HETEROARYL COMPOUNDS AND USES THEREOF

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds useful as inhibitors of protein kinases. The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

BACKGROUND OF THE INVENTION

[0002] The search for new therapeutic agents has been greatly aided in recent years by a better understanding of the structure of enzymes and other biomolecules associated with diseases. One important class of enzymes that has been the subject of extensive study is protein kinases.

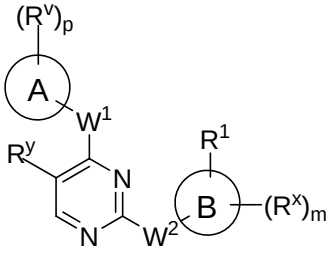
[0003] Protein kinases constitute a large family of structurally related enzymes that are responsible for the control of a variety of signal transduction processes within the cell. Protein kinases are thought to have evolved from a common ancestral gene due to the conservation of their structure and catalytic function. Almost all kinases contain a similar 250-300 amino acid catalytic domain. The kinases may be categorized into families by the substrates they phosphorylate (e.g., protein-tyrosine, protein-serine/threonine, lipids, etc.).

[0004] In general, protein kinases mediate intracellular signaling by effecting a phosphoryl transfer from a nucleoside triphosphate to a protein acceptor that is involved in a signaling pathway. These phosphorylation events act as molecular on/off switches that can modulate or regulate the target protein biological function. These phosphorylation events are ultimately triggered in response to a variety of extracellular and other stimuli. Examples of such stimuli include environmental and chemical stress signals (e.g., osmotic shock, heat shock, ultraviolet radiation, bacterial endotoxin, and H_2O_2), cytokines (e.g., interleukin-1 (IL-1) and tumor necrosis factor α (TNF-α)), and growth factors (e.g., granulocyte macrophage-colony-stimulating factor (GM-CSF), and fibroblast growth factor (FGF)). An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

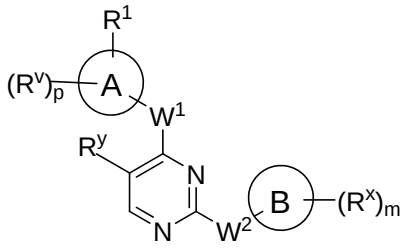
[0005] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY

[0006] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of one or more protein kinases. Such compounds have general formulae **I-a** and **I-b**:



I-a



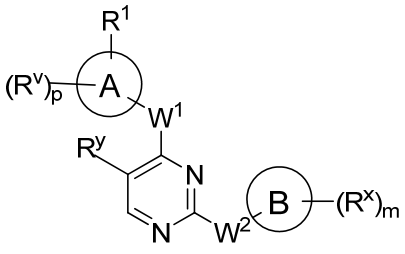
I-b

or a pharmaceutically acceptable salt thereof, wherein Ring A, Ring B, m, p, R^x, R^y, R^v,W^1, W^2, and R^1 are as defined herein.

[0007] Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with abnormal cellular responses triggered by protein kinase-mediated events. Such diseases, disorders, or conditions include those described herein.

[0008] Compounds provided by the present disclosureare also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

[0009A] In one aspect, the present disclosure refers to a compound of formula **I-b**:



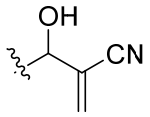
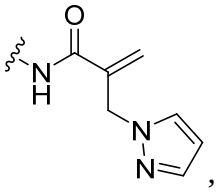
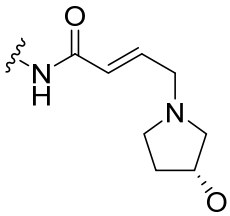
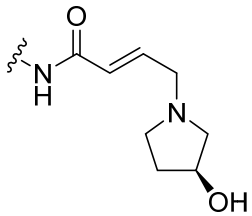
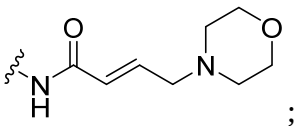
I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl;

Ring B is phenyl;

R^1 is a warhead group –L-Y, wherein R^1 is in a meta- or para-position of the phenyl ring relative to W^1;

-L-Y is  ,  ,  ,  or  ; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is -NRC(O)CH=CHCH$_2$N(CH$_3$)-, -NRC(O)CH=CHCH$_2$O- or -NRSO$_2$CH=CHCH$_2$-; and

Y is hydrogen, C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

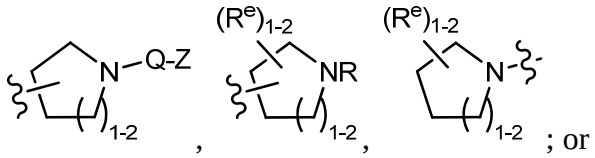
L is a bivalent C$_{2-8}$ straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are independently replaced by –C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, -SO$_2$N(R)-, –S-, -S(O)-, -SO$_2$-, -OC(O)-, or –C(O)O-; and Y is C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

L is a covalent bond and Y is:

(*ii*) C$_{2-6}$ alkenyl substituted with oxo, halogen, NO$_2$, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

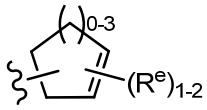
(*vi*) 

; or

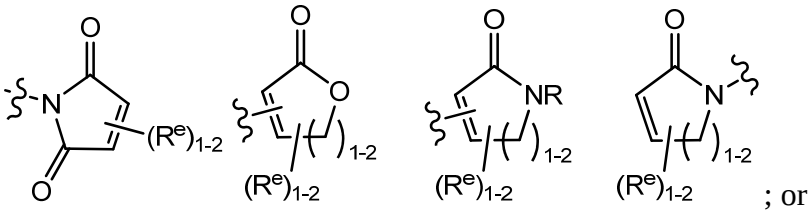
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

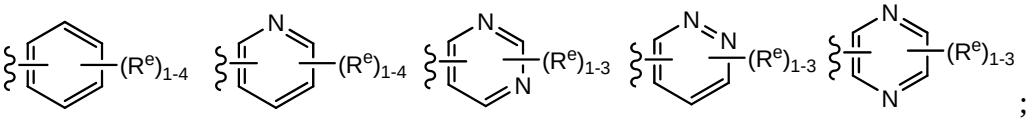
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

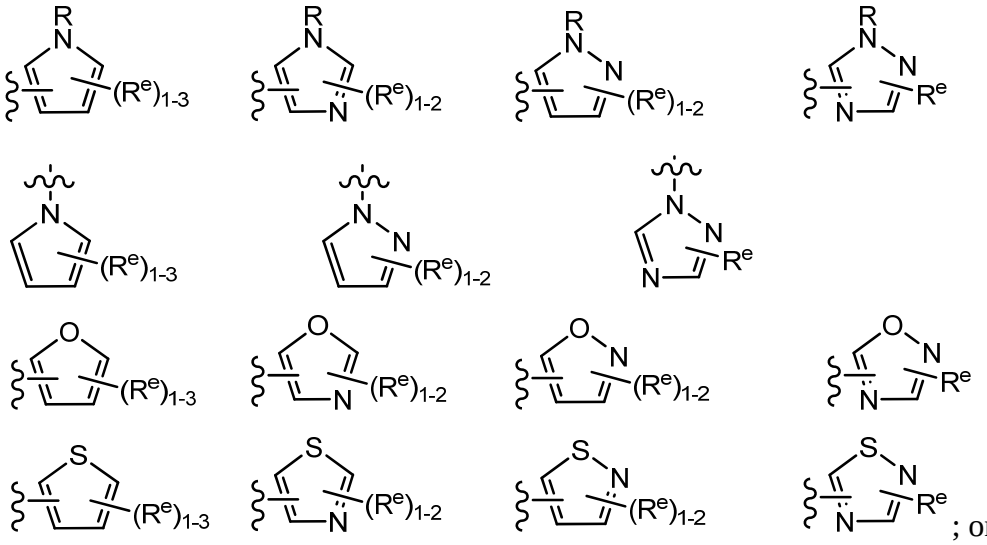
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ;

or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is –C(O)- and Y is:

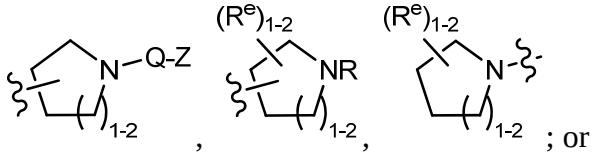
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

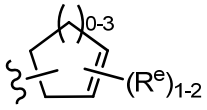
(*vi*) 

; or

(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

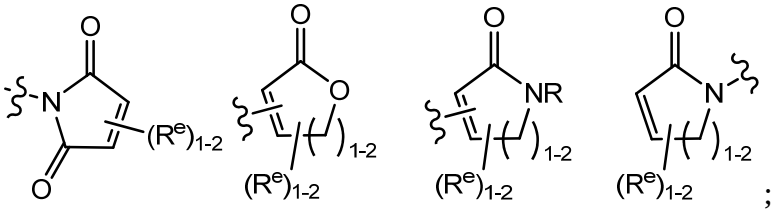
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*) 

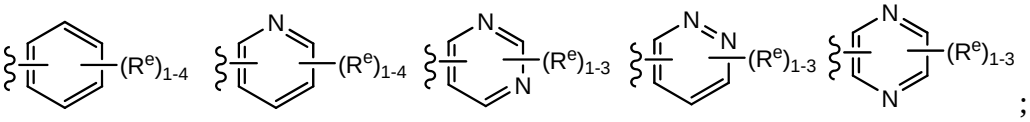
; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*) 

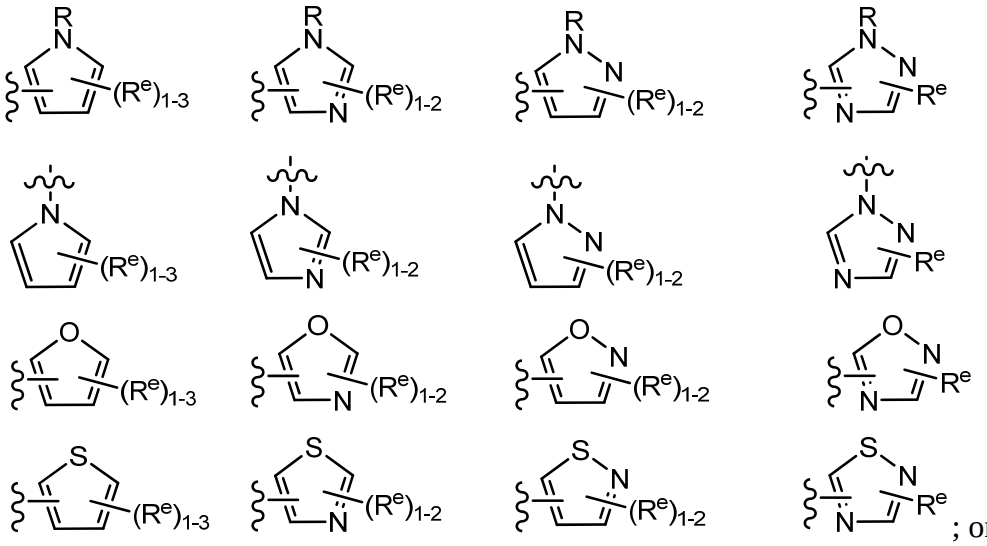
; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ;

or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is –N(R)C(O)- and Y is:

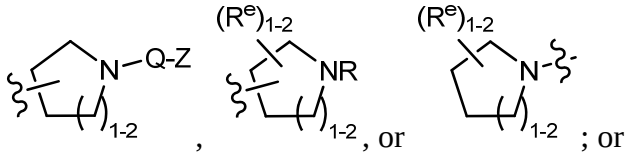
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

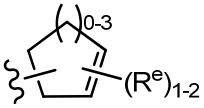
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

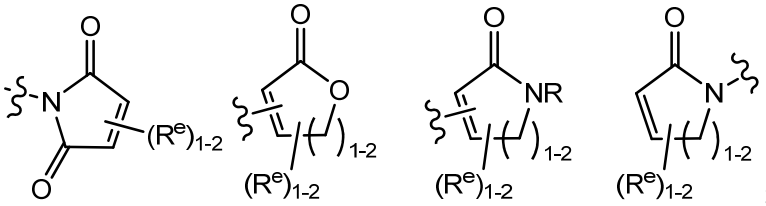
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

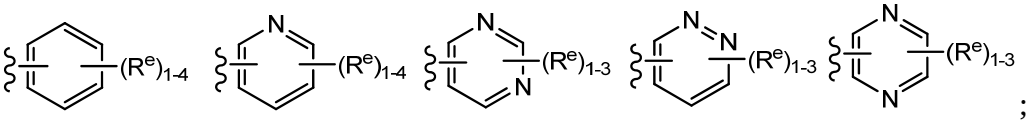
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

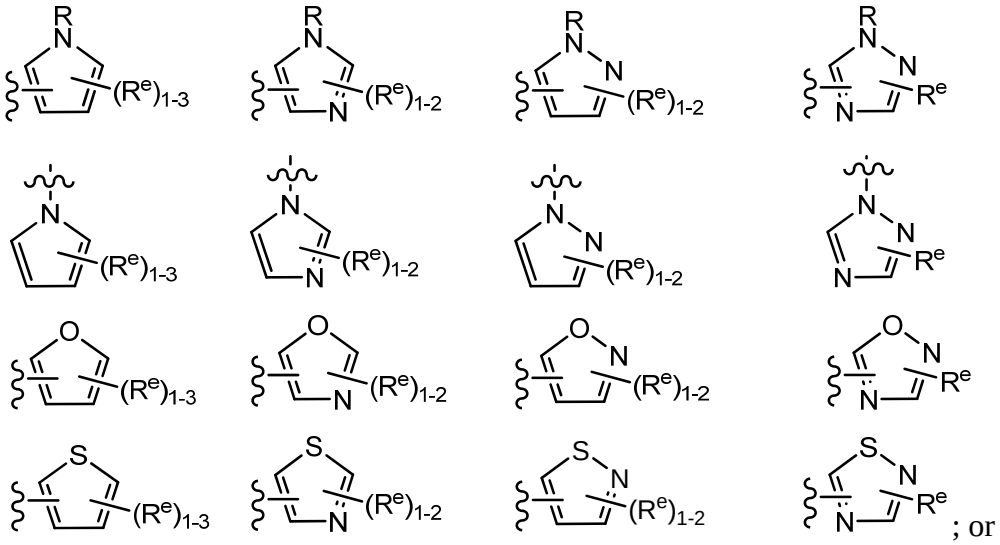
(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ;

or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*) ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and

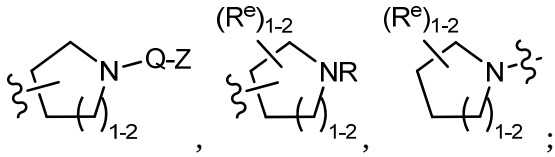
Y is:

(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

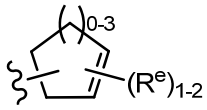
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*) ; or

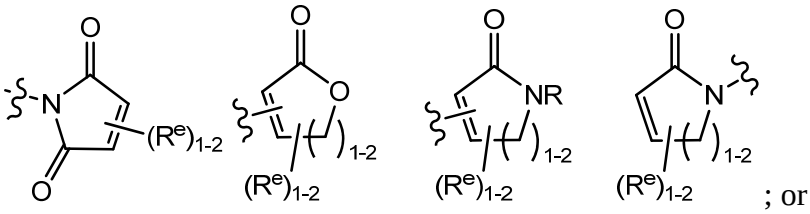
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

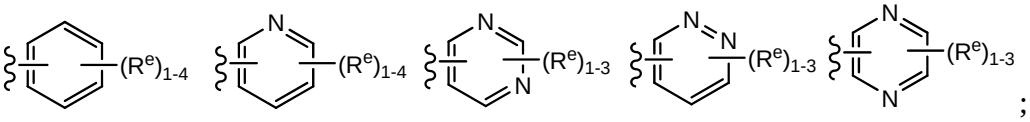
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

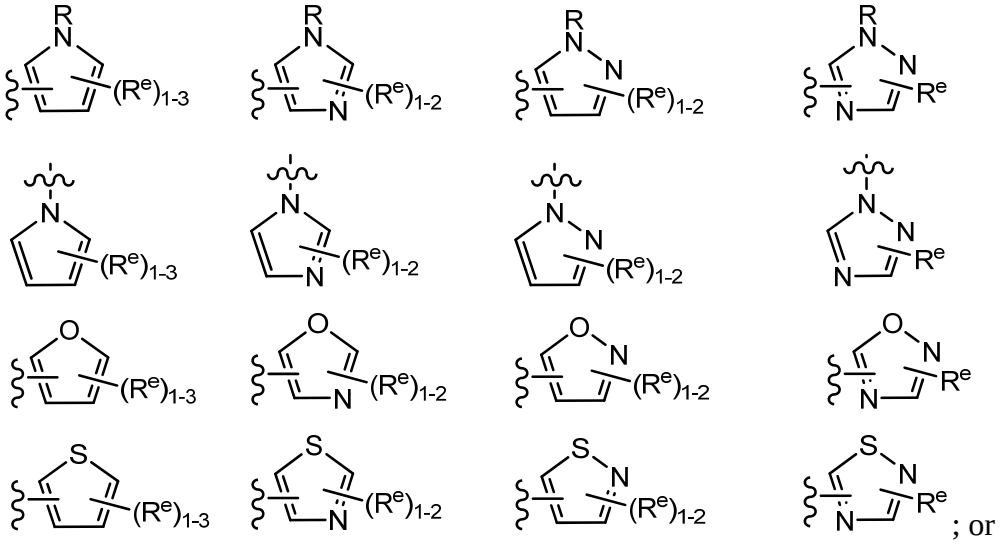
(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ;

or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*)  ; or

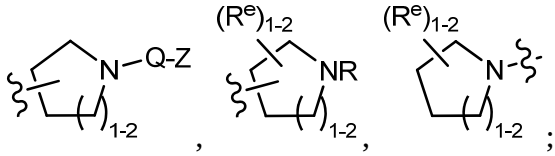
(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is $–CH_2$-, -NH-, -C(O)-, $-CH_2NH$-, $-NHCH_2$-, –NHC(O)-, $-NHC(O)CH_2OC(O)$-, $-CH_2NHC(O)$-, $-NHSO_2$-, $-NHSO_2CH_2$-, or $-SO_2NH$-; and Y is:

(*ii*) C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

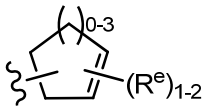
(*vi*) 

; or

(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

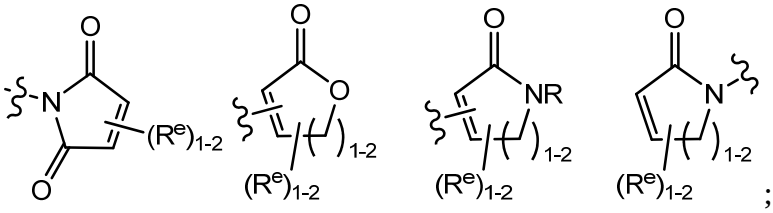
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*) 

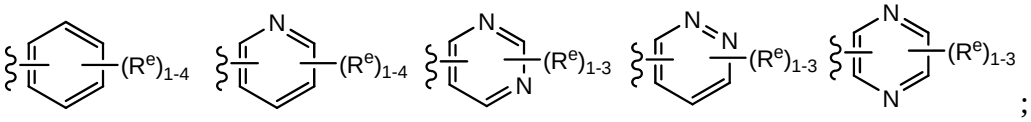
; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

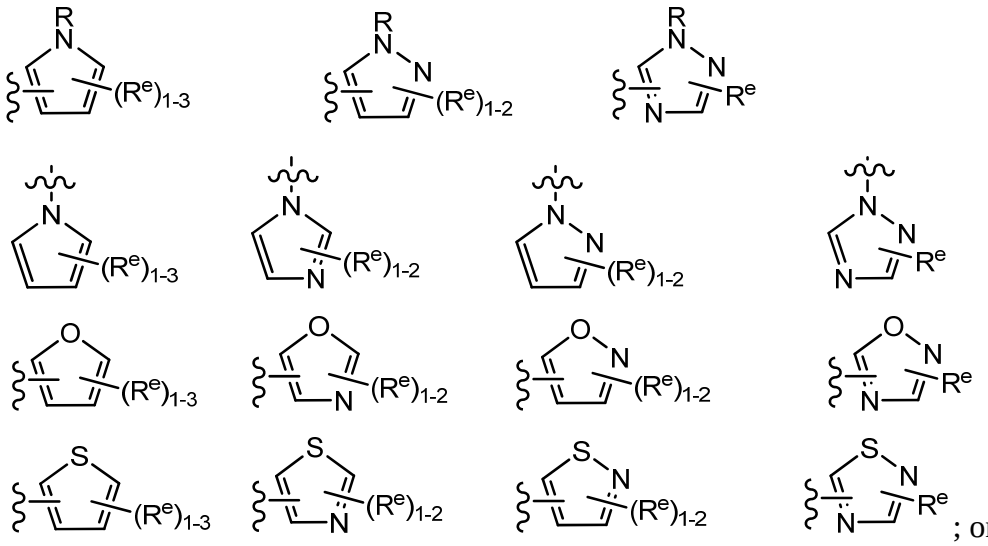
(*xii*) 

; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ;

or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups;

each R^e is independently–Q-Z, oxo, NO_2, halogen, CN, C_{1-6} saturated aliphatic substituted with oxo, halogen, NO_2, or CN, C_{2-6} unsaturated aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from the group consisting of alkoxy, sulfonyloxy, optionally substituted alkylsulfonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and diazonium, wherein:

Q is a bivalent C_{2-6} unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and

each Z is hydrogen or C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN;

R^y is halogen;

each R group is independently hydrogen or an optionally substituted group selected from the group consisting of $C_{1–6}$ aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

W^1 is $–NR^2$-;

W^2 is $–NR^2$-;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R;

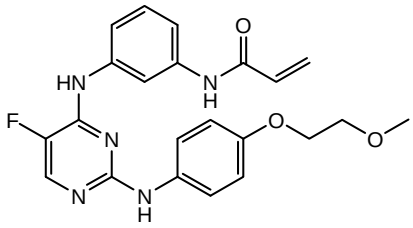
m is 0, 1, 2, 3 or 4;

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

each instance of R^x is independently–R, -OR, $-O(CH_2)_qOR$, or halogen, wherein q is 1, 2, 3 or 4; and

each instance of R^v is independently R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1, 2, 3 or 4.

[0009B] In another aspect, the present disclosure refers to a compound of the following structure:



or a pharmaceutically acceptable salt thereof.

[0009C] In a further aspect, the present disclosure refers to a pharmaceutical composition comprising the compound disclosed herein, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts dose-response inhibition of phospho-plc gamma2 (p-plc gamma 2) with compound **I-2** in Ramos Cells; and the results of compound **I-2** in a “washout” experiment.

Figure 2 depicts dose-response inhibition of p-plc gamma2 with compound **I-4** in Ramos Cells; and the results of compound **I-4** in a “washout” experiment.

Figure 3 depicts dose response inhibition of p-plc gamma2 with compound **I-7** in Ramos cells; and the results of compound **I-7** in a "washout" experiment.

Figure 4 depicts dose response inhibition of p-plc gamma2 with compound **I-35** in Ramos cells.

Figure 5 depicts dose response inhibition of p-plc gamma2 with compound **I-38** in Ramos cells.

Figure 6 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-2**.

Figure 7 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-4**.

Figure 8 depicts MS analysis confirming covalent modification of TEC kinase at Cys449 by compound **I-7**.

Figure 9 depicts the results of compound **I-2** in a "washout" experiment as compared to results of compound **I-4** and compound **I-7** in the same "washout" experiment in HCC827 cells containing EGFR deletion mutant.

Figure 10 depicts the results of compound **I-7** in a "washout" experiment as compared to results of an EGF control in A431 cells containing EGFR wild type.

Figure 11 depicts MS analysis confirming covalent modification of JAK-3 kinase at Cys909 by compound **I-7**.

Figure 12 depicts dose-response inhibition of P-Stat5 with compound **I-2** in IL-2 stimulated CTLL-2 cells; and dose-response inhibition of P-JAK-3 with compound **I-2** in IL-2 stimulated CTLL-2 cells.

Figure 13 depicts dose-response inhibition of P-Stat5 with compound **I-4** in IL-2 stimulated CTLL-2 cells; and dose-response inhibition of P-JAK-3 with compound **I-4** in IL-2 stimulated CTLL-2 cells.

Figure 14 depicts dose-response inhibition of P-Stat5 with compound **I-7** in IL-2 stimulated CTLL-2 cells.

Figure 15 depicts MS analysis confirming covalent modification of BTK by compound **I-7**.

Figure 16 depicts a Western blot showing BTK protein available to the probe compound **I-215** after treating with varying amounts of **I-7**.

Figure 17 depicts quantitation of the Western blot results in Figure 16.

Figure 18 depicts a Western blot for a washout experiment with compound **I-7** and probe compound **I-215**.

Figure 19 depicts quantitation of the Western blot results in Figure 18.

Figure 20 depicts an amino acid sequence for BTK (SEQ ID 1).

Figure 21 depicts an amino acid sequence for TEC (SEQ ID 2).

Figure 22 depicts an amino acid sequence for ITK (SEQ ID 3).

Figure 23 depicts an amino acid sequence for BMX (SEQ ID 4).

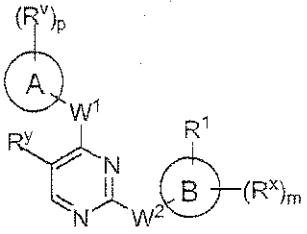
Figure 24 depicts an amino acid sequence for TXK (SEQ ID 5).

Figure 25 depicts an amino acid sequence for JAK3 (SEQ ID 6).

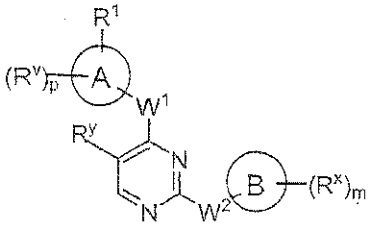
DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention

[0009] In certain embodiments, the present invention provides a compound of formula **I-a** or **I-b**:



I-a



I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is a warhead group;

R^y is hydrogen, halogen, -CN, $-CF_3$, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or $-C(O)N(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by $-NR^2-$, $-N(R^2)C(O)-$, $-C(O)N(R^2)-$, $-N(R^2)SO_2-$, $-SO_2N(R^2)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or $-SO_2-$;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring, or:

R^2 and R^y are taken together with their intervening atoms to form a 4-7 membered partially unsaturated or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^y are independently selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)NR_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1-4; or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, -CN, or C_{1-6} aliphatic; or

R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, -CN, or C_{1-6} aliphatic.

2. ***Compounds and Definitions***

[0010] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J.; John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[0011] The term "aliphatic" or "aliphatic group", as used herein, means a straight-chain (i.e., unbranched) or branched, substituted or unsubstituted hydrocarbon chain that is completely saturated or that contains one or more units of unsaturation, or a monocyclic hydrocarbon or bicyclic hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic (also referred to herein as "carbocycle" "cycloaliphatic" or "cycloalkyl"), that has a single point of attachment to the rest of the molecule. Unless otherwise specified, aliphatic groups contain 1-6 aliphatic carbon atoms. In some embodiments, aliphatic groups contain 1-5 aliphatic carbon atoms. In other embodiments, aliphatic groups contain 1-4 aliphatic carbon atoms. In still other embodiments, aliphatic groups contain 1-3 aliphatic carbon atoms, and in yet other embodiments, aliphatic groups contain 1-2 aliphatic carbon atoms. In some embodiments, "cycloaliphatic" (or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_6 hydrocarbon that is completely saturated or that contains one or more units of unsaturation, but which is not aromatic, that has a single point of attachment to the rest of the molecule. Suitable aliphatic groups include, but are not limited to, linear or branched, substituted or unsubstituted alkyl, alkenyl, alkynyl groups and hybrids thereof such as (cycloalkyl)alkyl, (cycloalkenyl)alkyl or (cycloalkyl)alkenyl.

[0012] The term "lower alkyl" refers to a C_{1-4} straight or branched alkyl group. Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert-butyl.

[0013] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

[0014] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0015] The term "unsaturated", as used herein, means that a moiety has one or more units of unsaturation.

[0016] As used herein, the term "bivalent C_{1-8} (or C_{1-6}) saturated or unsaturated, straight or branched, hydrocarbon chain", refers to bivalent alkylene, alkenylene, and alkynylene chains that are straight or branched as defined herein.

[0017] The term "alkylene" refers to a bivalent alkyl group. An "alkylene chain" is a polymethylene group, i.e., $-(CH_2)_n-$, wherein n is a positive integer, preferably from 1 to 6, from 1 to 4, from 1 to 3, from 1 to 2, or from 2 to 3. A substituted alkylene chain is a polymethylene group in which one or more methylene hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0018] The term "alkenylene" refers to a bivalent alkenyl group. A substituted alkenylene chain is a polymethylene group containing at least one double bond in which one or more hydrogen atoms are replaced with a substituent. Suitable substituents include those described below for a substituted aliphatic group.

[0019] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0020] The term "halogen" means F, Cl, Br, or I.

[0021] The term "aryl" used alone or as part of a larger moiety as in "aralkyl", "aralkoxy", or "aryloxyalkyl", refers to monocyclic and bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains three to seven ring members. The term "aryl" may be used interchangeably with

the term "aryl ring". In certain embodiments of the present invention, "aryl" refers to an aromatic ring system which includes, but not limited to, phenyl, biphenyl, naphthyl, anthracyl and the like, which may bear one or more substituents. Also included within the scope of the term "aryl", as it is used herein, is a group in which an aromatic ring is fused to one or more non–aromatic rings, such as indanyl, phthalimidyl, naphthimidyl, phenanthridinyl, or tetrahydronaphthyl, and the like.

[0022] The terms "heteroaryl" and "heteroar–", used alone or as part of a larger moiety, e.g., "heteroaralkyl", or "heteroaralkoxy", refer to groups having 5 to 10 ring atoms, preferably 5, 6, or 9 ring atoms; having 6, 10, or 14 π electrons shared in a cyclic array; and having, in addition to carbon atoms, from one to five heteroatoms. The term "heteroatom" refers to nitrogen, oxygen, or sulfur, and includes any oxidized form of nitrogen or sulfur, and any quaternized form of a basic nitrogen. Heteroaryl groups include, without limitation, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, purinyl, naphthyridinyl, and pteridinyl. The terms "heteroaryl" and "heteroar–", as used herein, also include groups in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Nonlimiting examples include indolyl, isoindolyl, benzothienyl, benzofuranyl, dibenzofuranyl, indazolyl, benzimidazolyl, benzthiazolyl, quinolyl, isoquinolyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, 4*H*–quinolizinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl, phenoxazinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, and pyrido[2,3–b]–1,4–oxazin–3(4H)–one. A heteroaryl group may be mono– or bicyclic. The term "heteroaryl" may be used interchangeably with the terms "heteroaryl ring", "heteroaryl group", or "heteroaromatic", any of which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0023] As used herein, the terms "heterocycle", "heterocyclyl", "heterocyclic radical", and "heterocyclic ring" are used interchangeably and refer to a stable 5– to 7–membered monocyclic or 7–10–membered bicyclic heterocyclic moiety that is either saturated or partially unsaturated, and having, in addition to carbon atoms, one or more, preferably one to four, heteroatoms, as defined above. When used in reference to a ring atom of a heterocycle, the term "nitrogen"

includes a substituted nitrogen. As an example, in a saturated or partially unsaturated ring having 0–3 heteroatoms selected from oxygen, sulfur or nitrogen, the nitrogen may be N (as in 3,4–dihydro–2*H*–pyrrolyl), NH (as in pyrrolidinyl), or $^{+}$NR (as in *N*–substituted pyrrolidinyl).

[0024] A heterocyclic ring can be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure and any of the ring atoms can be optionally substituted. Examples of such saturated or partially unsaturated heterocyclic radicals include, without limitation, tetrahydrofuranyl, tetrahydrothiophenyl pyrrolidinyl, piperidinyl, pyrrolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, oxazolidinyl, piperazinyl, dioxanyl, dioxolanyl, diazepinyl, oxazepinyl, thiazepinyl, morpholinyl, and quinuclidinyl. The terms "heterocycle", "heterocyclyl", "heterocyclyl ring", "heterocyclic group", "heterocyclic moiety", and "heterocyclic radical", are used interchangeably herein, and also include groups in which a heterocyclyl ring is fused to one or more aryl, heteroaryl, or cycloaliphatic rings, such as indolinyl, 3*H*–indolyl, chromanyl, phenanthridinyl, or tetrahydroquinolinyl, where the radical or point of attachment is on the heterocyclyl ring. A heterocyclyl group may be mono– or bicyclic. The term "heterocyclylalkyl" refers to an alkyl group substituted by a heterocyclyl, wherein the alkyl and heterocyclyl portions independently are optionally substituted.

[0025] As used herein, the term "partially unsaturated" refers to a ring moiety that includes at least one double or triple bond. The term "partially unsaturated" is intended to encompass rings having multiple sites of unsaturation, but is not intended to include aryl or heteroaryl moieties, as herein defined.

[0026] As described herein, compounds of the invention may contain "optionally substituted" moieties. In general, the term "substituted", whether preceded by the term "optionally" or not, means that one or more hydrogens of the designated moiety are replaced with a suitable substituent. Unless otherwise indicated, an "optionally substituted" group may have a suitable substituent at each substitutable position of the group, and when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position. Combinations of substituents envisioned by this invention are preferably those that result in the formation of stable or chemically feasible compounds. The term "stable", as used herein, refers to compounds that are not substantially altered when subjected to conditions to allow for their

production, detection, and, in certain embodiments, their recovery, purification, and use for one or more of the purposes disclosed herein.

[0027] Suitable monovalent substituents on a substitutable carbon atom of an "optionally substituted" group are independently halogen; $-(CH_2)_{0-4}R^\circ$; $-(CH_2)_{0-4}OR^\circ$; $-O(CH_2)_{0-4}R^\circ$, $-O-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}CH(OR^\circ)_2$; $-(CH_2)_{0-4}SR^\circ$; $-(CH_2)_{0-4}Ph$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}Ph$ which may be substituted with R°; $-CH=CHPh$, which may be substituted with R°; $-(CH_2)_{0-4}O(CH_2)_{0-1}$-pyridyl which may be substituted with R°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR^\circ$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; SiR°_3; $-(C_{1-4}$ straight or branched alkylene$)O-N(R^\circ)_2$; or $-(C_{1-4}$ straight or branched alkylene$)C(O)O-N(R^\circ)_2$, wherein each R° may be substituted as defined below and is independently hydrogen, C_{1-6} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, $-CH_2$-(5-6 membered heteroaryl ring), or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of R°, taken together with their intervening atom(s), form a 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, which may be substituted as defined below.

[0028] Suitable monovalent substituents on R° (or the ring formed by taking two independent occurrences of R° together with their intervening atoms), are independently halogen, $-(CH_2)_{0-2}R^\bullet$, $-(haloR^\bullet)$, $-(CH_2)_{0-2}OH$, $-(CH_2)_{0-2}OR^\bullet$, $-(CH_2)_{0-2}CH(OR^\bullet)_2$; $-O(haloR^\bullet)$, $-CN$, $-N_3$, $-(CH_2)_{0-2}C(O)R^\bullet$, $-(CH_2)_{0-2}C(O)OH$, $-(CH_2)_{0-2}C(O)OR^\bullet$, $-(CH_2)_{0-2}SR^\bullet$, $-(CH_2)_{0-2}SH$, $-(CH_2)_{0-2}NH_2$, $-(CH_2)_{0-2}NHR^\bullet$, $-(CH_2)_{0-2}NR^\bullet_2$, $-NO_2$, $-SiR^\bullet_3$, $-OSiR^\bullet_3$, $-C(O)SR^\bullet$, $-(C_{1-4}$ straight or branched alkylene$)C(O)OR^\bullet$, or $-SSR^\bullet$ wherein each $R^\bullet$ is

unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently selected from C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents on a saturated carbon atom of R° include =O and =S.

[0029] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O, =S, $=NNR^*_2$, $=NNHC(O)R^*$, $=NNHC(O)OR^*$, $=NNHS(O)_2R^*$, $=NR^*$, $=NOR^*$, $-O(C(R^*_2))_{2-3}O-$, or $-S(C(R^*_2))_{2-3}S-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Suitable divalent substituents that are bound to vicinal substitutable carbons of an "optionally substituted" group include: $-O(CR^*_2)_{2-3}O-$, wherein each independent occurrence of R^* is selected from hydrogen, C_{1-6} aliphatic which may be substituted as defined below, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0030] Suitable substituents on the aliphatic group of R^* include halogen, $-R^\bullet$, -(halo$R^\bullet$), -OH, $-OR^\bullet$, -O(halo$R^\bullet$), -CN, -C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0031] Suitable substituents on a substitutable nitrogen of an "optionally substituted" group include $-R^\dagger$, $-NR^\dagger_2$, $-C(O)R^\dagger$, $-C(O)OR^\dagger$, $-C(O)C(O)R^\dagger$, $-C(O)CH_2C(O)R^\dagger$, $-S(O)_2R^\dagger$, $-S(O)_2NR^\dagger_2$, $-C(S)NR^\dagger_2$, $-C(NH)NR^\dagger_2$, or $-N(R^\dagger)S(O)_2R^\dagger$; wherein each $R^\dagger$ is independently hydrogen, C_{1-6} aliphatic which may be substituted as defined below, unsubstituted –OPh, or an unsubstituted 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or, notwithstanding the definition above, two independent occurrences of $R^\dagger$, taken together with their intervening atom(s) form an unsubstituted 3–12–membered saturated, partially unsaturated, or aryl mono– or bicyclic ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0032] Suitable substituents on the aliphatic group of $R^{\dagger}$ are independently halogen, $-R^{\bullet}$, -(halo$R^{\bullet}$), –OH, $-OR^{\bullet}$, -O(halo$R^{\bullet}$), –CN, –C(O)OH, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or $-NO_2$, wherein each $R^{\bullet}$ is unsubstituted or where preceded by "halo" is substituted only with one or more halogens, and is independently C_{1-4} aliphatic, $-CH_2Ph$, $-O(CH_2)_{0-1}Ph$, or a 5–6–membered saturated, partially unsaturated, or aryl ring having 0–4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0033] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0034] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^{+}(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and

amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

[0035] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In some embodiments, the R^1 group of formula **I-a** and **I-b** comprises one or more deuterium atoms.

[0036] As used herein, the term "irreversible" or "irreversible inhibitor" refers to an inhibitor (i.e. a compound) that is able to be covalently bonded to a target protein kinase in a substantially non-reversible manner. That is, whereas a reversible inhibitor is able to bind to (but is generally unable to form a covalent bond) the target protein kinase, and therefore can become dissociated from the target protein kinase, an irreversible inhibitor will remain substantially bound to the target protein kinase once covalent bond formation has occurred. Irreversible inhibitors usually display *time dependency*, whereby the degree of inhibition increases with the time with which the inhibitor is in contact with the enzyme. Methods for identifying if a compound is acting as an irreversible inhibitor are known to one of ordinary skill in the art. Such methods include, but are not limited to, enzyme kinetic analysis of the inhibition profile of the compound with the protein kinase target, the use of mass spectrometry of the protein drug target modified in the presence of the inhibitor compound, discontinuous exposure, also known as "washout," experiments, and the use of labeling, such as radiolabelled inhibitor, to show covalent modification of the enzyme, as well as other methods known to one of skill in the art.

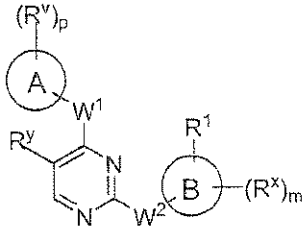
[0037] One of ordinary skill in the art will recognize that certain reactive functional groups can act as "warheads." As used herein, the term "warhead" or "warhead group" refers to a functional group present on a compound of the present invention wherein that functional group is capable of covalently binding to an amino acid residue (such as cysteine, lysine, histidine, or other residues capable of being covalently modified) present in the binding pocket of the target protein, thereby irreversibly inhibiting the protein. It will be appreciated that the –L-Y group, as defined and described herein, provides such warhead groups for covalently, and irreversibly, inhibiting the protein.

[0038] As used herein, the term "inhibitor" is defined as a compound that binds to and /or inhibits the target protein kinase with measurable affinity. In certain embodiments, an inhibitor has an IC_{50} and/or binding constant of less about 50 μM, less than about 1 μM, less than about 500 nM, less than about 100 nM, or less than about 10 nM.

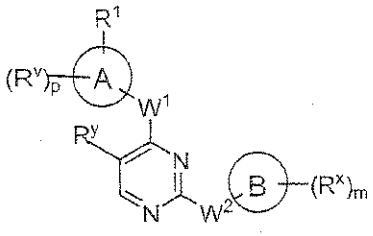
[0039] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3 activity between a sample comprising a compound of the present invention, or composition thereof, and at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, and an equivalent sample comprising at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, in the absence of said compound, or composition thereof.

3. ***Description of Exemplary Compounds***

[0040] According to one aspect, the present invention provides a compound of formula **I-a** or **I-b**,



I-a



I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms

independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^1 is –L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, –NR-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, -SO_2N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 groups independently selected from –Q-Z, oxo, NO_2, halogen, CN, or C_{1-6} aliphatic, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –NR-, -S-, -O-, -C(O)-, -SO-, or -SO_2-; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, or CN;

R^y is hydrogen, halogen, -CN, -CF_3, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or

$-C(O)N(R)_2$;

each R group is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by $-NR^2-$, $-N(R^2)C(O)-$, $-C(O)N(R^2)-$, $-N(R^2)SO_2-$, $-SO_2N(R^2)-$, $-O-$, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-S-$, $-SO-$ or $-SO_2-$;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or $-C(O)R$, or:

R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring; or

R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring;

m and p are independently 0-4; and

R^x and R^y are independently selected from -R, halogen, $-OR$, $-O(CH_2)_qOR$, $-CN$, $-NO_2$, $-SO_2R$, $-SO_2N(R)_2$, $-SOR$, $-C(O)R$, $-CO_2R$, $-C(O)N(R)_2$, $-NRC(O)R$, $-NRC(O)NR_2$, $-NRSO_2R$, or $-N(R)_2$, or:

R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, -CN, or C_{1-6} aliphatic; or

R^y and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, -CN, or C_{1-6} aliphatic.

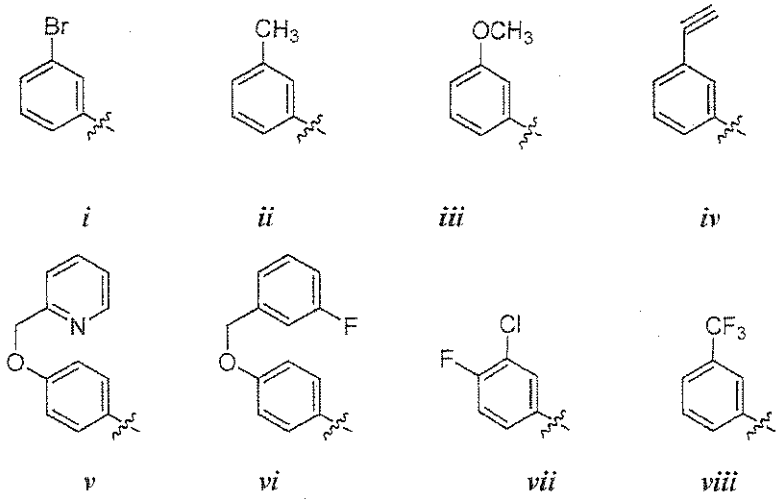
[0041] As defined generally above, Ring A is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered

saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring A is an optionally substituted phenyl group. In some embodiments, Ring A is an optionally substituted naphthyl ring or a bicyclic 8-10 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, Ring A is an optionally substituted 3-7 membered carbocyclic ring. In yet other embodiments, Ring A is an optionally substituted 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0042] In certain embodiments, Ring A is substituted as defined herein. In some embodiments, Ring A is substituted with one, two, or three groups independently selected from halogen, R°, or $-(CH_2)_{0-4}OR^{\circ}$, or $-O(CH_2)_{0-4}R^{\circ}$, wherein each R° is as defined herein. Exemplary substituents on Ring A include Br, I, Cl, methyl, $-CF_3$, $-C{\equiv}CH$, $-OCH_2$phenyl, $-OCH_2$(fluorophenyl), or $-OCH_2$pyridyl.

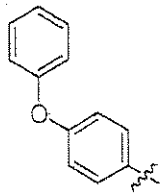
[0043] Exemplary Ring A groups are set forth in Table 1.

