 92, wherein X is CF_2.

94. The compound of any of embodiments 52-87, wherein X is NR^b, and R^b is H, or C_{1-8} alkyl optionally substituted with halo.

95. The compound of embodiment 94, wherein R^b is H.

96. The compound of embodiment 94, wherein R^b is C_{1-8} alkyl.

97. The compound of embodiment 96, wherein R^b is C_{1-4} alkyl.

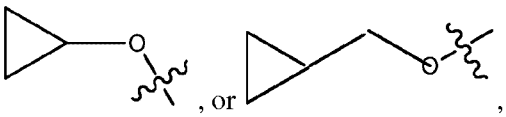
98. The compound of embodiment 96 or 97, wherein C_{1-4} alkyl or C_{1-8} alkyl is substituted with halo.

99. The compound of any of embodiments 52-98, wherein Y is CH.

100. The compound of any of embodiments 52-98, wherein Y is CF.

101. The compound of any of embodiments 52-98, wherein Y is N.

102. The compound of embodiment 52, wherein R^1 is OR^g wherein R^g is C_{1-4} alkyl substituted with CH_3O-, CH_3CH_2O-, $CH_3(O)_2S$-, CF_3O-,



, and R^2, R^3, R^5 and R^6 are H.

103. The compound of embodiment 102, wherein R^g is C_2 alkyl substituted with CH_3O-.

104. The compound of any of embodiments 52-103, wherein at least one of R^1, R^2, R^3, R^5 and R^6 is not H.

105. The compound of embodiment 52, which is selected from the group consisting of compound I-10, I-11, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, and I-40.

106. A pharmaceutical composition comprising a compound of any of embodiments 1-105 admixed with at least one pharmaceutically acceptable carrier or excipient.

107. A compound according to any of embodiments 1-105 for use in therapy.

108. A method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, which comprises administering to a subject in need thereof an effective amount of a compound of any of embodiments 1-105 or a pharmaceutical composition of embodiment 106.

109. Use of a compound according to any of embodiments 1-105 for the manufacture of a medicament.

110. A combination for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease in a subject, which combination comprises an effective amount of a compound of any of embodiments 1-105, or a pharmaceutically acceptable salt thereof, and an effective amount of a second prophylactic or therapeutic agent for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease in a subject.

111. A method for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease in a subject, which methods comprises administering to a subject in need thereof an effective amount of the combination of embodiment 110.

112. A method for inhibiting an activity of a Bruton's tyrosine kinase (Btk or BTK) or a Janus kinase (JAK) in a cell or subject, which methods comprises administering to a cell or subject in need thereof an effective amount of a compound of any of embodiments 1-105, or a pharmaceutical composition of claim 106, or a combination of embodiment 110.

113. The method of embodiment 112, wherein the JAK is JAK1, JAK2 or JAK3.

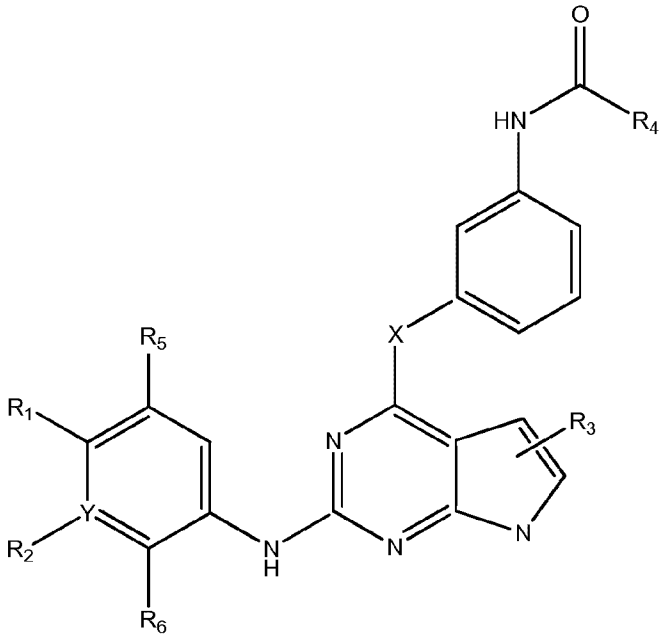
114. The method of embodiment 112 or 113, which is used for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease in the subject.

115. The method of embodiment 114, wherein the proliferation disorder is selected from the group consisting of sarcoma, epidermoid cancer, fibrosarcoma, cervical cancer, gastric carcinoma, skin cancer, leukemia, lymphoma, lung cancer, non- small cell lung cancer, colon

cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, breast cancer, liver cancer, head and neck cancers, and pancreatic cancer.

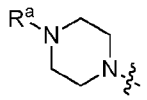
116. The method of any of embodiments 112-115, wherein the compound is selected from the group consisting of compound I-1, I-2, I-3, I-4, I-5, I-6, I-7, I-8, I-9, I-10, I-11, I-12, I-13, I-14, I-15, I-16, I-17, I-18, I-19, I-20, I-21, I-22, I-23, I-24, I-25, I-26, I-27, I-28, I-29, I-30, I-31, I-32, I-33, I-34, I-35, I-36, I-37, I-38, I-39, I-40, and I-41.

117. A compound of Formula (III):



(III)

wherein



R^1 is wherein R^a is CO-C_{1-4} alkyl-CONH-(C_{1-4} alkyl-O)$_m$-C_{1-4} alkyl-NH-(Detectable Label), m being an integer 1-4;

R^2 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^3 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;

R^5 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy;
R^6 is H, halo, C_{1-4} alkyl, or C_{1-4} alkoxy; or
R^1 and R^5 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^1 and R^2 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^2 and R^6 are part of 3-7 member cyclic ring, optionally substituted with C_{1-4} alkyl substituted with OZ, wherein Z is H or C_{1-4} alkyl,; or
R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$; and
X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo,
Y is CH optionally substituted with halo, or N,
or a pharmaceutically acceptable salt thereof.