Table 1. Exemplary Ring A Groups

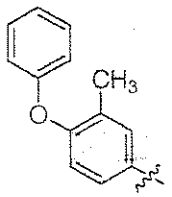


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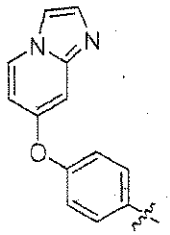
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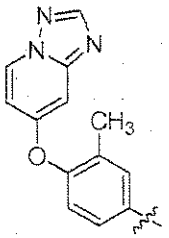
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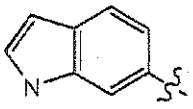
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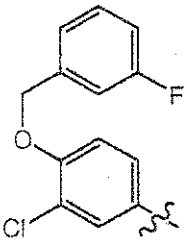
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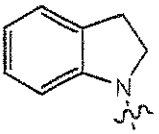
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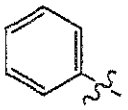
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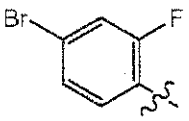
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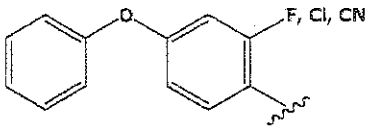
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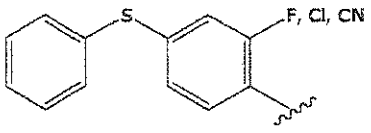
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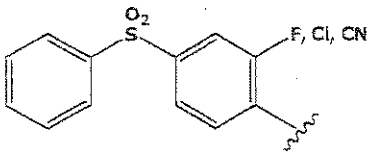
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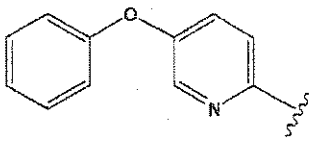
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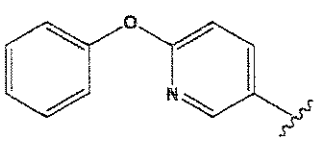
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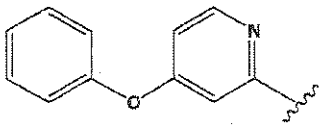
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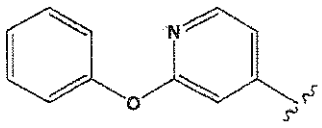
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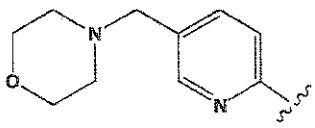
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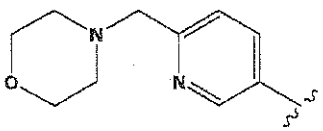
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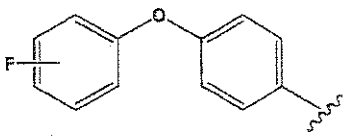
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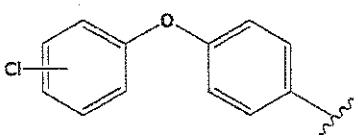
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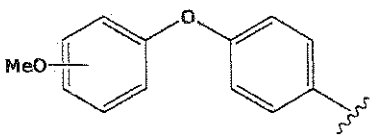
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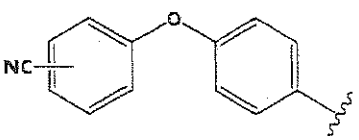
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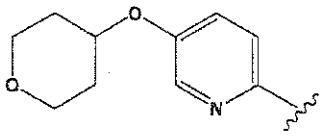
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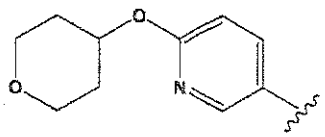
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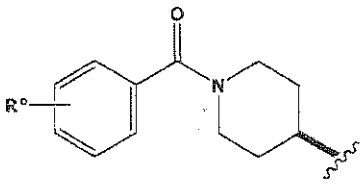
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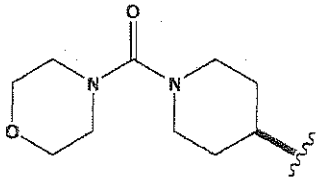
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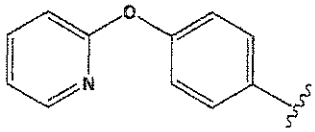
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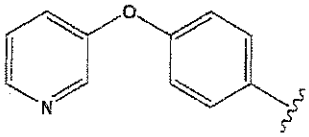
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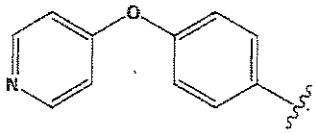
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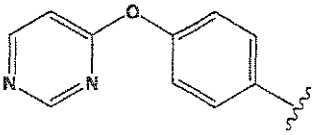
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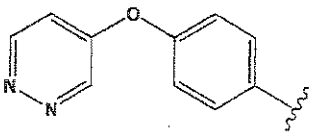
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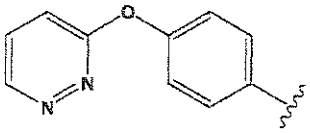
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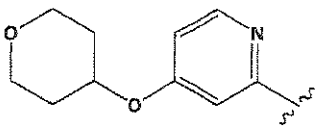
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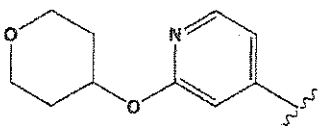
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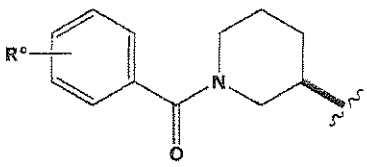
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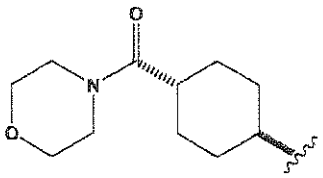
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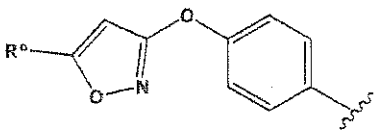
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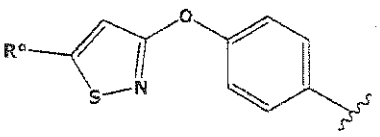
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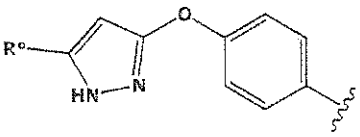
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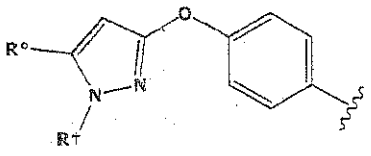
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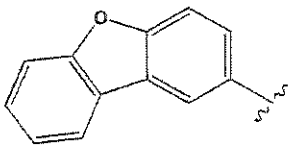
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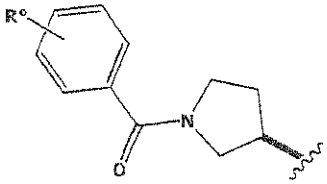
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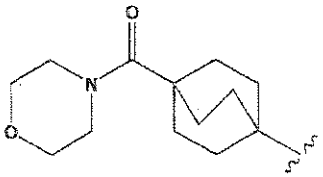
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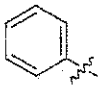
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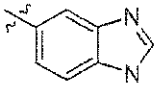
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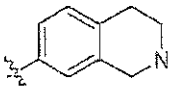
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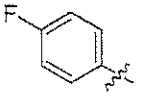
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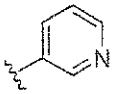
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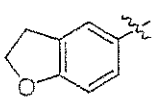
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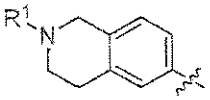
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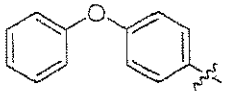
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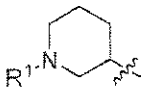
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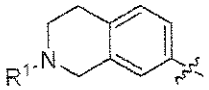
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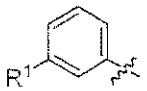
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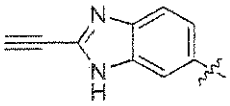
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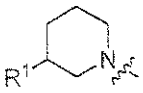
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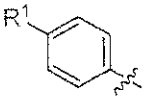
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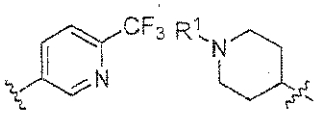
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lxv

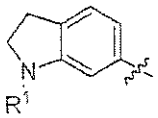


lxvi

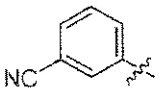


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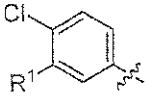
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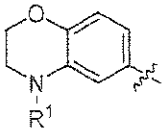
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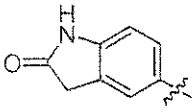
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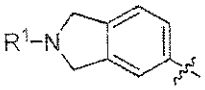
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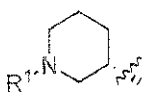
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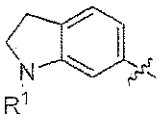
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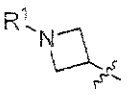
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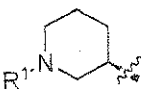
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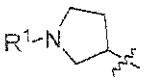
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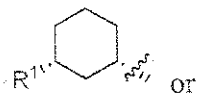
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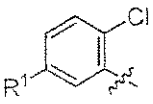
lxxviii



lxxix



or *lxxx*



lxxxi,

wherein each R°, R†, and R^1 is as defined above and described in classes and subclasses herein.

[0044] In certain embodiments, Ring A is selected from *i*, *ii*, *iv*, *v*, *vi*, *vii*, *ix*, *xiv*, *xvi*, *lii*, *lxiii*, *lxxi*, *lxxiv*, *lxxvi*, *lxxviii*, and *lxxxi*.

[0045] As defined generally above, Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, an 8-10 membered bicyclic saturated, partially unsaturated or aryl ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain embodiments, Ring B is an optionally substituted phenyl group. In some embodiments, Ring B is an optionally substituted naphthyl ring or a bicyclic 8-10 membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. In certain other embodiments, Ring B is an optionally substituted 3-7 membered carbocyclic ring. In yet other embodiments, Ring B is an optionally substituted 4-7 membered heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

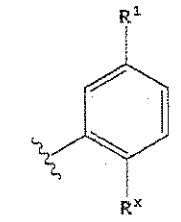
[0046] In some embodiments, Ring B is phenyl. In some embodiments, Ring B is a 6-membered heteroaryl ring having 1-3 nitrogens. In some embodiments, Ring B is a 5-membered heteroaryl ring having 1 or 2 or 3 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0047] In some embodiments, Ring B is a 5-6 membered saturated heterocyclic ring having 1 nitrogen. In some embodiments, Ring B is a 9-10 membered bicyclic partially saturated heteroaryl ring having 1-3 nitrogens. In some embodiments, Ring B is a 9-10 membered bicyclic partially saturated heteroaryl ring having 1 nitrogen. In some embodiments, Ring B is a 9-10 membered bicyclic partially saturated heteroaryl ring having 1 nitrogen and 1 oxygen.

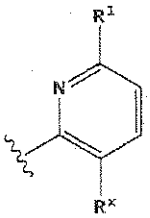
[0048] In some embodiments, Ring B is an optionally substituted group selected from phenyl, pyridyl, pyrazinyl, pyrimidinyl, imidazolyl, pyrrolidinyl, piperdinyl, indolinyl, indazolyl, and isoindolinyl.

[0049] Exemplary Ring B groups are set forth in Table 4.

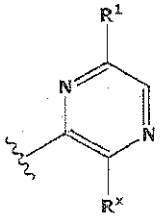
Table 2. Ring B Groups



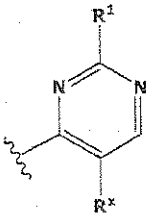
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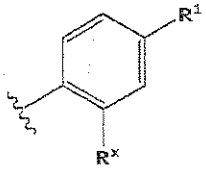
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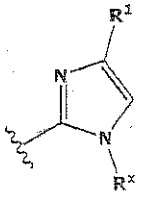
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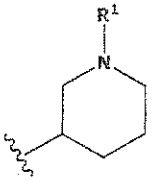
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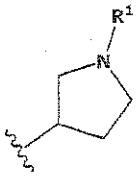
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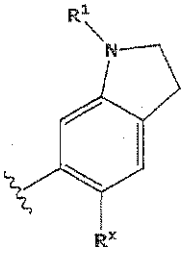
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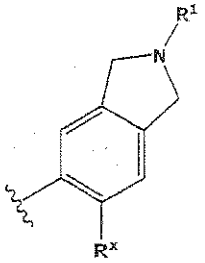
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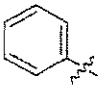
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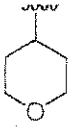
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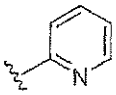
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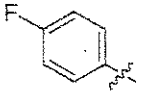
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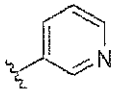
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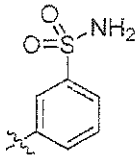
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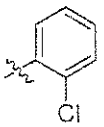
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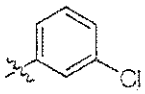
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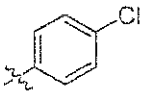
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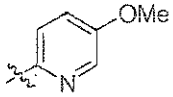
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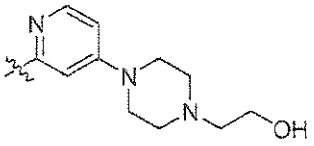
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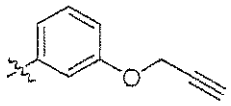
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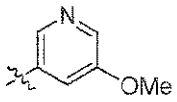
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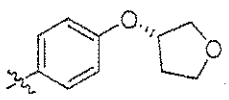
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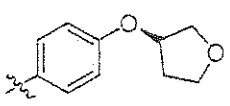
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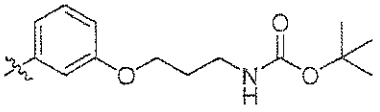
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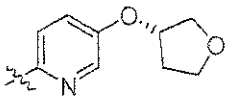
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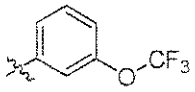
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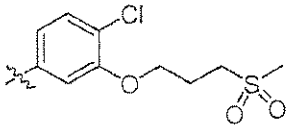
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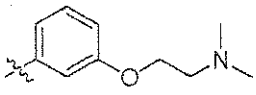
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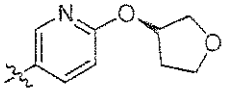
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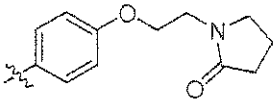
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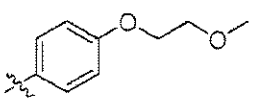
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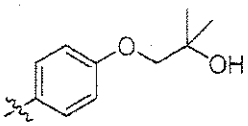
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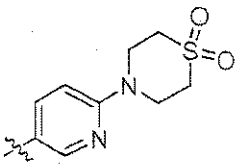
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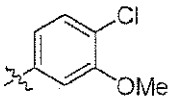
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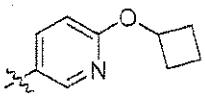
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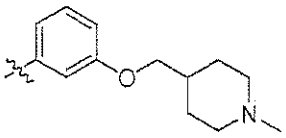
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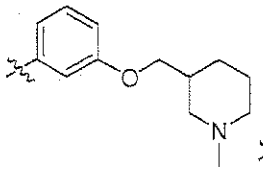
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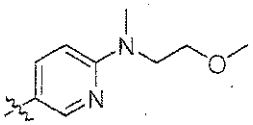
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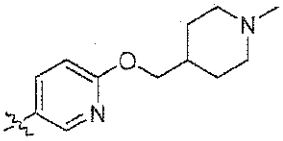
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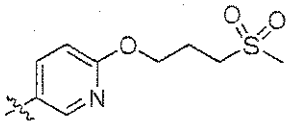
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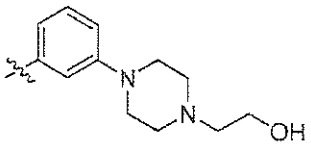
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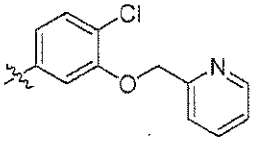
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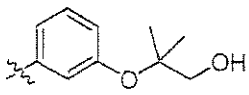
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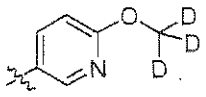
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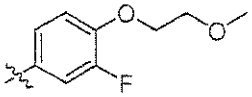
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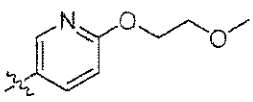
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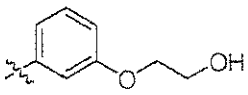
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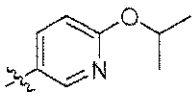
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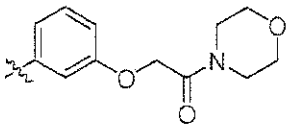
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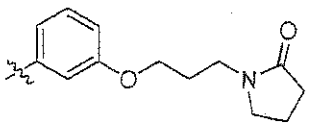
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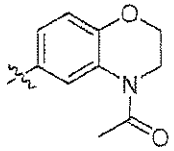
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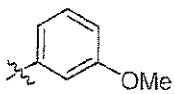
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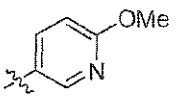
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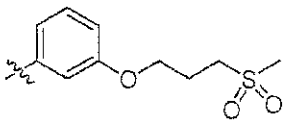
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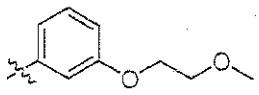
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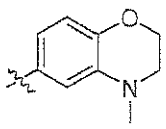
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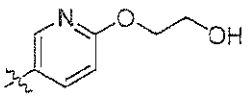
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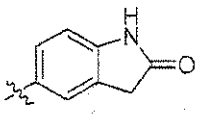
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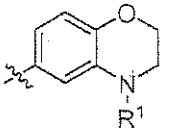
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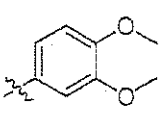
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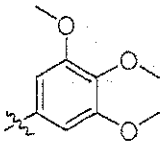
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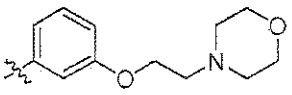
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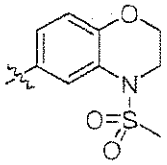
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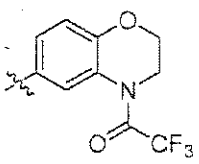
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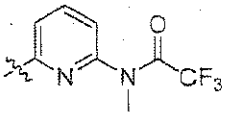
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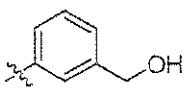
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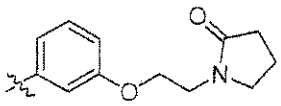
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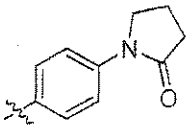
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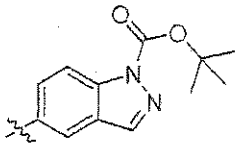
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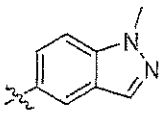
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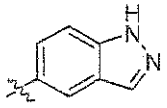
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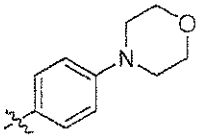
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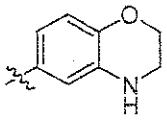
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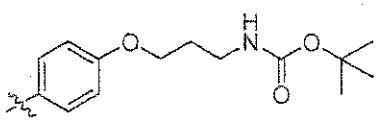
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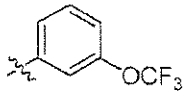
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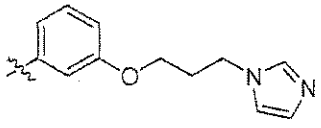
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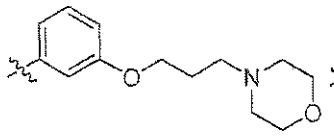
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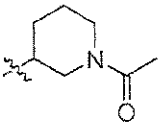
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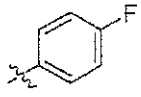
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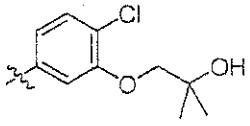
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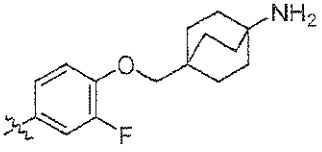
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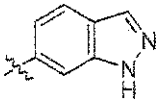
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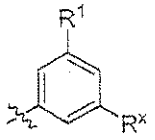
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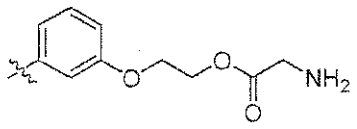
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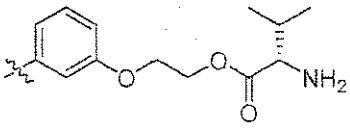
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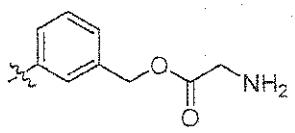
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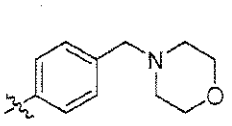
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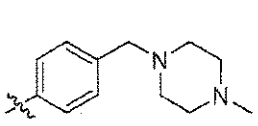
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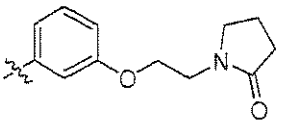
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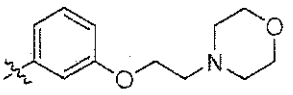
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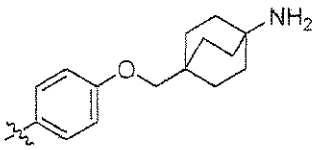
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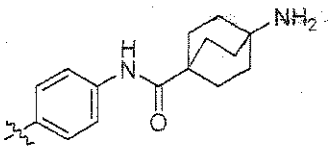
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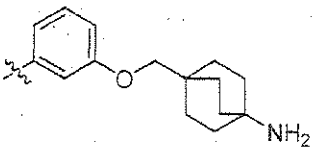
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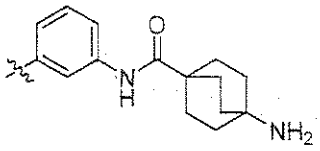
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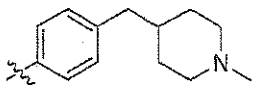
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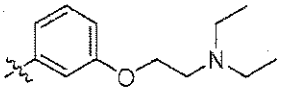
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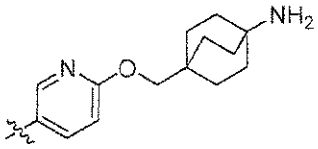
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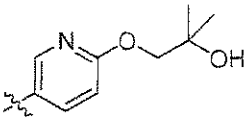
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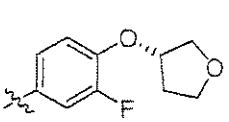
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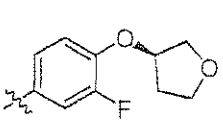
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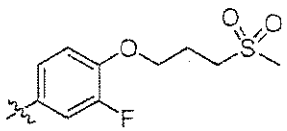
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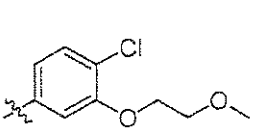
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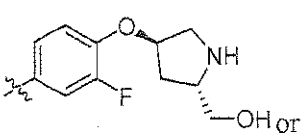
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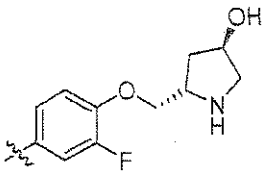
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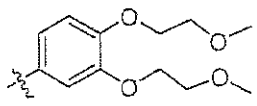
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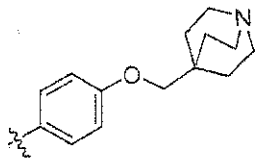
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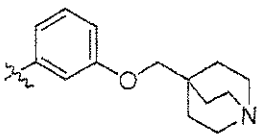
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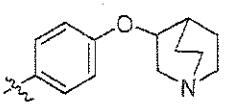
cviii



cix



cx



cxi,

wherein each R^1 and R^x is as defined above and described in classes and subclasses herein.

[0050] In certain embodiments, Ring B is selected from *i*, *ii*, *iii*, *iv*, *v*, *ix*, *x*, *xi*, *xiii*, *xvi*, *xvii*, *xix*, *xx*, *xxv*, *xxvi*, *xxxii*, *xxxiv*, *xxxv*, *xxxviii*, *xlii*, *xlvi*, *xlviii*, *l*, *lviii*, *lxiv*, *lxxviii*, *lxxxiii*, *lxxxvi*, *xciv*, *c*, *ci*, *cii*, *ciii*, *civ*, and *cv*.

[0051] In some embodiments, the m moiety of formula I is 1, 2, 3 or 4. In some embodiments, m is 1. In other embodiments, m is 0.

[0052] In some embodiments, the p moiety of formula I is 1, 2, 3 or 4. In some embodiments, p is 1. In other embodiments, p is 0.

[0053] As defined generally above, each R^x group of formula I is independently selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)NR_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1-4, or R^x and R^1 when concurrently present on Ring B are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic.

[0054] In some embodiments, each instance of R^x is independently selected from –R, -OR, $-O(CH_2)_qOR$, or halogen. In certain embodiments, R^x is lower alkyl, lower alkoxy, lower alkoxyalkoxy, or halogen. Exemplary R^x groups include methyl, methoxy, methoxyethoxy and fluoro. In some embodiments, R^x is hydrogen.

[0055] As defined generally above, each R^v group of formula I is independently selected from -R, halogen, –OR, $-O(CH_2)_qOR$, –CN, $–NO_2$, $-SO_2R$, $-SO_2N(R)_2$, -SOR, -C(O)R, $-CO_2R$, $–C(O)N(R)_2$, -NRC(O)R, $-NRC(O)NR_2$, $-NRSO_2R$, or $-N(R)_2$, wherein q is 1-4, or R^v and R^1 when concurrently present on Ring A are taken together with their intervening atoms to form a 5-7 membered saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with a warhead group and 0-3 groups independently selected from oxo, halogen, CN, or C_{1-6} aliphatic.

[0056] In some embodiments, each instance of R^v is independently selected from –R, -OR, $-O(CH_2)_qOR$, or halogen. In certain embodiments, R^v is lower alkyl, lower alkoxy, lower alkoxyalkoxy, or halogen. Exemplary R^v groups include methyl, methoxy, trifluoromethyl, methoxyethoxy, and chloro. In some embodiments, R^v is hydrogen.

[0057] In some embodiments, the q moiety is 1, 2, 3, or 4. In certain embodiments, q is 1. In certain other embodiments, q is 2.

[0058] As defined generally above, R^y is hydrogen, halogen, -CN, $-CF_3$, C_{1-4} aliphatic, C_{1-4} haloaliphatic, -OR, -C(O)R, or $–C(O)N(R)_2$, where R is as defined above and described herein. In certain embodiments, R^y is hydrogen, halogen, -CN, $-CF_3$, lower alkyl or lower haloalkyl, -

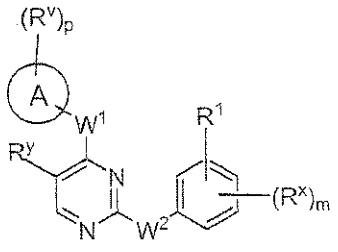
C≡CR and cyclopropyl. In other embodiments, R^y is -OR, -C(O)R, or $-C(O)N(R)_2$. In certain embodiments, R^y is $-OCH_3$. In certain other embodiments, R^y is $-C(O)CH_3$. In yet other embodiments, R^y is –C(O)NHR. In some embodiments, R^y is hydrogen. In certain embodiments, R^y is fluorine. In certain other embodiments, R^y is methyl.

[0059] As generally defined above, W^1 and W^2 are each independently a covalent bond or a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 or W^2 is optionally replaced by $-NR^2-$, $-N(R^2)C(O)-$, $-C(O)N(R^2)-$, $-N(R^2)SO_2-$, $-SO_2N(R^2)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or $-SO_2-$. In certain embodiments, W^1 and W^2 are the same. In some embodiments, W^1 and W^2 are different.

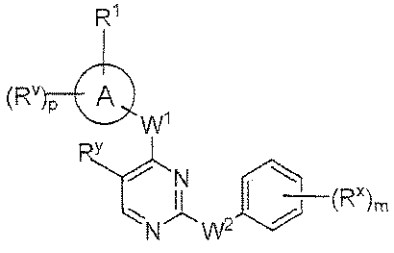
[0060] In some embodiments, W^1 is a covalent bond. In certain embodiments, W^1 is a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^1 is optionally replaced by $-NR^2-$, $-N(R^2)C(O)-$, $-C(O)N(R^2)-$, $-N(R^2)SO_2-$, $-SO_2N(R^2)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or $-SO_2-$. In certain embodiments, W^1 is –C(=O), $-NR^2-$, -S-, or -O-. In some embodiments, W^1 is $-NR^2-$. In other embodiments, W^1 is –O-. In certain embodiments, W^1 is –NH-, -S-, or –O–. In some embodiments, W^1 is $-CH_2O-$, $-CH_2S-$, or $-CH_2NH-$. In some aspects, W^1 is $-OCH_2-$, $-SCH_2-$, $-NHCH_2-$, or $-CH_2CH_2-$.

[0061] In certain embodiments, W^2 is a covalent bond. In some embodiments, W^2 is a bivalent C_{1-3} alkylene chain wherein one methylene unit of W^2 is optionally replaced by $-NR^2-$, $-N(R^2)C(O)-$, $-C(O)N(R^2)-$, $-N(R^2)SO_2-$, $-SO_2N(R^2)-$, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or $-SO_2-$. In certain embodiments, W^2 is –C(=O), $-NR^2-$, -S-, or -O-. In some embodiments, W^2 is $-NR^2-$. In other embodiments, W^2 is –O-. In certain embodiments, W^2 is –NH-, -S-, or –O–. In some embodiments, W^2 is $-CH_2O-$, $-CH_2S-$, or $-CH_2NH-$. In some aspects, W^2 is $-OCH_2-$, $-SCH_2-$, $-NHCH_2-$, or $-CH_2CH_2-$.

[0062] In some embodiments, Ring B is phenyl, thus forming a compound of formula **II-a** or **II-b**:



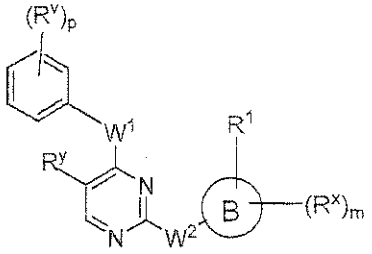
II-a



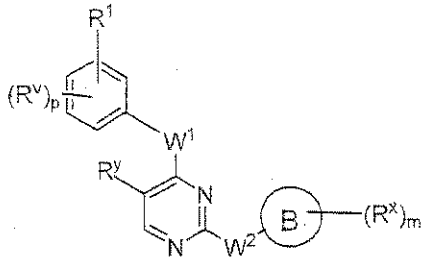
II-b

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, m, p, R^x, R^y, R^v,W^1, W^2, and R^1 is as defined above and described in classes and subclasses above and herein.

[0063] In certain embodiments, Ring A is phenyl, thus forming a compound of formula **III-a** or **III-b**:



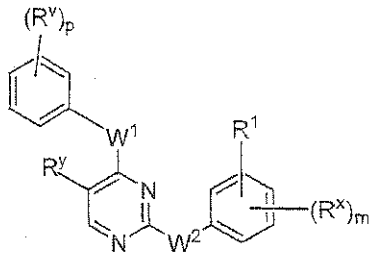
III-a



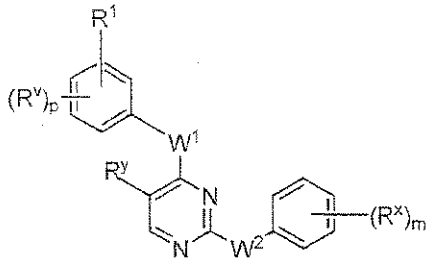
III-b

or a pharmaceutically acceptable salt thereof, wherein each of Ring B, m, p, R^x, R^y, R^v,W^1, W^2, and R^1 is as defined above and described in classes and subclasses above and herein.

[0064] In certain embodiments, Ring A is phenyl and Ring B is phenyl, thus forming a compound of formula **IV-a** or **IV-b**:



IV-a

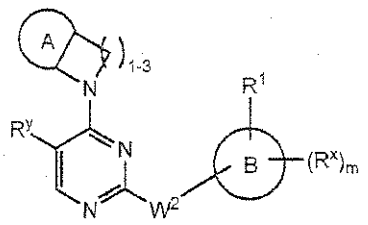


IV-b

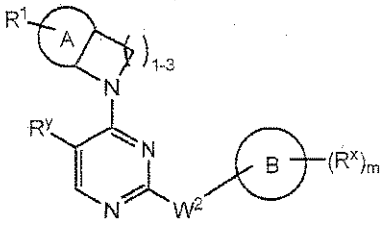
or a pharmaceutically acceptable salt thereof, wherein each of m, p, R^x, R^y, R^v,W^1, W^2, and R^1 is as defined above and described in classes and subclasses above and herein.

[0065] As defined generally above, each R^2 is independently hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R, or R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-6 membered partially unsaturated or aromatic fused ring, or R^2 and R^y are taken together with their intervening atoms to form a 4-6 membered saturated, partially unsaturated, or aromatic fused ring. According to one aspect, R^2 is hydrogen. According to another aspect, R^2 is –C(O)R, wherein R is an optionally substituted C_{1-6} aliphatic group.

[0066] According to some aspects, R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring, thus forming a compound of formula **I-a-*i*** or **I-b-*i***:



I-a-*i*

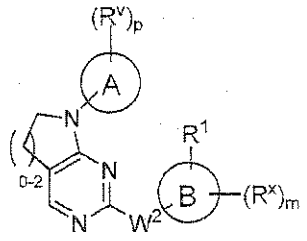


I-b-*i*

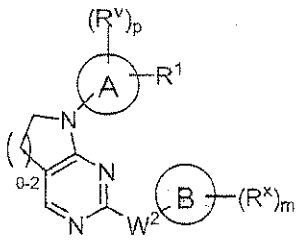
or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^x, and m are as defined above and described in classes and subclasses above and herein.

[0067] Similar to the formation of compounds of formulae **I-a-*i*** and **I-b-*i*** above, it will be understood by one skilled in the art that compounds of formulae **II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, and **IV-b**, will form corresponding compounds **II-a-*i***, **II-b-*i***, **III-a-*i***, **III-b-*i***, **IV-a-*i***, and **IV-b-*i*** when R^2 and a substituent on Ring A are taken together with their intervening atoms to form a 4-7 membered saturated or partially unsaturated ring.

[0068] According to some aspects, R^2 and R^y are taken together with their intervening atoms to form a 4-7 partially unsaturated ring, thus forming a compound of formula **I-a-*ii*** or **I-b-*ii***:



I-a-*ii*



I-b-*ii*

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, R^1, R^x, and m are as defined above and described in classes and subclasses above and herein.

[0069] Similar to the formation of compounds of formulae **I-a-*ii*** and **I-b-*ii*** above, it will be understood by one skilled in the art that compounds of formulae **II-a**, **II-b**, **III-a**, **III-b**, **IV-a**, and **IV-b**, will form corresponding compounds **II-a-*ii***, **II-b-*ii***, **III-a-*ii***, **III-b-*ii***, **IV-a-*ii***, and **IV-b-*ii*** when R^2 and R^y are taken together with their intervening atoms to form a 4-7 membered partially unsaturated ring.

[0070] As defined generally above, the R^1 group of formulae I and II is –L-Y, wherein:

L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by cyclopropylene, –NR-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, -SO_2N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, -N=N-, or -C(=N_2)-;

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with 1-4 R^e groups; and

each R^e is independently selected from –Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group, or a C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein:

Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and

Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[0071] In certain embodiments, L is a covalent bond.

[0072] In certain embodiments, L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain. In certain embodiments, L is –CH_2-.

[0073] In certain embodiments, L is a covalent bond, –CH_2-, -NH-, -CH_2NH-, -NHCH_2-, –NHC(O)-, -NHC(O)CH_2OC(O)-, -CH_2NHC(O)-, -NHSO_2-, -NHSO_2CH_2-, -NHC(O)CH_2OC(O)-, or -SO_2NH-.

[0074] In some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two additional methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-.

[0075] In certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-,

and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

[0076] In some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

[0077] As described above, in certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond. One of ordinary skill in the art will recognize that such a double bond may exist within the hydrocarbon chain backbone or may be "exo" to the backbone chain and thus forming an alkylidene group. By way of example, such an L group having an alkylidene branched chain includes $-CH_2C(=CH_2)CH_2-$. Thus, in some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond. Exemplary L groups include $-NHC(O)C(=CH_2)CH_2-$.

[0078] In certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-. In certain embodiments, L is $-C(O)CH=CH(CH_3)-$, $-C(O)CH=CHCH_2NH(CH_3)-$, $-C(O)CH=CH(CH_3)-$, –C(O)CH=CH-, $-CH_2C(O)CH=CH-$, $-CH_2C(O)CH=CH(CH_3)-$, $-CH_2CH_2C(O)CH=CH-$, $-CH_2CH_2C(O)CH=CHCH_2-$, $-CH_2CH_2C(O)CH=CHCH_2NH(CH_3)-$, or $-CH_2CH_2C(O)CH=CH(CH_3)-$, or $–CH(CH_3)OC(O)CH=CH-$.

[0079] In certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -OC(O)-.

[0080] In some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -NRC(O)-, -C(O)NR-, $-N(R)SO_2-$, $-SO_2N(R)-$, –S-, -S(O)-, $-SO_2-$, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-. In some embodiments, L is $–CH_2OC(O)CH=CHCH_2–$, $-CH_2-OC(O)CH=CH–$, or $-CH(CH=CH_2)OC(O)CH=CH–$.

[0081] In certain embodiments, L is $-NRC(O)CH=CH-$, $-NRC(O)CH=CHCH_2N(CH_3)-$, $-NRC(O)CH=CHCH_2O-$, $-CH_2NRC(O)CH=CH-$, $-NRSO_2CH=CH-$, $-NRSO_2CH=CHCH_2-$, $-NRC(O)(C=N_2)C(O)-$, $-NRC(O)CH=CHCH_2N(CH_3)-$, $-NRSO_2CH=CH-$, $-NRSO_2CH=CHCH_2-$,

-NRC(O)CH=CHCH$_2$O-, -NRC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NRC(O)-, -CH$_2$NRC(O)CH=CH-, -CH$_2$CH$_2$NRC(O)-, or -CH$_2$NRC(O)cyclopropylene-, wherein each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[0082] In certain embodiments, L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHC(O)CH=CHCH$_2$O-, -CH$_2$NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)(C=N$_2$)C(O)-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)CH=CHCH$_2$O-, -NHC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NHC(O)-, -CH$_2$NHC(O)CH=CH-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-.

[0083] In some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one triple bond. In certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one triple bond and one or two additional methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, –S-, -S(O)-, -SO$_2$-, -C(=S)-, -C(=NR)-, –O-, -N(R)-, or -C(O)-. In some embodiments, L has at least one triple bond and at least one methylene unit of L is replaced by -N(R)-, -N(R)C(O)-, -C(O)-, -C(O)O-, or –OC(O)-, or -O-.

[0084] Exemplary L groups include -C≡C-, -C≡CCH$_2$N(isopropyl)-, -NHC(O)C≡CCH$_2$CH$_2$-, -CH$_2$-C≡C-CH$_2$-, -C≡CCH$_2$O-, -CH$_2$C(O)C≡C-, -C(O)C≡C-, or -CH$_2$OC(=O)C≡C-.

[0085] In certain embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are independently replaced by –C(O)–, -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, or -SO$_2$N(R)-. Exemplary L groups include -NHC(O)-cyclopropylene-SO$_2$- and -NHC(O)-cyclopropylene-.

[0086] As defined generally above, Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, and wherein said ring is substituted with at 1-4 R^e groups, each R^e is independently selected from –Q-Z, oxo, NO$_2$, halogen, CN, a suitable leaving group, or C_{1-6} aliphatic, wherein Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO$_2$-, -N(R)C(O)-, -

C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and, Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

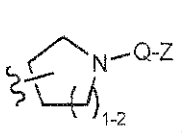
[0087] In certain embodiments, Y is hydrogen.

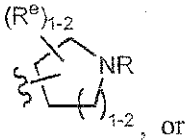
[0088] In certain embodiments, Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN. In some embodiments, Y is C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN. In other embodiments, Y is C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN. In some embodiments, Y is C_{2-6} alkenyl. In other embodiments, Y is C_{2-4} alkynyl.

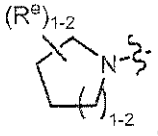
[0089] In other embodiments, Y is C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN. Such Y groups include –CH_2F, -CH_2Cl, –CH_2CN, and -CH_2NO_2.

[0090] In certain embodiments, Y is a saturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Y is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

[0091] In some embodiments, Y is a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein. Exemplary such rings are epoxide and oxetane rings, wherein each ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein.

[0092] In other embodiments, Y is a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. Such rings include piperidine and pyrrolidine, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is 

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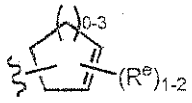
, or 

, wherein each R, Q, Z, and R^e is as defined above and described herein.

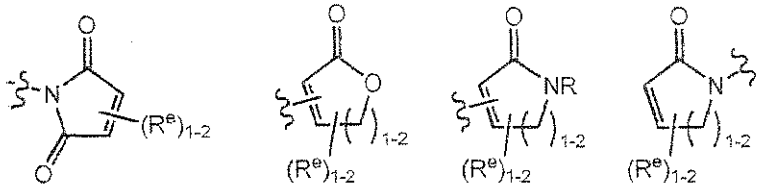
[0093] In some embodiments, Y is a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein..

In certain embodiments, Y is , wherein R^e is as defined above and described herein. In certain embodiments, Y is cyclopropyl optionally substituted with halogen, CN or NO_2.

[0094] In certain embodiments, Y is a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

[0095] In some embodiments, Y is a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In some embodiments, Y is cyclopropenyl, cyclobutenyl, cyclopentenyl, or cyclohexenyl wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is , wherein each R^e is as defined above and described herein.

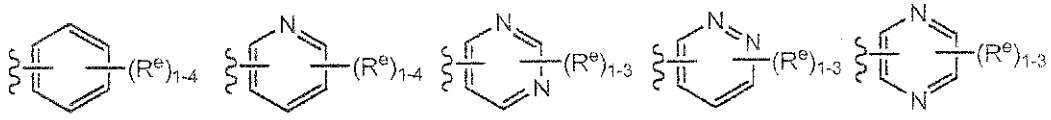
[0096] In certain embodiments, Y is a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is selected from:



wherein each R and R^e is as defined above and described herein.

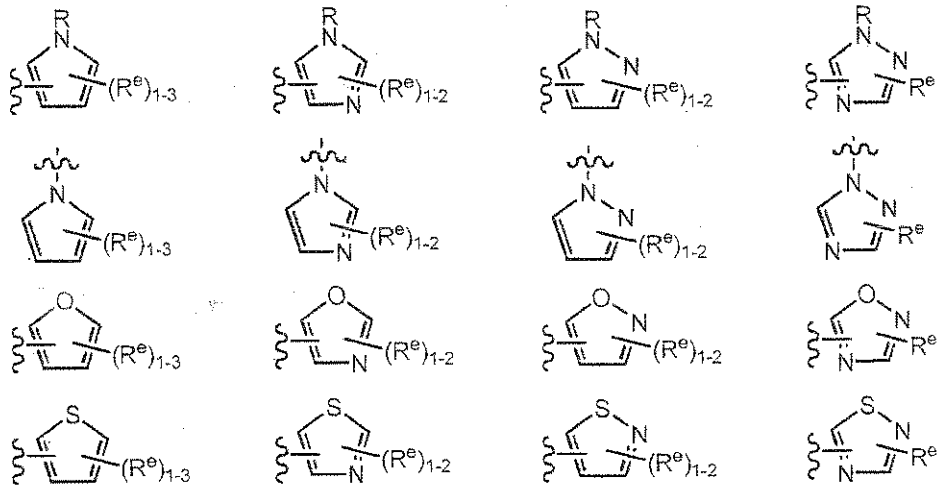
[0097] In certain embodiments, Y is a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein. In certain embodiments, Y is phenyl, pyridyl, or pyrimidinyl, wherein each ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

[0098] In some embodiments, Y is selected from:



wherein each R^e is as defined above and described herein.

[0099] In other embodiments, Y is a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein. In some embodiments, Y is a 5 membered partially unsaturated or aryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein. Exemplary such rings are isoxazolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyrrolyl, furanyl, thienyl, triazole, thiadiazole, and oxadiazole, wherein each ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein. In certain embodiments, Y is selected from:



wherein each R and R^e is as defined above and described herein.

[00100] In certain embodiments, Y is an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein. According to another aspect, Y is a 9-10 membered bicyclic, partially unsaturated, or aryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein. Exemplary such bicyclic rings include 2,3-dihydrobenzo[d]isothiazole, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein.

[00101] As defined generally above, each R^e group is independently selected from –Q-Z, oxo, NO_2, halogen, CN, a suitable leaving group, or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, wherein Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and Z is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[00102] In certain embodiments, R^e is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN. In other embodiments, R^e is oxo, NO_2, halogen, or CN.

[00103] In some embodiments, R^e is -Q-Z, wherein Q is a covalent bond and Z is hydrogen (i.e., R^e is hydrogen). In other embodiments, R^e is –Q-Z, wherein Q is a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by -NR-, -NRC(O)-, -C(O)NR-, -S-, -O-, -C(O)-, -SO-, or -SO_2-. In other embodiments, Q is a bivalent C_{2-6} straight or branched, hydrocarbon chain having at least one double bond, wherein one or two methylene units of Q are optionally and independently replaced by –NR-, -NRC(O)-, -C(O)NR-, -S-, -O-, -C(O)-, -SO-, or -SO_2-. In certain embodiments, the Z moiety of the R^e group is hydrogen. In some embodiments, -Q-Z is -NHC(O)CH=CH_2 or -C(O)CH=CH_2.

[00104] In certain embodiments, each R^e is independently selected from from oxo, NO_2, CN, fluoro, chloro, -NHC(O)CH=CH_2, -C(O)CH=CH_2, -CH_2CH=CH_2, -C≡CH, -C(O)OCH_2Cl, -C(O)OCH_2F, -C(O)OCH_2CN, -C(O)CH_2Cl, -C(O)CH_2F, -C(O)CH_2CN, or –CH_2C(O)CH_3.

[00105] In certain embodiments, R^e is a suitable leaving group, ie a group that is subject to nucleophilic displacement. A "suitable leaving" is a chemical group that is readily displaced by a desired incoming chemical moiety such as the thiol moiety of a cysteine of interest. Suitable leaving groups are well known in the art, e.g., see, "Advanced Organic Chemistry," Jerry March, 5th Ed., pp. 351-357, John Wiley and Sons, N.Y. Such leaving groups include, but are not limited to, halogen, alkoxy, sulphonyloxy, optionally substituted alkylsulphonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and diazonium moieties. Examples of suitable leaving groups include chloro, iodo, bromo, fluoro, acetoxy, methanesulfonyloxy (mesyloxy), tosyloxy, triflyloxy, nitro-phenylsulfonyloxy (nosyloxy), and bromo-phenylsulfonyloxy (brosyloxy).