118. The compound of embodiment 117, wherein in R^a C_{1-4} alkyl is C_2 alkyl.

119. The compound of embodiment 117 or 118, wherein m is 3.

120. The compound of any of embodiments 117-119, wherein the Detectable Label is biotin.

121. The compound of embodiment 117, which is compound I-42.

122. A compound according to any of embodiments 117-121 for use in testing.

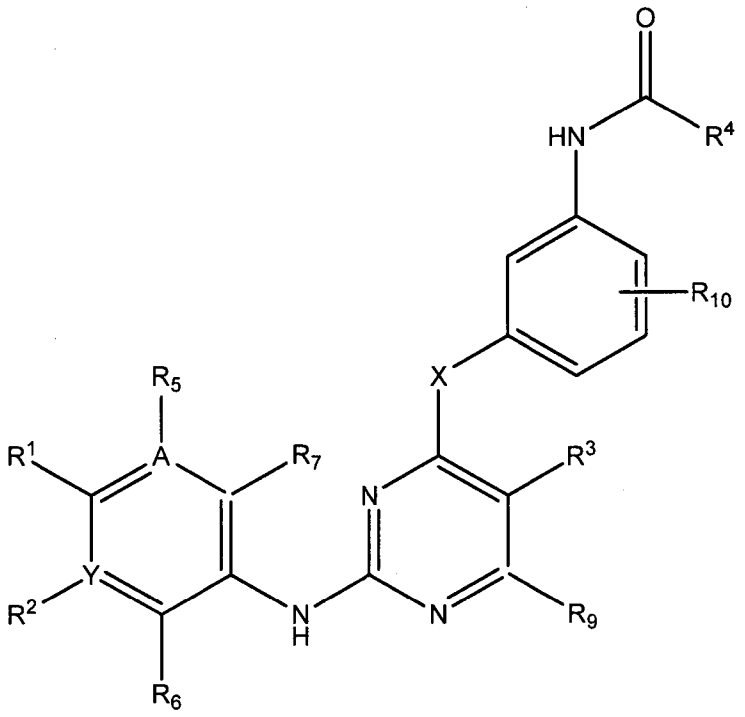
[00479] The detailed description set-forth above is provided to aid those skilled in the art in practicing the present invention. However, the invention described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed because these embodiments are intended as illustration of several aspects of the invention. Any equivalent embodiments are intended to be within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description which do not depart from the spirit or scope of the present

inventive discovery. Such modifications are also intended to fall within the scope of the appended claims.

[00480] Citation of a reference herein shall not be construed as an admission that such is prior art to the present invention.

CLAIMS:

1. A compound of Formula (Ia):



(Ia)

wherein

R^1 is NR^cR^d wherein

R^c is a 3-7 member cyclic ring, said 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl,

or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl,

or said 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4,

or said 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4, or

said 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl, and

R^d is H, C_{1-4} alkyl, C_{1-4} alkenyl, or 3-7 member cyclic ring, said C_{1-4} alkyl, C_{1-4} alkenyl or 3-7 member cyclic ring being optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are

independently H or C_{1-4} alkyl;R^2 is absent, H, halo, C_{1-4} alkyl, C_{2-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^3 is C_{1-4} alkoxy;

R^5 is absent, H, halo, C_{1-4} alkyl, C_{2-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^6 is H, halo, C_{1-4} alkyl, C_{2-4} alkoxy; or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^7 is H, halo, C_{1-4} alkyl, C_{2-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^9 is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^{10} is H, hydroxyl, halo, C_{1-4} alkyl, C_{1-4} alkoxy, or alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl;

R^4 is C_2 alkenyl optionally substituted with C_{1-4} alkyl, $-CH_2OCH_3$, or $-CH_2N(CH_3)_2$;

X is O, C_{1-4} alkyl optionally substituted with halo, or NR^b, wherein R^b is H, or C_{1-8} alkyl optionally substituted with halo;

Y is C, CH optionally substituted with halo, or N; and

A is C, CH optionally substituted with halo or N;

or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

3. The compound of claim 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

4. The compound of claim 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4.

5. The compound of claim 4, wherein the 3-7 member cyclic ring is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with $SO_2(CH_2)_qH$, wherein q is 1-4.

6. The compound of claim 5, wherein q is 1.

7. The compound of claim 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with C_{1-4} alkyl that is further optionally substituted with $SO_2(CH_2)_qH$, wherein q is 1-4.

8. The compound of claim 7, wherein the 3-7 member cyclic ring is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with C_{1-4} alkyl that is further substituted with $SO_2(CH_2)_qH$, wherein q is 1-4.

9. The compound of claim 8, wherein the H linked to the N atom is substituted with C_2 alkyl that is further substituted with SO_2CH_3.

10. The compound of claim 1, wherein R^1 is NR^cR^d and R^c is 3-7 member cyclic ring being optionally substituted with R_8CO, wherein R_8 is C_{1-4} alkyl.

11. The compound of claim 10, wherein R^1 is NR^cR^d and R^c is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with R_8CO, wherein R_8 is C_{1-4} alkyl.

12. The compound of claim 11, wherein the H linked to the N atom is substituted with CH_3CO.

13. The compound of any one of claims 2 to 12, wherein R^d is H.

14. The compound of any one of claims 2 to 12, wherein R^d is C_{1-4} alkyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

15. The compound of any one of claims 2 to 12, wherein R^d is C_{1-4} alkenyl, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

16. The compound of any one of claims 2 to 12, wherein R^d is 3-7 member cyclic ring, optionally substituted with OZ or $NR_{11}R_{12}$, wherein Z, R_{11}, R_{12} are independently H or C_{1-4} alkyl.

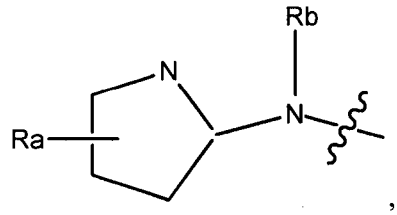
17. The compound of claim 16, wherein R^c is a 5 member cyclic ring that comprises a N atom, the H linked to the N atom is substituted with C_{1-4} alkyl that is further substituted with OZ, wherein Z is independently C_{1-4} alkyl, and R^d is 3-7 member cyclic ring.

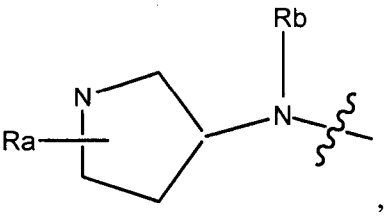
18. The compound of claim 1, wherein R^1 is a 3-7 member cyclic ring substituted with R^a wherein R^a is C_{2-4} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4.

19. The compound of claim 18, wherein the 3-7 member cyclic ring comprises a N atom.

20. The compound of claim 19, wherein the 3-7 member cyclic ring is substituted at the N atom with $SO_2(CH_2)_qH$, wherein q is 1-4.

21. The compound of any one of claims 18 to 20, wherein R^1 is selected from the group consisting of



,


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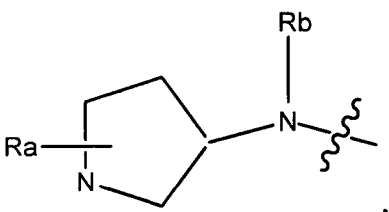

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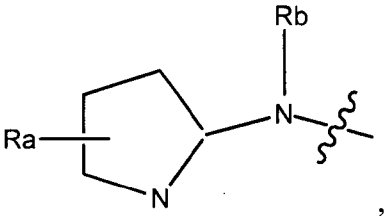
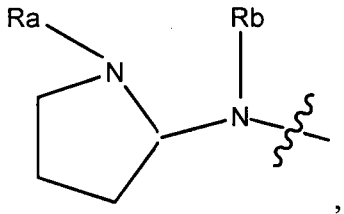


, R^a is C_{2-4} alkyl optionally

substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4, and R^b is H or C_{1-4} alkyl optionally substituted with halo, C_{1-4} alkoxy or $SO_2(CH_2)_qH$, wherein q is 1-4.

22. The compound of claim 21, wherein R^1 is selected from the group consisting of



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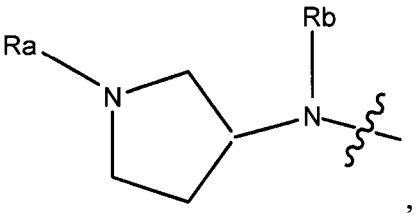

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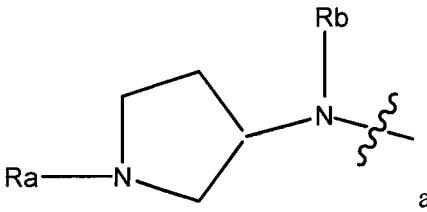
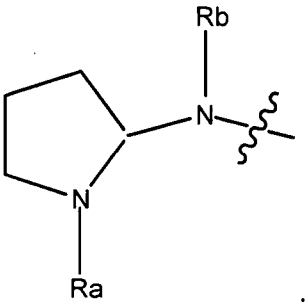


and


.

23. The compound of any one of claims 1 to 22, wherein R^2 is H or halo.

24. The compound of any one of claims 1 to 22, wherein R^2 is C_{1-4} alkyl or C_{2-4} alkoxy.

25. The compound of any one of claims 1 to 22, wherein R^2 is alkylamine ($NR_{11}R_{12}$), and R_{11} and R_{12} are independently H or C_{1-4} alkyl.

26. The compound of any one of claims 1 to 25, wherein R^5 is H.

27. The compound of any one of claims 1 to 25, wherein R^5 is halo.

28. The compound of any one of claims 1 to 25, wherein R^5 is C_{1-4} alkyl.

29. The compound of any one of claims 1 to 25, wherein R^5 is C_{2-4} alkoxy.

30. The compound of any one of claims 1 to 25, wherein R^5 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

31. The compound of any one of claims 1 to 30, wherein R^6 is H.

32. The compound of any one of claims 1 to 30, wherein R^6 is halo.

33. The compound of any one of claims 1 to 30, wherein R^6 is C_{1-4} alkyl.

34. The compound of any one of claims 1 to 30, wherein R^6 is C_{2-4} alkoxy.

35. The compound of any one of claims 1 to 30, wherein R^6 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

36. The compound of any one of claims 1 to 35, wherein R^7 is H.

37. The compound of any one of claims 1 to 35, wherein R^7 is halo.

38. The compound of any one of claims 1 to 35, wherein R^7 is C_{1-4} alkyl.

39. The compound of any one of claims 1 to 35, wherein R^7 is C_{2-4} alkoxy.

40. The compound of any one of claims 1 to 35, wherein R^7 is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

41. The compound of any one of claims 1 to 40, wherein R^9 is H.

42. The compound of any one of claims 1 to 40, wherein R^9 is hydroxyl.

43. The compound of any one of claims 1 to 40, wherein R^9 is halo.

44. The compound of any one of claims 1 to 40, wherein R^9 is C_{1-4} alkyl.

45. The compound of any one of claims 1 to 40, wherein R^9 is C_{1-4} alkoxy.

46. The compound of any one of claims 1 to 40, wherein R^9 is C_{1-4} alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

47. The compound of any one of claims 1 to 46, wherein R^{10} is H.

48. The compound of any one of claims 1 to 46, wherein R^{10} is hydroxyl.

49. The compound of any one of claims 1 to 46, wherein R^{10} is halo.

50. The compound of any one of claims 1 to 46, wherein R^{10} is C_{1-4} alkyl.

51. The compound of any one of claims 1 to 46, wherein R^{10} is C_{1-4} alkoxy.

52. The compound of any one of claims 1 to 46, wherein R^{10} is alkylamine ($NR_{11}R_{12}$), wherein R_{11} and R_{12} are independently H or C_{1-4} alkyl.

53. The compound of any one of claims 1 to 52, wherein R^4 is unsubstituted C_2 alkenyl.

54. The compound of any one of claims 1 to 52, wherein R^4 is C_2 alkenyl substituted with C_{1-4} alkyl.

55. The compound of any one of claims 1 to 52, wherein R^4 is C_2 alkenyl substituted with $-CH_2OCH_3$.

56. The compound of any one of claims 1 to 52, wherein R^4 is C_2 alkenyl substituted with $-CH_2N(CH_3)_2$.

57. The compound of any one of claims 1 to 56, wherein X is O.

58. The compound of any one of claims 1 to 56, wherein X is unsubstituted C_{1-4} alkyl or C_{1-4} alkyl substituted with halo.

59. The compound of any one of claims 1 to 56, wherein X is NR^b, and R^b is H, or C_{1-8} alkyl optionally substituted with halo.

60. The compound of any one of claims 1 to 59, wherein Y is C.

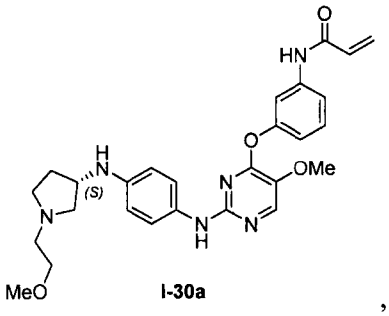
61. The compound of claim 60, wherein Y is CH or CH substituted with halo.

62. The compound of claim 60, wherein Y is N.

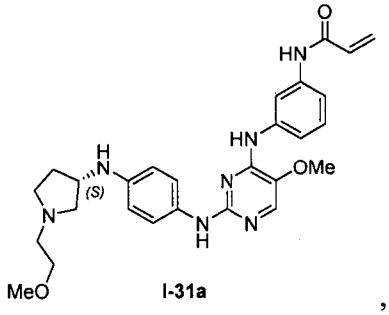
63. The compound of any one of claims 1 to 62, wherein A is C.