[00106] In certain embodiments, the following embodiments and combinations of –L-Y apply:

(a) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two additional methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)- ; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(b) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(c) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -C(O)-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(d) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by –C(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(e) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and at least one methylene unit of L is replaced by -OC(O)-; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(f) L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O-, -CH_2NRC(O)CH=CH-, -NRSO_2CH=CH-, -NRSO_2CH=CHCH_2-, -NRC(O)(C=N_2)-, -NRC(O)(C=N_2)C(O)-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRSO_2CH=CH-, -NRSO_2CH=CHCH_2-, -NRC(O)CH=CHCH_2O-, -NRC(O)C(=CH_2)CH_2-, -CH_2NRC(O)-, -CH_2NRC(O)CH=CH-, -CH_2CH_2NRC(O)-, or -CH_2NRC(O)cyclopropylene-; wherein R is H or optionally substituted C_{1-6} aliphatic; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

(g) L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHC(O)CH=CHCH$_2$O-, -CH$_2$NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)(C=N$_2$)-, -NHC(O)(C=N$_2$)C(O)-, -NHC(O)CH=CHCH$_2$N(CH$_3$)-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH$_2$-, -NHC(O)CH=CHCH$_2$O-, -NHC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NHC(O)-, -CH$_2$NHC(O)CH=CH-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-; and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(h) L is a bivalent C$_{2-8}$ straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, -SO$_2$N(R)-, –S-, -S(O)-, -SO$_2$-, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(i) L is a bivalent C$_{2-8}$ straight or branched, hydrocarbon chain wherein L has at least one triple bond and one or two additional methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, -SO$_2$N(R)-, –S-, -S(O)-, -SO$_2$-, -OC(O)-, or –C(O)O-, and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(j) L is -C≡C-, -C≡CCH$_2$N(isopropyl)-, -NHC(O)C≡CCH$_2$CH$_2$-, -CH$_2$-C≡C-CH$_2$-, -C≡CCH$_2$O-, -CH$_2$C(O)C≡C-, -C(O)C≡C-, or -CH$_2$OC(=O)C≡C-; and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(k) L is a bivalent C$_{2-8}$ straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO$_2$-, -SO$_2$N(R)-, –S-, -S(O)-, -SO$_2$-, -OC(O)-, or –C(O)O-; and Y is hydrogen or C$_{1-6}$ aliphatic optionally substituted with oxo, halogen, NO$_2$, or CN; or

(l) L is a covalent bond and Y is selected from:

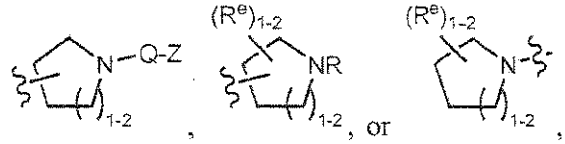
(*i*) C$_{1-6}$ alkyl substituted with oxo, halogen, NO$_2$, or CN;

(*ii*) C$_{2-6}$ alkenyl optionally substituted with oxo, halogen, NO$_2$, or CN; or

(*iii*) C$_{2-6}$ alkynyl optionally substituted with oxo, halogen, NO$_2$, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

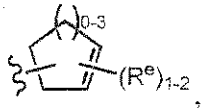
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*vi*) , wherein each R, Q, Z, and R^e is as defined above and described herein; or

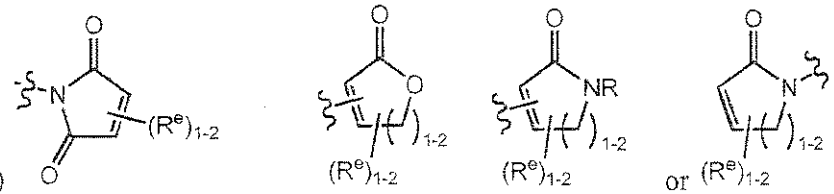
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

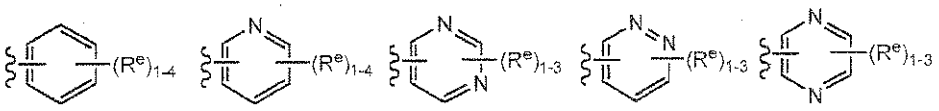
(*x*) , wherein each R^e is as defined above and described herein; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*xii*) 

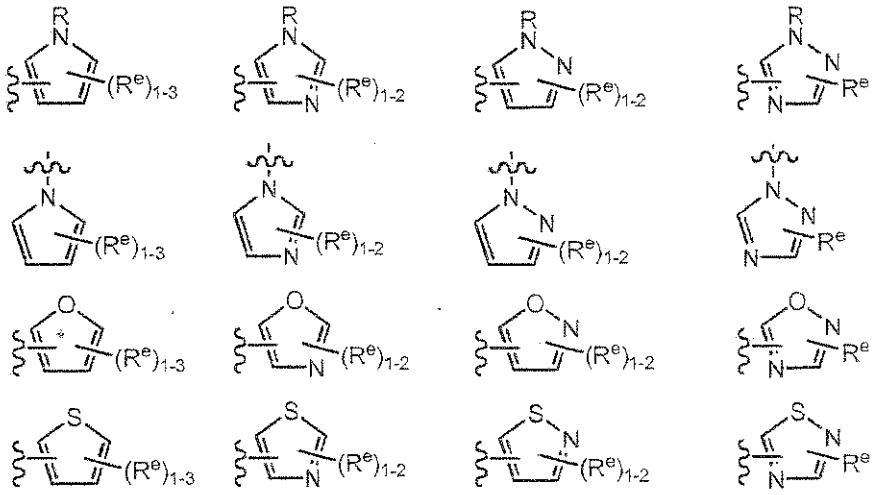
wherein each R and R^e is as defined above and described herein; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xiv*) 

wherein each R^e is as defined above and described herein; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xvi*) 

wherein each R and R^e is as defined above and described herein; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(m) L is –C(O)- and Y is selected from:

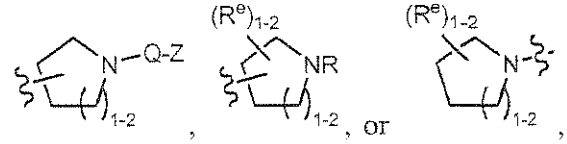
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

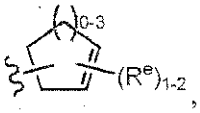
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*vi*) , wherein each R, Q, Z, and R^e is as defined above and described herein; or

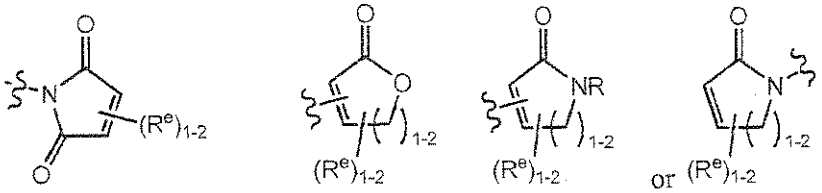
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

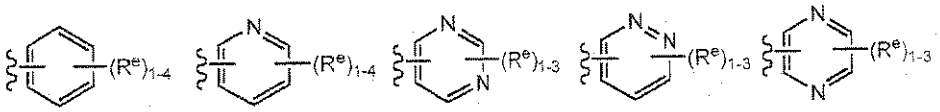
(*x*) , wherein each R^e is as defined above and described herein; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*xii*) 

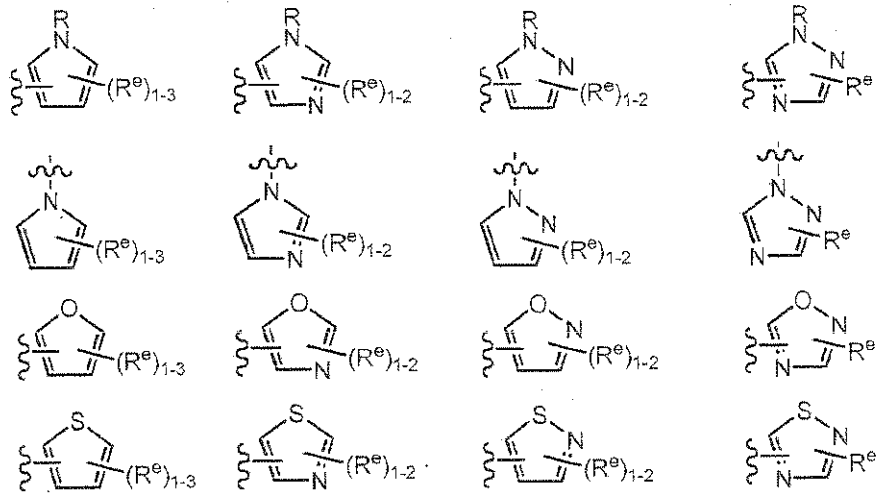
wherein each R and R^e is as defined above and described herein; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xiv*) 

wherein each R^e is as defined above and described herein; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xvi*) 

wherein each R and R^e is as defined above and described herein; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(n) L is –N(R)C(O)- and Y is selected from:

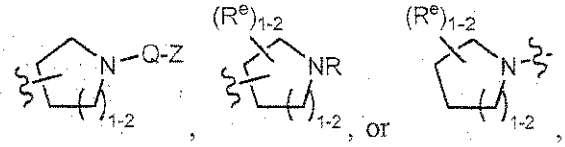
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

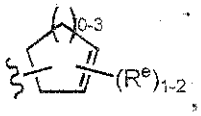
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*vi*)  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

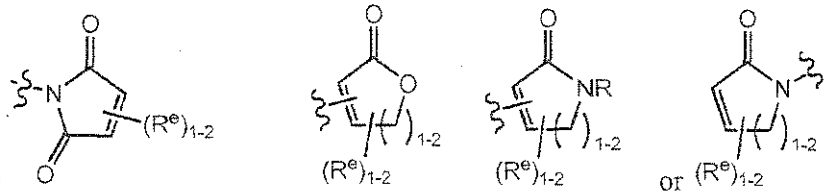
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

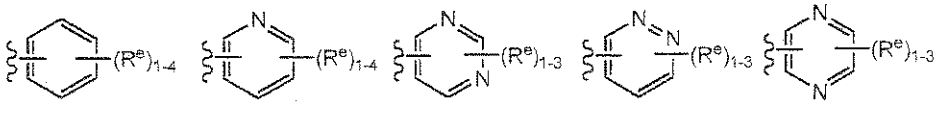
(*x*)  , wherein each R^e is as defined above and described herein; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*xii*) 

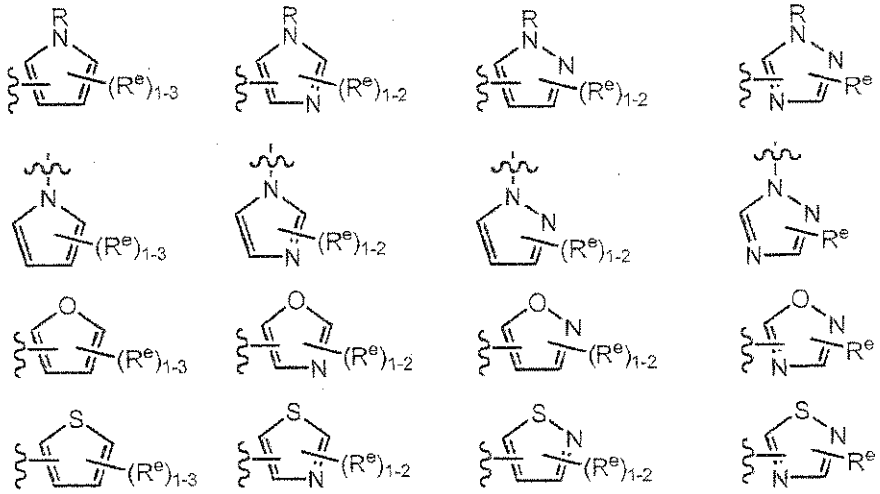
wherein each R and R^e is as defined above and described herein; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xiv*) 

wherein each R^e is as defined above and described herein; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xvi*) 

wherein each R and R^e is as defined above and described herein; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(o) L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is selected from:

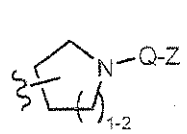
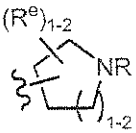
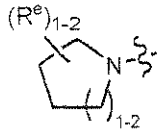
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

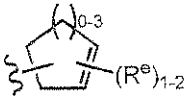
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*vi*)  , , or  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

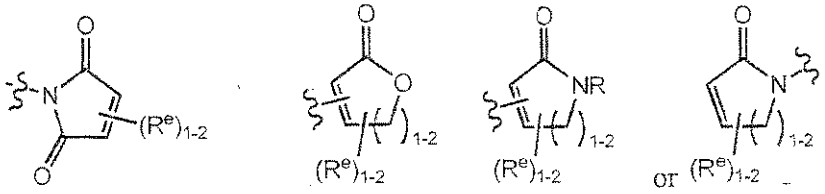
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

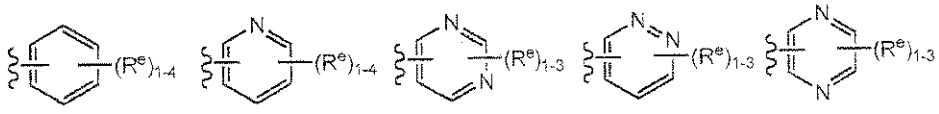
(*x*) , wherein each R^e is as defined above and described herein; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*xii*) 

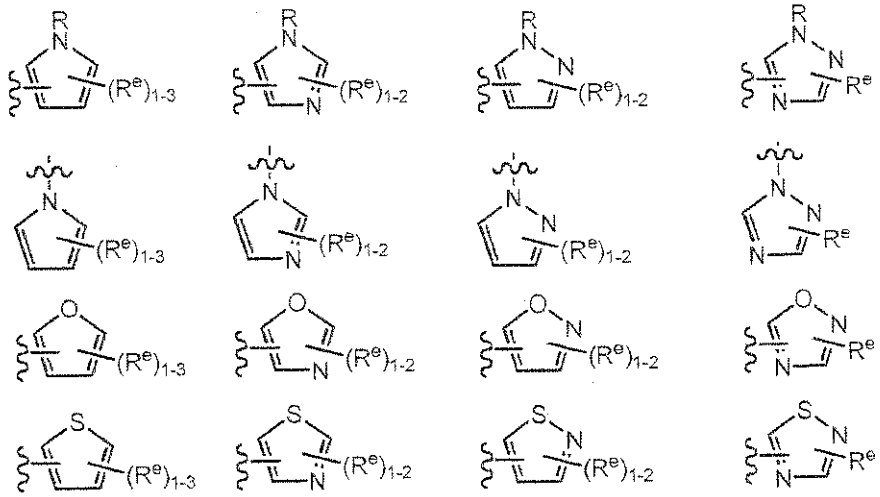
wherein each R and R^e is as defined above and described herein; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xiv*) 

wherein each R^e is as defined above and described herein; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xvi*) 

wherein each R and R^e is as defined above and described herein; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein;

(p) L is a covalent bond, $-CH_2-$, -NH-, -C(O)-, $-CH_2NH-$, $-NHCH_2-$, $-NHC(O)-$, $-NHC(O)CH_2OC(O)-$, $-CH_2NHC(O)-$, $-NHSO_2-$, $-NHSO_2CH_2-$, $-NHC(O)CH_2OC(O)-$, or $-SO_2NH-$; and Y is selected from:

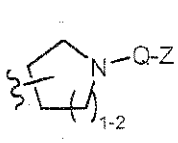
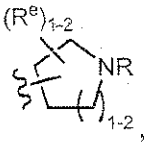
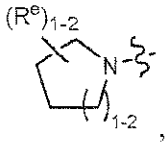
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups, wherein each R^e is as defined above and described herein; or

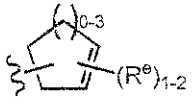
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*vi*)  , , or  , wherein each R, Q, Z, and R^e is as defined above and described herein; or

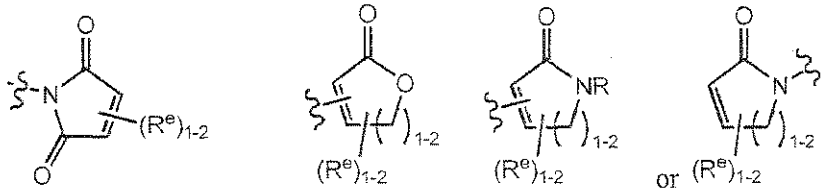
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

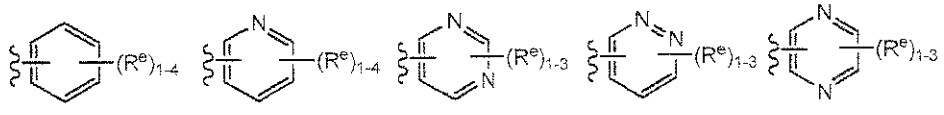
(*x*) , wherein each R^e is as defined above and described herein; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*xii*) 

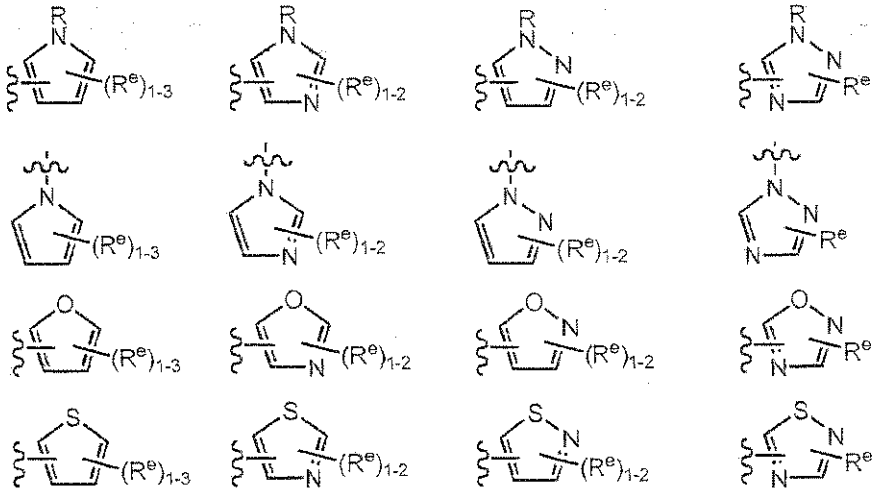
wherein each R and R^e is as defined above and described herein; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*xiv*) 

wherein each R^e is as defined above and described herein; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-3 R^e groups, wherein each R^e group is as defined above and described herein; or

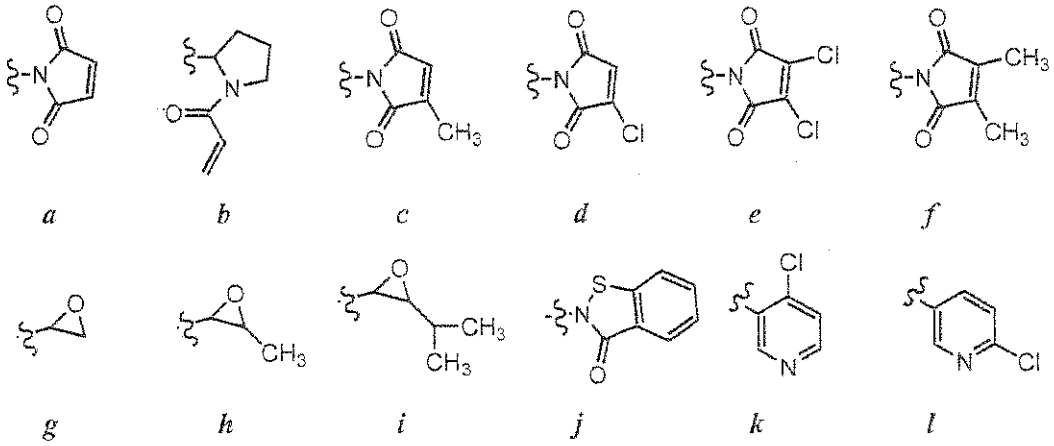
(*xvi*) 

wherein each R and R^e is as defined above and described herein; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein.

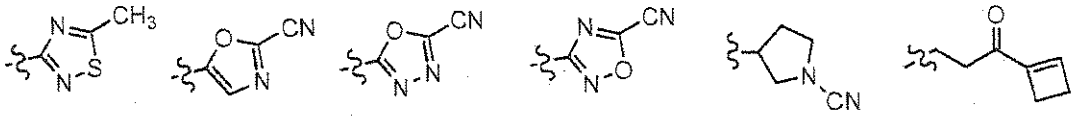
[00107] In certain embodiments, the Y group of formula **Ia** or **Ib** is selected from those set forth in Table 3, below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

Table 3. Exemplary Y groups:

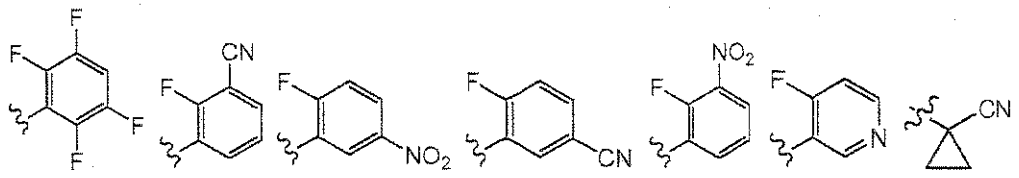


a *b* *c* *d* *e* *f*

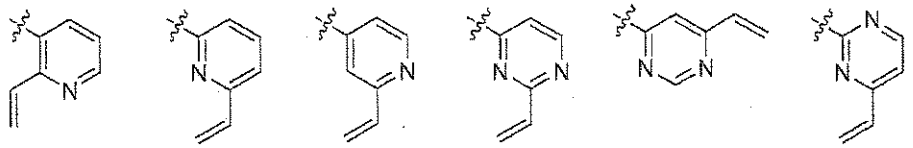
g *h* *i* *j* *k* *l*



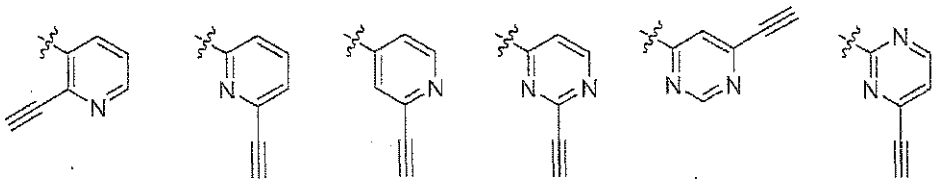
m *n* *o* *p* *q* *r*



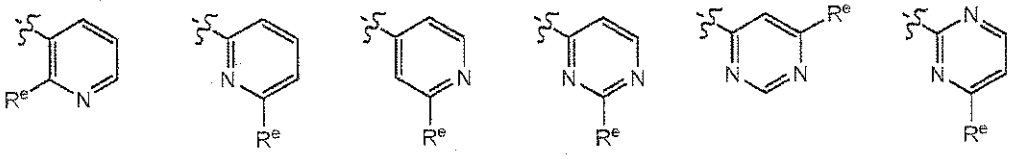
s *t* *u* *v* *w* *x* *y*



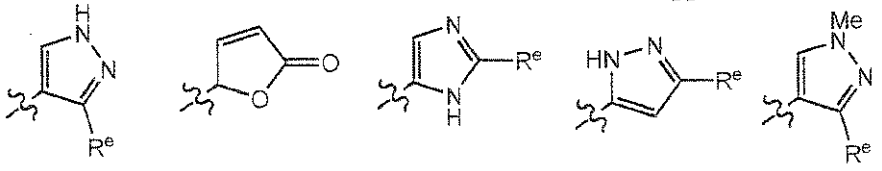
z *aa* *bb* *cc* *dd* *ee*



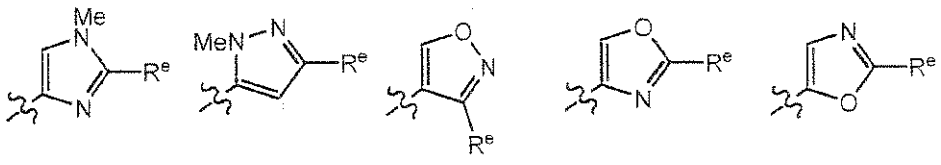
ff *gg* *hh* *ii* *jj* *kk*



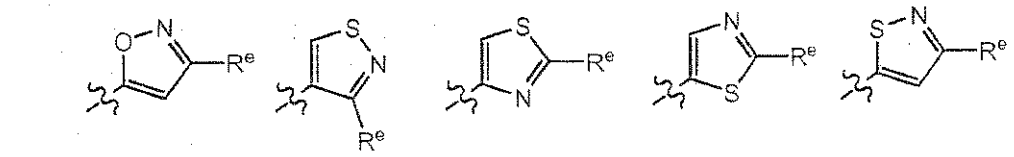
ll *mm* *nn* *oo* *pp* *qq*



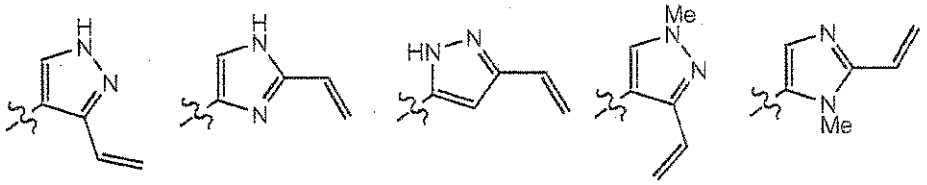
rr *ss* *tt* *uu* *vv*



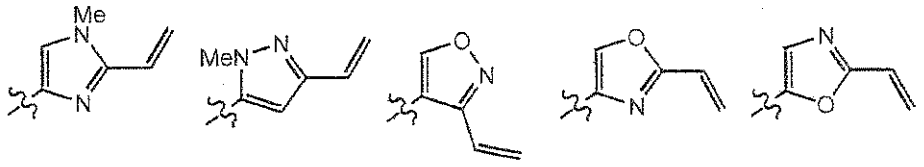
ww *xx* *yy* *zz* *aaa*



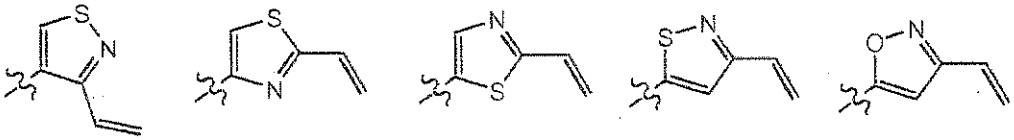
bbb *ccc* *ddd* *eee* *fff*



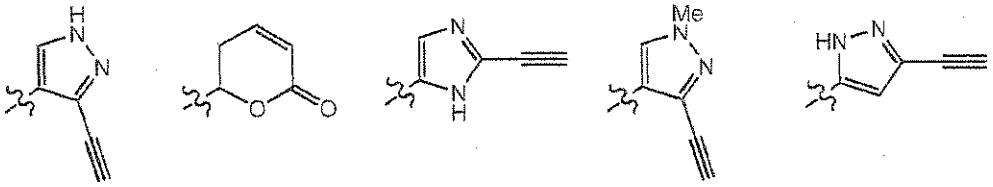
ggg *hhh* *iii* *jjj* *kkk*



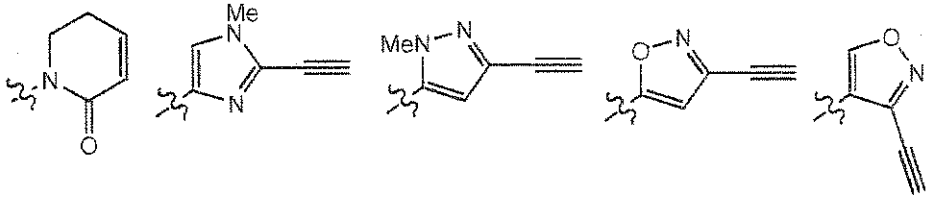
lll *mmm* *nnn* *ooo* *ppp*



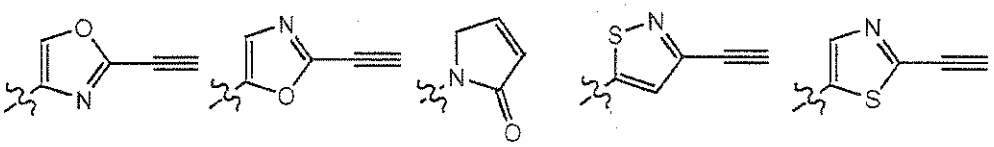
qqq *rrr* *sss* *ttt* *uuu*



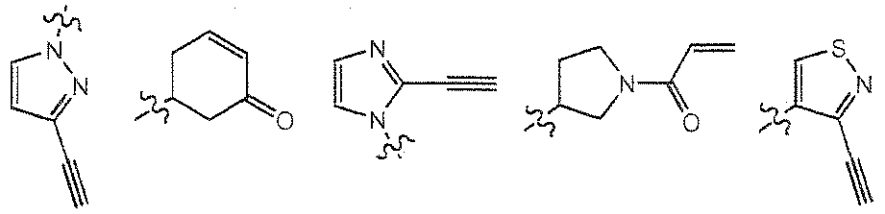
vvv *qqq* *www* *xxx* *yyy*



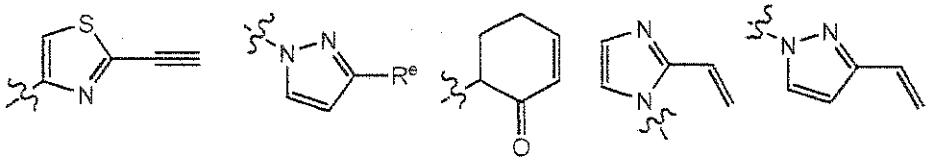
zzz *aaaa* *bbbb* *cccc* *dddd*



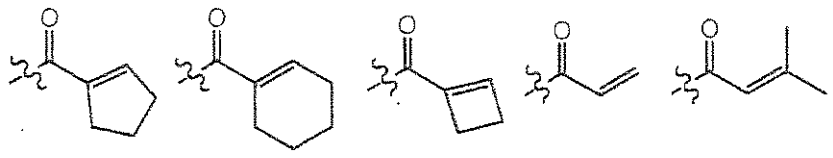
eeee *ffff* *gggg* *hhhh* *iiii*



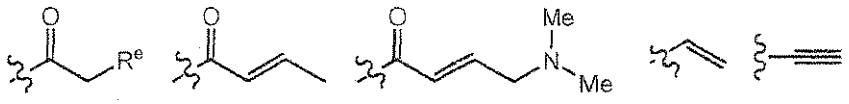
jjjj *kkkk* *llll* *mmmm* *nnnn*



oooo *pppp* *qqqq* *rrrr* *ssss*



tttt *uuuu* *vvvv* *wwww* *xxxx*



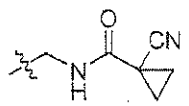
yyyy *zzzz* *aaaaa* *bbbbb* *ccccc*

wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

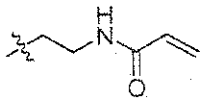
[00108] In certain embodiments, R^1 is -C≡CH, -C≡CCH_2NH(isopropyl), -NHC(O)C≡CCH_2CH_3, -CH_2-C≡C-CH_3, -C≡CCH_2OH, -CH_2C(O)C≡CH, -C(O)C≡CH, or -CH_2OC(=O)C≡CH. In some embodiments, R^1 is selected from -NHC(O)CH=CH_2, -NHC(O)CH=C$HCH_2N(CH_3)_2$, or -CH_2NHC(O)CH=CH_2.

[00109] In certain embodiments, R^1 is selected from those set forth in Table 4, below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

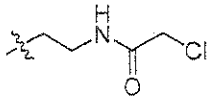
Table 4: Exemplary R^1 Groups



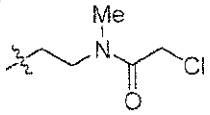
a



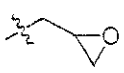
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c



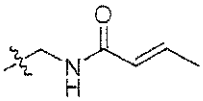
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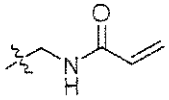
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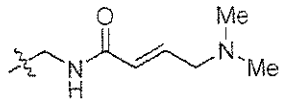
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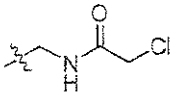
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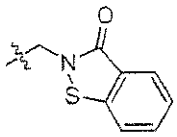
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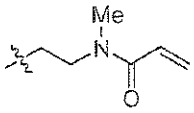
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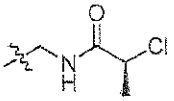
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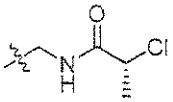
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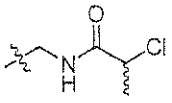
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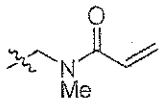
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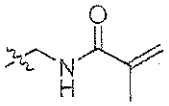
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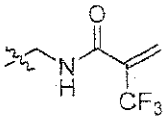
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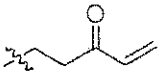
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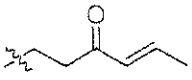
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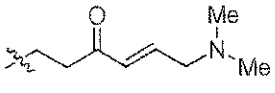
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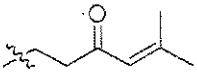
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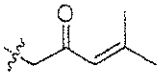
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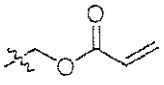
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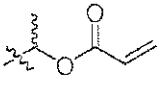
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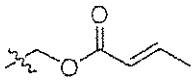
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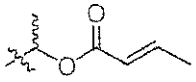
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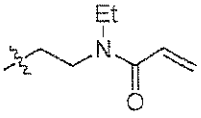
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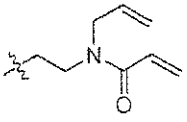
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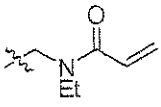
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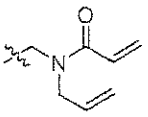
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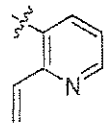
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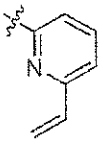
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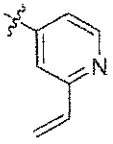
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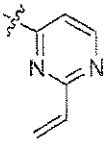
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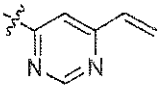
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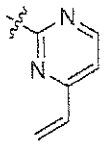
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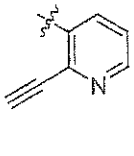
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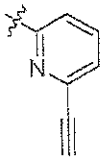
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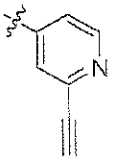
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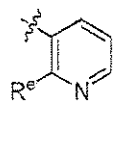


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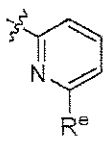
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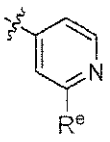
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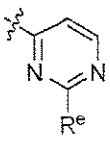
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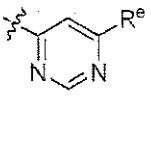
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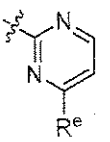
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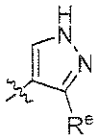
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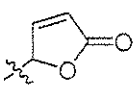
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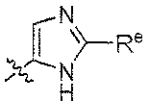
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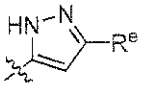
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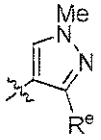
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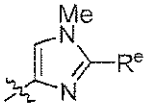
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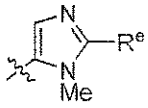
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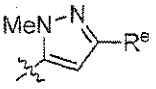
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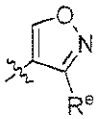
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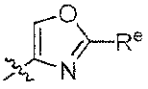
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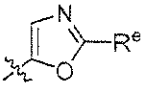
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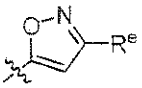
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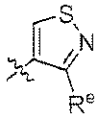
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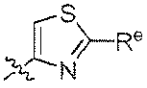
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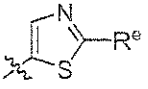
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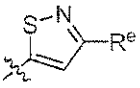
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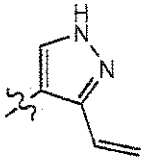
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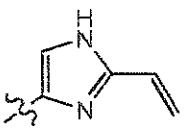
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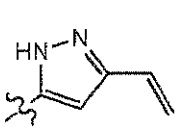
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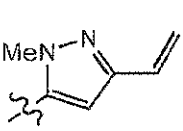
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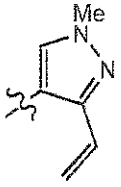
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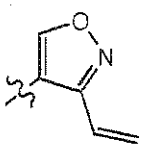
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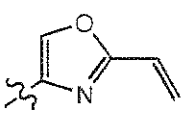
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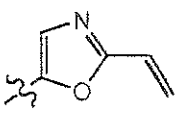
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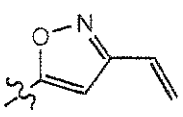
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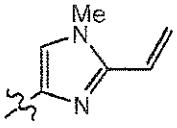
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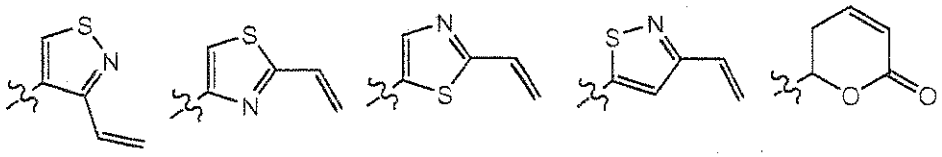


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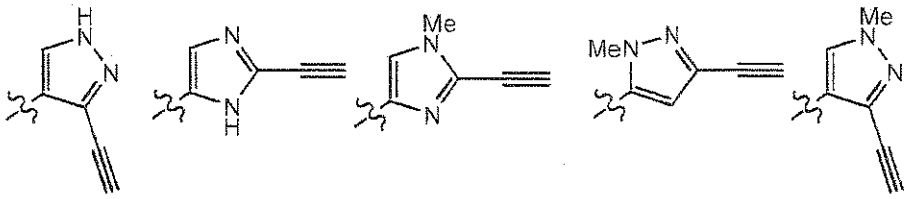


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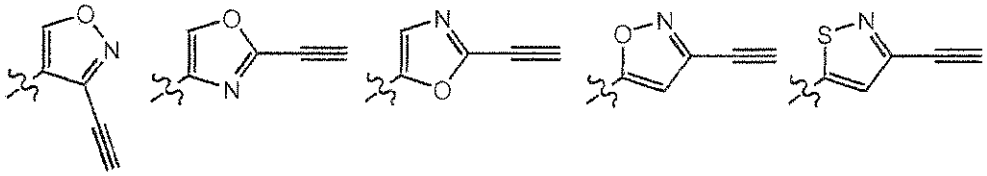




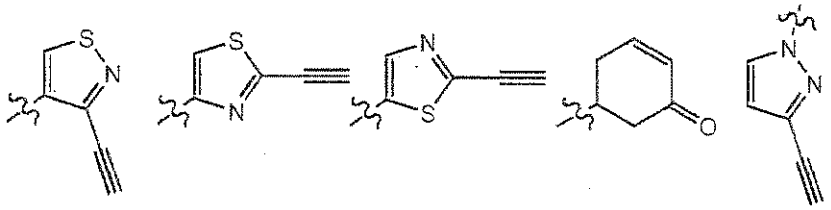
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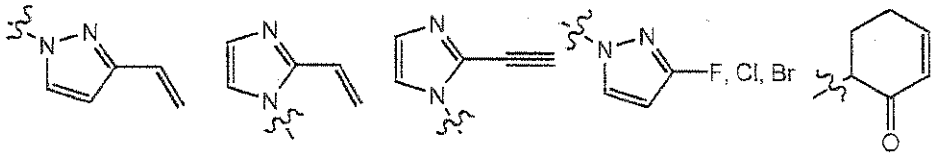
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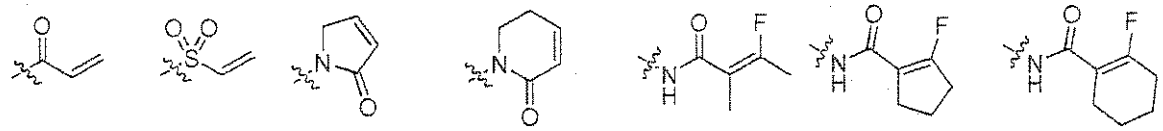
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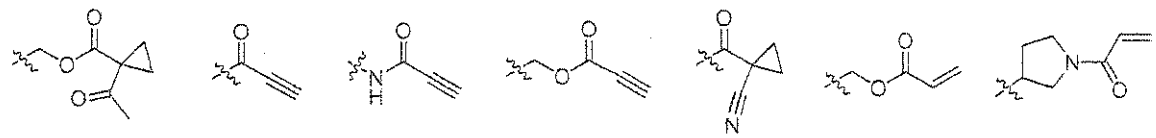
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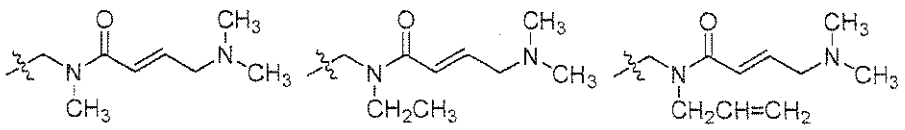
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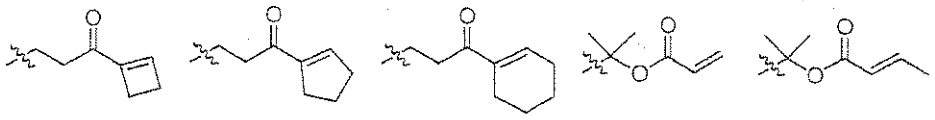
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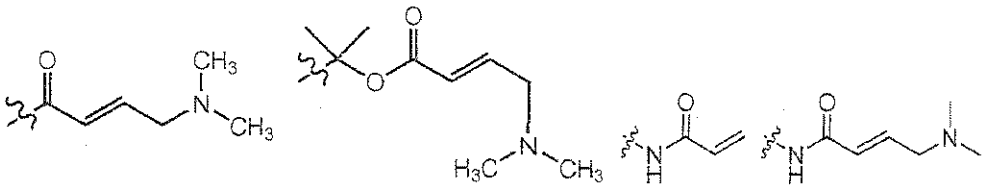
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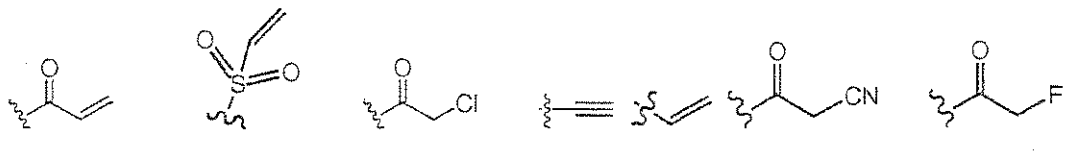
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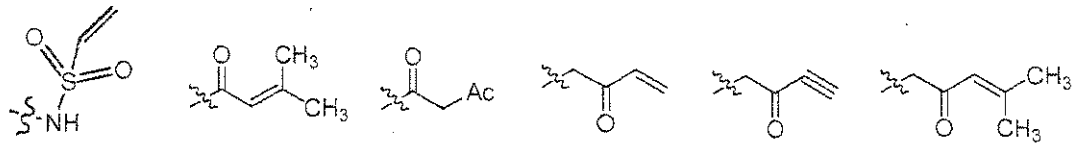
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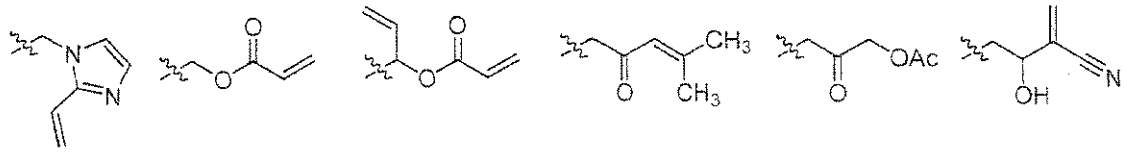
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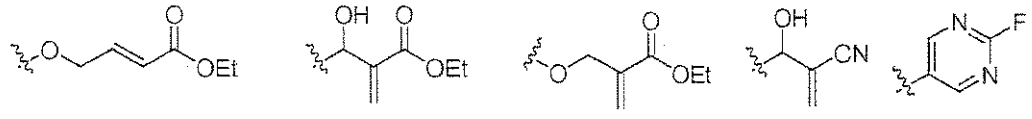
vvvvv *wwwww* *xxxxxx* *yyyyy* *zzzzz* *aaaaaa* *bbbbbb*



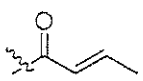
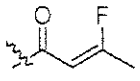
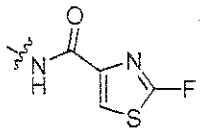
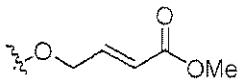
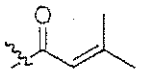
cccccc *dddddd* *eeeeee* *ffffff* *gggggg* *hhhhhh*



iiiiii *jjjjjj* *kkkkkk* *llllll* *mmmmmm* *nnnnnn*



oooooo *pppppp* *qqqqqq* *rrrrrr* *ssssss*

ttttt *uuuuuu* *vvvvvv* *wwwwww* or *xxxxxx*

wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

[00110] As defined generally above, R^1 is a warhead group, or, when R^1 and R^x form a ring, then -Q-Z is a warhead group. Without wishing to be bound by any particular theory, it is believed that such R^1 groups, i.e. warhead groups, are particularly suitable for covalently binding to a key cysteine residue in the binding domain of certain protein kinases. Protein kinases having a cysteine residue in the binding domain are known to one of ordinary skill in the art and include ErbB1, ErbB2, and ErbB4, or a mutant thereof. In certain embodiments, compounds of the present invention have a warhead group characterized in that inventive compounds target one or more of the following cysteine residues:

ERBB1	ITQLMPFG<u>C</u>LLDYVREH
ERBB2	VTQLMPYG<u>C</u>LLDHVREN
ERBB4	VTQLMPHG<u>C</u>LLEYVHEH

[00111] Thus, in some embodiments, R^1 is characterized in that the -L-Y moiety is capable of covalently binding to a cysteine residue thereby irreversibly inhibiting the enzyme. In certain embodiments, the cysteine residue is Cys797 of ErbB1, Cys805 of ErbB2 and Cys803 of ErbB4, or a mutant thereof, where the provided residue numbering is in accordance with Uniprot (code POO533 for ErbB1; code PO4626 for ErbB2, and Q15303 for ErbB4). It will be understood that the Cys of ErbB1 (EGFR) is variably called 773 or 797 depending on whether the parent sequence contains the signal peptide or not. Thus, in accordance with the present invention, the relevant cysteine residue of ErbB1 may be described as Cys 773 or Cys 797 and these terms are used interchangeably.

[00112] One of ordinary skill in the art will recognize that a variety of warhead groups, as defined herein, are suitable for such covalent bonding. Such R^1 groups include, but are not limited to, those described herein and depicted in Table 3, *infra*.

[00113] As depicted in formulae **I-a** and **I-b** *supra*, the R^1 warhead group can be in an ortho-, meta-, or para-position. In certain embodiments, the R^1 warhead group is in a meta-position of the phenyl ring relative to the rest of the molecule.

[00114] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of TEC, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 449.

[00115] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of BTK, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 481.

[00116] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of ITK, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 442.

[00117] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of BMX, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 496.

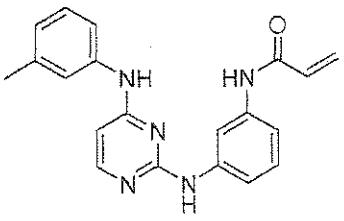
[00118] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of JAK3, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 909.

[00119] In certain embodiments, R^1 is characterized in that the –L-Y moiety is capable of covalently binding to a cysteine residue of TXK, thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys 350.