64. The compound of any one of claims 1 to 62, wherein A is N.

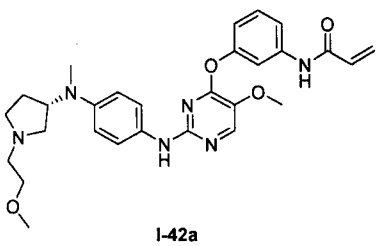
65. The compound of claim 1, which is selected from the group consisting of compound



I-30a ,



I-31a ,



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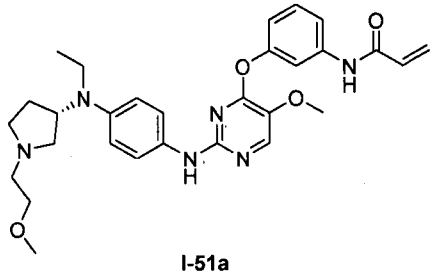
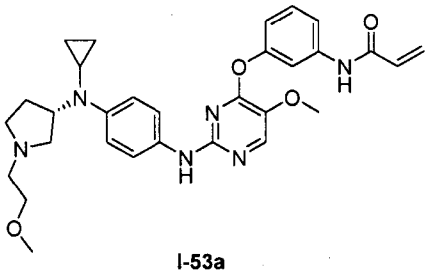
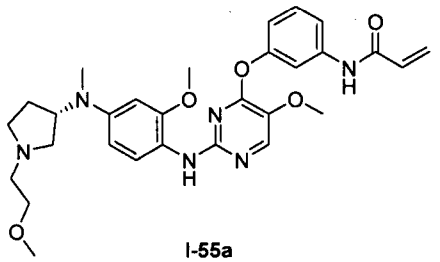


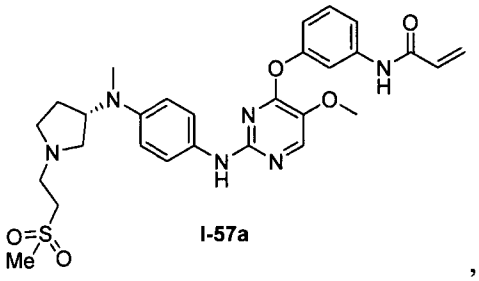
I-51a ,



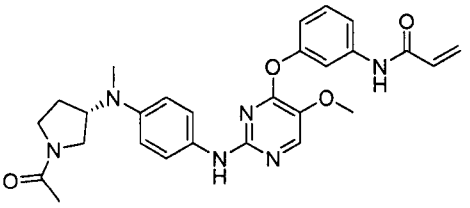
I-53a ,



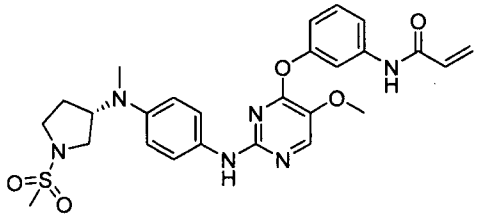
I-55a ,



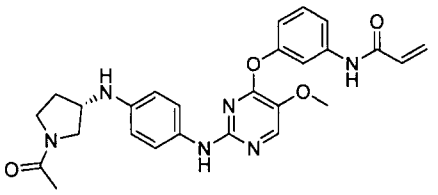
I-57a ,



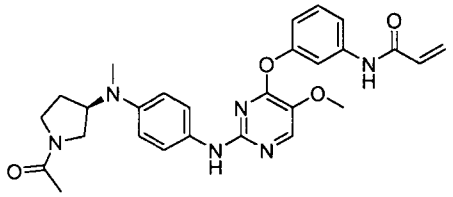
I-58a ,



I-60a ,



I-66a , and



I-72a .

66. A pharmaceutical composition comprising a compound of any one of claims 1 to 65, admixed with at least one pharmaceutically acceptable carrier or excipient.

67. A compound according to any one of claims 1 to 65, for treating a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease, or lupus.

68. A combination for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject, which combination comprises an effective amount of a compound of any one of claims 1 to 65, or a pharmaceutically acceptable salt thereof, and an effective amount of a second prophylactic or therapeutic agent for treating and/or preventing a proliferation disorder, a cancer, a tumor, an inflammatory disease, an autoimmune disease, psoriasis, dry eye or an immunologically related disease or lupus in a subject.

Figure 1A

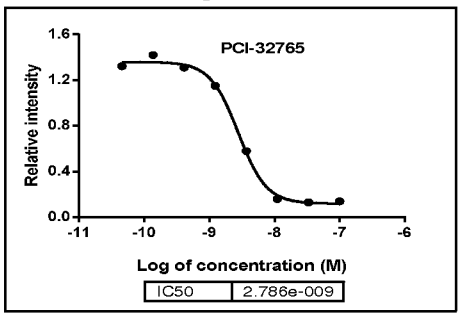


Figure 1B

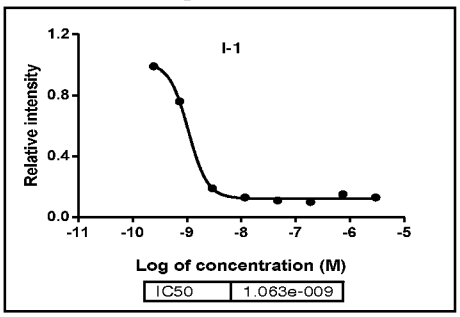


Figure 1C

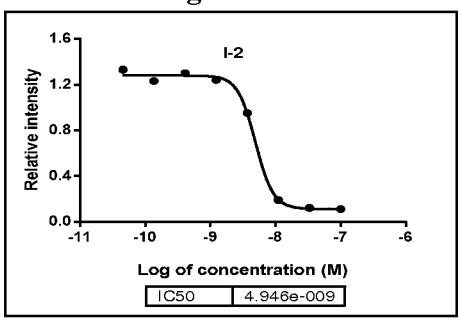


Figure 2A

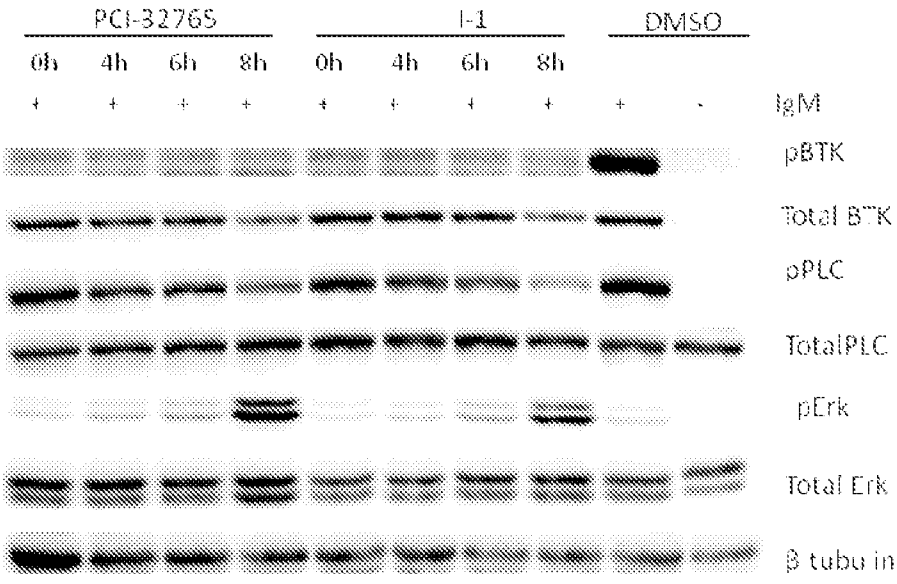


Figure 2B

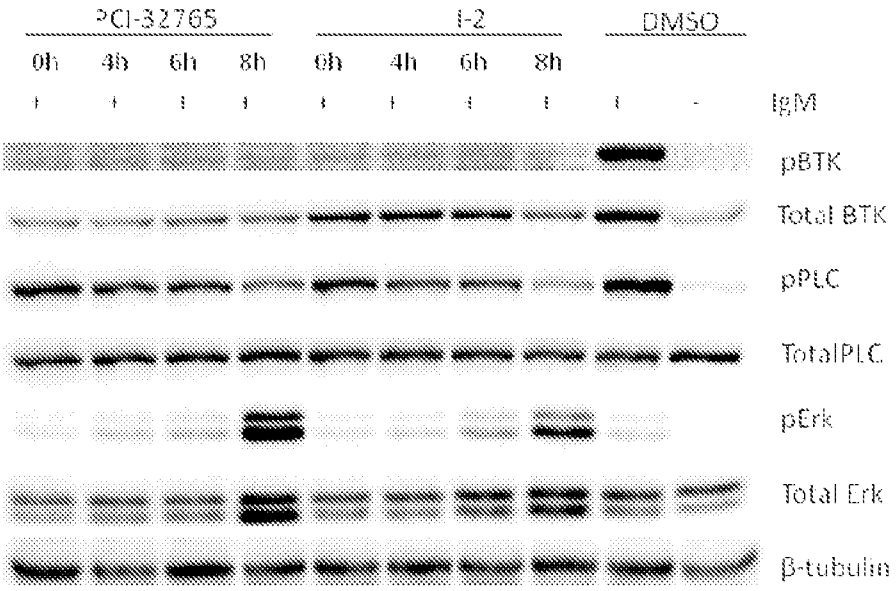


Figure 3

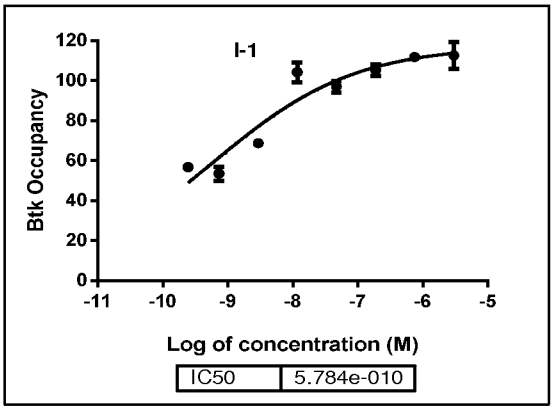


Figure 4A

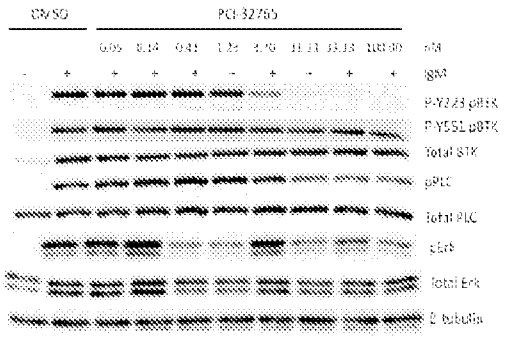


Figure 4B

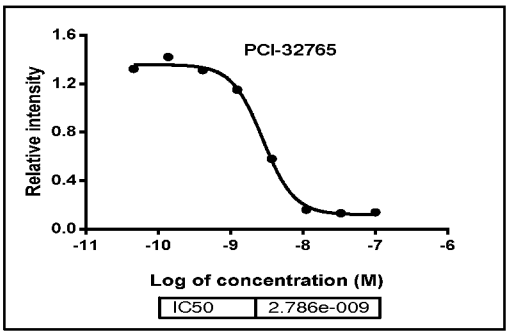


Figure 4C

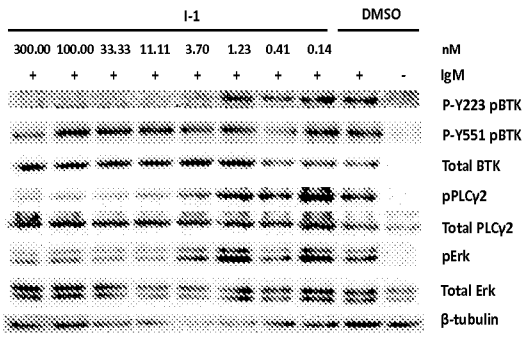