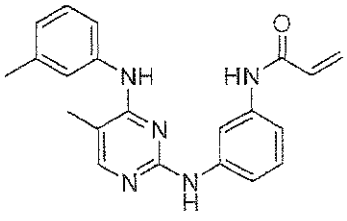
[00120] One of ordinary skill in the art will recognize that a variety of warhead groups, as defined herein, are suitable for such covalent bonding. Such R^1 groups include, but are not limited to, those described herein and depicted in Table 3, *infra*.

[00121] Exemplary compounds of the present invention are set forth in Table 5 below.

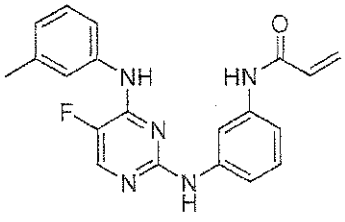
Table 5. Exemplary Compounds



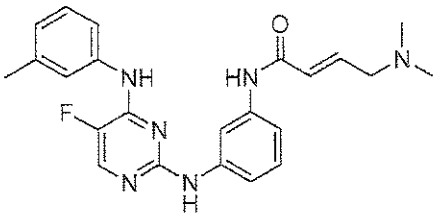
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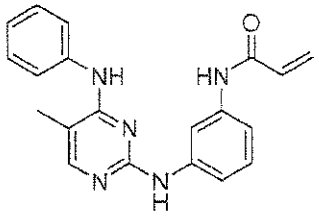
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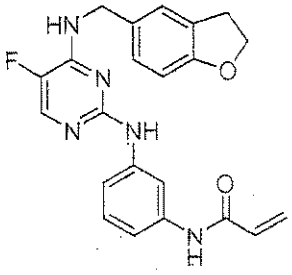
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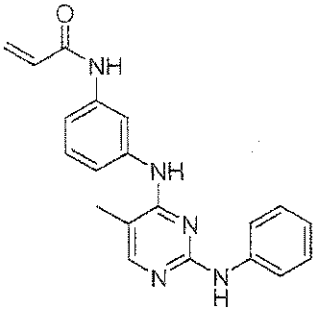
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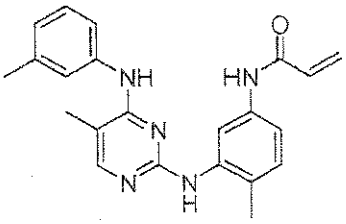
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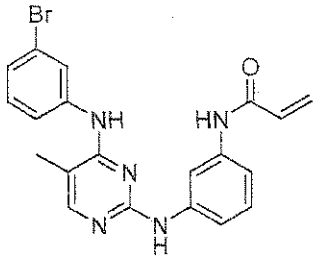
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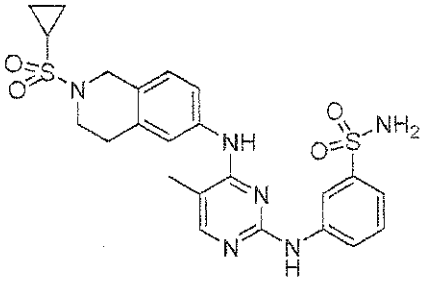
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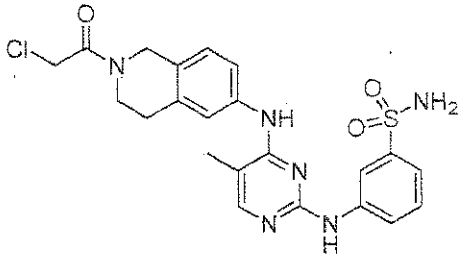
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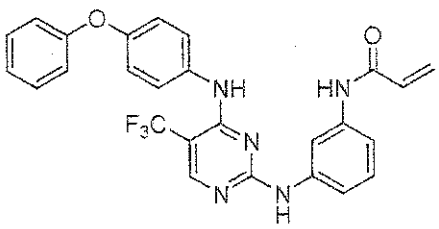
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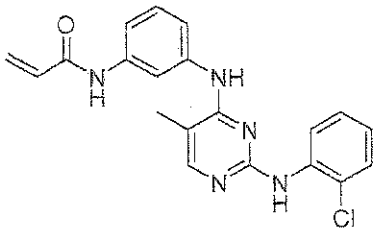
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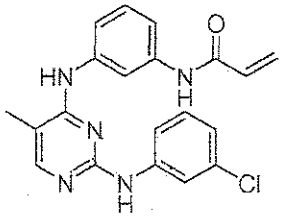
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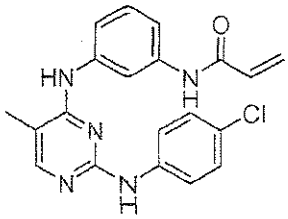
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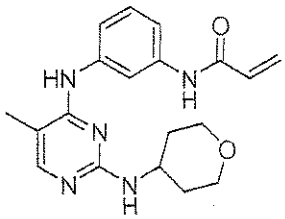
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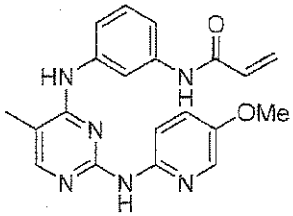
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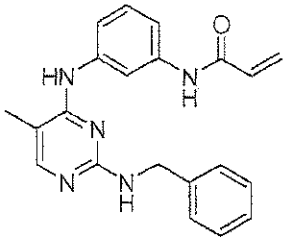
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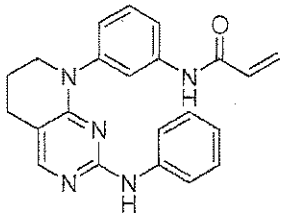
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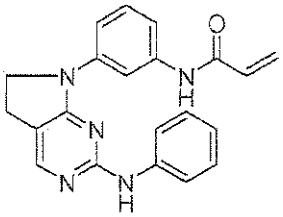
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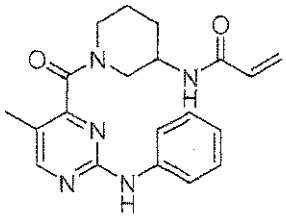
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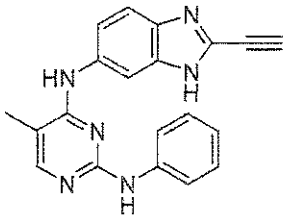
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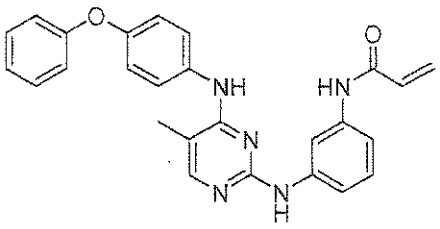
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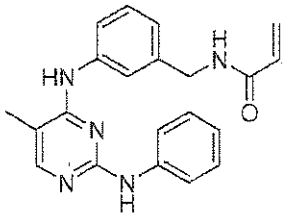
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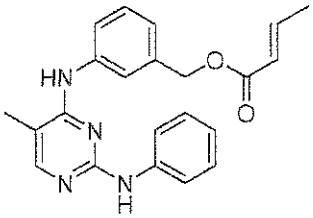
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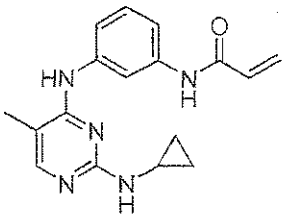
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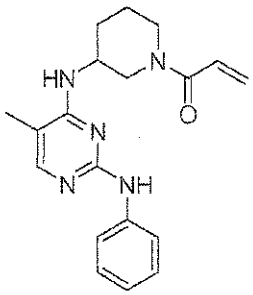
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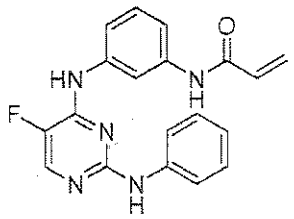
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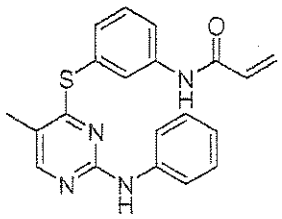
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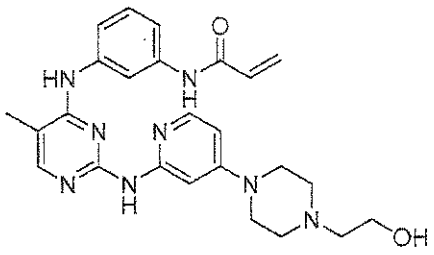
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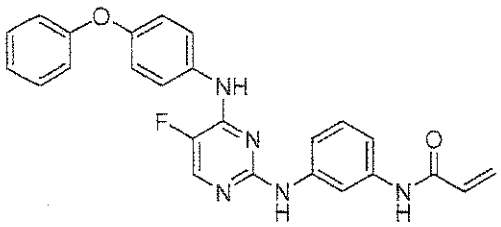
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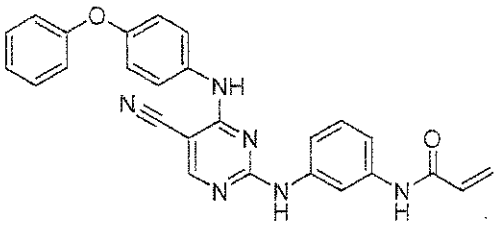
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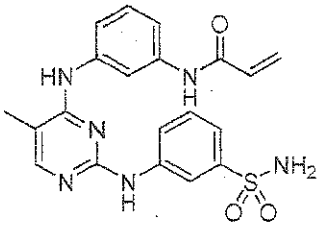
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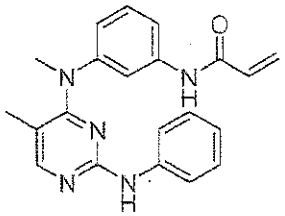
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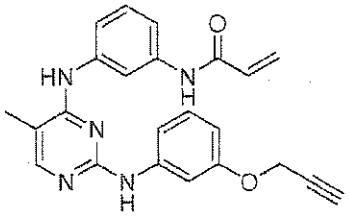
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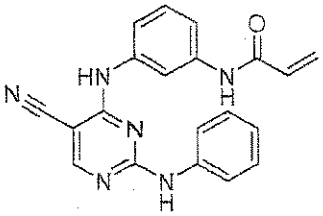
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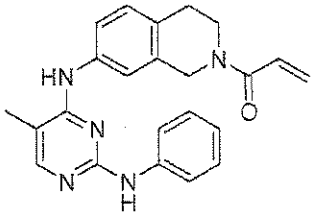
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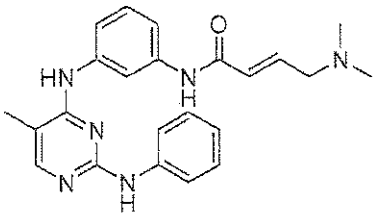
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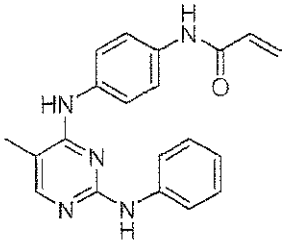
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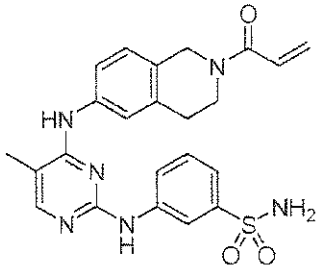
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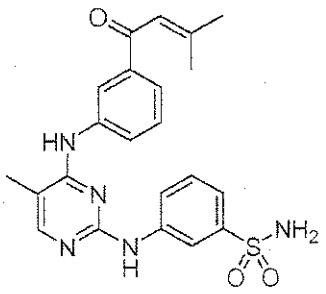
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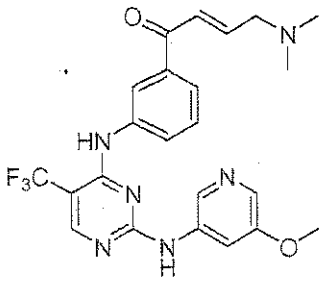
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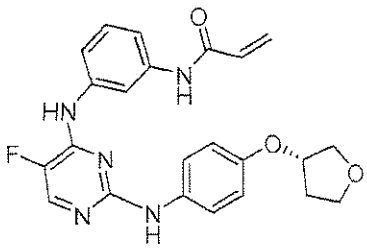
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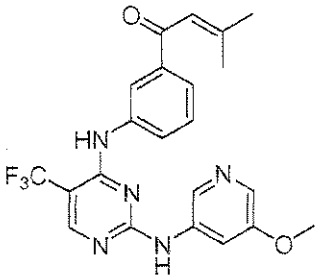
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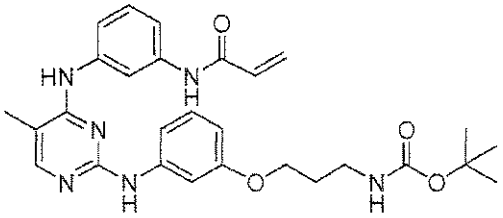
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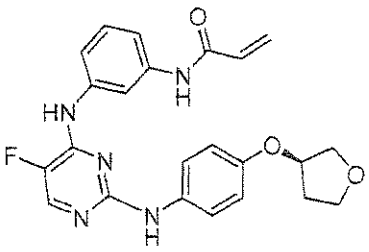
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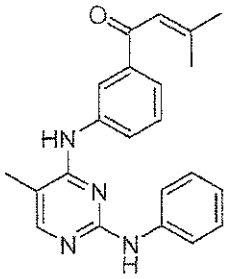
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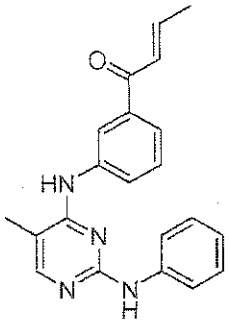
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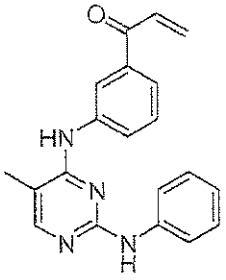
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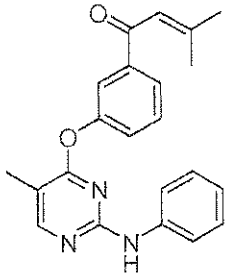
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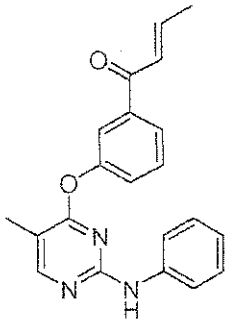
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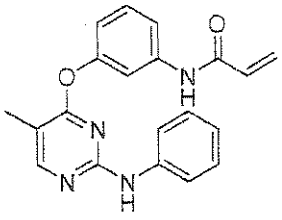
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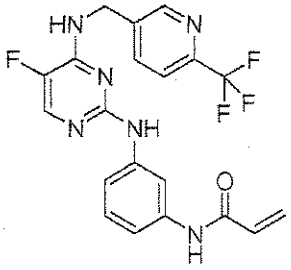
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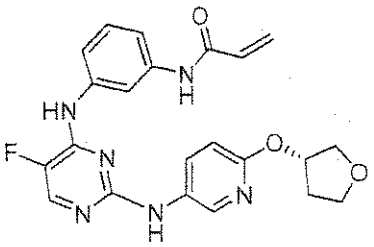
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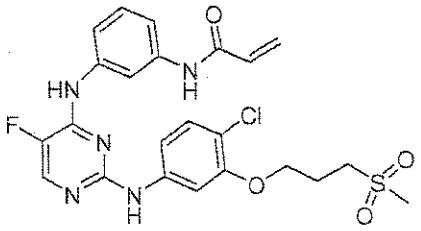
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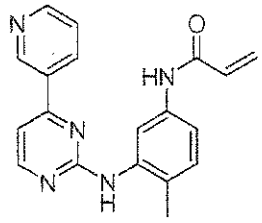
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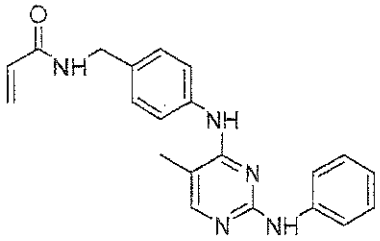
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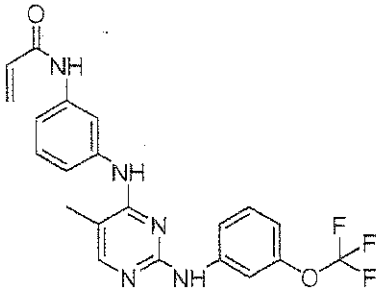
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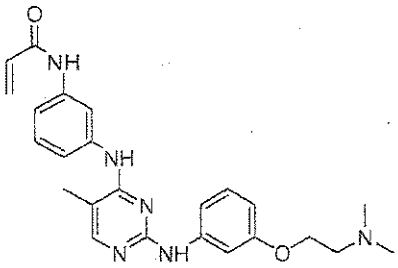
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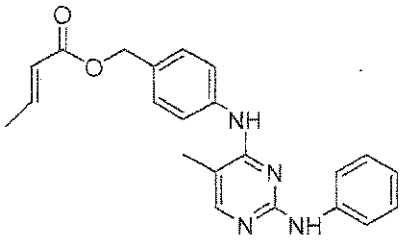
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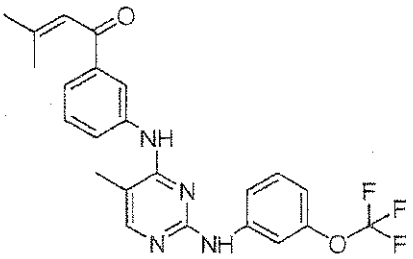
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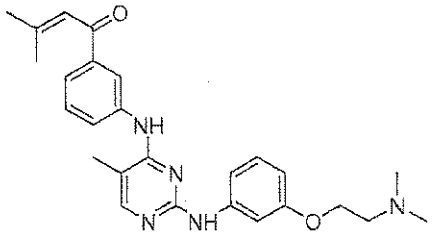
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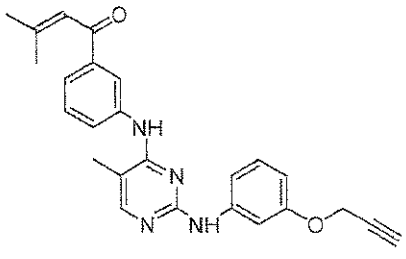
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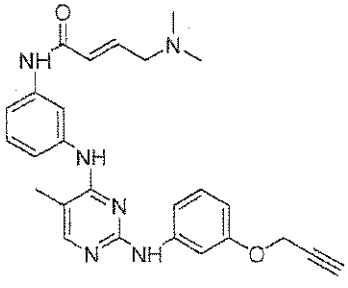
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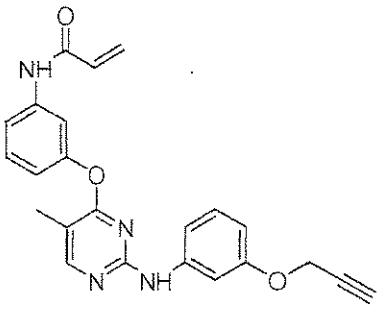
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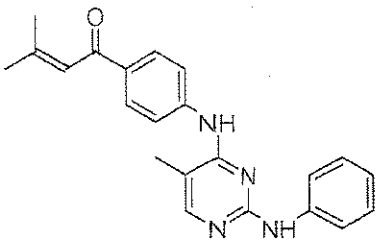
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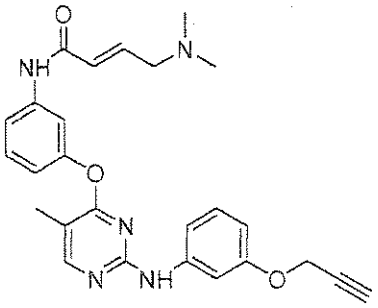
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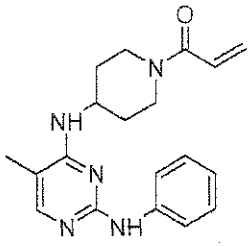
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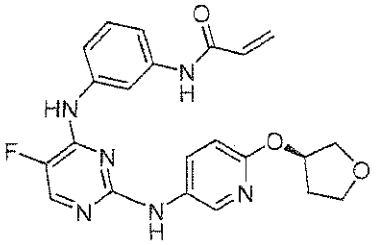
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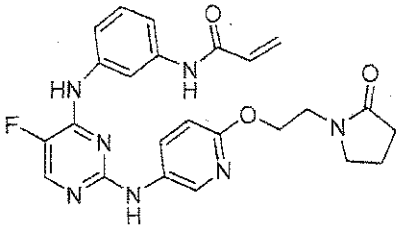
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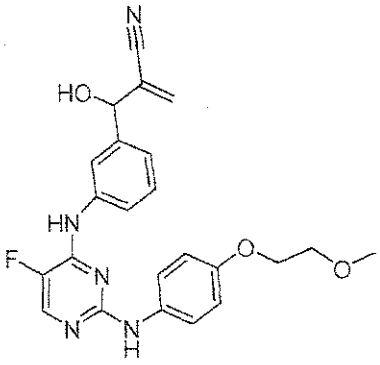
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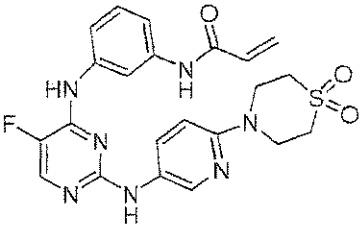
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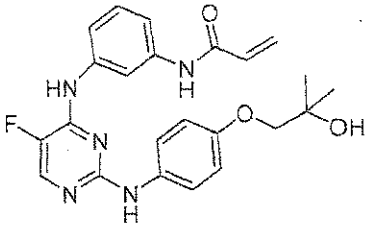
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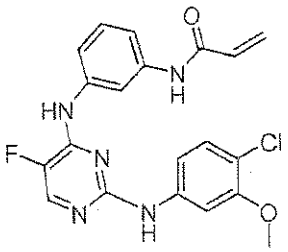
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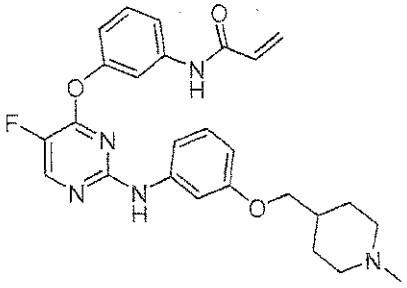
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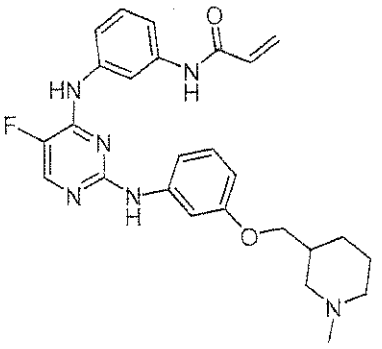
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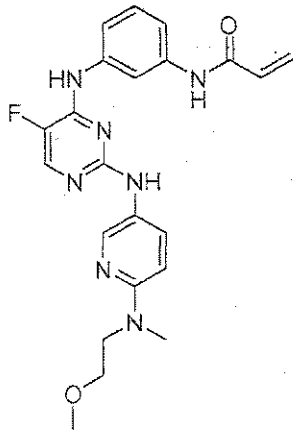
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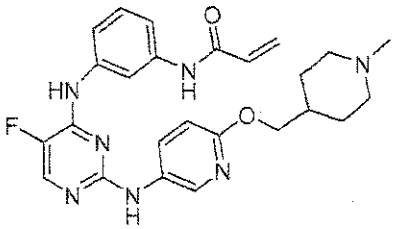
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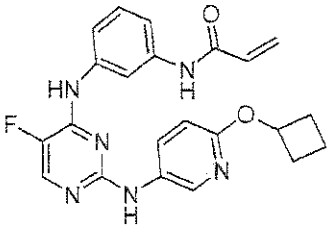
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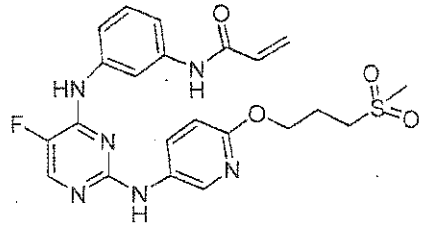
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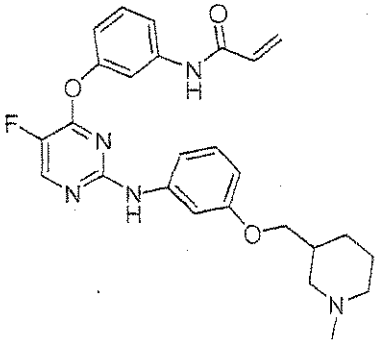
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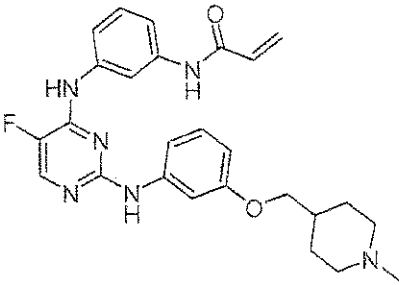
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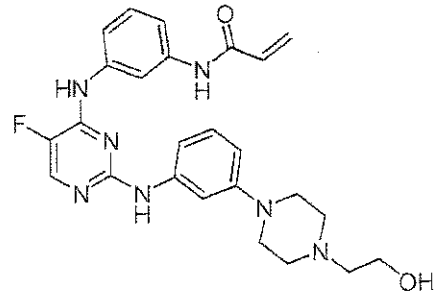
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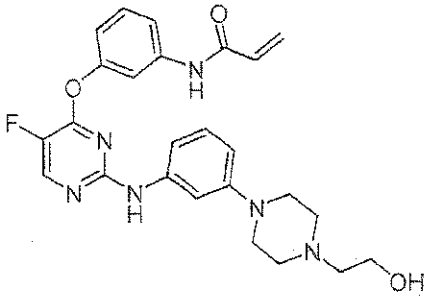
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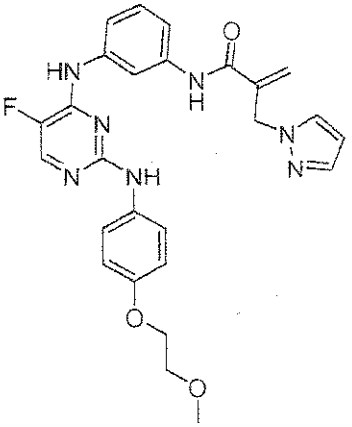
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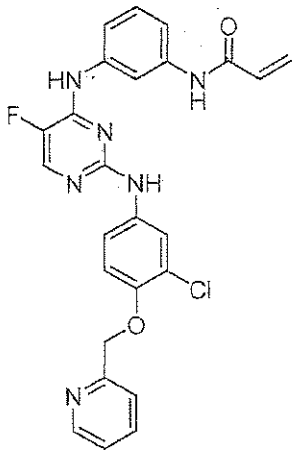
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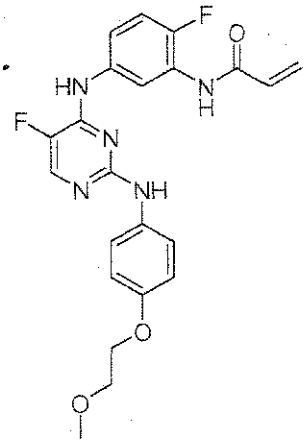
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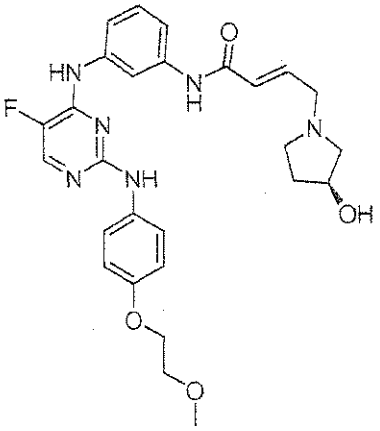
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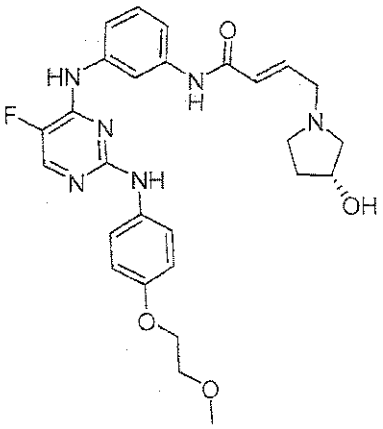
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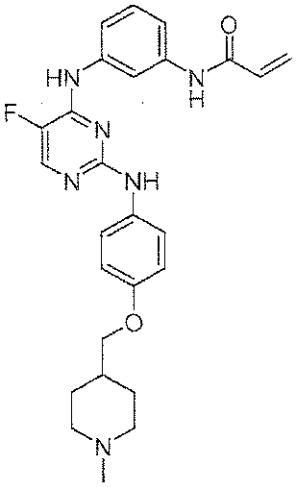
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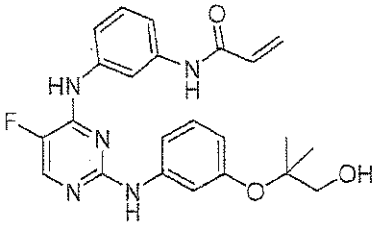
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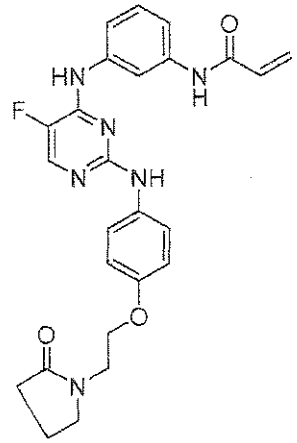
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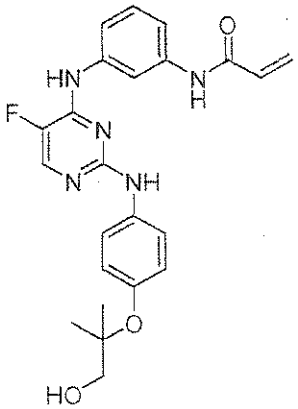
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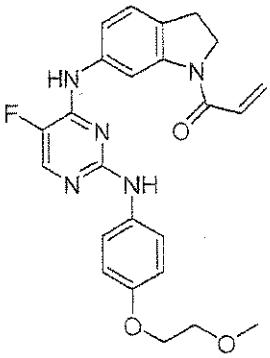
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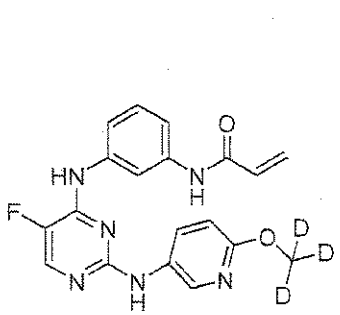
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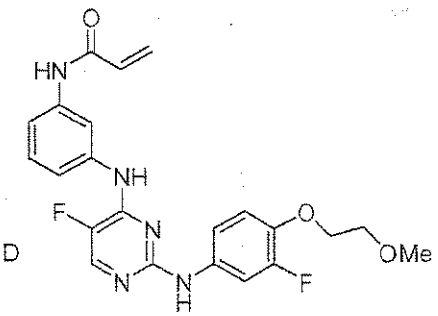
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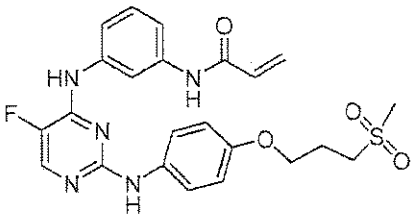
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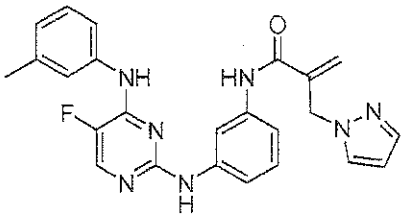
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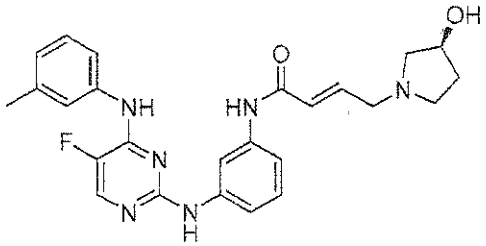
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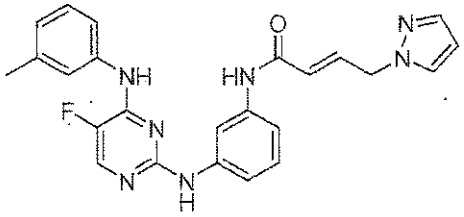
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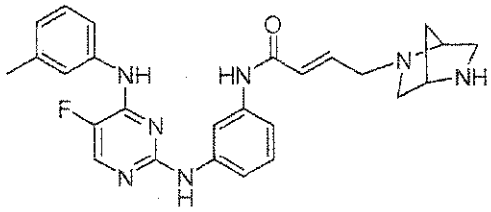
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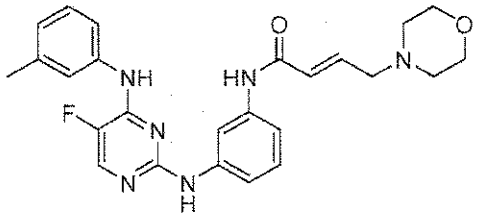
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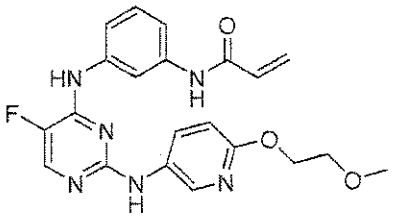
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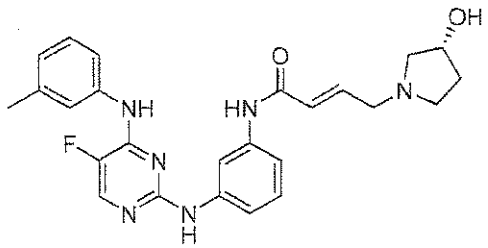
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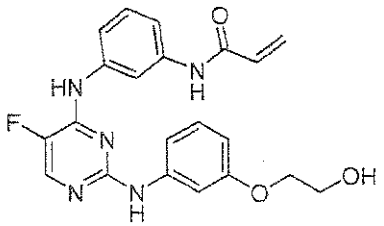
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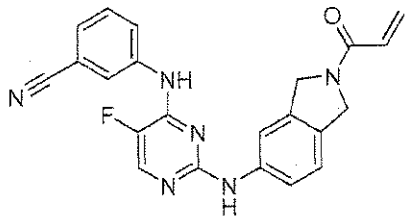
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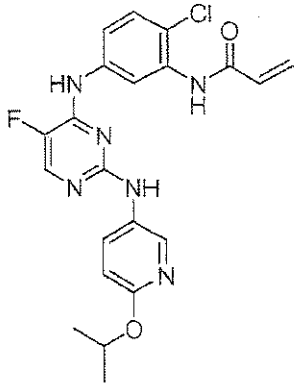
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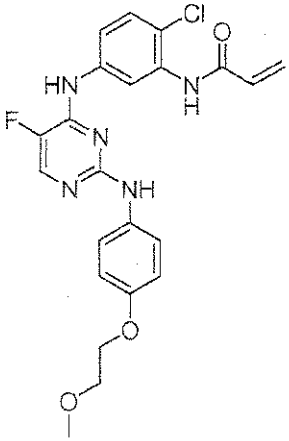
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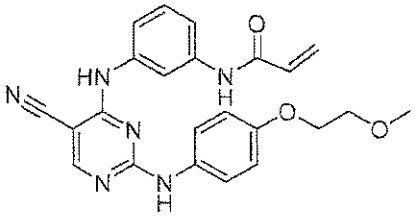
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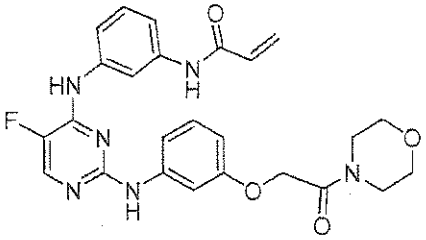
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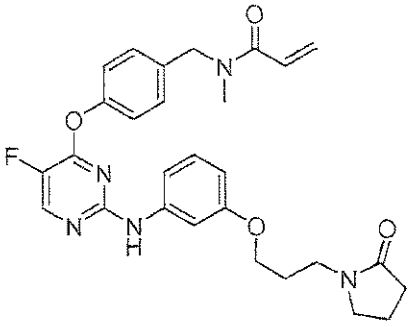
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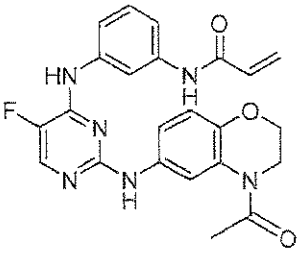
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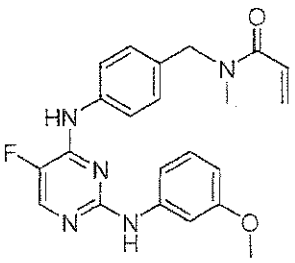
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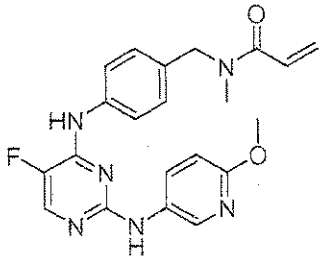
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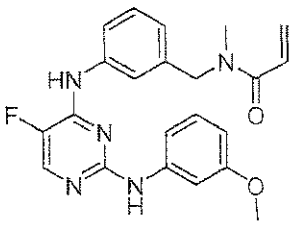
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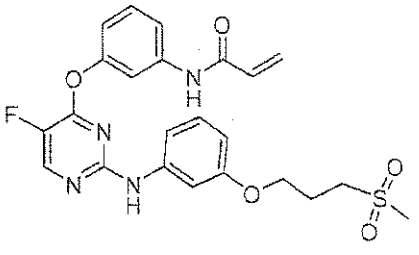
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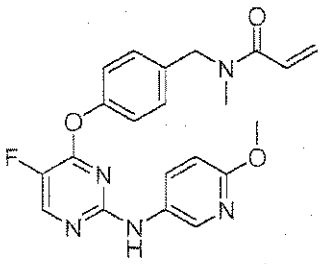
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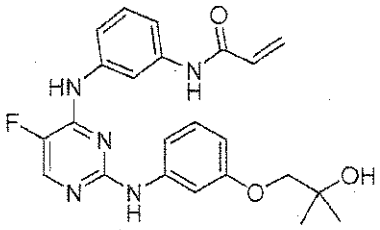
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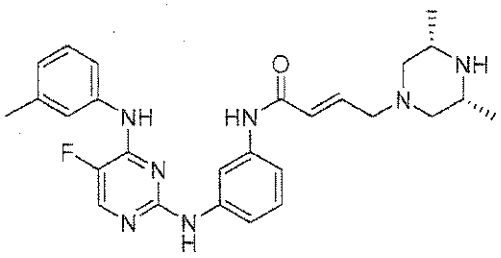
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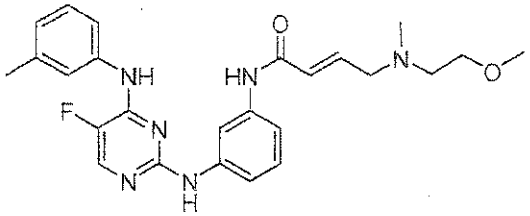
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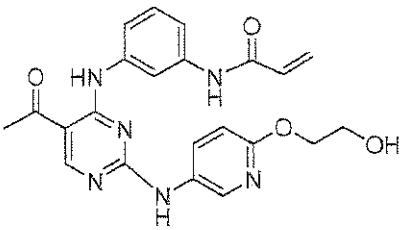
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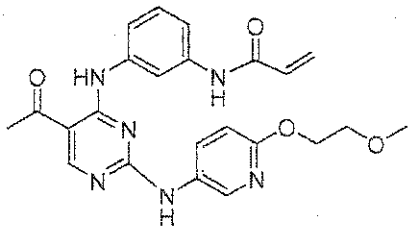
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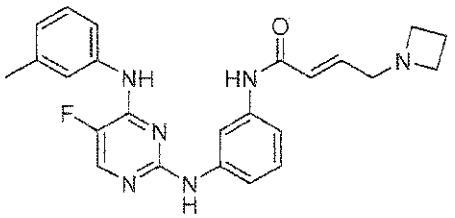
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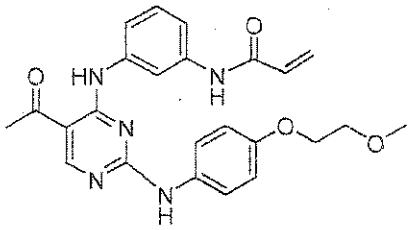
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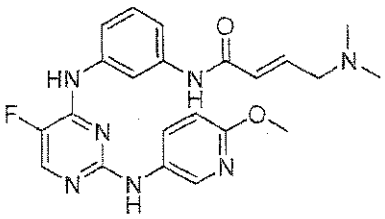
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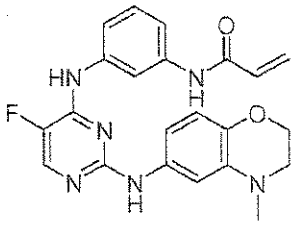
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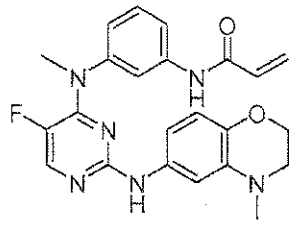
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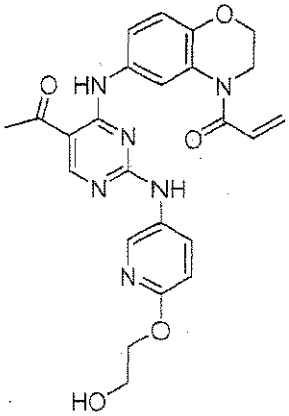
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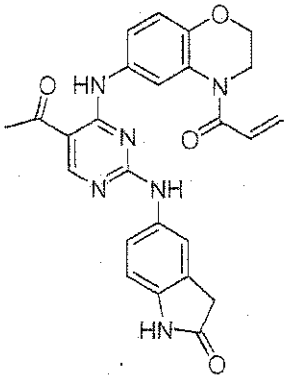
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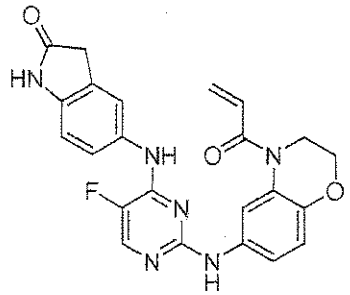
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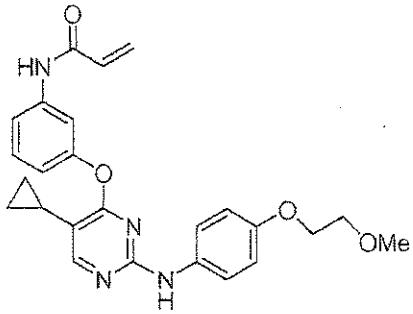
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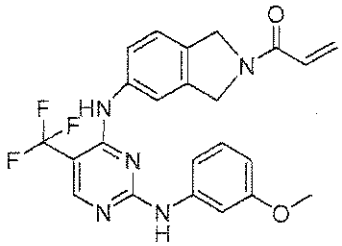
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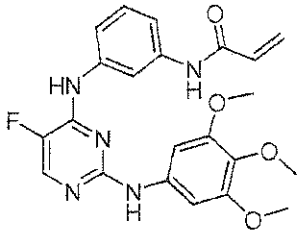
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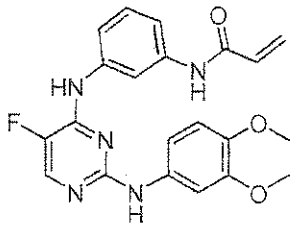
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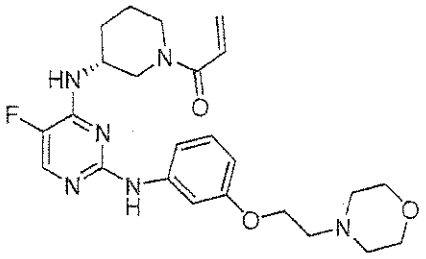
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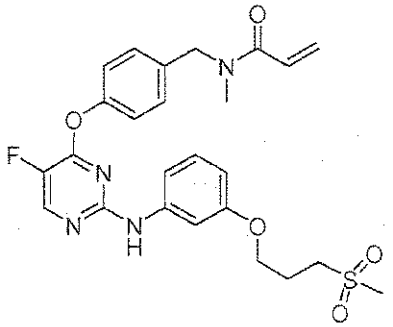
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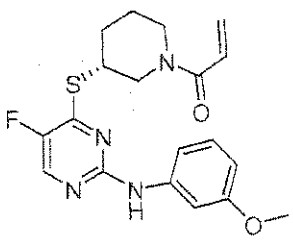
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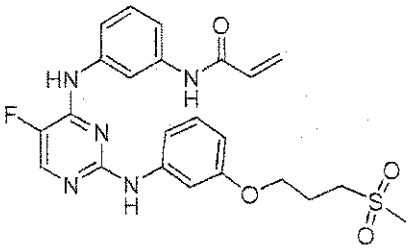
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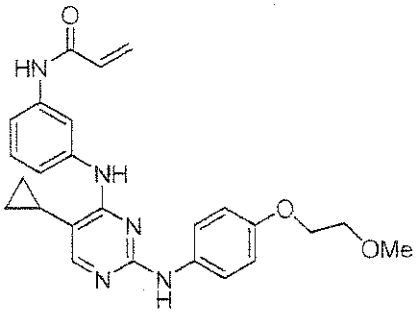
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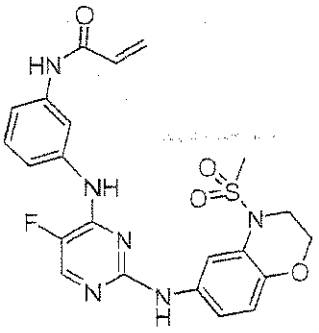
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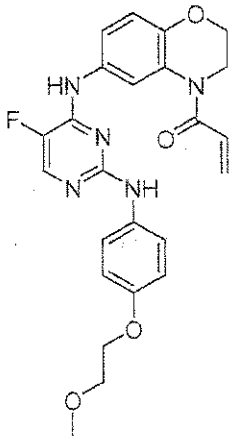
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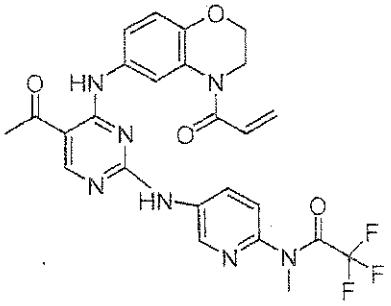
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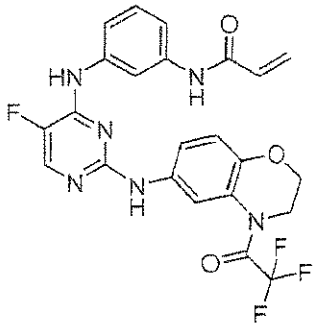
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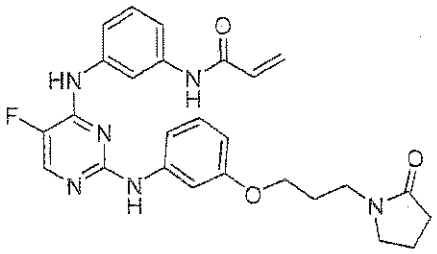
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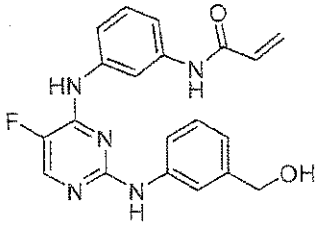
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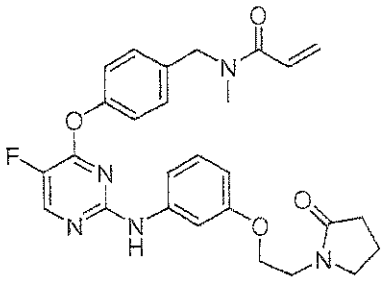
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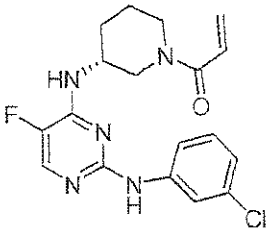
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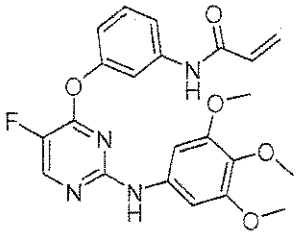
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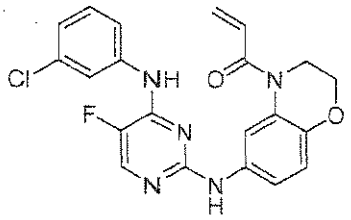
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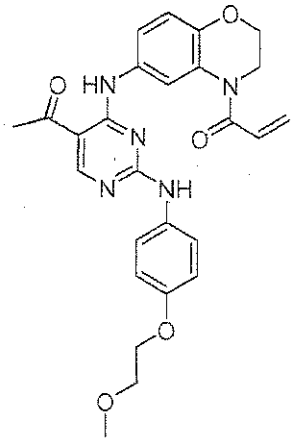
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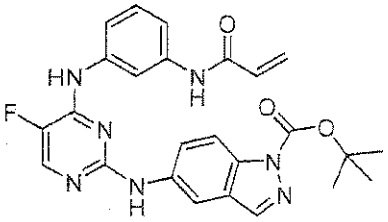
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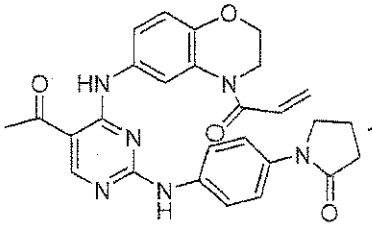
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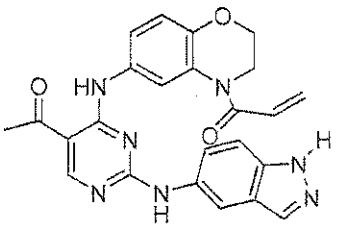
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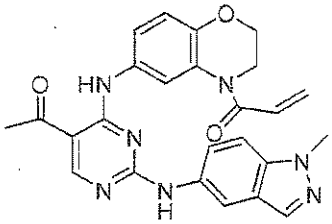
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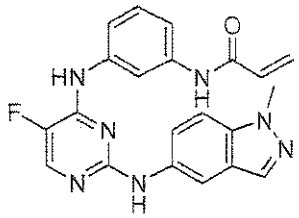
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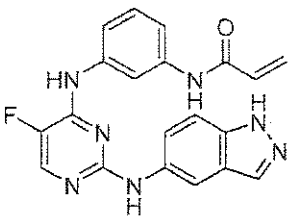
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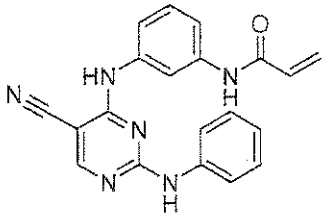
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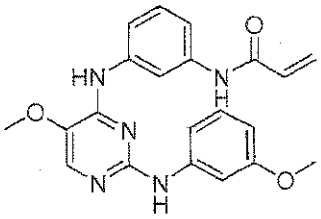
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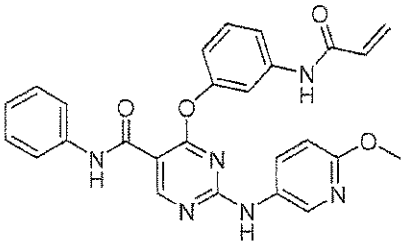
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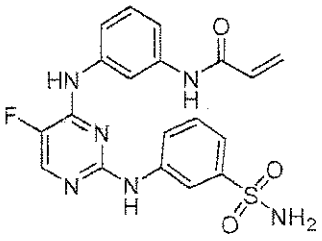
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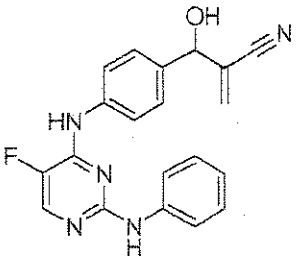
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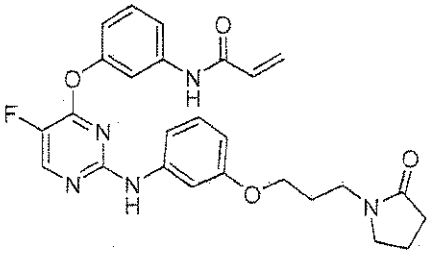
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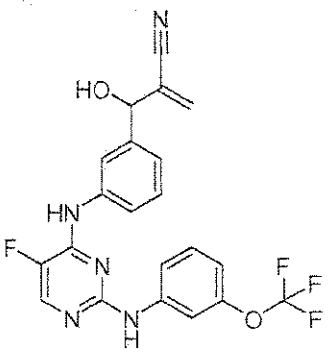
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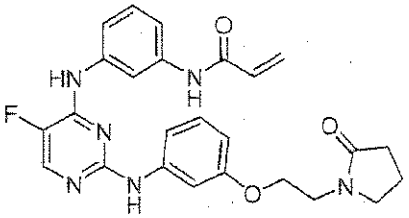
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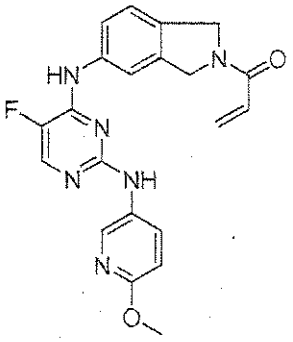
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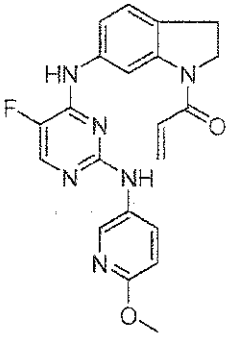
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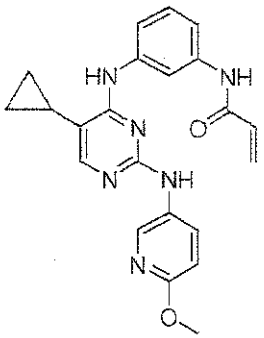
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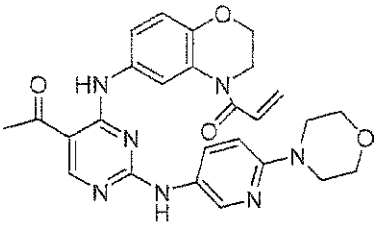
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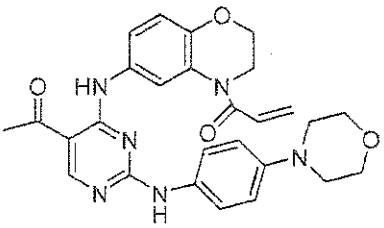
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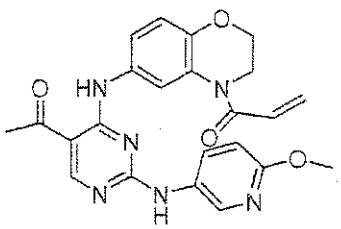
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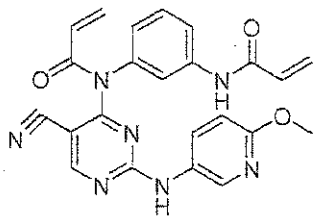
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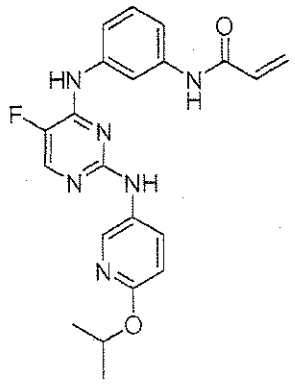
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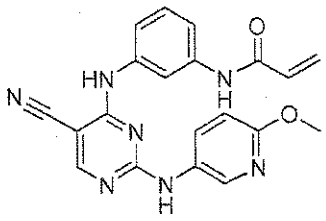
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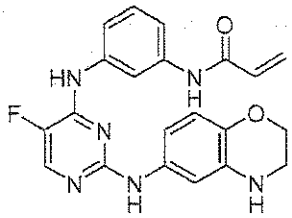
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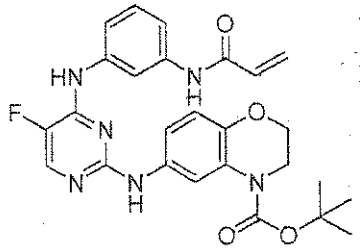
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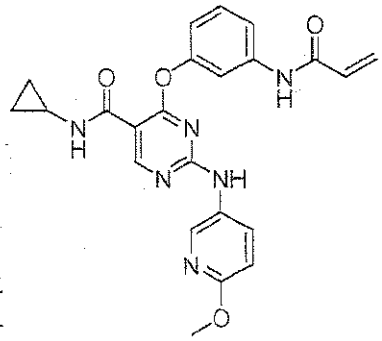
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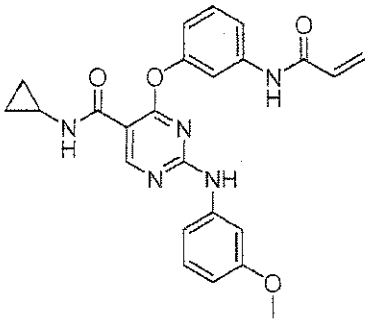
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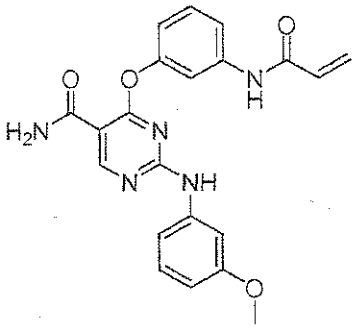
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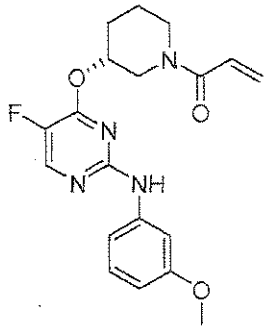
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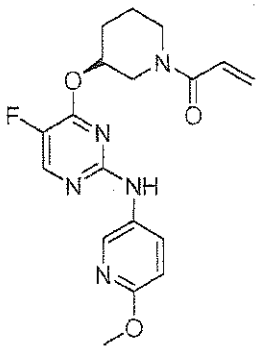
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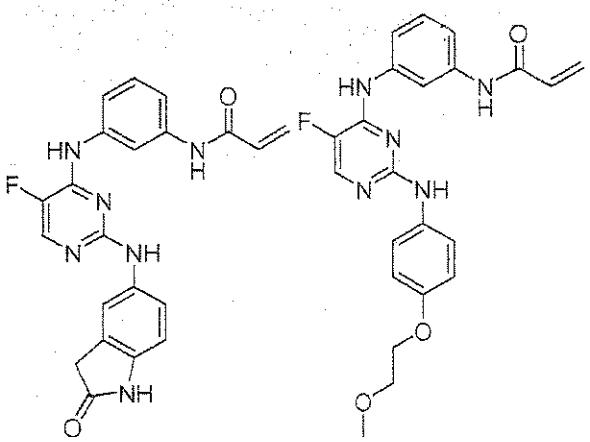
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I-179