Figure 4D

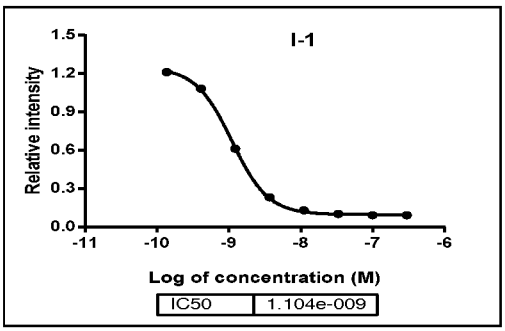


Figure 4E

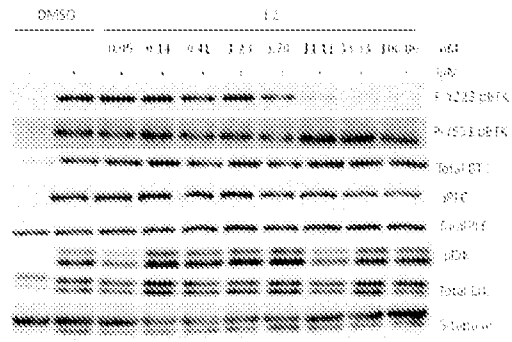


Figure 4F

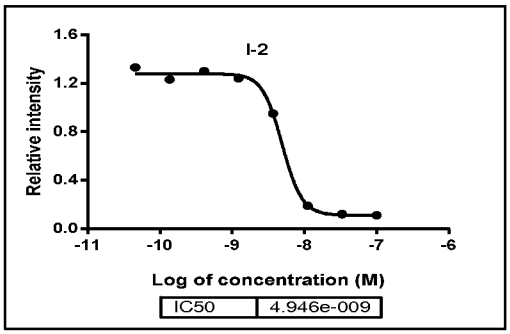


Figure 4G

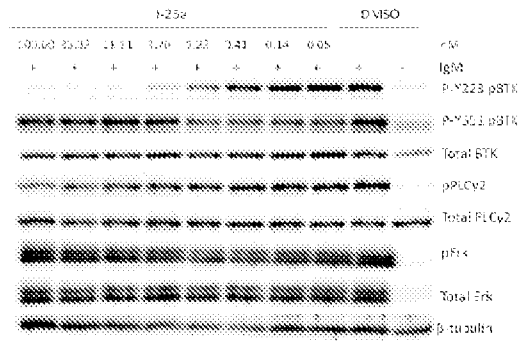


Figure 4H

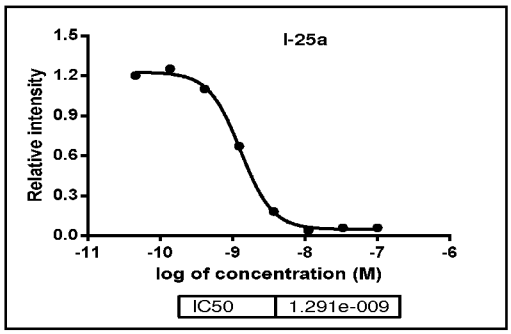


Figure 4I

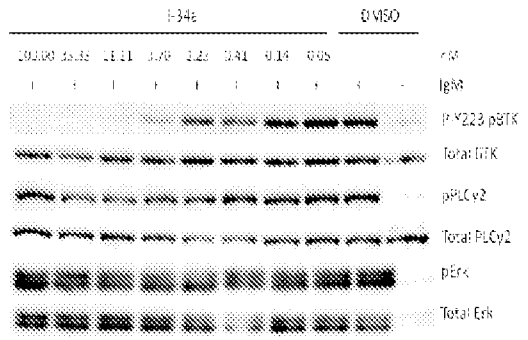


Figure 4J

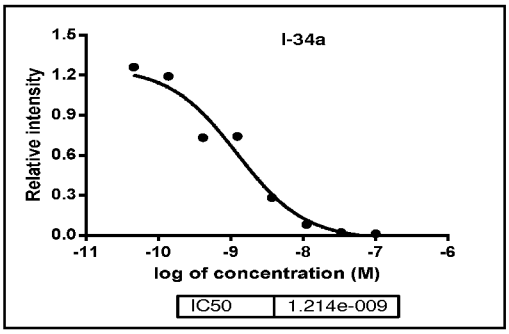


Figure 4K

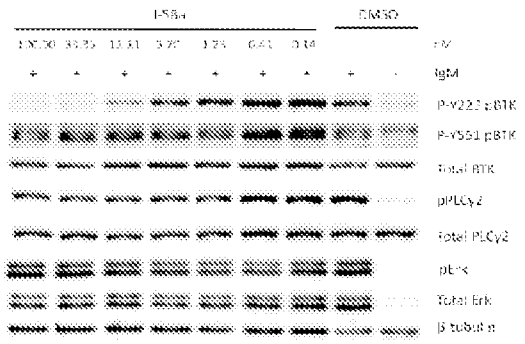


Figure 4L