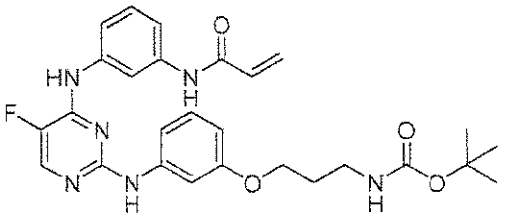


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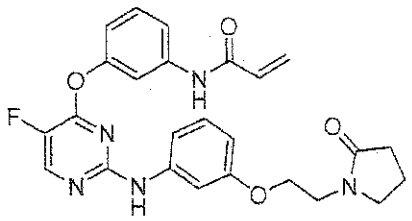


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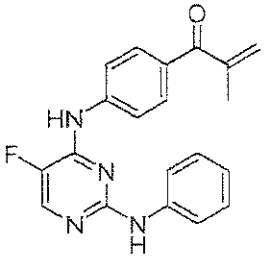
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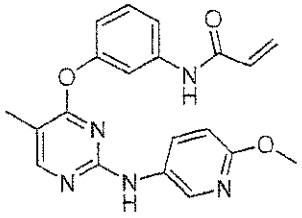
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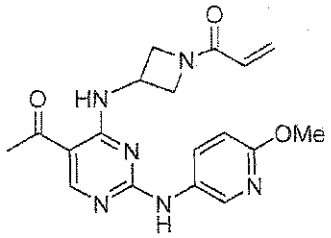
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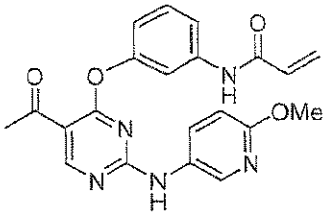
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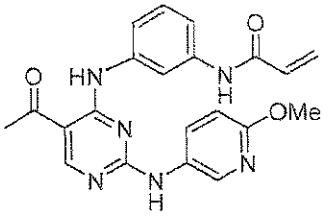
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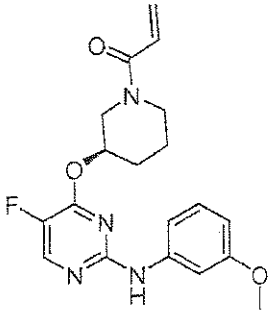
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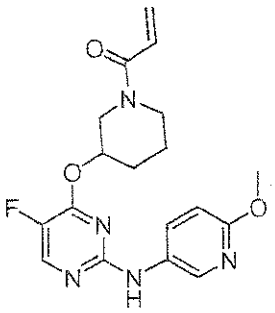
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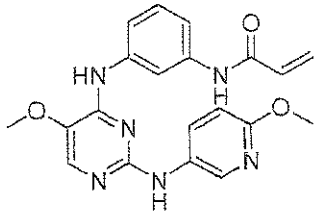
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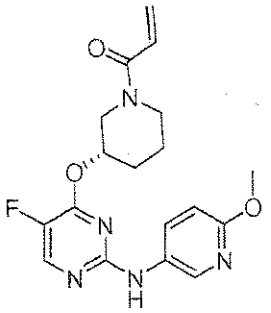
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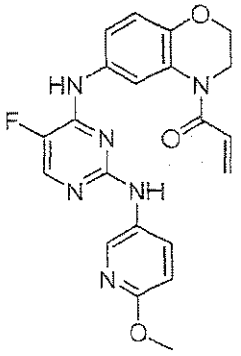
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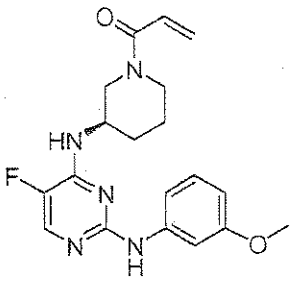
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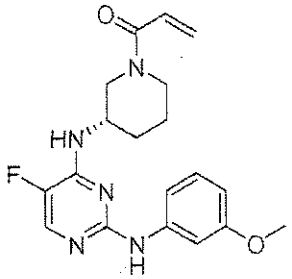
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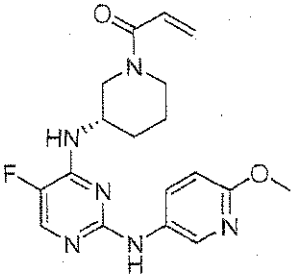
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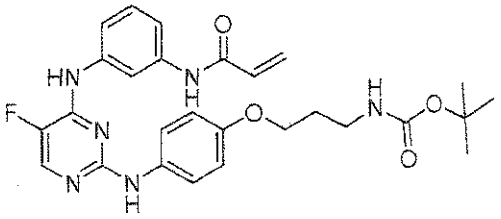
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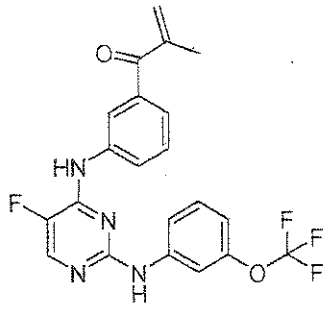
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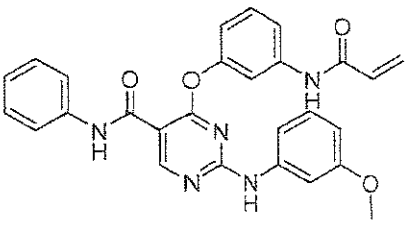
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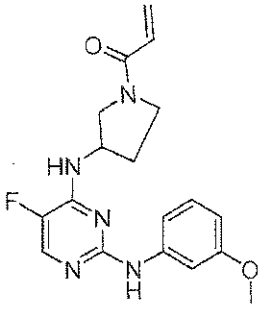
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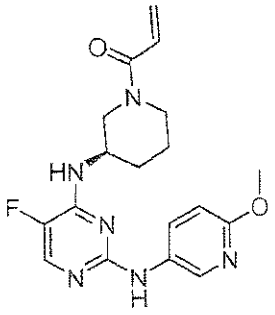
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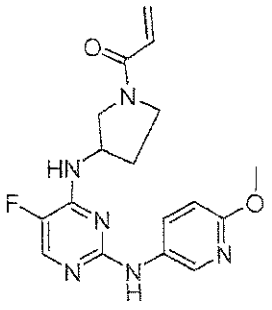
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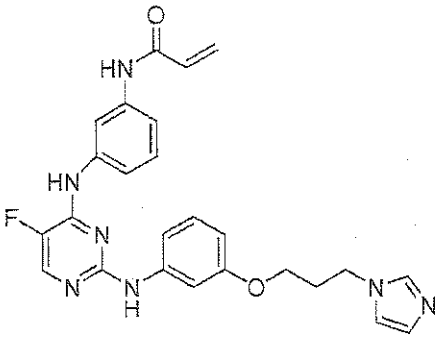
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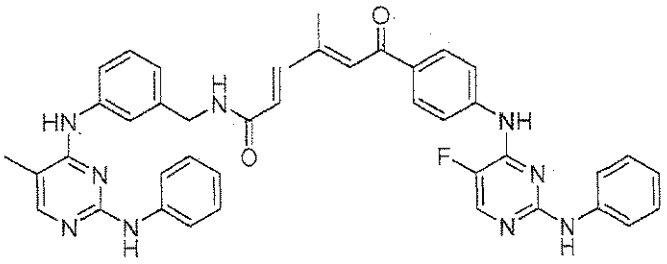
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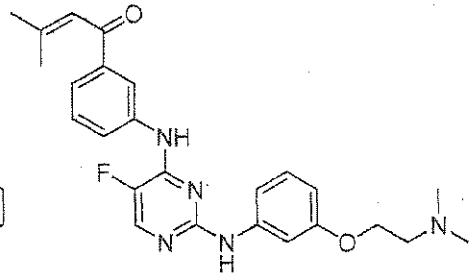
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I-204

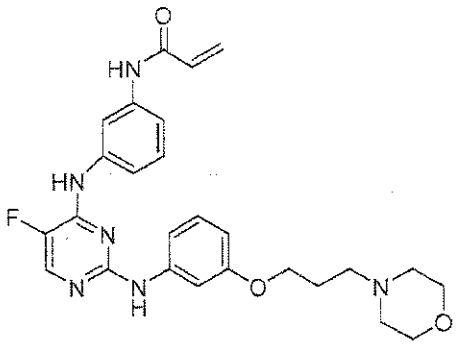


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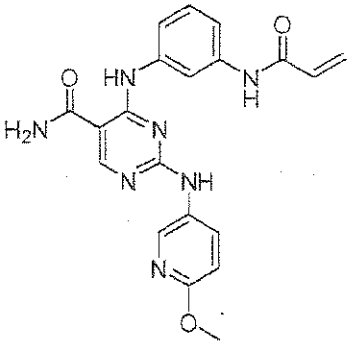


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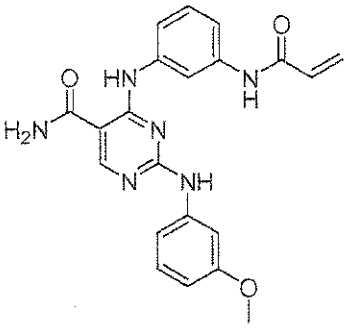
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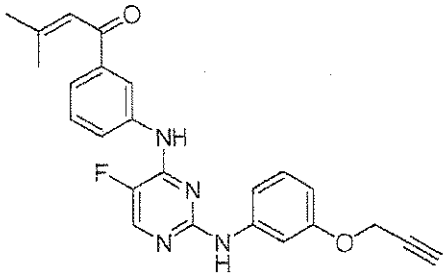
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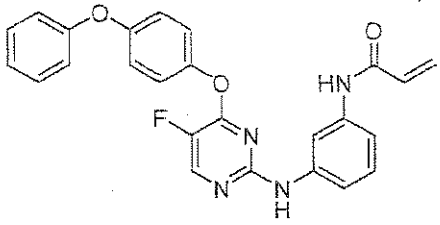
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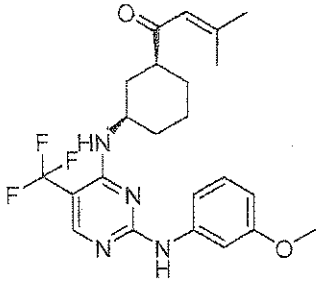
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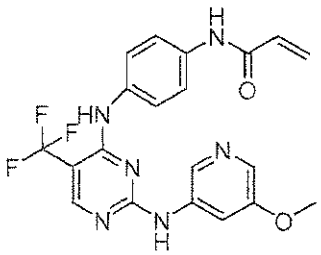
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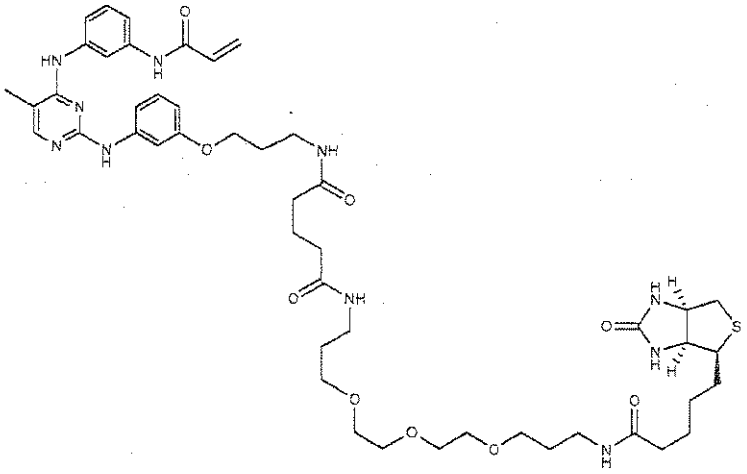
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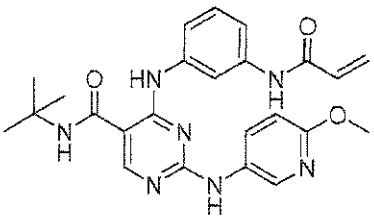
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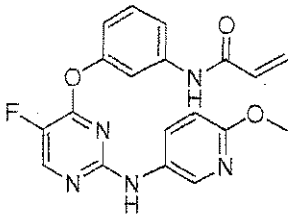
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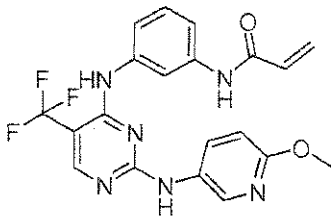
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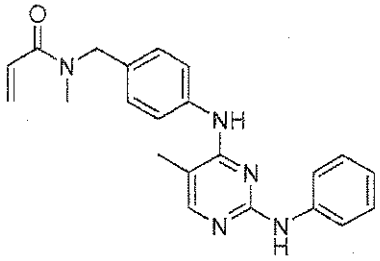
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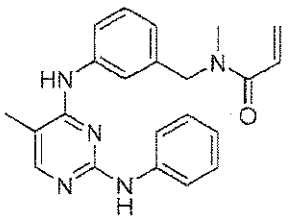
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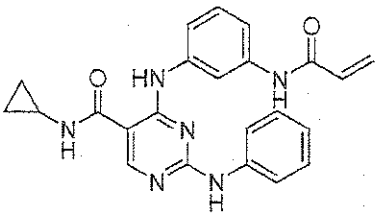
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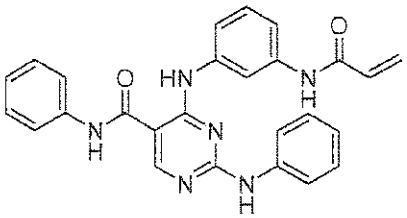
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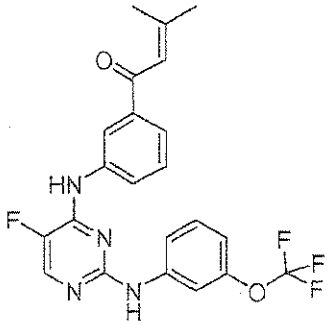
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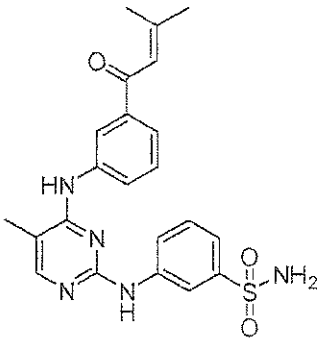
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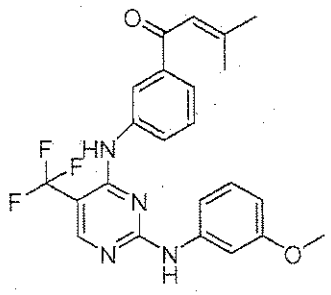
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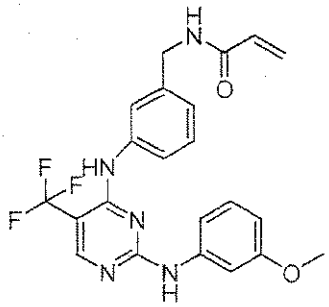
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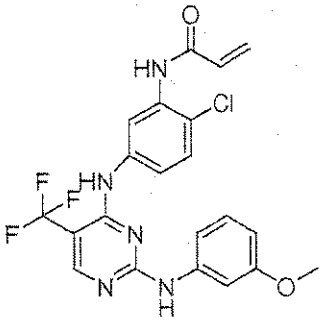
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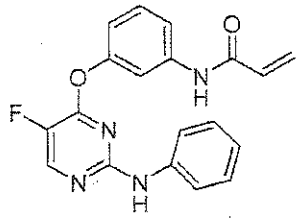
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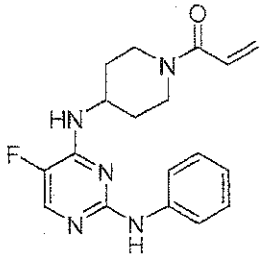
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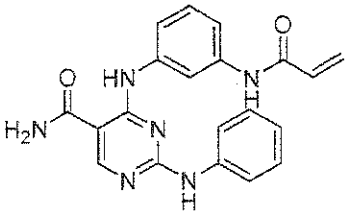
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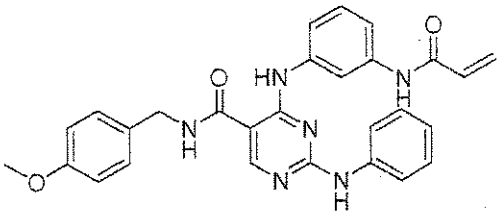
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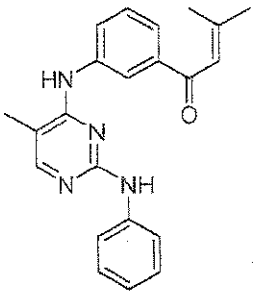
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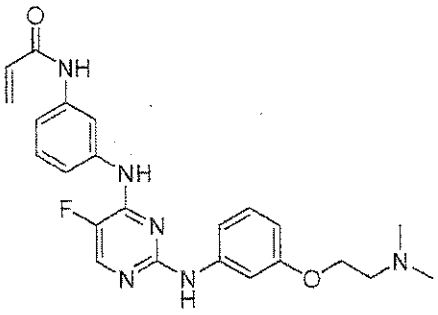
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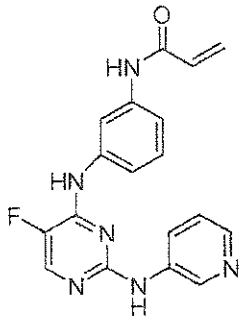
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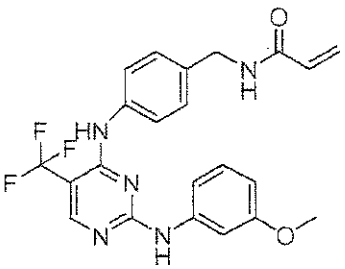
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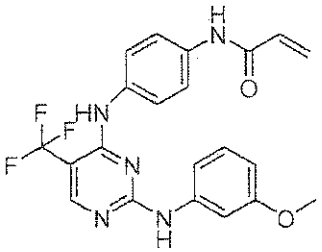
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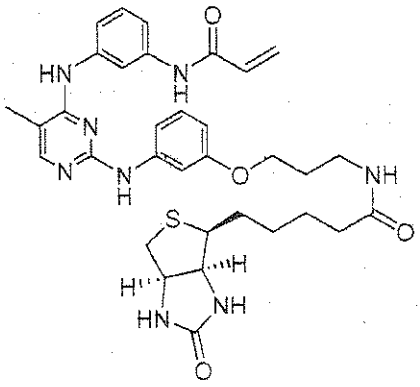
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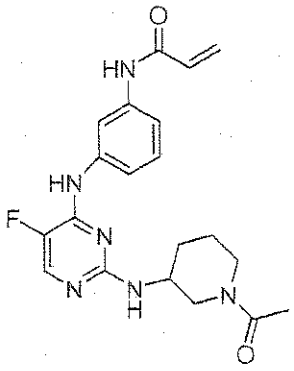
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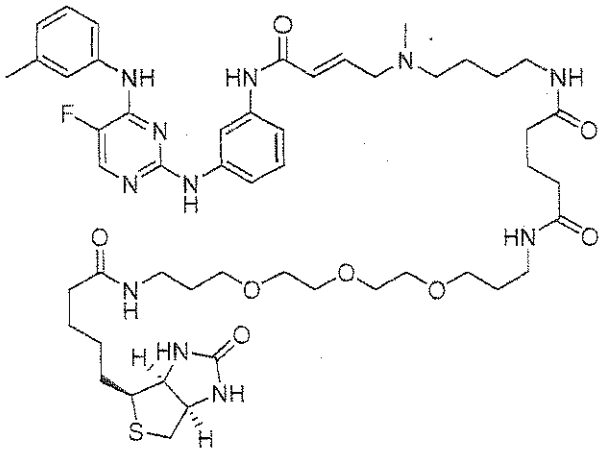
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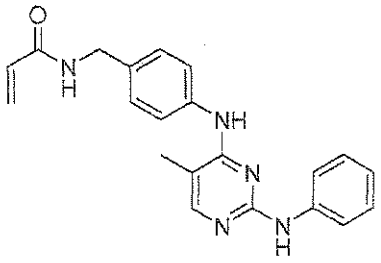
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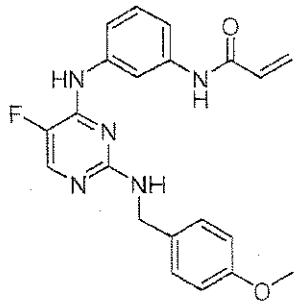
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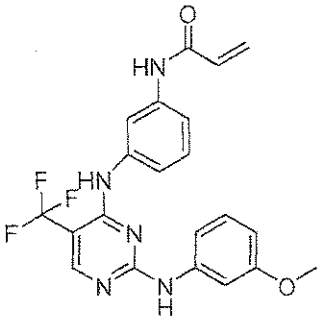
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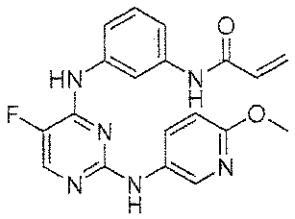
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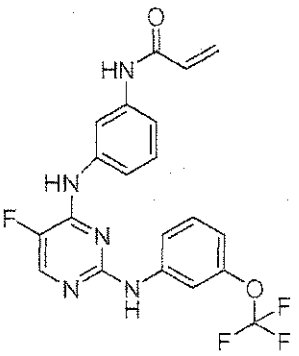
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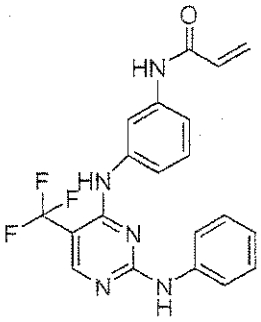
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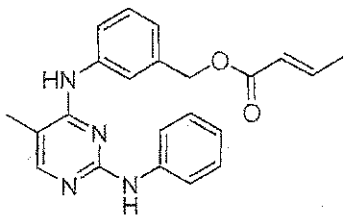
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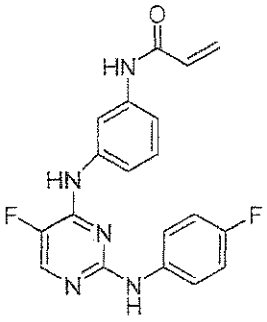
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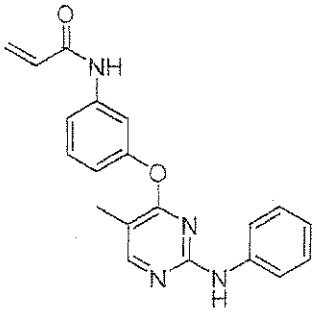
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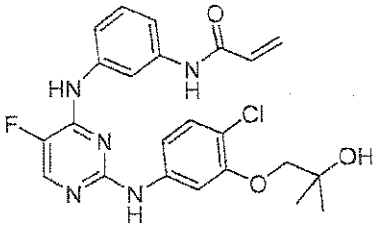
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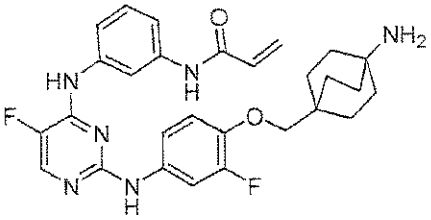
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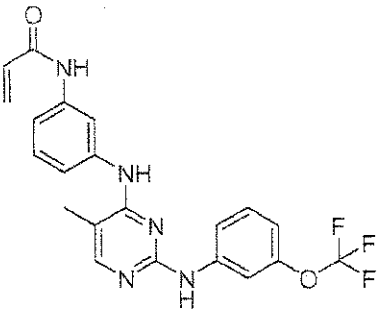
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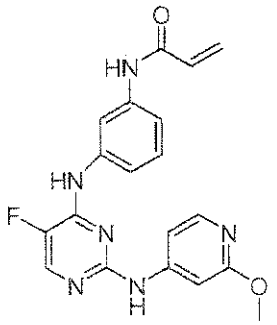
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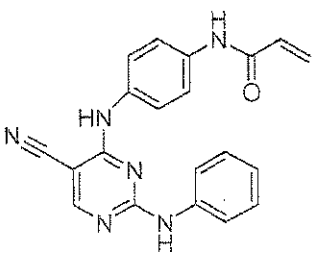
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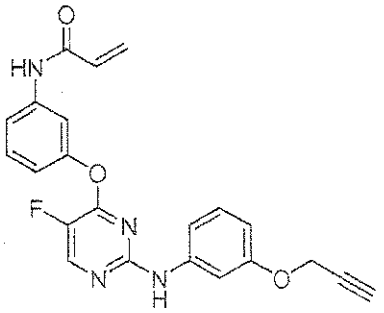
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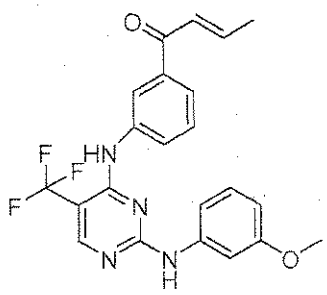
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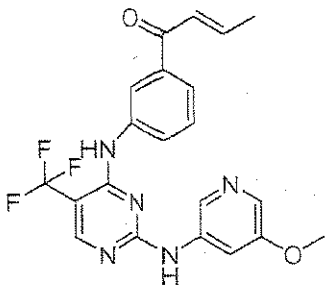
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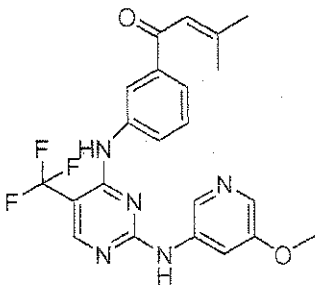
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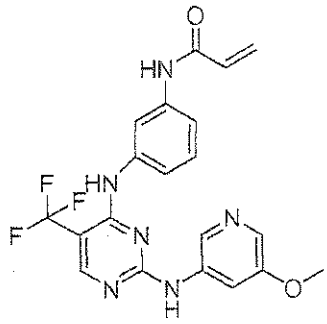
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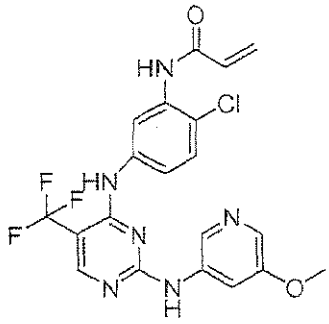
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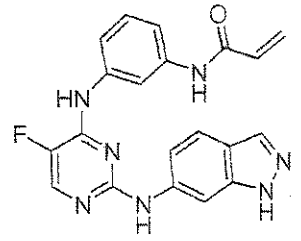
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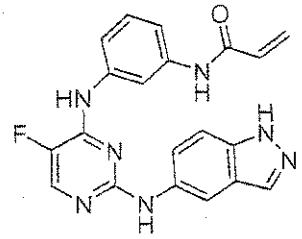
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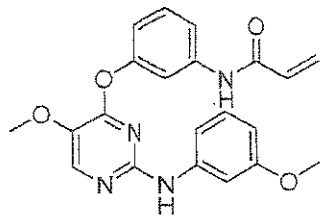
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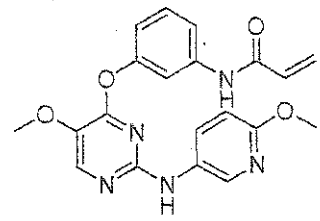
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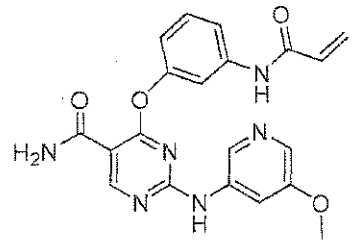
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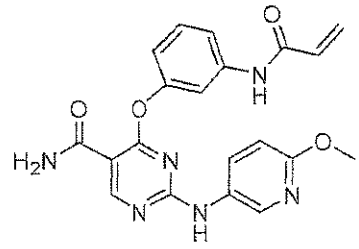
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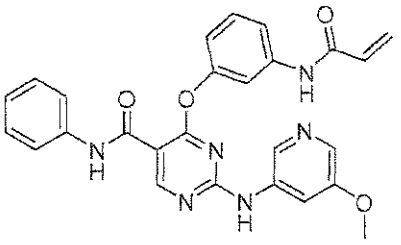
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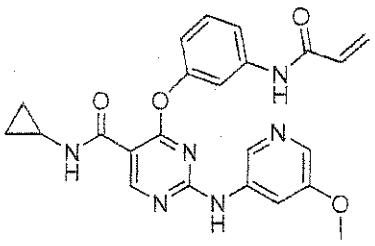
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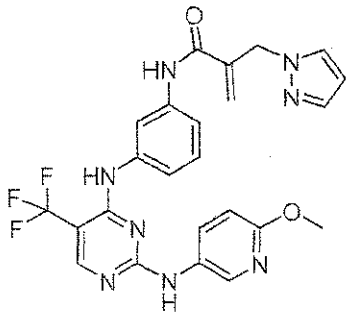
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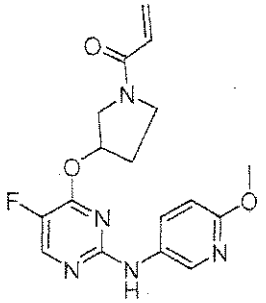
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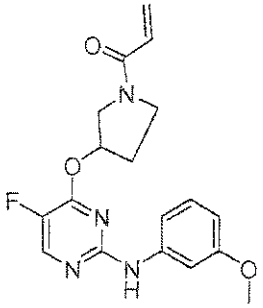
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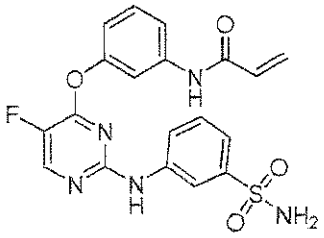
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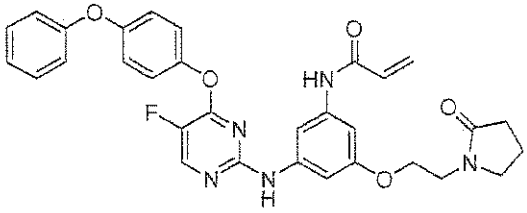
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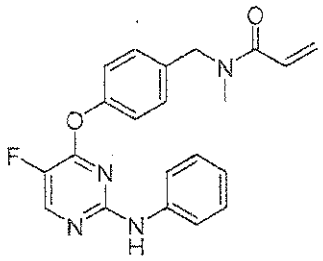
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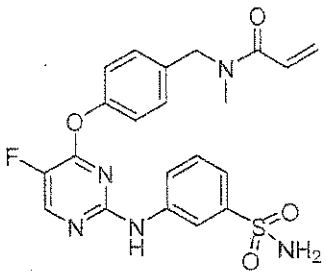
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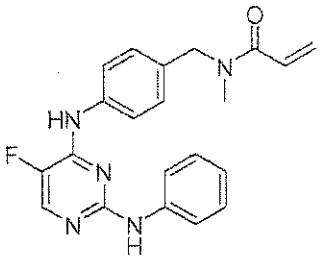
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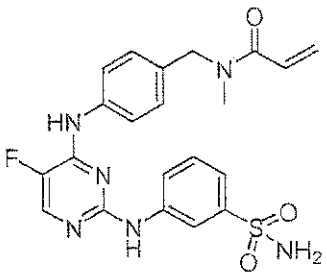
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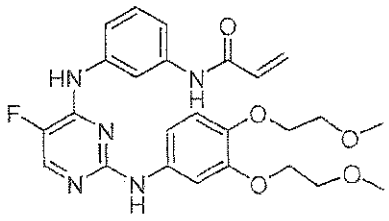
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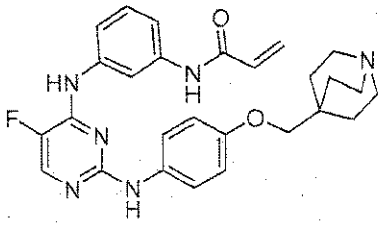
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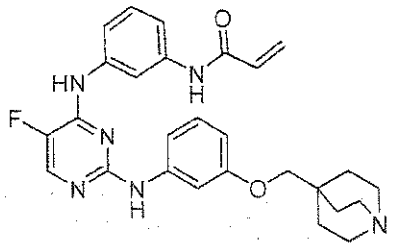
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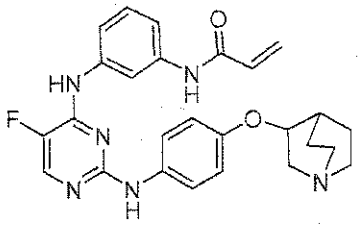
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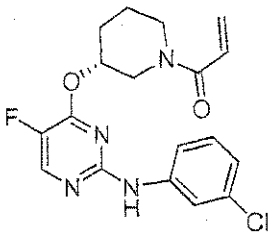
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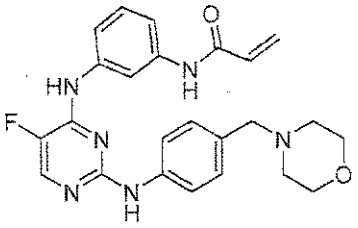
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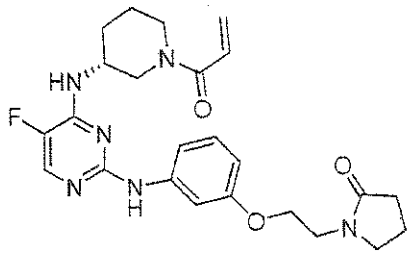
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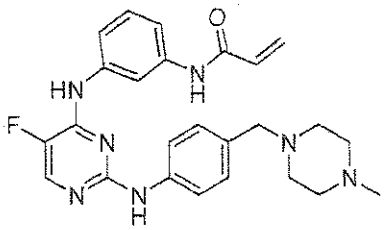
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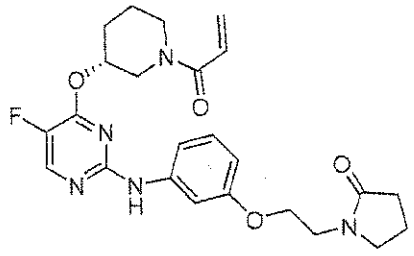
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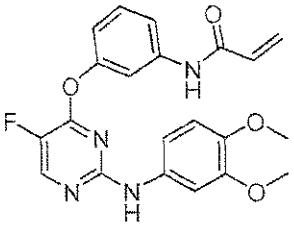
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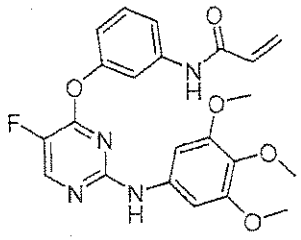
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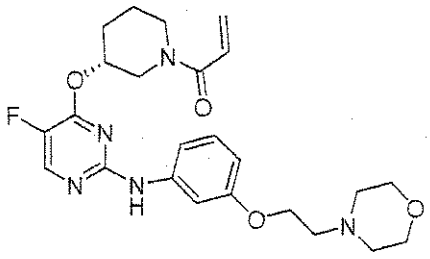
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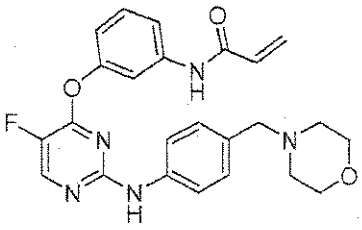
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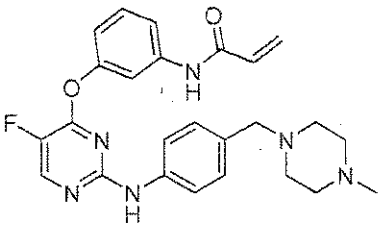
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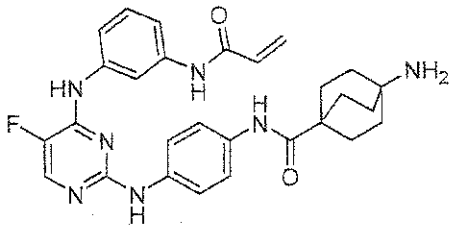
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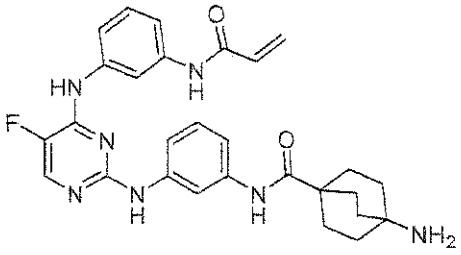
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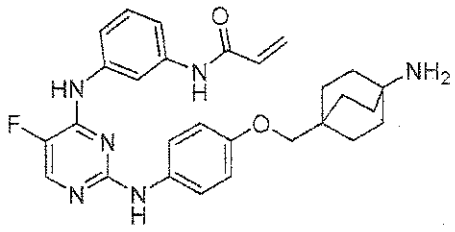
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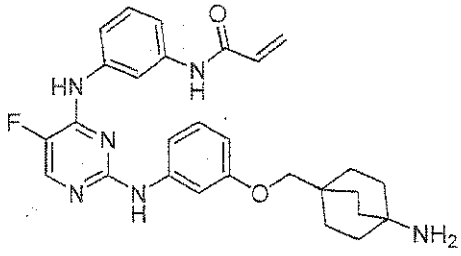
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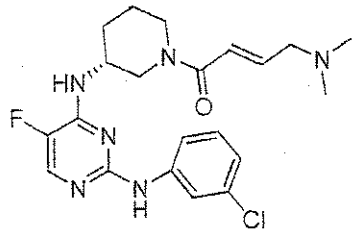
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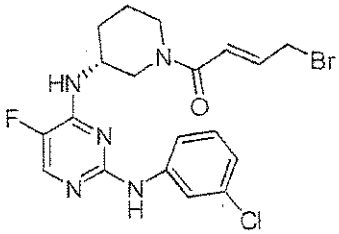
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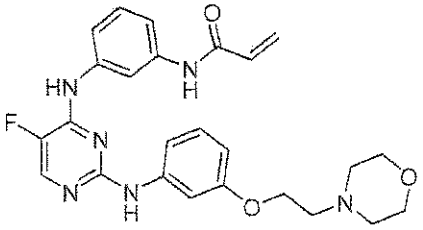
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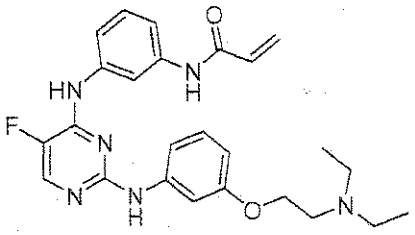
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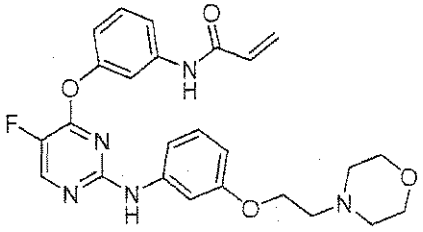
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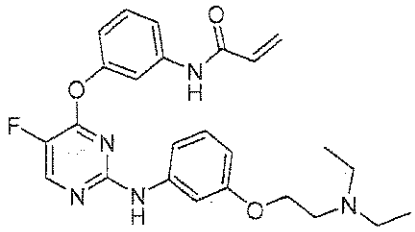
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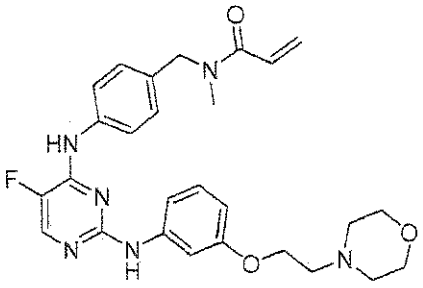
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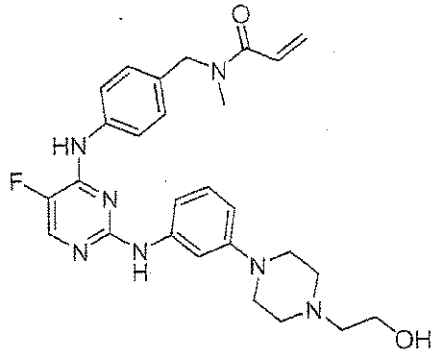
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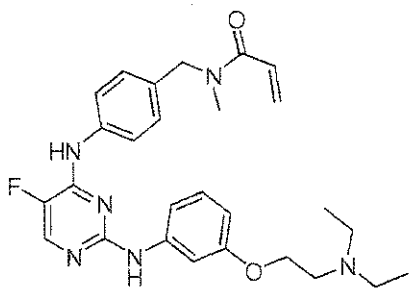
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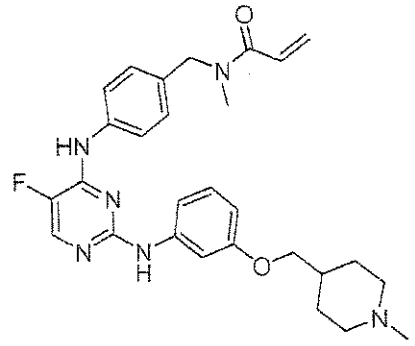
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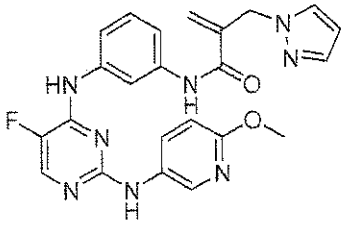
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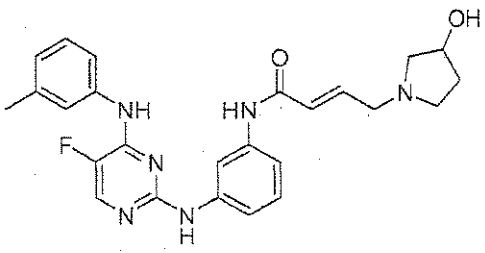
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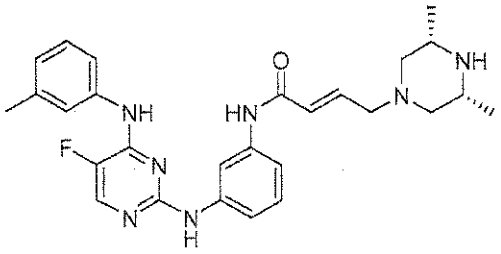
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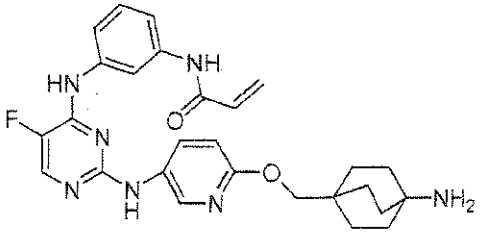
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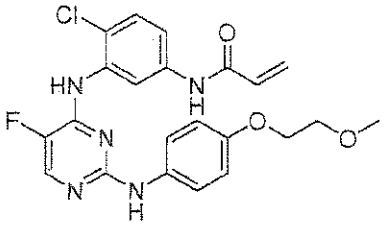
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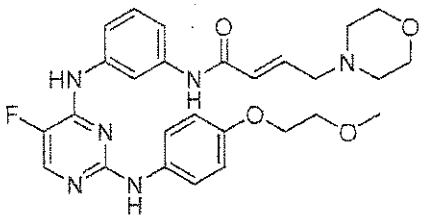
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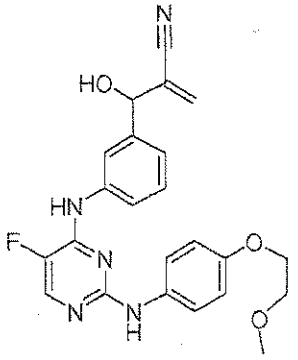
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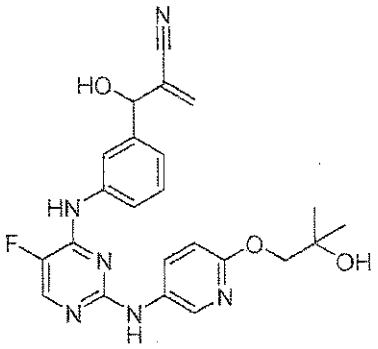
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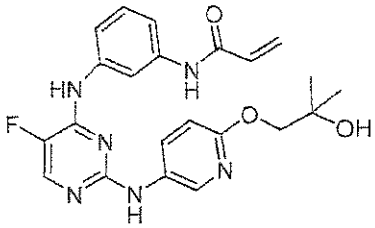
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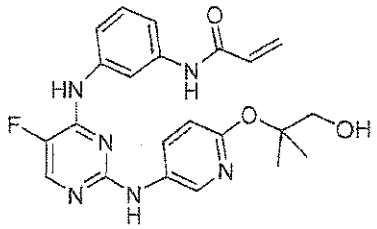
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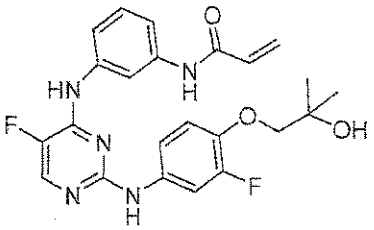
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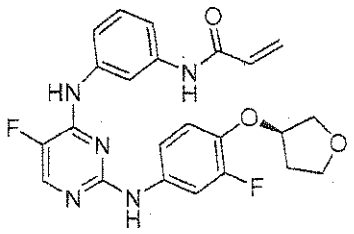
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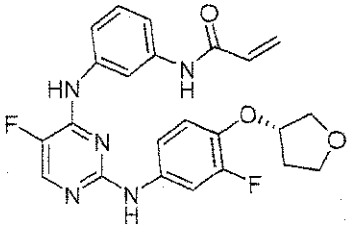
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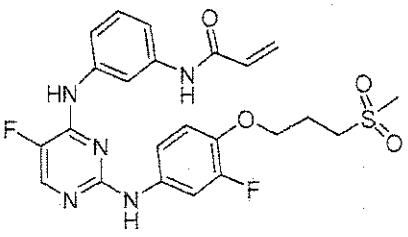
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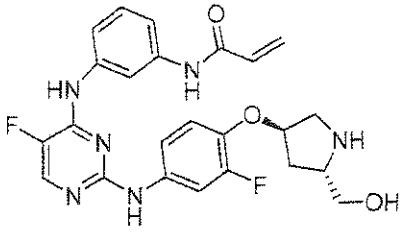
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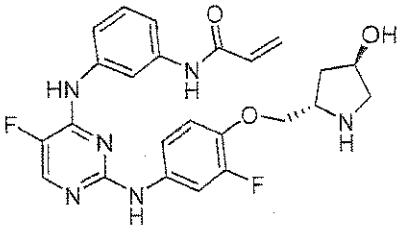
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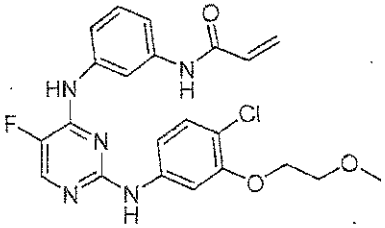
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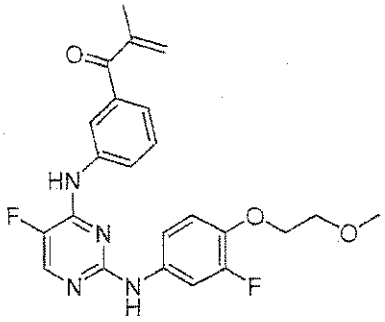
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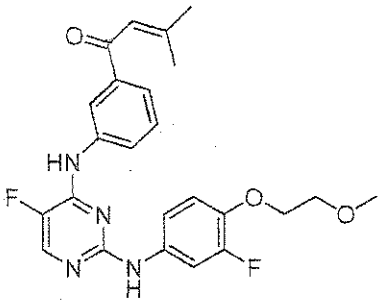
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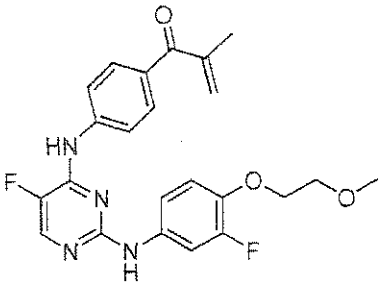
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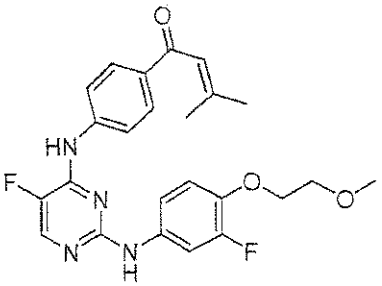
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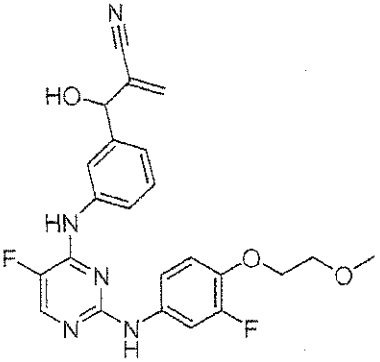
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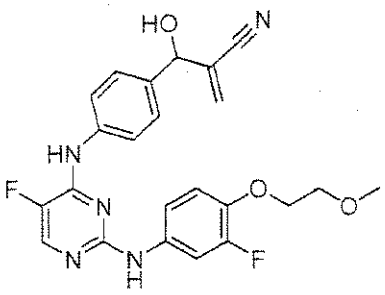
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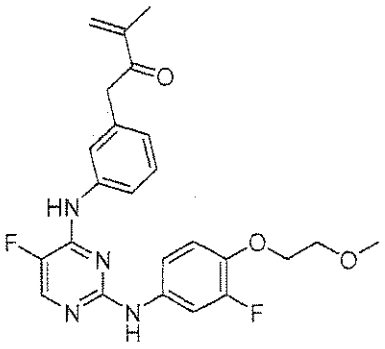
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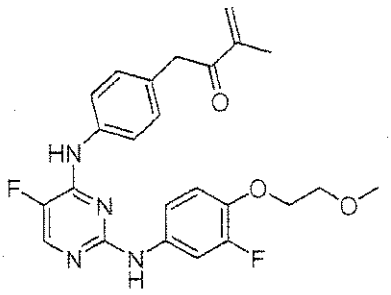
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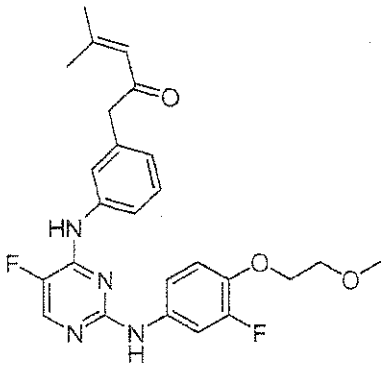
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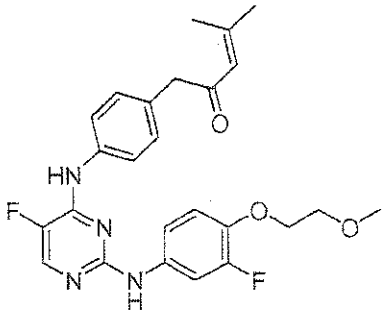
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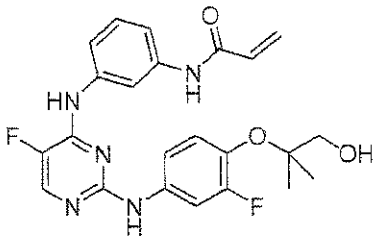
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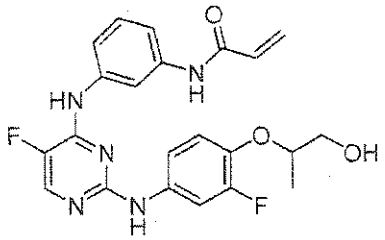
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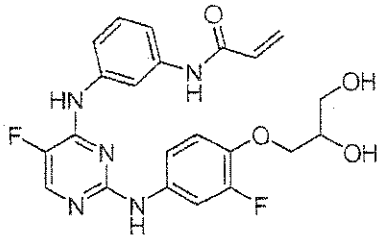
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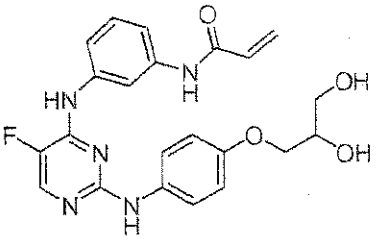
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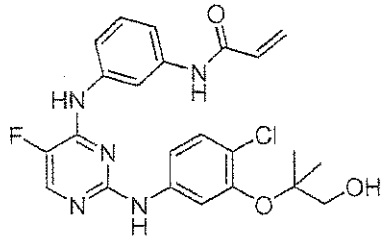
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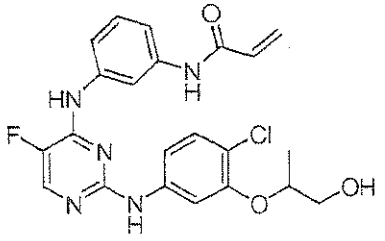
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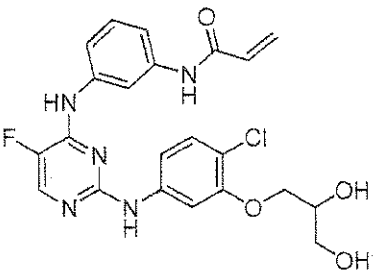
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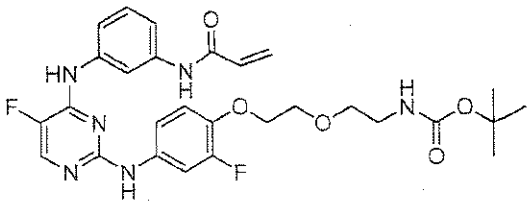
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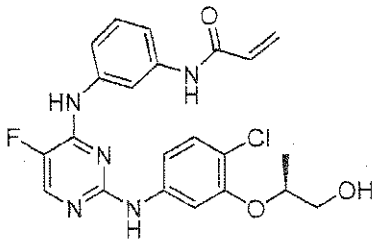
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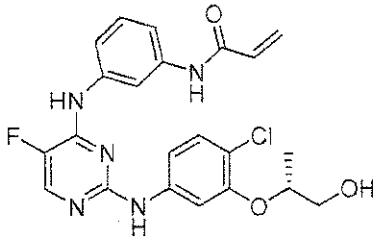
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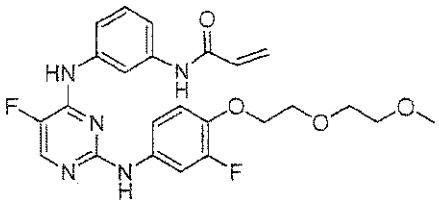
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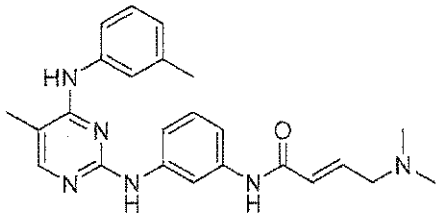
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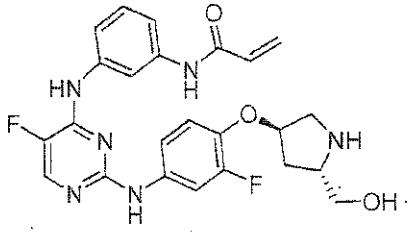
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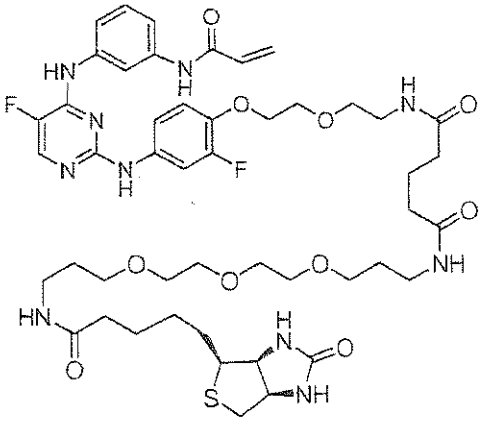
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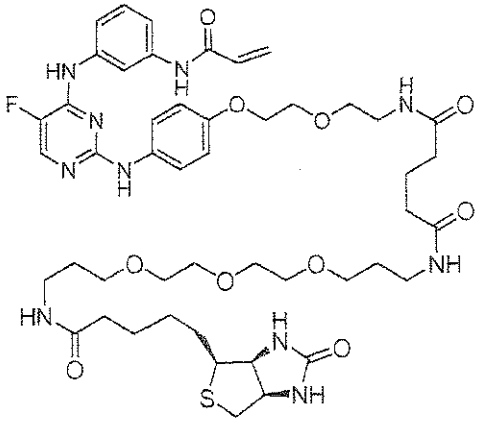
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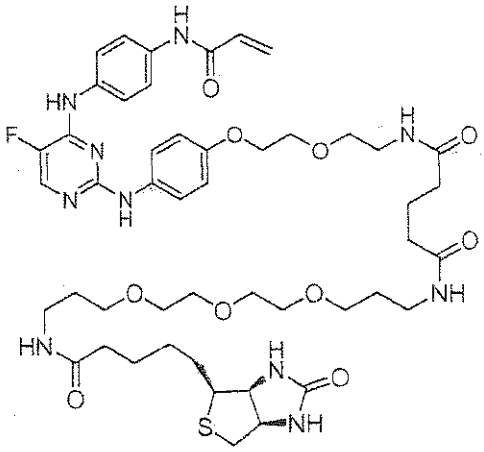
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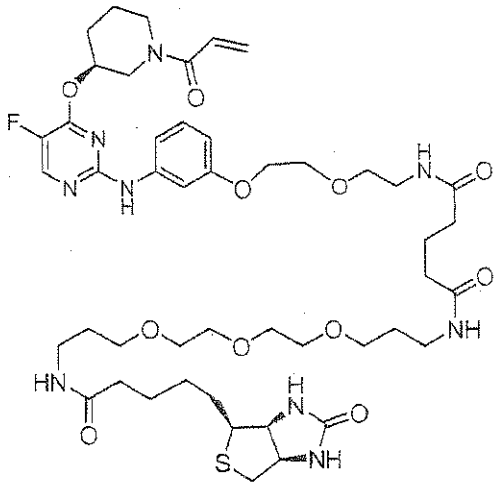
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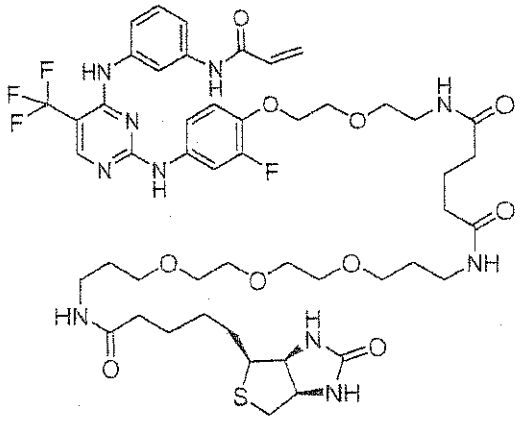
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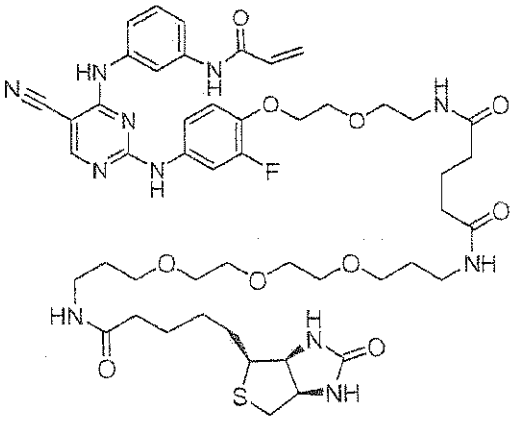
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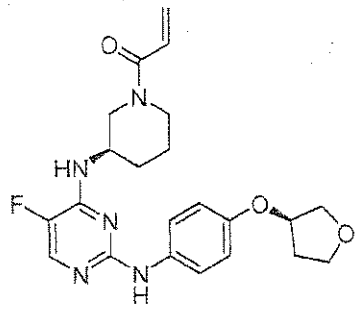
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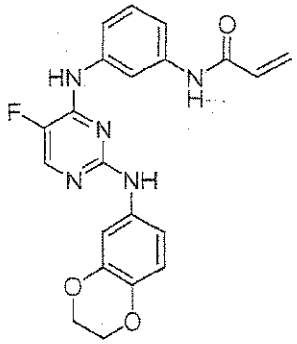
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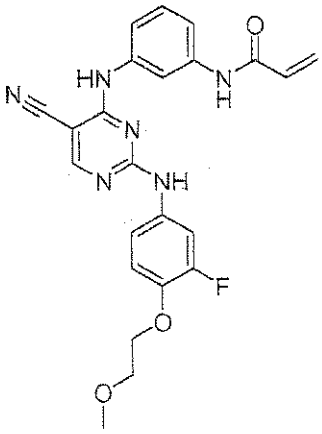
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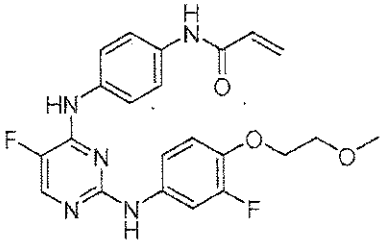
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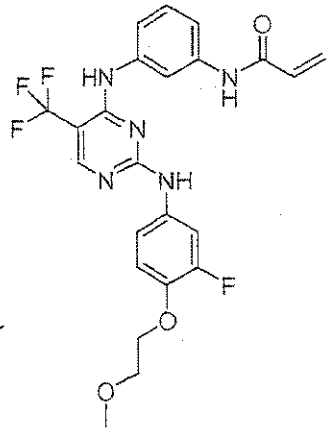
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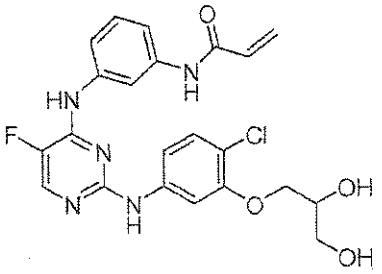
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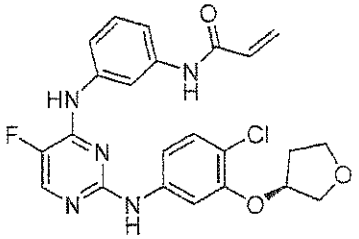
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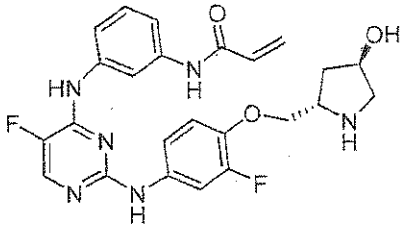
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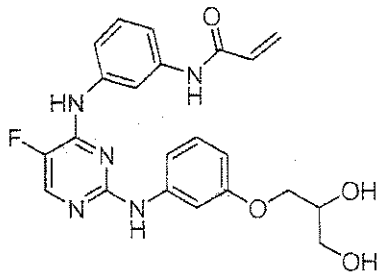
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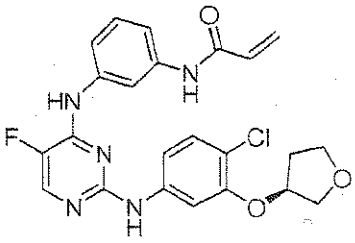
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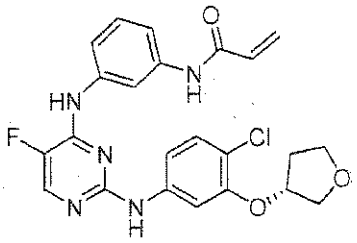
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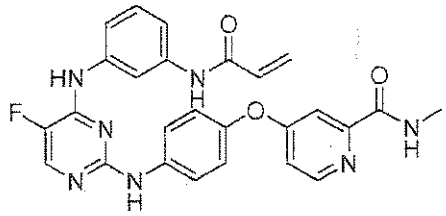
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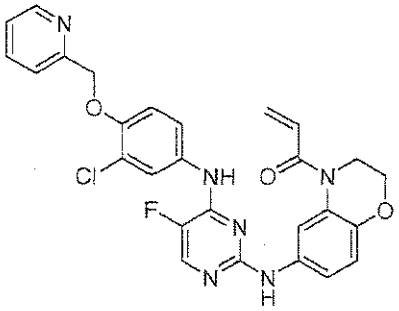
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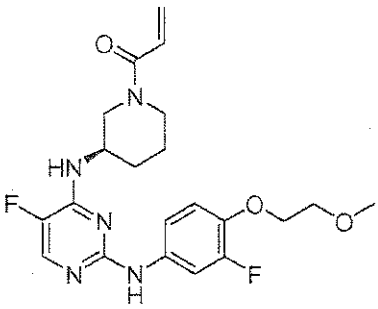
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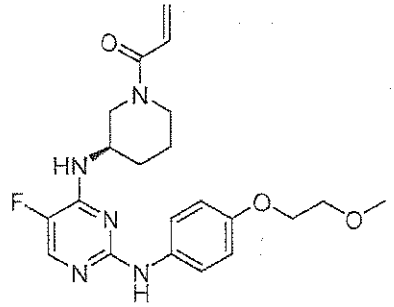
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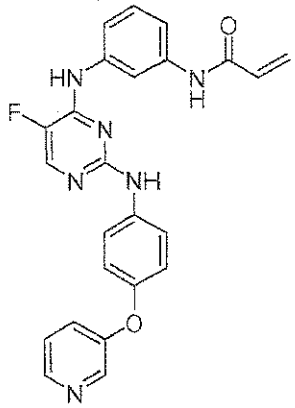
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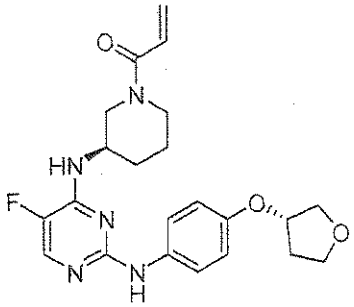
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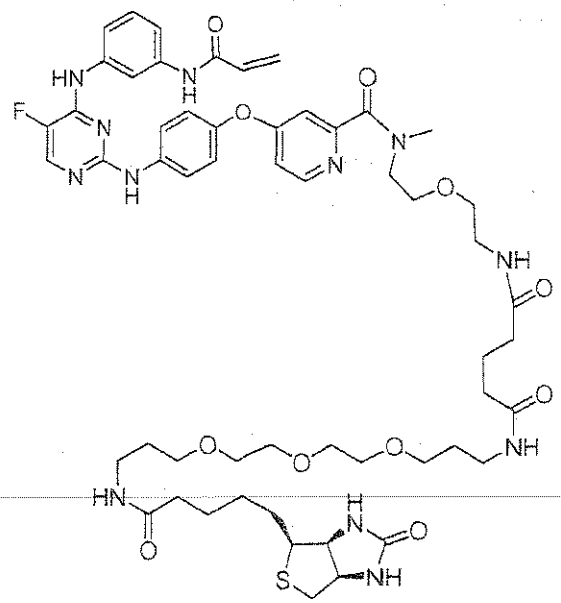
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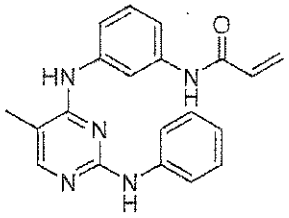
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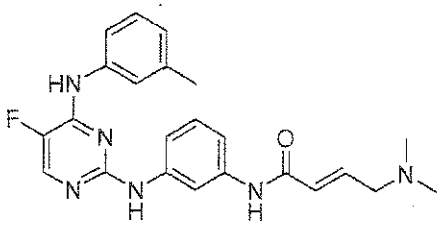
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[00122] In certain embodiments, the present invention provides any compound depicted in Table 5, above, or a pharmaceutically acceptable salt thereof.

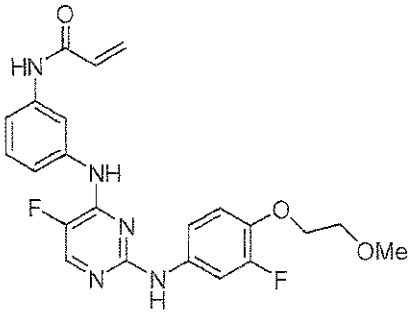
[00123] In certain embodiments, the present invention provides a compound selected from:



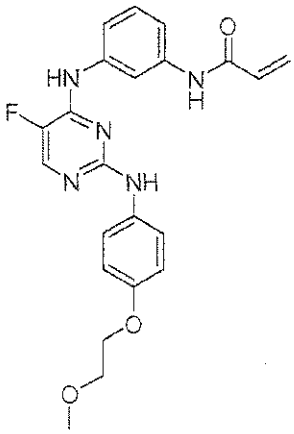
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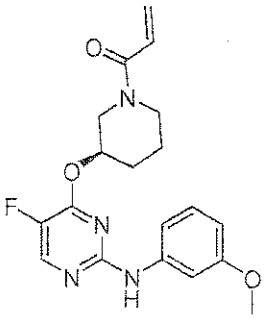
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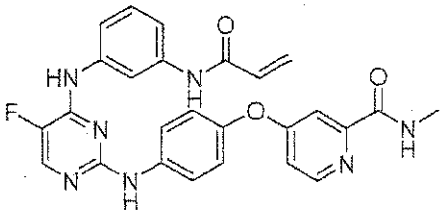
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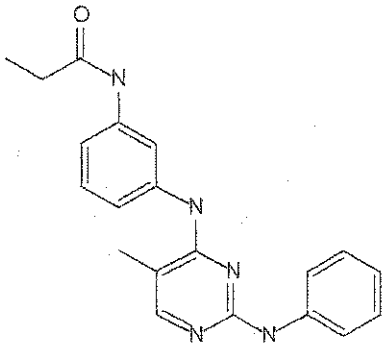
I-190



I-342

or a pharmaceutically acceptable salt thereof.

[00124] As described herein, compounds of the present invention are irreversible inhibitors of at least one of ErbB1, ErbB2, ErbB3 and ErbB4, or a mutant thereof. In some embodiments, provided compounds are irreversible inhibitors of a TEC-kinase (e.g. BTK) and JAK3. One of ordinary skill in the art will recognize that certain compounds of the present invention are reversible inhibitors. In certain embodiments, such compounds are useful as assay comparator compounds. In other embodiments, such reversible compounds are useful as inhibitors of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, and therefore useful for treating one or disorders as described herein. An exemplary reversible compound of the present invention has the following structure.



I^R-7

or a pharmaceutically acceptable salt thereof.

4. ***Uses, Formulation and Administration***

Pharmaceutically Acceptable Compositions

[00125] According to another embodiment, the invention provides a composition comprising a compound of this invention or a pharmaceutically acceptable derivative thereof and a pharmaceutically acceptable carrier, adjuvant, or vehicle. The amount of compound in compositions of this invention is such that is effective to measurably inhibit a protein kinase,

particularly at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, the amount of compound in compositions of this invention is such that is effective to measurably inhibit at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, in a biological sample or in a patient. In certain embodiments, a composition of this invention is formulated for administration to a patient in need of such composition. In some embodiments, a composition of this invention is formulated for oral administration to a patient.

[00126] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00127] The term "pharmaceutically acceptable carrier, adjuvant, or vehicle" refers to a non-toxic carrier, adjuvant, or vehicle that does not destroy the pharmacological activity of the compound with which it is formulated. Pharmaceutically acceptable carriers, adjuvants or vehicles that may be used in the compositions of this invention include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

[00128] A "pharmaceutically acceptable derivative" means any non-toxic salt, ester, salt of an ester or other derivative of a compound of this invention that, upon administration to a recipient, is capable of providing, either directly or indirectly, a compound of this invention or an inhibitorily active metabolite or residue thereof.

[00129] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of at least one of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof.

[00130] Compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial

injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously. Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium.

[00131] For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as carboxymethyl cellulose or similar dispersing agents that are commonly used in the formulation of pharmaceutically acceptable dosage forms including emulsions and suspensions. Other commonly used surfactants, such as Tweens, Spans and other emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

[00132] Pharmaceutically acceptable compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried cornstarch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening, flavoring or coloring agents may also be added.

[00133] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but

[00140] The amount of compounds of the present invention that may be combined with the carrier materials to produce a composition in a single dosage form will vary depending upon the host treated, the particular mode of administration. Preferably, provided compositions should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of the inhibitor can be administered to a patient receiving these compositions.

[00141] It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease being treated. The amount of a compound of the present invention in the composition will also depend upon the particular compound in the composition.

Uses of Compounds and Pharmaceutically Acceptable Compositions

[00142] Compounds and compositions described herein are generally useful for the inhibition of protein kinase activity of one or more enzymes.

[00143] Drug resistance is emerging as a significant challenge for targeted therapies. For example, drug resistance has been reported for Gleevec® and Iressa®, as well as several other kinase inhibitors in development. In addition, drug resistance has been reported for the cKit and PDGFR receptors. It has been reported that irreversible inhibitors may be effective against drug resistant forms of protein kinases (Kwak, E. L., R. Sordella, et al. (2005). "Irreversible inhibitors of the EGF receptor may circumvent acquired resistance to gefitinib." PNAS **102**(21): 7665-7670.) Without wishing to be bound by any particular theory, it is believed that compounds of the present invention may be effective inhibitors of drug resistant forms of protein kinases.

[00144] As used herein, the term "clinical drug resistance" refers to the loss of susceptibility of a drug target to drug treatment as a consequence of mutations in the drug target.

[00145] As used herein, the term "resistance" refers to changes in the wild-type nucleic acid sequence coding a target protein, and/or the protein sequence of the target, which changes decrease or abolish the inhibitory effect of the inhibitor on the target protein.

[00146] Examples of kinases that are inhibited by the compounds and compositions described herein and against which the methods described herein are useful include ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase (including BTK, ITK, TEC, BMX and RLK), and/or JAK3, or a mutant thereof.

liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00134] Pharmaceutically acceptable compositions of this invention may also be administered topically, especially when the target of treatment includes areas or organs readily accessible by topical application, including diseases of the eye, the skin, or the lower intestinal tract. Suitable topical formulations are readily prepared for each of these areas or organs.

[00135] Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-transdermal patches may also be used.

[00136] For topical applications, provided pharmaceutically acceptable compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, provided pharmaceutically acceptable compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

[00137] For ophthalmic use, provided pharmaceutically acceptable compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with or without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutically acceptable compositions may be formulated in an ointment such as petrolatum.

[00138] Pharmaceutically acceptable compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

[00139] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration.

domain that serve as docking sites for adaptor proteins and downstream effectors. In some contexts, activation of phosphatidyl-inositol 3-kinase (PI3K) and mitogen-activated protein kinase pathways occur, leading to cell proliferation and survival (Lin, N. U.; Winer, E. P., Breast Cancer Res 6: 204-210, 2004).

[00150] Interaction between family members is necessitated by deficiencies in ErbB2, which has no known ligand, and ErbB3, which is kinase dead. EGFR, ErbB3, and ErbB4 bind ligand to induce ErbB receptor homodimerization or heterodimerization, whereas ErbB2 functions as the preferred dimerization partner. The composition of the pairwise combinations is important for signal diversification, as dimer identity determines which downstream pathways are activated. Representative downstream gene products in the ErbB signal transduction pathway include Shc, Grb2, SOS1, Ras, Raf1, Mek, ERK1, ERK2, ERα, Akt, mTOR, FKHR, p27, Cyclin D1, FasL, GSK-3, Bad, and STAT3.

[00151] There is strong precedent for involvement of the EGFR and other members of the ErbB family in human cancer because over 60% of all solid tumors overexpress at least one of these proteins or their ligands. Constitutively active, tumorigenic EGFR vIII, a mutant possessing a truncated extracellular domain, has been reported to be present in up to 78% of breast carcinomas and has also been found in glioblastomas. Overexpression of EGFR is commonly found in breast, lung, head and neck, bladder tumors, while ErbB2 expression is frequently elevated in human tumors of epithelial origin. Activating mutations in the tyrosine kinase domain have been identified in patients with non-small cell lung cancer (Lin, N. U.; Winer, E. P., Breast Cancer Res 6: 204-210, 2004). ErbB1 and/or ErbB2 amplification has also been implicated in squamous cell carcinomas, salivary gland carcinomas, ovarian carcinomas, and pancreatic cancers (Cooper, G.C. Oncogenes. 2nd ed. Sudbury: Jones and Barlett, 1995; Zhang, Y., et al., Cancer Res 66 : 1025-32, 2006). Overexpression of ErbB2 has potent transforming activity, likely due to its ability to cooperate with other ErbB receptors (Sherman, L., et al., Oncogene 18: 6692-99, 1999). In fact, some human cancers that overexpress both EGFR and ErbB2 have a poorer prognosis than cancers that overexpress either receptor alone.

[00152] The ErbB signaling network is often a key component in the pathogenesis of breast cancer. Amplification of ErbB2 is associated with an aggressive tumor phenotype that is characterized by relatively rapid tumor growth, metastatic spread to visceral sites, and drug resistance. ErbB2 has been shown to be amplified in 20% of axillary node-negative ("ANN")

[00147] The activity of a compound utilized in this invention as an inhibitor of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of either the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of activated ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof. Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3. Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/ErbB1, inhibitor/ErbB2, inhibitor/ErbB3, inhibitor/ErbB4, inhibitor/TEC-kinase (i.e., TEC, BTK, ITK, RLK and BMX), or inhibitor/JAK3 complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3 bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, are set forth in the Examples below.

[00148] Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to a tyrosine residue located on a protein substrate. Receptor tyrosine kinases act to transmit signals from the outside of a cell to the inside by activating secondary messaging effectors via a phosphorylation event. A variety of cellular processes are promoted by these signals, including proliferation, carbohydrate utilization, protein synthesis, angiogenesis, cell growth, and cell survival.

(a) ***ErbB Family***

[00149] ErbB receptors, a major family of receptor tyrosine kinases, are composed of an extracellular ligand binding domain, a single transmembrane domain, and an intracellular domain with tyrosine kinase activity. The ErbB family comprises ErbB1 (commonly known as EGFR), ErbB2 (commonly known as HER2 or *neu*), ErbB3 (commonly known as HER3), and ErbB4 (commonly known as HER4). More than 10 ligands (including EGF, TGFα, AR, BTC, EPR, HB-EGF, NRG-1, NRG-2, NRG-3, NRG-4) have been identified for the various receptor family members. Upon ligand binding the extracellular domain undergoes conformational change, allowing the formation of homodimers or heterodimers with other members of the ErbB family. Dimerization induces tyrosine phosphorylation of specific residues in the intracellular

[00157] In both *in vitro* and *in vivo* models, strategies that employ a dual ErbB approach seem to have greater antitumor activity than agents targeting a single ErbB receptor. Thus, agents that target multiple members of ErbB family are likely to provide therapeutic benefit to a broader patient population (Zhang, Y., et al., Cancer Res 66: 1025-32, 2006). In certain embodiments, provided compounds inhibit one or more of ErbB1, ErbB2, ErbB3, and ErbB4. In some embodiments, provided compounds inhibit two or more of ErbB1, ErbB2, ErbB3, and ErbB4, or a mutant thereof, and are therefore pan-ErbB inhibitors.

[00158] Clearly, there is growing evidence to support the concurrent inhibition of two or more ErbB (i.e., pan-ErbB) receptors in cancer therapy. Possible pan-ErbB approaches with small molecules include using combinations of agents that target individual ErbB receptors, using single agents that target multiple ErbB receptors, or using agents that interfere with ErbB receptor interactions (e.g., dimerization). Additional strategies include therapies utilizing a small molecule in combination with antibodies, or chemoprevention therapies (Lin, N. U.; Winer, E. P., Breast Cancer Res 6: 204-210, 2004).

[00159] An example of small molecule pan-ErbB inhibition is CI-1033, an irreversible pan-ErbB inhibitor that covalently binds to the ATP binding site of the intracellular kinase domain. Another irreversible pan-ErbB receptor tyrosine kinase inhibitor is HKI-272, which inhibits the growth of tumor cells that express ErbB-1 (EGFR) and ErbB-2 (HER-2) in culture and xenografts, and has antitumor activity in HER-2-positive breast cancer (Andrulis, I.L., et al., J Clin Oncol 16: 1340-9, 1998). Irreversible inhibitors have demonstrated superior antitumor activity in comparison with reversible inhibitors.