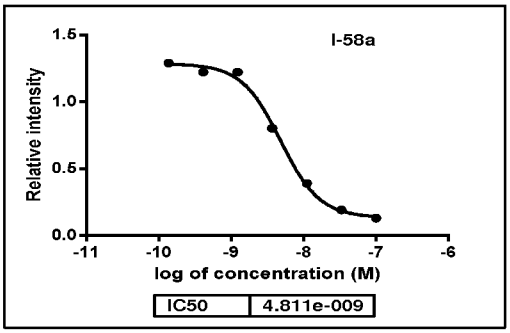


Figure 4M

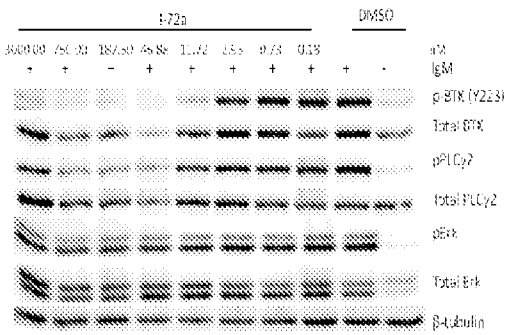


Figure 4N

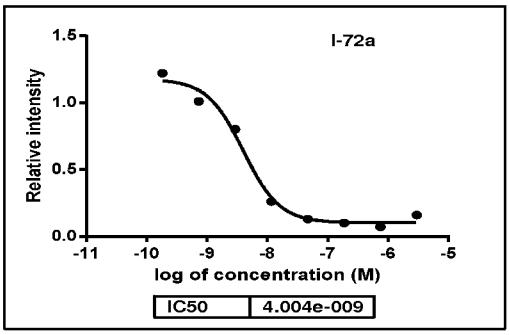


Figure 5A

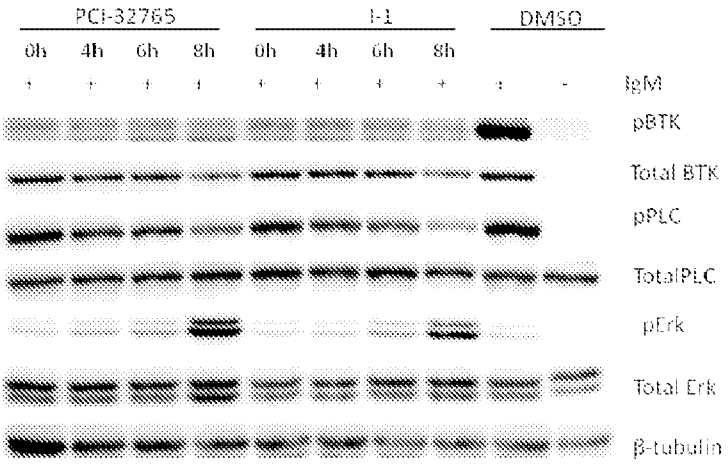


Figure 5B

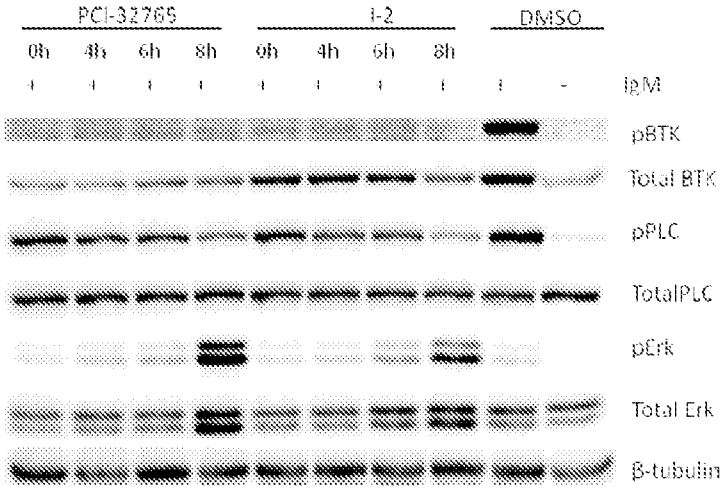


Figure 6A

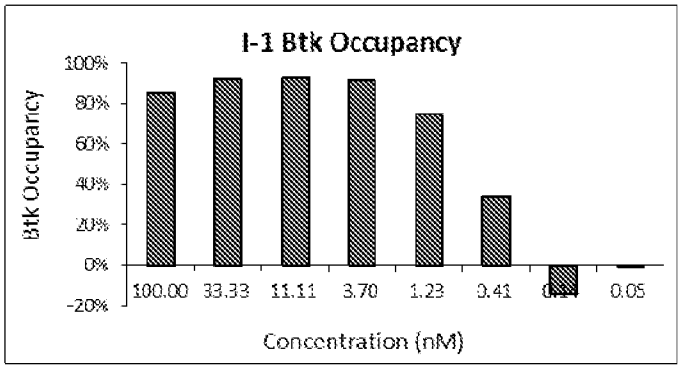


Figure 6B

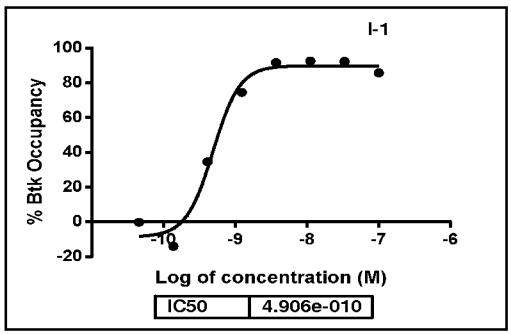


Figure 6C

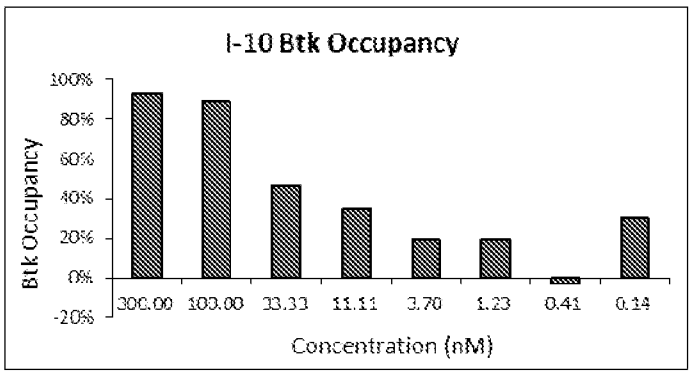


Figure 6D

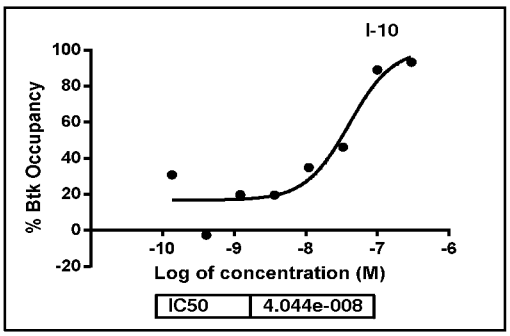


Figure 6E