[00160] Neurofibromatosis type I (NF1) is a dominantly inherited human disease affecting one in 2500-3500 individuals. Several organ systems are affected, including bones, skin, iris, and the central nervous system, as manifested in learning disabilities and gliomas. A hallmark of NF1 is the development of benign tumors of the peripheral nervous system (neurofibromas), which vary greatly in both number and size among patients. Neurofibromas are heterogeneous tumors composed of Schwann cells, neurons, fibroblasts and other cells, w/ Schwann cells being the major (60-80%) cell type.

[00161] Abberant expression of the EGFR is associated with tumor development in NF1 and in animal models of NF1, suggesting a role in pathogenesis and representing a novel potential therapeutic target. EGFR expression affects the growth of tumor cell lines derived from NF1

breast cancer cases, and this amplification has been identified as an independent prognostic factor for risk of recurrence in ANN breast cancer. (Andrulis, I.L., et al., J Clin Oncol 16: 1340-9, 1998).

[00153] Targeted blockade of ErbB signaling with trastuzumab (Herceptin), a monoclonal antibody directed at ErbB2, has been shown to improve survival in women with ErbB2-positive, advanced breast cancer. Other monoclonal antibodies directed against ErbB receptors include cetuximab (Erbitux) and panitumumab (Vectibix).

[00154] Several small molecule tyrosine kinase inhibitors (TKIs) have been found to act selectively upon ErbB family members. Notable examples include gefitinib (Iressa) and erlotinib (Tarceva), both of which target the EGFR. These small molecules compete with ATP for binding to the kinase domain of the receptor. Compared to monoclonal antibodies, TKIs have several advantages in that they are orally bioavailable, well-tolerated, and appear to be active against truncated forms of ErbB2 and EGFR receptors (e.g., EGFR vIII) *in vitro*. In addition, the small size of small molecule TKIs may allow them to penetrate sanctuary sites such as the central nervous system. Finally, the homology between kinase domains of ErbB receptors allows for development of TKIs that target more than one member of the ErbB family simultaneously, the advantages of which are described herein.

[00155] Although certain malignancies have been linked to the overexpression of individual receptors, efficient signal transduction relies on the coexpression of ErbB receptor family members. This cooperation of ErbB receptor family members in signal transduction and malignant transformation may limit the success of agents that target individual receptors in the treatment of cancer; a potential mechanism of resistance to agents targeting a single ErbB receptor is upregulation of other members of the receptor family (Britten, C. D., Mol Cancer Ther 3: 1335-42, 2004).

[00156] Agents that target two or more ErbB receptors are called pan-ErbB regulators. ERRP is a pan-ErbB negative regulator that is expressed in most benign pancreatic ductal epithelium and islet cells. Tumors have been found to experience a progressive loss in ERRP expression. That Erbitux and Herceptin show success in a limited patient base (tumors having increased expression of EGFR or ErbB2) could be partly due to coexpression of multiple ErbB family members.

patients under conditions where EGF is not the primary factor driving growth of the cells. These data suggest that EGFR may play an important role in NF1 tumorigenesis and Schwann cell transformation (DeClue, J. E., et al., J Clin Invest 105: 1233-41, 2000).

[00162] Patients with NF1 develop aggressive Schwann cell neoplasmas known as malignant peripheral nerve sheath tumors (MPNSTs). Schwann cells are the major supportive cell population in the peripheral nervous system. Neoplastic Schwann cells within these neoplasms variably express the ErbB tyrosine kinases mediating NRG-1 responses (ErbB2, ErbB3, ErbB4). Neuregulin-1 (NRG-1) proteins promote the differentiation, survival, and/or proliferation of many cell types in the developing nervous system, and overexpression of NRG-1 in myelinating Schwann cells induces the formation of malignant peripheral nerve sheath tumors (MPNSTs) (Fallon, K. B., et al., J Neuro Oncol 66: 273-84, 2004).

[00163] Deregulation of Schwann cell growth is a primary defect driving the development of both benign neurofibromas and MPNST in neurofibromatosis type I (NF1) patients. Growth of MPNSTs and transformed mouse Schwann cells *in vitro* is highly EGF-dependent and can be blocked by EGFR inhibitors under conditions where EGF is the primary growth factor. Some human MPNST cell lines have been found to demonstrate constitutive ErbB phosphorylation. While treatment with ErbB inhibitors abolishes ErbB phosphorylation and reduces DNA synthesis in these lines, effective chemotherapeutic regimens for MPNST remain elusive (Stonecypher, M. S., et al., Oncogene 24: 5589-5605, 2005).

[00164] Schwannomas are peripheral nerve tumors comprised almost entirely of Schwann-like cells, and typically have mutations in the neurofibromatosis type II (NF2) tumor suppressor gene. Ninety percent of NF2 patients develop bilateral vestibular schwannomas and/or spinal schwannomas. Enlarging schwannomas can compress adjacent structures, resulting in deafness and other neurologic problems. Surgical removal of these tumors is difficult, often resulting in increased patient morbidity.

[00165] Both normal human Schwann cells and schwannoma cells express neuregulin receptors (i.e., ErbB receptors), and schwannoma cells proliferate in response to neuregulin. It is possible that aberrant neuregulin production or response contributes to aberrant schwannoma cell proliferation (Pelton, P. D., et al., Oncogene 17: 2195-2209, 1998).

[00166] The NF2 tumor suppressor, Merlin, is a membrane/cytoskeleton-associated protein implicated in the regulation of tyrosine kinase activity. Genetic interactions between a Merlin

mutation and EGFR pathway mutations have been documented in *Drosophila* (LaJeunesse, D. R., et al., Genetics 158: 667-79, 2001). Other evidence suggests Merlin can inhibit EGFR internalization and signaling upon cell-cell contact by restraining the EGFR into a membrane compartment from which it can neither signal nor be internalized (McClatchey, A. I., et al., Genes and Development 19: 2265-77, 2005; Curto, M. C., et al., J Cell Biol 177: 893-903, 2007).

[00167] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00168] Provided compounds are inhibitors of one or more of ErbB1, ErbB2, ErbB3, and ErbB4 and are therefore useful for treating one or more disorders associated with activity of one of more of ErbB1, ErbB2, ErbB3, and ErbB4. Thus, in certain embodiments, the present invention provides a method for treating an ErbB1-mediated, an ErbB2-mediated, an ErbB3-mediated, and/or ErbB4-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00169] As used herein, the terms "ErbB1-mediated", "ErbB2-mediated," "ErbB3-mediated," and/or "ErbB4-mediated" disorders or conditions as used herein means any disease or other deleterious condition in which one or more of ErbB1, ErbB2, ErbB3, and/or ErbB4, or a mutant thereof, are known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which one or more of ErbB1, ErbB2, ErbB3, and/or ErbB4, or a mutant thereof, are known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from a proliferative disorder, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

[00170] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from a cancer. In some embodiments,

the cancer is associated with a solid tumor. In certain embodiments, the cancer is breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, or non-small cell lung cancer. In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, or pancreatic cancer.

[00171] In certain embodiments, the present invention provides a method for treating or lessening the severity of neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms (e.g. MPNST's), or Schwannomas.

(b) *TEC Family*

[00172] The TEC family of non-receptor tyrosine kinases, referred to herein as "TEC-kinases," plays a central role in signaling through antigen-receptors such as the TCR, BCR and Fc receptors (reviewed in Miller A, et al. Current Opinion in Immunology 14; 331-340 (2002). TEC-kinases are essential for T cell activation. Three members of the family, Itk, Rlk and, are activated downstream of antigen receptor engagement in T cells and transmit signals to downstream effectors, including PLC-γ. Combined deletion of Itk and Rlk in mice leads to a profound inhibition of TCR responses including proliferation, cytokine production and immune responses to an intracellular parasite (Toxoplasma gondii) (Schaeffer et al., Science 284; 638-641 (1999)). Intracellular signalling following TCR engagement is effected in ITK/RLK deficient T cells; inositol triphosphate production, calcium mobilization and MAP kinase activation are all reduced. Tec-kinases are also essential for B cell development and activation.

[00173] TEC-kinases include five family members, which are expressed primarily in hematopoietic cells: TEC, BTK, ITK (also known as TSK and EMT), RLK (also known as TXK), and BMX (also known as ETK). Additional related TEC-kinases have been found in Drosophila melanogaster, zebrafish (Danio rerió), skate (Raja eglanteria), and sea urchin (Anthocidaris crassispina).

[00174] Provided compounds are inhibitors of one of more TEC-kinases and are therefore useful for treating one or more disorders associated with activity of one or more TEC-kinases. Thus, in certain embodiments, the present invention provides a method for treating a TEC-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00175] The term "TEC-mediated condition", as used herein means any disease or other deleterious condition in which TEC-kinases are known to play a role. Such conditions include those described herein and in Melcher, M *et al.*, "The Role of TEC Family Kinases in Inflammatory Processes", *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, Vol. 6, No. 1, pp. 61-69 (Feb. 2007). Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which TEC-kinases are known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from autoimmune, inflammatory, proliferative, and hyperproliferative diseases and immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS)(also known as HIV), wherein said method comprises administering to a patient in need thereof a composition of the present invention.

[00176] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including diseases of the respiratory tract including, without limitation, reversible obstructive airways diseases including asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g., late asthma airways hyper-responsiveness) and bronchitis. In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including those conditions characterized by inflammation of the nasal mucus membrane, including acute rhinitis, allergic, atrophic rhinitis and chronic rhinitis including rhinitis caseosa, hypertrophic rhinitis, rhinitis purulenta, rhinitis sicca and rhinitis medicamentosa; membranous rhinitis including croupous, fibrinous and pseudomembranous rhinitis and scrofoulous rhinitis, seasonal rhinitis including rhinitis nervosa (hay fever) and vasomotor rhinitis, sarcoidosis, farmer's lung and related diseases, fibroid lung, and idiopathic interstitial pneumonia.

[00177] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and

Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, and bone metastasis.

[00178] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including diseases and disorders of the skin, including, without limitation, psoriasis, systemic sclerosis, atopical dermatitis, contact dermatitis and other eczematous dermatitis, seborrhoetic dermatitis, Lichen planus, pemphigus, bullous pemphigus, epidermolysis bullosa, urticaria, angiodermas, vasculitides, erythemas, cutaneous eosinophilias, uveitis, alopecia, areata and vernal conjunctivitis.

[00179] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including diseases and disorders of the gastrointestinal tract, including, without limitation, celiac disease, proctitis, eosinophilic gastro-enteritis, mastocytosis, pancreatitis, Crohn's disease, ulcerative colitis, food-related allergies which have effects remote from the gut, e. g. migraine, rhinitis and eczema.

[00180] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including those diseases and disorders of other tissues and systemic disease, including, without limitation, multiple sclerosis, artherosclerosis, lupus erythematosus, systemic lupus erythematosus, Hashimoto's thyroiditis, myasthenia gravis, type I diabetes, nephrotic syndrome, eosinophilia fascitis, hyper IgE syndrome, lepromatous leprosy, sezary syndrome and idiopathic thrombocytopenia purpura, restenosis following angioplasty, tumours (for example leukemia, lymphomas, and prostate cancers), and artherosclerosis.

[00181] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with TEC-kinases including allograft rejection including, without limitation, acute and chronic allograft rejection following for example transplantation of kidney, heart, liver, lung, bone marrow, skin and cornea; and chronic graft versus host disease.

[00182] In some embodiments, the present invention relates to a method of treating or lessening the severity of one or more of the diseases or conditions associated with TEC-kinases,

as recited above, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

(c) ***Bruton's tyrosine kinase (BTK)***

[00183] Bruton's tyrosine kinase ("BTK"), a member of TEC-kinases, is a key signaling enzyme expressed in all hematopoietic cell types except T lymphocytes and natural killer cells. BTK plays an essential role in the B-cell signaling pathway linking cell surface B-cell receptor (BCR) stimulation to downstream intracellular responses.

[00184] BTK is a key regulator of B-cell development, activation, signaling, and survival (Kurosaki, Curr Op Imm, 2000, 276-281; Schaeffer and Schwartzberg, Curr Op Imm 2000, 282-288). In addition, BTK plays a role in a number of other hematopoietic cell signaling pathways, e.g., Toll like receptor (TLR) and cytokine receptor-mediated TNF-α production in macrophages, IgE receptor (Fc_epsilon_RI) signaling in mast cells, inhibition of Fas/APO-1 apoptotic signaling in B-lineage lymphoid cells, and collagen-stimulated platelet aggregation. See, e.g., C. A. Jeffries, et al., (2003), Journal of Biological Chemistry 278:26258-26264; N. J. Horwood, et al., (2003), The Journal of Experimental Medicine 197: 1603- 1611 ; Iwaki et al. (2005), Journal of Biological Chemistry 280(48):40261 -40270; Vassilev et al. (1999), Journal of Biological Chemistry 274(3): 1646-1656, and Quek et al. (1998), Current Biology 8(20): 1137-1140.

[00185] Patients with mutations in BTK have a profound block in B cell development, resulting in the almost complete absence of mature B lymphocytes and plasma cells, severely reduced Ig levels and a profound inhibition of humoral response to recall antigens (reviewed in Vihinen et al Frontiers in Bioscience 5 : d917-928). Mice deficient in BTK also have a reduced number of peripheral B cells and greatly decreased serum levels of IgM and IgG3. BTK deletion in mice has a profound effect on B cell proliferation induced by anti-IgM, and inhibits immune responses to thymus-independent type II antigens (Ellmeier et al, J Exp Med 192: 1611-1623 (2000)). BTK also plays a crucial role in mast cell activation through the high-affinity IgE receptor (Fc_epsilon_RI). BTK deficient murine mast cells have reduced degranulation and decreased production of proinflammatory cytokines following Fc_epsilon_RI cross-linking (Kawakami et al. Journal of Leukocyte Biology 65: 286-290).

[00186] Provided compounds are inhibitors of BTK and are therefore useful for treating one or more disorders associated with activity of BTK. Thus, in some embodiments, the present invention provides a method for treating a BTK-mediated disorder comprising the step of

administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00187] As used herein, the term "BTK-mediated" disorders or conditions as used herein means any disease or other deleterious condition in which BTK, or a mutant thereof, is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which BTK, or a mutant thereof, is known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from a proliferative disorder or an autoimmune disorder, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

[00188] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK. In some embodiments, the disease or condition is an autoimmune disease, e.g., inflammatory bowel disease, arthritis, lupus, rheumatoid arthritis, psoriatic arthritis, osteoarthritis, Still's disease, juvenile arthritis, diabetes, myasthenia gravis, Hashimoto's thyroiditis, Ord's thyroiditis, Graves' disease, Sjogren's syndrome, multiple sclerosis, Guillain-Barre syndrome, acute disseminated encephalomyelitis, Addison's disease, opsoclonus-myoclonus syndrome, ankylosing spondylosis, antiphospholipid antibody syndrome, aplastic anemia, autoimmune hepatitis, celiac disease, Goodpasture's syndrome, idiopathic thrombocytopenic purpura, optic neuritis, scleroderma, primary biliary cirrhosis, Reiter's syndrome, Takayasu's arteritis, temporal arteritis, warm autoimmune hemolytic anemia, Wegener's granulomatosis, psoriasis, alopecia universalis, Behcet's disease, chronic fatigue, dysautonomia, endometriosis, interstitial cystitis, neuromyotonia, scleroderma, or vulvodynia. In some embodiments, the disease or condition is a hyperproliferative disease or immunologically-mediated diseases including rejection of transplanted organs or tissues and Acquired Immunodeficiency Syndrome (AIDS, also known as HIV).

[00189] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, wherein the disease or condition is selected from heteroimmune conditions or diseases, which include, but are not limited to graft versus host disease, transplantation, transfusion, anaphylaxis, allergies (e.g., allergies to plant pollens, latex, drugs, foods, insect poisons, animal hair, animal dander,

dust mites, or cockroach calyx), type I hypersensitivity, allergic conjunctivitis, allergic rhinitis, and atopic dermatitis.

[00190] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, wherein the disease or condition is selected from an inflammatory disease, e.g., asthma, appendicitis, blepharitis, bronchiolitis, bronchitis, bursitis, cervicitis, cholangitis, cholecystitis, colitis, conjunctivitis, cystitis, dacryoadenitis, dermatitis, dermatomyositis, encephalitis, endocarditis, endometritis, enteritis, enterocolitis, epicondylitis, epididymitis, fasciitis, fibrositis, gastritis, gastroenteritis, hepatitis, hidradenitis suppurativa, laryngitis, mastitis, meningitis, myelitis myocarditis, myositis, nephritis, oophoritis, orchitis, osteitis, otitis, pancreatitis, parotitis, pericarditis, peritonitis, pharyngitis, pleuritis, phlebitis, pneumonitis, pneumonia, proctitis, prostatitis, pyelonephritis, rhinitis, salpingitis, sinusitis, stomatitis, synovitis, tendonitis, tonsillitis, uveitis, vaginitis, vasculitis, or vulvitis.

[00191] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, wherein the disease or condition is selected from a cancer. In one embodiment, the cancer is a B-cell proliferative disorder, e.g., diffuse large B cell lymphoma, follicular lymphoma, chronic lymphocytic lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, B-cell prolymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia, splenic marginal zone lymphoma, multiple myeloma (also known as plasma cell myeloma), non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmacytoma, extranodal marginal zone B cell lymphoma, nodal marginal zone B cell lymphoma, mantle cell lymphoma, mediastinal (thymic) large B cell lymphoma, intravascular large B cell lymphoma, primary effusion lymphoma, Burkitt lymphoma/leukemia, or lymphomatoid granulomatosis. In some embodiments, the cancer is breast cancer, prostate cancer, or cancer of the mast cells (e.g., mastocytoma, mast cell leukemia, mast cell sarcoma, systemic mastocytosis). In one embodiment, the cancer is bone cancer. In another embodiment, the cancer is of other primary origin and metastasizes to the bone.

[00192] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases or conditions associated with BTK including diseases of the bone and joints including, without limitation, rheumatoid arthritis, seronegative

spondyloarthropathies (including ankylosing spondylitis, psoriatic arthritis and Reiter's disease), Behcet's disease, Sjogren's syndrome, systemic sclerosis, osteoporosis, bone cancer, and bone metastasis.

[00193] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, wherein the disease or condition is selected from a thromboembolic disorder, e.g., myocardial infarct, angina pectoris, reocclusion after angioplasty, restenosis after angioplasty, reocclusion after aortocoronary bypass, restenosis after aortocoronary bypass, stroke, transitory ischemia, a peripheral arterial occlusive disorder, pulmonary embolism, or deep venous thrombosis.

[00194] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, including infectious and noninfectious inflammatory events and autoimmune and other inflammatory diseases. These autoimmune and inflammatory diseases, disorders, and syndromes include inflammatory pelvic disease, urethritis, skin sunburn, sinusitis, pneumonitis, encephalitis, meningitis, myocarditis, nephritis, osteomyelitis, myositis, hepatitis, gastritis, enteritis, dermatitis, gingivitis, appendicitis, pancreatitis, cholocystitus, agammaglobulinemia, psoriasis, allergy, Crohn's disease, irritable bowel syndrome, ulcerative colitis, Sjogren's disease, tissue graft rejection, hyperacute rejection of transplanted organs, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome), autoimmune alopecia, pernicious anemia, glomerulonephritis, dermatomyositis, multiple sclerosis, scleroderma, vasculitis, autoimmune hemolytic and thrombocytopenic states, Goodpasture's syndrome, atherosclerosis, Addison's disease, Parkinson's disease, Alzheimer's disease, type I diabetes, septic shock, systemic lupus erythematosus (SLE), rheumatoid arthritis, psoriatic arthritis, juvenile arthritis, osteoarthritis, chronic idiopathic thrombocytopenic purpura, Waldenstrom macroglobulinemia, myasthenia gravis, Hashimoto's thyroiditis, atopic dermatitis, degenerative joint disease, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, Behcet's disease, scleraderma, mycosis fungoides, acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury), and Graves' disease.

[00195] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with BTK, selected from

rheumatoid arthritis, multiple sclerosis, B-cell chronic lymphocytic leukemia, acute lymphocytic leukemia, hairy cell leukemia, non-Hodgkin's lymphoma, Hodgkin's lymphoma, multiple myeloma, bone cancer, bone metastasis, osteoporosis, irritable bowel syndrome, Crohn's disease, lupus and renal transplant.

(d) ***ITK***

[00196] Interleukin-2 inducible T-cell kinase ("ITK") is expressed in T cells, mast cells and natural killer cells. It is activated in T cells upon stimulation of the T cell receptor (TCR), and in mast cells upon activation of the high affinity IgE receptor. Following receptor stimulation in T cells, Lck, a Src tyrosine kinase family member, phosphorylates Y511 in the kinase domain activation loop of ITK (S. D. Heyeck et al., 1997, J. Biol. Chem, 272, 25401-25408). Activated ITK, together with Zap-70 is required for phosphorylation and activation of PLC-gamma (S. C. Bunnell et al., 2000, J. Biol. Chem., 275, 2219-2230). PLC-gamma catalyzes the formation of inositol 1,4,5-triphosphate and diacylglycerol, leading to calcium mobilization and PKC activation, respectively. These events activate numerous downstream pathways and lead ultimately to degranulation (mast cells) and cytokine gene expression (T cells) (Y. Kawakami et al., 1999, J. Leukocyte Biol., 65, 286-290).

[00197] The role of ITK in T cell activation has been confirmed in ITK knockout mice. $CD4^+$ T cells from ITK knockout mice have a diminished proliferative response in a mixed lymphocyte reaction or upon Con A or anti-CD3 stimulation. (X. C. Liao and D. R. Littman, 1995, Immunity, 3, 757-769). Also, T cells from ITK knockout mice produced little IL-2 upon TCR stimulation resulting in reduced proliferation of these cells. In another study, ITK deficient $CD4^+$ T cells produced reduced levels of cytokines including IL-4, IL-5 and IL-13 upon stimulation of the TCR, even after priming with inducing conditions (D. J. Fowell, 1999, Immunity, 11, 399-409).

[00198] The role of ITK in PLC-gamma activation and in calcium mobilization was also confirmed in the T cells of these knockout mice, which had severely impaired IP_3 generation and no extracellular calcium influx upon TCR stimulation (K. Liu et al., 1998, J. Exp. Med. 187, 1721-1727). Such studies support a key role for ITK in activation of T cells and mast cells. Thus an inhibitor of ITK would be of therapeutic benefit in diseases mediated by inappropriate activation of these cells.

[00199] It has been well established that T cells play an important role in regulating the immune response (Powrie and Coffman, 1993, Immunology Today, 14, 270-274). Indeed,

activation of T cells is often the initiating event in immunological disorders. Following activation of the TCR, there is an influx of calcium that is required for T cell activation. Upon activation, T cells produce cytokines, including IL-2, 4, 5, 9, 10, and 13 leading to T cell proliferation, differentiation, and effector function. Clinical studies with inhibitors of IL-2 have shown that interference with T cell activation and proliferation effectively suppresses immune response in vivo (Waldmann, 1993, Immunology Today, 14, 264-270). Accordingly, agents that inhibit T lymphocyte activation and subsequent cytokine production, are therapeutically useful for selectively suppressing the immune response in a patient in need of such immunosuppression.

[00200] Mast cells play a critical roll in asthma and allergic disorders by releasing pro-inflammatory mediators and cytokines. Antigen-mediated aggregation of Fc.epsilon.RI, the high-affinity receptor for IgE, results in activation of mast cells (D. B. Corry et al., 1999, Nature, 402, B18-23). This triggers a series of signaling events resulting in the release of mediators, including histamine, proteases, leukotrienes and cytokines (J. R. Gordon et al., 1990, Immunology Today, 11, 458-464.) These mediators cause increased vascular permeability, mucus production, bronchoconstriction, tissue degradation and inflammation thus playing key roles in the etiology and symptoms of asthma and allergic disorders.

[00201] Published data using ITK knockout mice suggests that in the absence of ITK function, increased numbers of memory T cells are generated (A. T. Miller et al., 2002 The Journal of Immunology, 168, 2163-2172). One strategy to improve vaccination methods is to increase the number of memory T cells generated (S. M. Kaech et al., Nature Reviews Immunology, 2, 251-262). In addition, deletion of ITK in mice results in reduced T cell receptor (TCR)-induced proliferation and secretion of the cytokines IL-2, IL-4, IL-5, IL-10 and IFN-y (Schaeffer et al, Science 284; 638-641 (1999)), Fowell et al, Immunity 11, 399-409 (1999), Schaeffer et al, Nature Immunology 2 (12): 1183-1188 (2001))). The immunological symptoms of allergic asthma are attenuated in ITK-/-mice. Lung inflammation, eosinophil infiltration and mucus production are drastically reduced in ITK-/-mice in response to challenge with the allergen OVA (Mueller et al, Journal of Immunology 170: 5056-5063 (2003)). ITK has also been implicated in atopic dermatitis. This gene has been reported to be more highly expressed in peripheral blood T cells from patients with moderate and/or severe atopic dermatitis than in controls or patients with mild atopic dermatitis (Matsumoto et al, International Archives of Allergy and Immunology 129: 327-340 (2002)).

[00202] Splenocytes from RLK-/-mice secrete half the IL-2 produced by wild type animals in response to TCR engagement (Schaeffer et al, Science 284: 638-641 (1999)), while combined deletion of ITK and RLK in mice leads to a profound inhibition of TCR-induced responses including proliferation and production of the cytokines IL-2, IL-4, IL-5 and IFN-γ (Schaeffer et al, Nature Immunology 2 (12): 1183-1188 (2001), Schaeffer et al, Science 284: 638-641 (1999)). Intracellular signalling following TCR engagement is effected in ITK/RLK deficient T cells; inositol triphosphate production, calcium mobilization, MAP kinase activation, and activation of the transcription factors NFAT and AP-1 are all reduced (Schaeffer et al, Science 284: 638-641 (1999), Schaeffer et al, Nature Immunology 2 (12): 1183-1188 (2001)).

[00203] Provided compounds are inhibitors of ITK and are therefore useful for treating one or more disorders associated with activity of ITK. Thus, in some embodiments, the present invention provides a method for treating an ITK-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[00204] As used herein, the term "ITK-mediated" disorders or conditions as used herein means any disease or other deleterious condition in which ITK, or a mutant thereof, is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which ITK, or a mutant thereof, is known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from a mast cell-mediated condition, a basophil-mediated disorder, an immune or allergic disorder, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

[00205] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with ITK, wherein the disease or condition is an immune disorder, including inflammatory diseases, autoimmune diseases, organ and bone marrow transplant rejection and other disorders associated with T cell-mediated immune response or mast cell-mediated immune response.

[00206] In certain embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with ITK, wherein the disease or condition is acute or chronic inflammation, an allergy, contact dermatitis, psoriasis, rheumatoid arthritis, multiple sclerosis, type 1 diabetes, inflammatory bowel disease, Guillain-

Barre syndrome, Crohn's disease, ulcerative colitis, cancer, graft versus host disease (and other forms of organ or bone marrow transplant rejection) or lupus erythematosus.

[00207] In certain embodiments, the present invention provides a method for treating or lessening the severity of one or more diseases and conditions associated with ITK, wherein the disease or condition is a mast cell driven conditions, a basophil-mediated disorder, reversible obstructive airway disease, asthma, rhinitis, chronic obstructive pulmonary disease (COPD), peripheral T-cell lymphomas or HIV [also known as Acquired Immunodeficiency Syndrome (AIDS)]. Such conditions include those described in Readinger, et al., PNAS 105: 6684-6689 (2008).

(e) ***JAK Family***

[00208] The Janus kinases (JAK) are a family of tyrosine kinases consisting of JAK1, JAK2, JAK3 and TYK2. The JAKs play a critical role in cytokine signaling. The down-stream substrates of the JAK family of kinases include the signal transducer and activator of transcription (STAT) proteins. JAK/STAT signaling has been implicated in the mediation of many abnormal immune responses such as allergies, asthma, autoimmune diseases such as transplant rejection, rheumatoid arthritis, amyotrophic lateral sclerosis and multiple sclerosis as well as in solid and hematologic malignancies such as leukemias and lymphomas. The pharmaceutical intervention in the JAK/STAT pathway has been reviewed [Frank, Mol. Med. 5 : 432-456 (1999) & Seidel, et al, Oncogene 19 : 2645-2656 (2000)].

[00209] JAK1, JAK2, and TYK2 are ubiquitously expressed, while JAK3 is predominantly expressed in hematopoietic cells. JAK3 binds exclusively to the common cytokine receptor gamma chain (yc) and is activated by IL-2, IL-4, IL-7, IL-9, and IL-15.

[00210] The proliferation and survival of murine mast cells induced by IL-4 and IL-9 have, in fact, been shown to be dependent on JAK3-and yc-signaling [Suzuki et al, Blood 96 : 2172-2180 (2000)].

[00211] Cross-linking of the high-affinity immunoglobulin (Ig) E receptors of sensitized mast cells leads to a release of proinflammatory mediators, including a number of vasoactive cytokines resulting in acute allergic, or immediate (type I) hypersensitivity reactions [Gordon et al, Nature 346 : 274-276 (1990) & Galli, N. Engl. J. Med., 328 : 257- 265 (1993)]. A crucial role for JAK3 in IgE receptor-mediated mast cell responses in vitro and in vivo has been established [Malaviya, et al, Biochem. Biophys. Res. Commun. 257 : 807-813 (1999)]. In

addition, the prevention of type I hypersensitivity reactions, including anaphylaxis, mediated by mast cell-activation through inhibition of JAK3 has also been reported [Malaviya et al, J. Biol. Chem. 274 : 27028-27038 (1999)]. Targeting mast cells with JAK3 inhibitors modulated mast cell degranulation in vitro and prevented IgE receptor/antigen-mediated anaphylactic reactions in vivo.

[00212] A recent study described the successful targeting of JAK3 for immune suppression and allograft acceptance. The study demonstrated a dose-dependent survival of buffalo heart allograft in Wistar Furth recipients upon administration of inhibitors of JAK3 indicating the possibility of regulating unwanted immune responses in graft versus host disease [Kirken, Transpl. Proc. 33: 3268-3270 (2001)].

[00213] IL-4-mediated STAT-phosphorylation has been implicated as the mechanism involved in early and late stages of rheumatoid arthritis (RA). Up-regulation of proinflammatory cytokines in RA synovium and synovial fluid is a characteristic of the disease. It has been demostrated that IL-4-mediated activation of IL-4/STAT pathway is mediated through the Janus kinases (JAK 1 & 3) and that IL-4-associated JAK kinases are expressed in the RA synovium [Muller-Ladner, et al, J. Immunol. 164 : 3894-3901 (2000)].

[00214] Familial amyotrophic lateral sclerosis (FALS) is a fatal neurodegenerative disorder affecting about 10% of ALS patients. The survival rates of FALS mice were increased upon treatment with a JAK3 specific inhibitor. This confirmed that JAK3 plays a role in FALS [Trieu, et al, Biochem. Biophys. Res. Commun. 267 : 22-25 (2000)].

[00215] Signal transducer and activator of transcription (STAT) proteins are activated by, among others, the JAK family kinases. Results form a recent study suggested the possibility of intervention in the JAK/STAT signaling pathway by targeting JAK family kinases with specific inhibitors for the treatment of leukemia [Sudbeck, et al., Clin. Cancer Res. 5 : 1569-1582 (1999)]. JAK3 specific compounds were shown to inhibit the clonogenic growth of JAK3-expressing cell lines DAUDI, RAMOS, LC1 ; 19, NALM-6, MOLT-3 and HL-60. Inhibition of JAK3 and TYK 2 abrogated tyrosine phosphorylation of STAT3, and inhibited cell growth of mycosis fungoides, a form of cutaneous T cell lymphoma.

[00216] According to another embodiment, the invention provides a method for treating or lessening the severity of a JAK3-mediated disease or condition in a patient comprising the step of administering to said patient a composition according to the present invention.

[00217] The term "JAK3-mediated disease", as used herein means any disease or other deleterious condition in which a JAK3 kinase is known to play a role. Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which JAK3 is known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from immune responses such as allergic or type I hypersensitivity reactions, asthma, autoimmune diseases such as transplant rejection, graft versus host disease, rheumatoid arthritis, amyotrophic lateral sclerosis, and multiple sclerosis, neurodegenerative disorders such as familial amyotrophic lateral sclerosis (FALS), as well as in solid and hematologic malignancies such as leukemias and lymphomas, wherein said method comprises administering to a patient in need thereof a composition according to the present invention.

[00218] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of cancer, an autoimmune disorder, a neurodegenerative or neurological disorder, schizophrenia, a bone-related disorder, liver disease, or a cardiac disorder. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection, the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[00219] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg and preferably from about 1 mg/kg to about 25 mg/kg, of subject body weight per day, one or more times a day, to obtain the desired therapeutic effect.

[00220] Liquid dosage forms for oral administration include, but are not limited to, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00221] Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution, suspension or emulsion in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P. and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[00222] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00223] In order to prolong the effect of a compound of the present invention, it is often desirable to slow the absorption of the compound from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the compound then depends upon its rate of dissolution that, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered compound form is accomplished by dissolving or suspending the compound in an oil vehicle. Injectable depot forms are made by forming microencapsule matrices of the compound in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of compound to polymer and the nature of the particular polymer employed, the rate of compound release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the compound in liposomes or microemulsions that are compatible with body tissues.

[00224] Compositions for rectal or vaginal administration are preferably suppositories which can be prepared by mixing the compounds of this invention with suitable non-irritating excipients or carriers such as cocoa butter, polyethylene glycol or a suppository wax which are solid at ambient temperature but liquid at body temperature and therefore melt in the rectum or vaginal cavity and release the active compound.

[00225] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar--agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00226] Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other coatings well known in the pharmaceutical formulating art. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polethylene glycols and the like.

[00227] The active compounds can also be in micro-encapsulated form with one or more excipients as noted above. The solid dosage forms of tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings, release controlling coatings and other coatings well known in the pharmaceutical formulating art. In such solid dosage forms the active compound may be admixed with at least one inert diluent such as sucrose, lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., tableting lubricants and other tableting aids such a magnesium stearate and microcrystalline cellulose. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. They may optionally contain opacifying agents and can also be of a composition that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes.

[00228] Dosage forms for topical or transdermal administration of a compound of this invention include ointments, pastes, creams, lotions, gels, powders, solutions, sprays, inhalants or patches. The active component is admixed under sterile conditions with a pharmaceutically acceptable carrier and any needed preservatives or buffers as may be required. Ophthalmic formulation, ear drops, and eye drops are also contemplated as being within the scope of this invention. Additionally, the present invention contemplates the use of transdermal patches, which have the added advantage of providing controlled delivery of a compound to the body. Such dosage forms can be made by dissolving or dispensing the compound in the proper

medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate can be controlled by either providing a rate controlling membrane or by dispersing the compound in a polymer matrix or gel.

[00229] According to one embodiment, the invention relates to a method of inhibiting protein kinase activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00230] According to another embodiment, the invention relates to a method of inhibiting ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound. In certain embodiments, the invention relates to a method of irreversibly inhibiting ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3,, or a mutant thereof, activity in a biological sample comprising the step of contacting said biological sample with a compound of this invention, or a composition comprising said compound.

[00231] The term "biological sample", as used herein, includes, without limitation, cell cultures or extracts thereof; biopsied material obtained from a mammal or extracts thereof; and blood, saliva, urine, feces, semen, tears, or other body fluids or extracts thereof.

[00232] Inhibition of protein kinase, or a protein kinase selected from ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, activity in a biological sample is useful for a variety of purposes that are known to one of skill in the art. Examples of such purposes include, but are not limited to, blood transfusion, organ transplantation, biological specimen storage, and biological assays.

[00233] Another embodiment of the present invention relates to a method of inhibiting protein kinase activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound.

[00234] According to another embodiment, the invention relates to a method of inhibiting one or more of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3,, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of irreversibly inhibiting one or more of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3,, or a mutant thereof, activity in a patient

comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of ErbB1, ErbB2, ErbB3, ErbB4, a TEC-kinase, and/or JAK3, or a mutant thereof, in a patient in need thereof, comprising the step of administering to said patient a compound according to the present invention or pharmaceutically acceptable composition thereof. Such disorders are described in detail herein.

[00235] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00236] For example, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with chemotherapeutic agents to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane (e.g., paclitaxel), vinca alkaloids (e.g., vinblastine), anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), cisplatin, an mTOR inhibitor (e.g., a rapamycin), methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents (e.g., chlorambucil), 5-fluorouracil, campthothecin, cisplatin, metronidazole, and Gleevec™, among others. In other embodiments, a compound of the present invention is administered in combination with a biologic agent, such as Avastin or VECTIBIX.

[00237] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with an antiproliferative or chemotherapeutic agent selected from any one or more of abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, erlotinib, estramustine,

etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, or zoledronic acid.

[00238] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as donepezil hydrochloride (Aricept®) and rivastigmine (Exelon®); treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), glatiramer acetate (Copaxone®), and mitoxantrone; treatments for asthma such as albuterol and montelukast (Singulair®); agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids, TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00239] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00240] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00241] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a provided compound, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00242] The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above)) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

[00243] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00244] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of

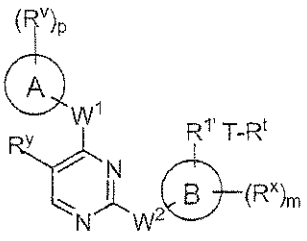
the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00245] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

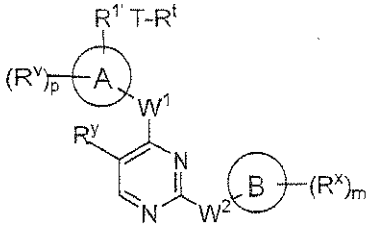
5. ***Probe Compounds***

[00246] In certain aspects, a compound of the present invention may be tethered to a detectable moiety to form a probe compound. In one aspect, a probe compound of the invention comprises an irreversible protein kinase inhibitor of formula **I-a** or **I-b**, as described herein, a detectable moiety, and a tethering moiety that attaches the inhibitor to the detectable moiety.

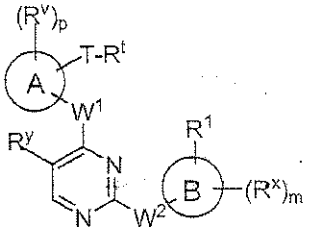
[00247] In some embodiments, such probe compounds of the present invention comprise a provided compound of formula **I-a** or **I-b** tethered to a detectable moiety, R^t, by a bivalent tethering moiety, -T-. The tethering moiety may be attached to a compound of formula **I-a** or **I-b** *via* Ring A, Ring B, or R^1. One of ordinary skill in the art will appreciate that when a tethering moiety is attached to R^1, R^1 is a bivalent warhead group denoted as $R^{1'}$. In certain embodiments, a provided probe compound is selected from any of formula **V-a**, **V-b**, **VI-a**, **VI-b**, **VII-a**, or **VII-b**:



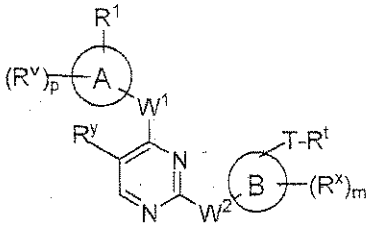
V-a



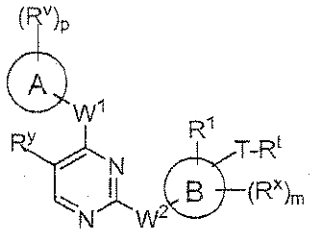
V-b



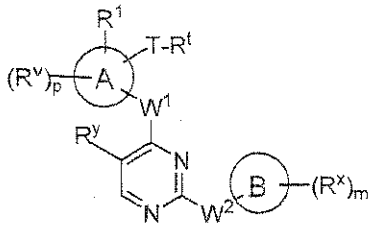
VI-a



VI-b



VII-a



VII-b,

wherein each of Ring A, Ring B, R^1, m, p, R^x, R^y, R^v,W^1, and W^2 is as defined above with respect to formulae **I-a** and **I-b**, and described in classes and subclasses herein, $R^{1'}$ is a bivalent warhead group, T is a bivalent tethering moiety; and R^t is a detectable moiety.

[00248] In some embodiments, R^t is a detectable moiety selected from a primary label or a secondary label. In certain embodiments, R^t is a detectable moiety selected from a fluorescent label (e.g., a fluorescent dye or a fluorophore), a mass-tag, a chemiluminescent group, a chromophore, an electron dense group, or an energy transfer agent.

[00249] As used herein, the term "detectable moiety" is used interchangeably with the term "label" and "reporter" and relates to any moiety capable of being detected, e.g., primary labels and secondary labels. A presence of a detectable moiety can be measured using methods for quantifying (in absolute, approximate or relative terms) the detectable moiety in a system under study. In some embodiments, such methods are well known to one of ordinary skill in the art and include any methods that quantify a reporter moiety (e.g., a label, a dye, a photocrosslinker, a cytotoxic compound, a drug, an affinity label, a photoaffinity label, a reactive compound, an antibody or antibody fragment, a biomaterial, a nanoparticle, a spin label, a fluorophore, a metal-containing moiety, a radioactive moiety, quantum dot(s), a novel functional group, a group that covalently or noncovalently interacts with other molecules, a photocaged moiety, an actinic radiation excitable moiety, a ligand, a photoisomerizable moiety, biotin, a biotin analog (e.g., biotin sulfoxide), a moiety incorporating a heavy atom, a chemically cleavable group, a

photocleavable group, a redox-active agent, an isotopically labeled moiety, a biophysical probe, a phosphorescent group, a chemiluminescent group, an electron dense group, a magnetic group, an intercalating group, a chromophore, an energy transfer agent, a biologically active agent, a detectable label, and any combination of the above).

[00250] Primary labels, such as radioisotopes (e.g., tritium, ^{32}P, ^{33}P, ^{35}S, ^{14}C, ^{123}I, ^{124}I, ^{125}I, or ^{131}I), mass-tags including, but not limited to, stable isotopes (e.g., ^{13}C, ^{2}H, ^{17}O, ^{18}O, ^{15}N, ^{19}F, and ^{127}I), positron emitting isotopes (e.g., ^{11}C, ^{18}F, ^{13}N, ^{124}I, and ^{15}O), and fluorescent labels are signal generating reporter groups which can be detected without further modifications. Detectable moities may be analyzed by methods including, but not limited to fluorescence, positron emission tomography, SPECT medical imaging, chemiluminescence, electron-spin resonance, ultraviolet/visible absorbance spectroscopy, mass spectrometry, nuclear magnetic resonance, magnetic resonance, flow cytometry, autoradiography, scintillation counting, phosphoimaging, and electrochemical methods.

[00251] The term "secondary label" as used herein refers to moieties such as biotin and various protein antigens that require the presence of a second intermediate for production of a detectable signal. For biotin, the secondary intermediate may include streptavidin-enzyme conjugates. For antigen labels, secondary intermediates may include antibody-enzyme conjugates. Some fluorescent groups act as secondary labels because they transfer energy to another group in the process of nonradiative fluorescent resonance energy transfer (FRET), and the second group produces the detected signal.

[00252] The terms "fluorescent label", "fluorescent dye", and "fluorophore" as used herein refer to moieties that absorb light energy at a defined excitation wavelength and emit light energy at a different wavelength. Examples of fluorescent labels include, but are not limited to: Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY TR, BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD

800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X, 5(6)-Carboxyfluorescein, 2,7-Dichlorofluorescein, N,N-Bis(2,4,6-trimethylphenyl)-3,4:9,10-perylenebis(dicarboximide, HPTS, Ethyl Eosin, DY-490XL MegaStokes, DY-485XL MegaStokes, Adirondack Green 520, ATTO 465, ATTO 488, ATTO 495, YOYO-1,5-FAM, BCECF, dichlorofluorescein, rhodamine 110, rhodamine 123, YO-PRO-1, SYTOX Green, Sodium Green, SYBR Green I, Alexa Fluor 500, FITC, Fluo-3, Fluo-4, fluoro-emerald, YoYo-1 ssDNA, YoYo-1 dsDNA, YoYo-1, SYTO RNASelect, Diversa Green-FP, Dragon Green, EvaGreen, Surf Green EX, Spectrum Green, NeuroTrace 500525, NBD-X, MitoTracker Green FM, LysoTracker Green DND-26, CBQCA, PA-GFP (post-activation), WEGFP (post-activation), FlASH-CCXXCC, Azami Green monomeric, Azami Green, green fluorescent protein (GFP), EGFP (Campbell Tsien 2003), EGFP (Patterson 2001), Kaede Green, 7-Benzylamino-4-Nitrobenz-2-Oxa-1,3-Diazole, Bexl, Doxorubicin, Lumio Green, and SuperGlo GFP.

[00253] The term "mass-tag" as used herein refers to any moiety that is capable of being uniquely detected by virtue of its mass using mass spectrometry (MS) detection techniques. Examples of mass-tags include electrophore release tags such as N-[3-[4'-[(p-Methoxytetrafluorobenzyl)oxy]phenyl]-3-methylglyceronyl]isonipecotic Acid, 4'-[2,3,5,6-Tetrafluoro-4-(pentafluorophenoxyl)]methyl acetophenone, and their derivatives. The synthesis and utility of these mass-tags is described in United States Patents 4,650,750, 4,709,016, 5,360,8191, 5,516,931, 5,602,273, 5,604,104, 5,610,020, and 5,650,270. Other examples of mass-tags include, but are not limited to, nucleotides, dideoxynucleotides, oligonucleotides of varying length and base composition, oligopeptides, oligosaccharides, and other synthetic polymers of varying length and monomer composition. A large variety of organic molecules, both neutral and charged (biomolecules or synthetic compounds) of an appropriate mass range (100-2000 Daltons) may also be used as mass-tags. Stable isotopes (e.g., ^{13}C, ^{2}H, ^{17}O, ^{18}O, and ^{15}N) may also be used as mass-tags.

[00254] The term "chemiluminescent group," as used herein, refers to a group which emits light as a result of a chemical reaction without the addition of heat. By way of example, luminol

(5-amino-2,3-dihydro-1,4-phthalazinedione) reacts with oxidants like hydrogen peroxide (H_2O_2) in the presence of a base and a metal catalyst to produce an excited state product (3-aminophthalate, 3-APA).

[00255] The term "chromophore," as used herein, refers to a molecule which absorbs light of visible wavelengths, UV wavelengths or IR wavelengths.

[00256] The term "dye," as used herein, refers to a soluble, coloring substance which contains a chromophore.