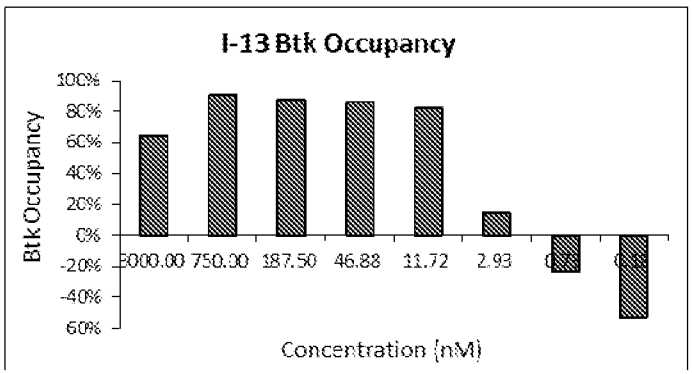


Figure 6F

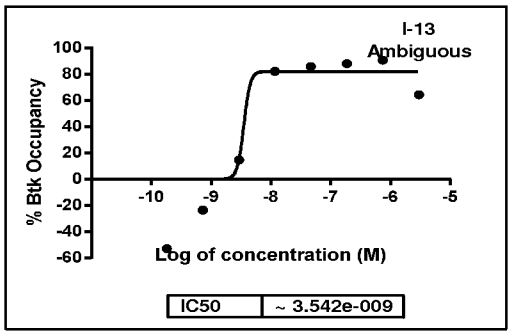


Figure 6G

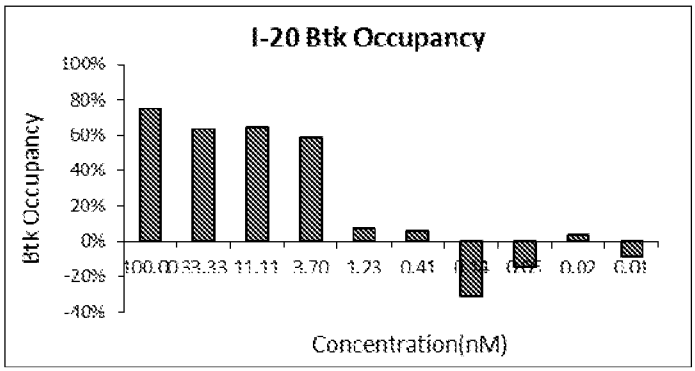


Figure 6H

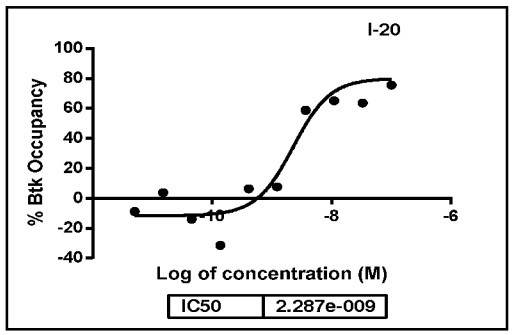


Figure 6I

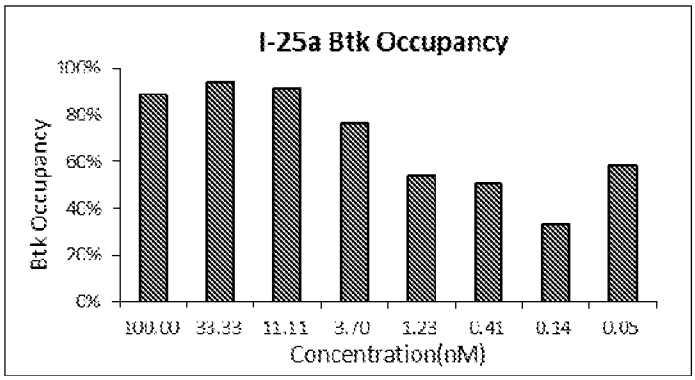


Figure 6J

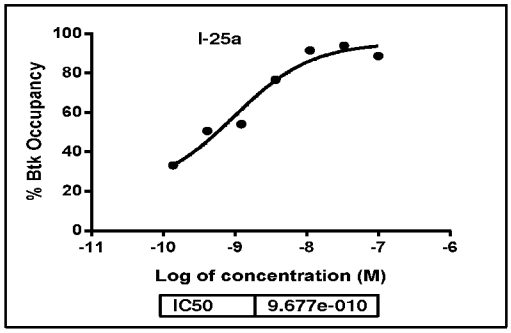


Figure 6K

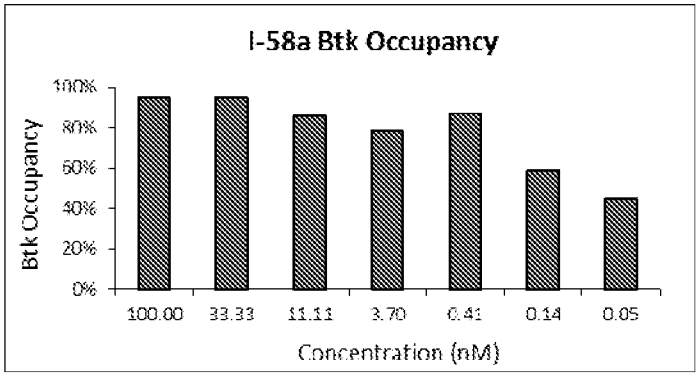
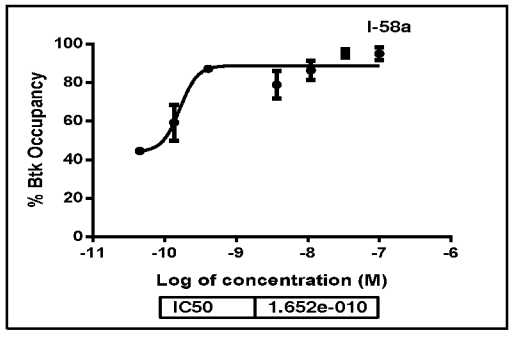
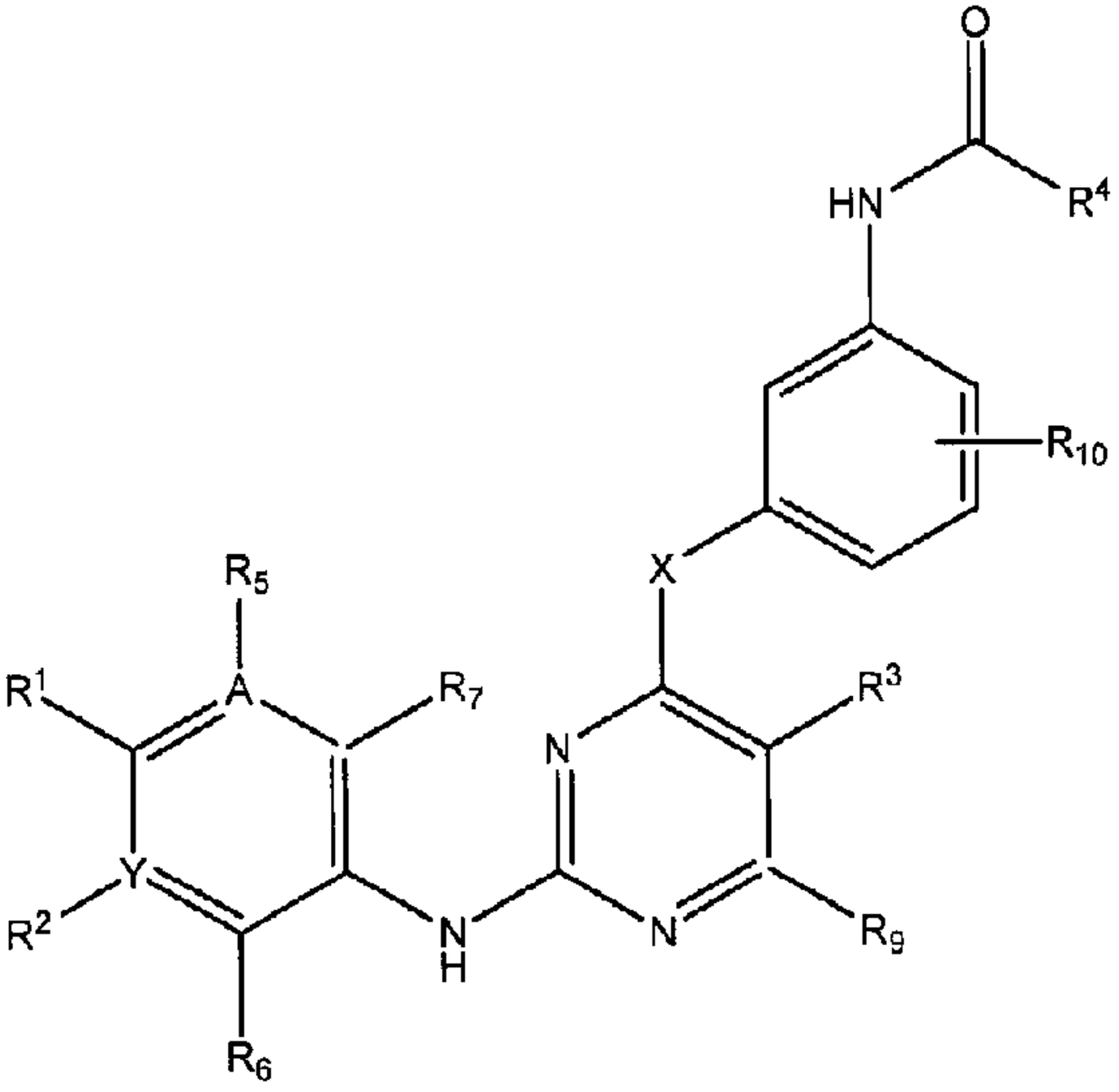


Figure 6L





(Ia)