[00257] The term "electron dense group," as used herein, refers to a group which scatters electrons when irradiated with an electron beam. Such groups include, but are not limited to, ammonium molybdate, bismuth subnitrate, cadmium iodide, carbohydrazide, ferric chloride hexahydrate, hexamethylene tetramine, indium trichloride anhydrous, lanthanum nitrate, lead acetate trihydrate, lead citrate trihydrate, lead nitrate, periodic acid, phosphomolybdic acid, phosphotungstic acid, potassium ferricyanide, potassium ferrocyanide, ruthenium red, silver nitrate, silver proteinate (Ag Assay: 8.0-8.5%) "Strong", silver tetraphenylporphin (S-TPPS), sodium chloroaurate, sodium tungstate, thallium nitrate, thiosemicarbazide (TSC), uranyl acetate, uranyl nitrate, and vanadyl sulfate.

[00258] The term "energy transfer agent," as used herein, refers to a molecule which either donates or accepts energy from another molecule. By way of example only, fluorescence resonance energy transfer (FRET) is a dipole-dipole coupling process by which the excited-state energy of a fluorescence donor molecule is non-radiatively transferred to an unexcited acceptor molecule which then fluorescently emits the donated energy at a longer wavelength.

[00259] The term "moiety incorporating a heavy atom," as used herein, refers to a group which incorporates an ion of atom which is usually heavier than carbon. In some embodiments, such ions or atoms include, but are not limited to, silicon, tungsten, gold, lead, and uranium.

[00260] The term "photoaffinity label," as used herein, refers to a label with a group, which, upon exposure to light, forms a linkage with a molecule for which the label has an affinity.

[00261] The term "photocaged moiety," as used herein, refers to a group which, upon illumination at certain wavelengths, covalently or non-covalently binds other ions or molecules.

[00262] The term "photoisomerizable moiety," as used herein, refers to a group wherein upon illumination with light changes from one isomeric form to another.

[00263] The term "radioactive moiety," as used herein, refers to a group whose nuclei spontaneously give off nuclear radiation, such as alpha, beta, or gamma particles; wherein, alpha particles are helium nuclei, beta particles are electrons, and gamma particles are high energy photons.

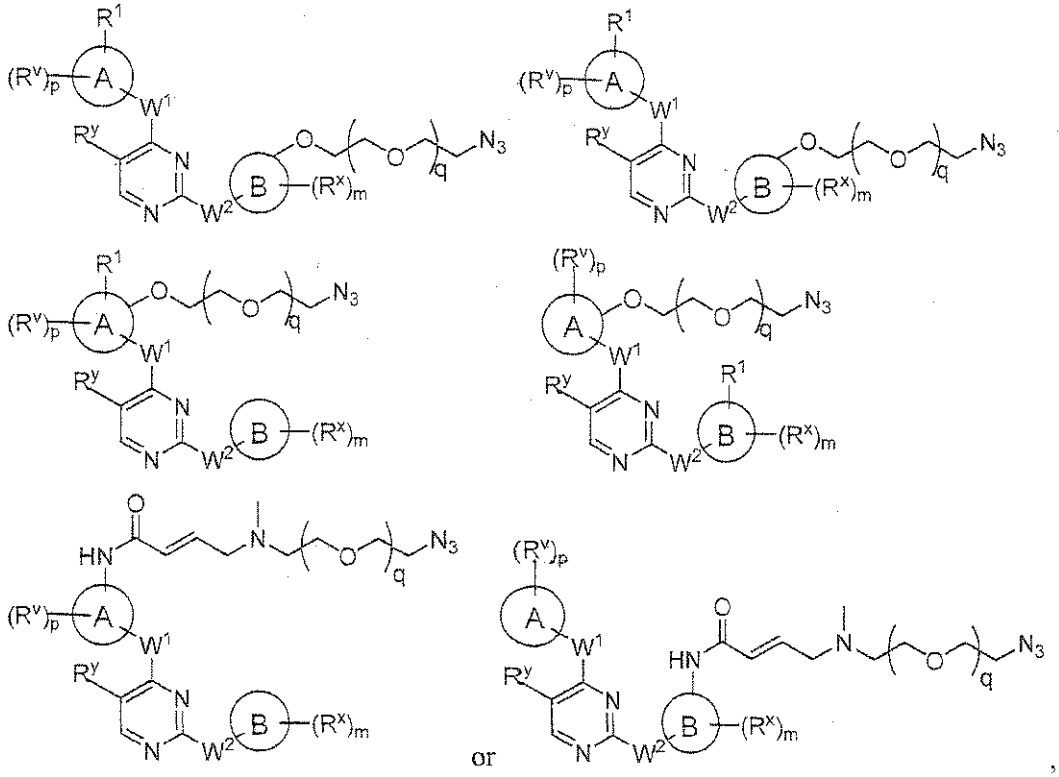
[00264] The term "spin label," as used herein, refers to molecules which contain an atom or a group of atoms exhibiting an unpaired electron spin (i.e. a stable paramagnetic group) that in some embodiments are detected by electron spin resonance spectroscopy and in other embodiments are attached to another molecule. Such spin-label molecules include, but are not limited to, nitryl radicals and nitroxides, and in some embodiments are single spin-labels or double spin-labels.

[00265] The term "quantum dots," as used herein, refers to colloidal semiconductor nanocrystals that in some embodiments are detected in the near-infrared and have extremely high quantum yields (i.e., very bright upon modest illumination).

[00266] One of ordinary skill in the art will recognize that a detectable moiety may be attached to a provided compound *via* a suitable substituent. As used herein, the term "suitable substituent" refers to a moiety that is capable of covalent attachment to a detectable moiety. Such moieties are well known to one of ordinary skill in the art and include groups containing, e.g., a carboxylate moiety, an amino moiety, a thiol moiety, or a hydroxyl moiety, to name but a few. It will be appreciated that such moieties may be directly attached to a provided compound or *via* a tethering moiety, such as a bivalent saturated or unsaturated hydrocarbon chain.

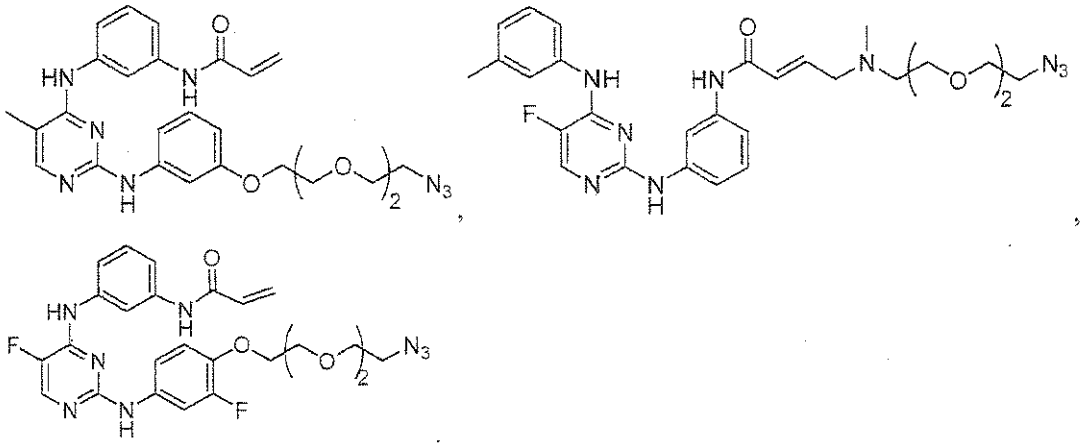
[00267] In some embodiments, detectable moieties are attached to a provided compound via click chemistry. In some embodiments, such moieties are attached via a 1,3-cycloaddition of an azide with an alkyne, optionally in the presence of a copper catalyst. Methods of using click chemistry are known in the art and include those described by Rostovtsev *et al.*, Angew. Chem. Int. Ed. 2002, 41, 2596-99 and Sun *et al.*, Bioconjugate Chem., 2006, 17, 52-57. In some embodiments, a click ready inhibitor moiety is provided and reacted with a click ready $-T-R^t$ moiety. As used herein, "click ready" refers to a moiety containing an azide or alkyne for use in a click chemistry reaction. In some embodiments, the click ready inhibitor moiety comprises an azide. In certain embodiments, the click ready $-T-R^t$ moiety comprises a strained cyclooctyne for use in a copper-free click chemistry reaction (for example, using methods described in Baskin *et al.*, Proc. Natl. Acad. Sci. USA 2007, 104, 16793-16797).

[00268] In certain embodiments, the click ready inhibitor moiety is of one of the following formulae:

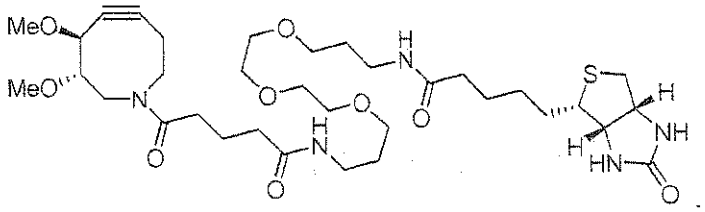


wherein Ring A, Ring B, W^1, W^2, R^y, R^v, p, R^x, and m are as defined above with respect to Formula I and described herein, and q is 1, 2, or 3.

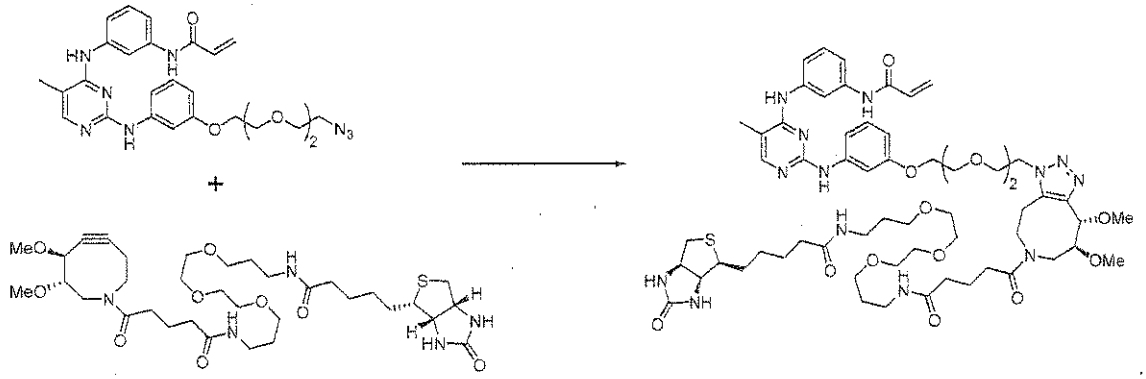
[00269] Exemplary click ready inhibitors include:



[00270] In some embodiments, the click ready $-T-R^t$ moiety is of formula:



[00271] An exemplary reaction in which a click ready inhibitor moiety and a click ready -T-R^t moiety are joined through a [2+3]-cycloaddition is as follows:



[00272] In some embodiments, the detectable moiety, R^t, is selected from a label, a dye, a photocrosslinker, a cytotoxic compound, a drug, an affinity label, a photoaffinity label, a reactive compound, an antibody or antibody fragment, a biomaterial, a nanoparticle, a spin label, a fluorophore, a metal-containing moiety, a radioactive moiety, quantum dot(s), a novel functional group, a group that covalently or noncovalently interacts with other molecules, a photocaged moiety, an actinic radiation excitable moiety, a ligand, a photoisomerizable moiety, biotin, a biotin analog (e.g., biotin sulfoxide), a moiety incorporating a heavy atom, a chemically cleavable group, a photocleavable group, a redox-active agent, an isotopically labeled moiety, a biophysical probe, a phosphorescent group, a chemiluminescent group, an electron dense group, a magnetic group, an intercalating group, a chromophore, an energy transfer agent, a biologically active agent, a detectable label, or a combination thereof.

[00273] In some embodiments, R^t is biotin or an analog thereof. In certain embodiments, R^t is biotin. In certain other embodiments, R^t is biotin sulfoxide.

[00274] In another embodiment, R^t is a fluorophore. In a further embodiment, the fluorophore is selected from Alexa Fluor dyes (Alexa Fluor 350, Alexa Fluor 488, Alexa Fluor 532, Alexa Fluor 546, Alexa Fluor 568, Alexa Fluor 594, Alexa Fluor 633, Alexa Fluor 660 and Alexa Fluor 680), AMCA, AMCA-S, BODIPY dyes (BODIPY FL, BODIPY R6G, BODIPY TMR, BODIPY

TR, BODIPY 493/503, BODIPY 530/550, BODIPY 558/568, BODIPY 564/570, BODIPY 576/589, BODIPY 581/591, BODIPY 630/650, BODIPY 650/665), Carboxyrhodamine 6G, carboxy-X-rhodamine (ROX), Cascade Blue, Cascade Yellow, Coumarin 343, Cyanine dyes (Cy3, Cy5, Cy3.5, Cy5.5), Dansyl, Dapoxyl, Dialkylaminocoumarin, 4',5'-Dichloro-2',7'-dimethoxy-fluorescein, DM-NERF, Eosin, Erythrosin, Fluorescein, FAM, Hydroxycoumarin, IRDyes (IRD40, IRD 700, IRD 800), JOE, Lissamine rhodamine B, Marina Blue, Methoxycoumarin, Naphthofluorescein, Oregon Green 488, Oregon Green 500, Oregon Green 514, Pacific Blue, PyMPO, Pyrene, Rhodamine B, Rhodamine 6G, Rhodamine Green, Rhodamine Red, Rhodol Green, 2',4',5',7'-Tetra-bromosulfone-fluorescein, Tetramethyl-rhodamine (TMR), Carboxytetramethylrhodamine (TAMRA), Texas Red, Texas Red-X, 5(6)-Carboxyfluorescein, 2,7-Dichlorofluorescein, N,N-Bis(2,4,6-trimethylphenyl)-3,4:9,10-perylenebis(dicarboximide, HPTS, Ethyl Eosin, DY-490XL MegaStokes, DY-485XL MegaStokes, Adirondack Green 520, ATTO 465, ATTO 488, ATTO 495, YOYO-1,5-FAM, BCECF, dichlorofluorescein, rhodamine 110, rhodamine 123, YO-PRO-1, SYTOX Green, Sodium Green, SYBR Green I, Alexa Fluor 500, FITC, Fluo-3, Fluo-4, fluoro-emerald, YoYo-1 ssDNA, YoYo-1 dsDNA, YoYo-1, SYTO RNASelect, Diversa Green-FP, Dragon Green, EvaGreen, Surf Green EX, Spectrum Green, NeuroTrace 500525, NBD-X, MitoTracker Green FM, LysoTracker Green DND-26, CBQCA, PA-GFP (post-activation), WEGFP (post-activation), FlASH-CCXXCC, Azami Green monomeric, Azami Green, green fluorescent protein (GFP), EGFP (Campbell Tsien 2003), EGFP (Patterson 2001), Kaede Green, 7-Benzylamino-4-Nitrobenz-2-Oxa-1,3-Diazole, Bexl, Doxorubicin, Lumio Green, or SuperGlo GFP.

[00275] As described generally above, a provided probe compound comprises a tethering moiety, -T-, that attaches the irreversible inhibitor to the detectable moiety. As used herein, the term "tether" or "tethering moiety" refers to any bivalent chemical spacer including, but not limited to, a covalent bond, a polymer, a water soluble polymer, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkenyl, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted heterocycloalkylalkenylalkyl, an optionally substituted amide moiety, an ether moiety, an ketone moiety, an ester moiety, an optionally substituted carbamate

moiety, an optionally substituted hydrazone moiety, an optionally substituted hydrazine moiety, an optionally substituted oxime moiety, a disulfide moiety, an optionally substituted imine moiety, an optionally substituted sulfonamide moiety, a sulfone moiety, a sulfoxide moiety, a thioether moiety, or any combination thereof.

[00276] In some embodiments, the tethering moiety, -T-, is selected from a covalent bond, a polymer, a water soluble polymer, optionally substituted alkyl, optionally substituted heteroalkyl, optionally substituted heterocycloalkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkylalkyl, optionally substituted heterocycloalkylalkenyl, optionally substituted aryl, optionally substituted heteroaryl, and optionally substituted heterocycloalkylalkenylalkyl. In some embodiments, the tethering moiety is an optionally substituted heterocycle. In other embodiments, the heterocycle is selected from aziridine, oxirane, episulfide, azetidine, oxetane, pyrroline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, pyrazole, pyrrole, imidazole, triazole, tetrazole, oxazole, isoxazole, oxirene, thiazole, isothiazole, dithiolane, furan, thiophene, piperidine, tetrahydropyran, thiane, pyridine, pyran, thiapyrane, pyridazine, pyrimidine, pyrazine, piperazine, oxazine, thiazine, dithiane, and dioxane. In some embodiments, the heterocycle is piperazine. In further embodiments, the tethering moiety is optionally substituted with halogen, -CN, -OH, $-NO_2$, alkyl, S(O), and $S(O)_2$. In other embodiments, the water soluble polymer is a PEG group.

[00277] In other embodiments, the tethering moiety provides sufficient spatial separation between the detectable moiety and the protein kinase inhibitor moiety. In further embodiments, the tethering moiety is stable. In yet a further embodiment, the tethering moiety does not substantially affect the response of the detectable moiety. In other embodiments, the tethering moiety provides chemical stability to the probe compound. In further embodiments, the tethering moiety provides sufficient solubility to the probe compound.

[00278] In some embodiments, a tethering moiety, -T-, such as a water soluble polymer is coupled at one end to a provided irreversible inhibitor and to a detectable moiety, R^t, at the other end. In other embodiments, a water soluble polymer is coupled via a functional group or substituent of the provided irreversible inhibitor. In further embodiments, a water soluble polymer is coupled via a functional group or substituent of the reporter moiety.

[00279] In some embodiments, examples of hydrophilic polymers, for use in tethering moiety –T-, include, but are not limited to: polyalkyl ethers and alkoxy-capped analogs thereof (e.g.,

polyoxyethylene glycol, polyoxyethylene/propylene glycol, and methoxy or ethoxy-capped analogs thereof, polyoxyethylene glycol, the latter is also known as polyethylene glycol or PEG); polyvinylpyrrolidones; polyvinylalkyl ethers; polyoxazolines, polyalkyl oxazolines and polyhydroxyalkyl oxazolines; polyacrylamides, polyalkyl acrylamides, and polyhydroxyalkyl acrylamides (e.g., polyhydroxypropylmethacrylamide and derivatives thereof); polyhydroxyalkyl acrylates; polysialic acids and analogs thereof, hydrophilic peptide sequences; polysaccharides and their derivatives, including dextran and dextran derivatives, e.g., carboxymethyldextran, dextran sulfates, aminodextran; cellulose and its derivatives, e.g., carboxymethyl cellulose, hydroxyalkyl celluloses; chitin and its derivatives, e.g., chitosan, succinyl chitosan, carboxymethylchitin, carboxymethylchitosan; hyaluronic acid and its derivatives; starches; alginates; chondroitin sulfate; albumin; pullulan and carboxymethyl pullulan; polyaminoacids and derivatives thereof, e.g., polyglutamic acids, polylysines, polyaspartic acids, polyaspartamides; maleic anhydride copolymers such as: styrene maleic anhydride copolymer, divinylethyl ether maleic anhydride copolymer; polyvinyl alcohols; copolymers thereof, terpolymers thereof, mixtures thereof, and derivatives of the foregoing. In other embodiments, a water soluble polymer is any structural form including but not limited to linear, forked or branched. In further embodiments, multifunctional polymer derivatives include, but are not limited to, linear polymers having two termini, each terminus being bonded to a functional group which is the same or different.

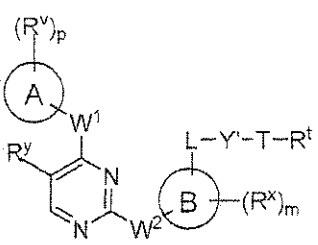
[00280] In some embodiments, a water polymer comprises a poly(ethylene glycol) moiety. In further embodiments, the molecular weight of the polymer is of a wide range, including but not limited to, between about 100 Da and about 100,000 Da or more. In yet further embodiments, the molecular weight of the polymer is between about 100 Da and about 100,000 Da, including but not limited to, about 100,000 Da, about 95,000 Da, about 90,000 Da, about 85,000 Da, about 80,000 Da, about 75,000 Da, about 70,000 Da, about 65,000 Da, about 60,000 Da, about 55,000 Da, about 50,000 Da, about 45,000 Da, about 40,000 Da, about 35,000 Da, 30,000 Da, about 25,000 Da, about 20,000 Da, about 15,000 Da, about 10,000 Da, about 9,000 Da, about 8,000 Da, about 7,000 Da, about 6,000 Da, about 5,000 Da, about 4,000 Da, about 3,000 Da, about 2,000 Da, about 1,000 Da, about 900 Da, about 800 Da, about 700 Da, about 600 Da, about 500 Da, about 400 Da, about 300 Da, about 200 Da, and about 100 Da. In some embodiments, the molecular weight of the polymer is between about 100 Da and 50,000 Da. In some

embodiments, the molecular weight of the polymer is between about 100 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is between about 1,000 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is between about 5,000 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is between about 10,000 Da and 40,000 Da. In some embodiments, the poly(ethylene glycol) molecule is a branched polymer. In further embodiments, the molecular weight of the branched chain PEG is between about 1,000 Da and about 100,000 Da, including but not limited to, about 100,000 Da, about 95,000 Da, about 90,000 Da, about 85,000 Da, about 80,000 Da, about 75,000 Da, about 70,000 Da, about 65,000 Da, about 60,000 Da, about 55,000 Da, about 50,000 Da, about 45,000 Da, about 40,000 Da, about 35,000 Da, about 30,000 Da, about 25,000 Da, about 20,000 Da, about 15,000 Da, about 10,000 Da, about 9,000 Da, about 8,000 Da, about 7,000 Da, about 6,000 Da, about 5,000 Da, about 4,000 Da, about 3,000 Da, about 2,000 Da, and about 1,000 Da. In some embodiments, the molecular weight of a branched chain PEG is between about 1,000 Da and about 50,000 Da. In some embodiments, the molecular weight of a branched chain PEG is between about 1,000 Da and about 40,000 Da. In some embodiments, the molecular weight of a branched chain PEG is between about 5,000 Da and about 40,000 Da. In some embodiments, the molecular weight of a branched chain PEG is between about 5,000 Da and about 20,000 Da. The foregoing list for substantially water soluble backbones is by no means exhaustive and is merely illustrative, and in some embodiments, polymeric materials having the qualities described above are suitable for use in methods and compositions described herein.

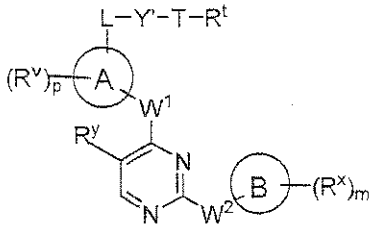
[00281] One of ordinary skill in the art will appreciate that when $-T-R^1$ is attached to a compound of formula **I-a** or **I-b** *via* the R^1 warhead group, then the resulting tethering moiety comprises the R^1 warhead group. As used herein, the phrase "comprises a warhead group" means that the tethering moiety formed by $-R^{1'}-T-$ of formula **V-a** or **V-b** is either substituted with a warhead group or has such a warhead group incorporated within the tethering moiety. For example, the tethering moiety formed by $-R^{1'}-T-$ may be substituted with an -L-Y warhead group, wherein such groups are as described herein. Alternatively, the tethering moiety formed by $-R^{1'}-T-$ has the appropriate features of a warhead group incorporated within the tethering moiety. For example, the tethering moiety formed by $-R^{1'}-T-$ may include one or more units of unsaturation and optional substituents and/or heteroatoms which, in combination, result in a

moiety that is capable of covalently modifying a protein kinase in accordance with the present invention. Such $-R^{1}$-T- tethering moiety are depicted below.

[00282] In some embodiments, a methylene unit of an $-R^{1'}$-T- tethering moiety is replaced by a bivalent -L-Y'- moiety to provide a compound of formula **V-a-*iii*** or **V-b-*iii***:



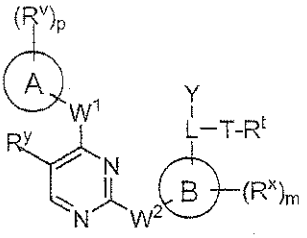
V-a-*iii*



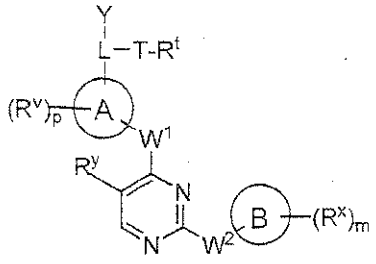
V-b-*iii*

wherein each of Ring A, Ring B, m, p, R^{x}, R^{y}, R^{v},W^{1}, W^{2}, T, L, Y', and R^{t} is as defined above and described in classes and subclasses herein and Y' is a bivalent version of the Y group defined above and described in classes and subclasses herein.

[00283] In some embodiments, a methylene unit of an $-R^{1'}$-T- tethering moiety is replaced by an –L(Y)- moiety to provide a compound of formula **V-a-*iv*** or **V-b-*iv***:



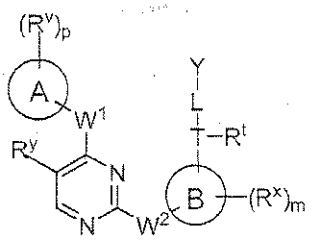
V-a-*iv*



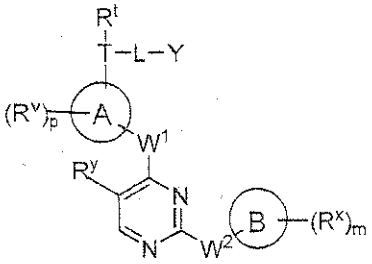
V-b-*iv*

wherein each of Ring A, Ring B, m, p, R^{x}, R^{y}, R^{v},W^{1}, W^{2}, T, L, Y, and R^{t} is as defined above and described in classes and subclasses herein.

[00284] In some embodiments, a tethering moiety is substituted with an L-Y moiety to provide a compound of formula **V-a-*v*** or **V-b-*v***:



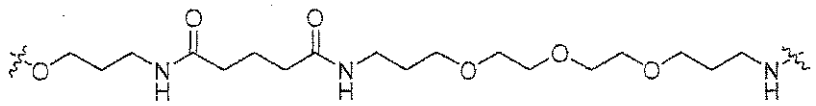
V-a-v



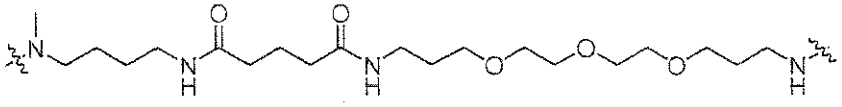
V-b-v

wherein each of Ring A, Ring B, m, p, R^x, R^y, R^v,W^1, W^2, T, L, Y, and R^t is as defined above and described in classes and subclasses herein.

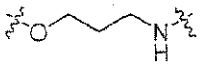
[00285] In certain embodiments, the tethering moiety, -T-, has one of the following structures:



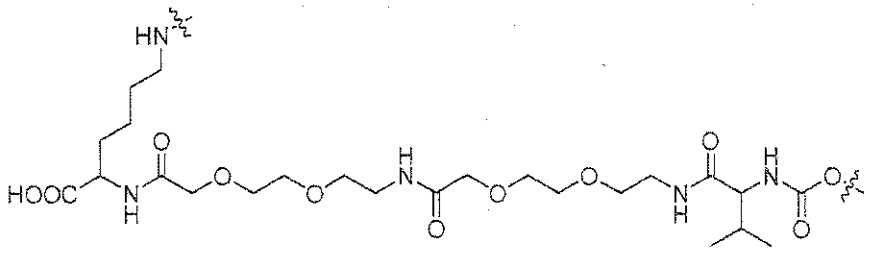
[00286] In some embodiments, the tethering moiety, -T-, has the following structure:



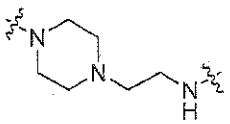
[00287] In other embodiments, the tethering moiety, -T-, has the following structure:



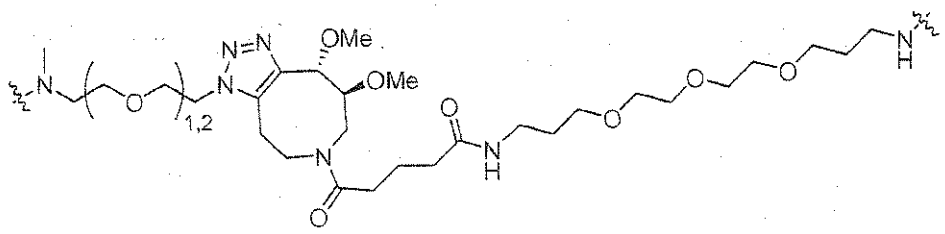
[00288] In certain other embodiments, the tethering moiety, -T-, has the following structure:



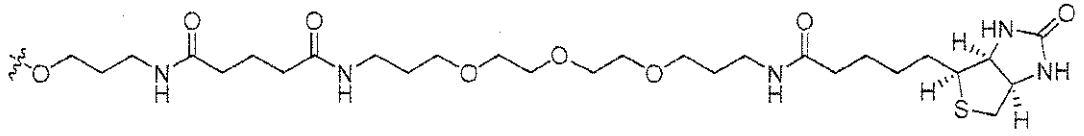
[00289] In yet other embodiments, the tethering moiety, -T-, has the following structure:



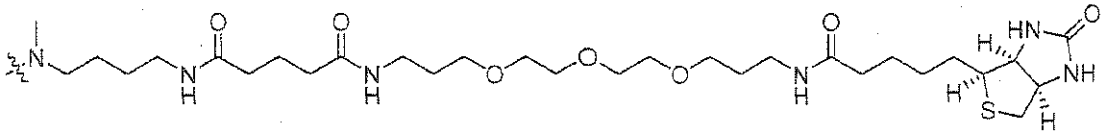
[00290] In some embodiments, the tethering moiety, -T-, has the following structure:



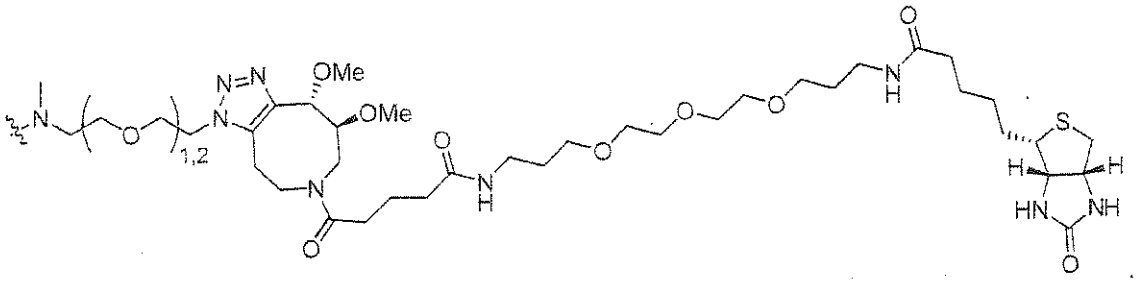
[00291] In some embodiments, -T-R^1 is of the following structure:



[00292] In other embodiments, -T-R^1 is of the following structure:

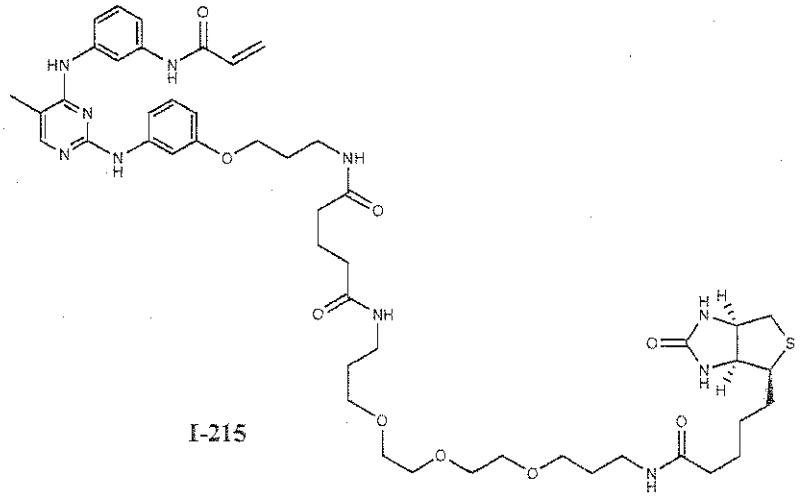


[00293] In certain embodiments, -T-R^1 is of the following structure:

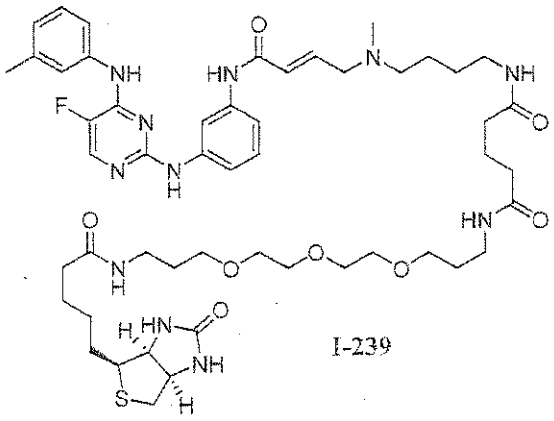


[00294] In some embodiments, a probe compound of formula **V-a**, **V-b**, **VI-a**, **VI-b**, **VII-a**, or **VII-b** is derived from any compound of Table 5.

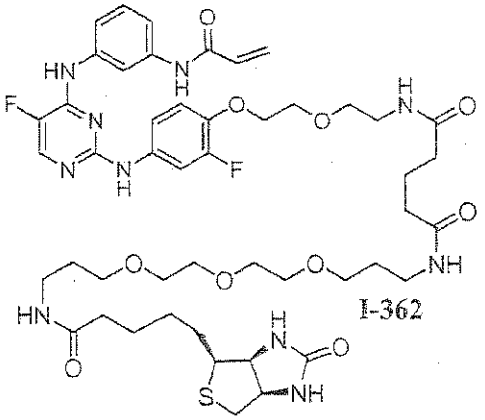
[00295] In certain embodiments, the probe compound is one of the following structures:



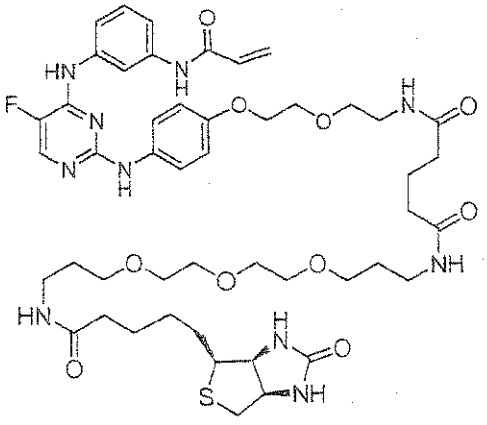
I-215



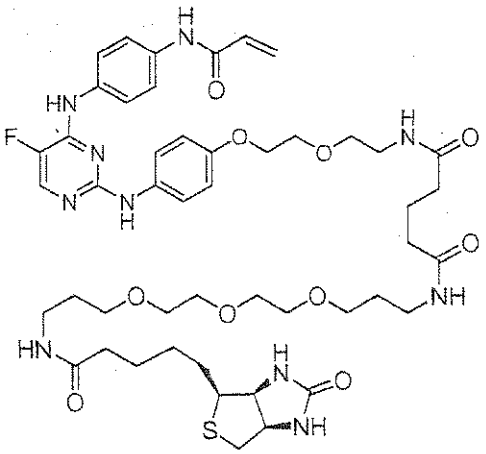
I-239



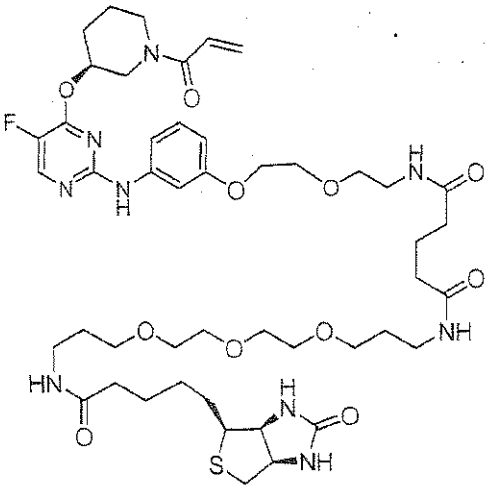
I-362



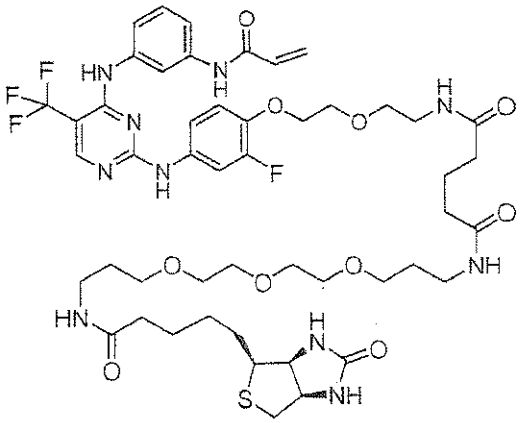
I-363



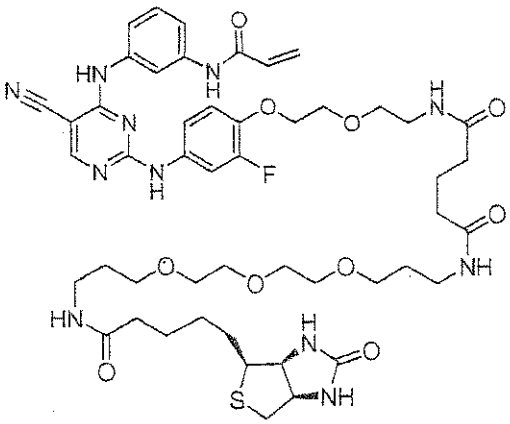
I-364



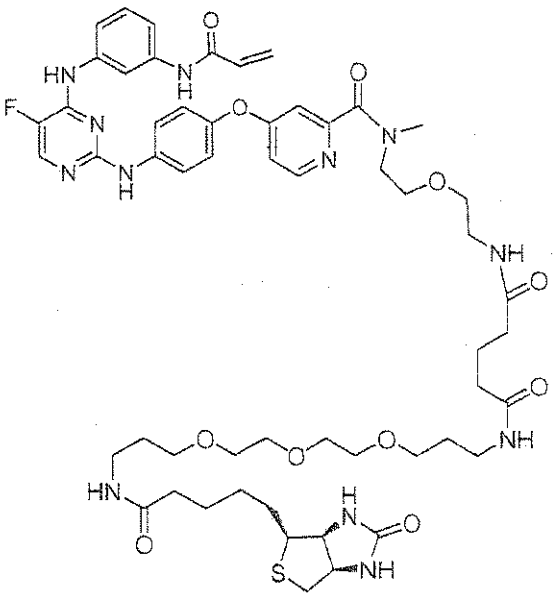
I-365



I-366



I-367



I-368.

[00296] It will be appreciated that many –T-R^1 reagents are commercially available. For example, numerous biotinylating reagents are available from, e.g., Thermo Scientific having varying tether lengths. Such reagents include NHS-PEG_4-Biotin and NHS-PEG_{12}-Biotin.

[00297] In some embodiments, analogous probe structures to the ones exemplified above are prepared using click-ready inhibitor moieties and click-ready –T-R^1 moieties, as described herein.

[00298] In some embodiments, a provided probe compound covalently modifies a phosphorylated conformation of a protein kinase. In one aspect, the phosphorylated conformation of the protein kinase is either an active or inactive form of the protein kinase. In certain embodiments, the phosphorylated conformation of the protein kinase is an active form of said kinase. In certain embodiments, the probe compound is cell permeable.

[00299] In some embodiments, the present invention provides a method for determining occupancy of a protein kinase by a provided irreversible inhibitor (i.e., a compound of formula I-a or I-b) in a patient, comprising providing one or more tissues, cell types, or a lysate thereof, obtained from a patient administered at least one dose of a compound of said irreversible inhibitor, contacting said tissue, cell type or lysate thereof with a probe compound (i.e., a compound of formula V-a, V-b, VI-a, VI-b, VII-a, or VII-b) to covalent modify at least one protein kinase present in said lysate, and measuring the amount of said protein kinase covalently

modified by the probe compound to determine occupancy of said protein kinase by said compound of formula **I-a** or **I-b** as compared to occupancy of said protein kinase by said probe compound. In certain embodiments, the method further comprises the step of adjusting the dose of the compound of formula **I-a** or **I-b** to increase occupancy of the protein kinase. In certain other embodiments, the method further comprises the step of adjusting the dose of the compound of formula **I-a** or **I-b** to decrease occupancy of the protein kinase.

[00300] As used herein, the terms "occupancy" or "occupy" refer to the extent to which a protein kinase is modified by a provided covalent inhibitor compound. One of ordinary skill in the art would appreciate that it is desirable to administer the lowest dose possible to achieve the desired efficacious occupancy of the protein kinase.

[00301] In some embodiments, the protein kinase to be modified is BTK. In other embodiments, the protein kinase to be modified is EGFR. In certain embodiments, the protein kinase is JAK. In certain other embodiments, the protein kinase is one or more of ErbB1, ErbB2, or ErbB4. In yet other embodiments, the protein kinase is TEC, ITK, or BMX.

[00302] In some embodiments, the probe compound comprises the irreversible inhibitor for which occupancy is being determined.

[00303] In some embodiments, the present invention provides a method for assessing the efficacy of a provided irreversible inhibitor in a mammal, comprising administering a provided irreversible inhibitor to the mammal, administering a provided probe compound to tissues or cells isolated from the mammal, or a lysate thereof, measuring the activity of the detectable moiety of the probe compound, and comparing the activity of the detectable moiety to a standard.

[00304] In other embodiments, the present invention provides a method for assessing the pharmacodynamics of a provided irreversible inhibitor in a mammal, comprising administering a provided irreversible inhibitor to the mammal, administering a probe compound presented herein to one or more cell types, or a lysate thereof, isolated from the mammal, and measuring the activity of the detectable moiety of the probe compound at different time points following the administration of the inhibitor.

[00305] In yet other embodiments, the present invention provides a method for *in vitro* labeling of a protein kinase comprising contacting said protein kinase with a probe compound

described herein. In one embodiment, the contacting step comprises incubating the protein kinase with a probe compound presented herein.

[00306] In certain embodiments, the present invention provides a method for *in vitro* labeling of a protein kinase comprising contacting one or more cells or tissues, or a lysate thereof, expressing the protein kinase with a probe compound described herein.

[00307] In certain other embodiments, the present invention provides a method for detecting a labeled protein kinase comprising separating proteins, the proteins comprising a protein kinase labeled by probe compound described herein, by electrophoresis and detecting the probe compound by fluorescence.

[00308] In some embodiments, the present invention provides a method for assessing the pharmacodynamics of a provided irreversible inhibitor *in vitro*, comprising incubating the provided irreversible inhibitor with the target protein kinase, adding the probe compound presented herein to the target protein kinase, and determining the amount of target modified by the probe compound.

[00309] In certain embodiments, the probe compound is detected by binding to avidin, streptavidin, neutravidin, or captavidin.

[00310] In some embodiments, the probe is detected by Western blot. In other embodiments, the probe is detected by ELISA. In certain embodiments, the probe is detected by flow cytometry.

[00311] In other embodiments, the present invention provides a method for probing the kinome with irreversible inhibitors comprising incubating one or more cell types, or a lysate thereof, with a biotinylated probe compound to generate proteins modified with a biotin moiety, digesting the proteins, capturing with avidin or an analog thereof, and performing multi-dimensional LC-MS-MS to identify protein kinases modified by the probe compound and the adduction sites of said kinases.

[00312] In certain embodiments, the present invention provides a method for measuring protein synthesis in cells comprising incubating cells with an irreversible inhibitor of the target protein, forming lysates of the cells at specific time points, and incubating said cell lysates with an inventive probe compound to measure the appearance of free protein over an extended period of time.

[00313] In other embodiments, the present invention provides a method for determining a dosing schedule in a mammal for maximizing occupancy of a target protein kinase comprising assaying a one or more cell types, or a lysate thereof, isolated from the mammal, (derived from, e.g., splenocytes, peripheral B cells, whole blood, lymph nodes, intestinal tissue, or other tissues) from a mammal administered a provided irreversible inhibitor of formula **I-a** or **I-b**, wherein the assaying step comprises contacting said one or more tissues, cell types, or a lysate thereof, with a provided probe compound and measuring the amount of protein kinase covalently modified by the probe compound.

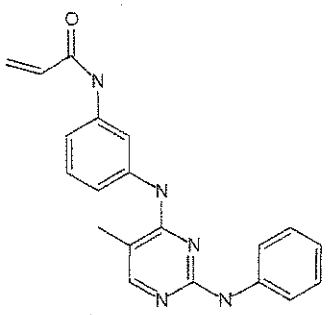
EXEMPLIFICATION

[00314] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00315] Compound numbers utilized in the Examples below correspond to compound numbers set forth in Table 5, *supra*.

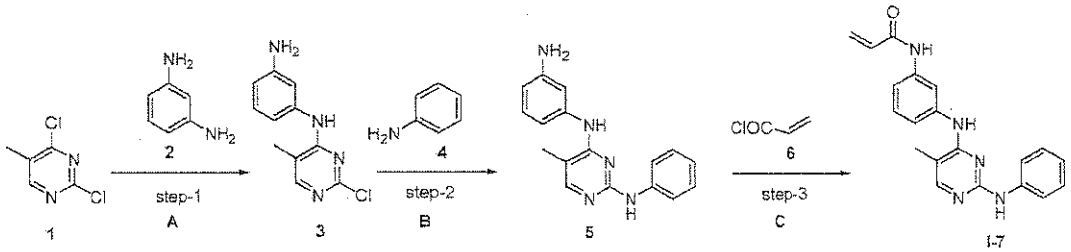
EXAMPLE 1

[00316] Preparation of N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl) acrylamide **I-7**



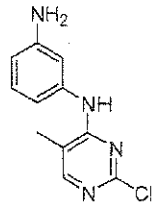
I-7

[00317] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 120 ^{0}C, 30 min, MW; **B)** NMP, 200 ^{0}C, 10 min, MW; **C)** NMP, 0 ^{0}C-30 min, rt-30 min.

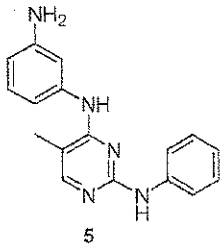
[00318] **Step-1**



3

[00319] A solution of **1** (2.0 g, 0.012 mol), 1,3-phenylenediamine (2.0 g, 0.018 mmol), DIPEA (2.33 g, 0.018 mol) in n-BuOH (20 mL) was subjected to microwave irradiation at 120 ^{0}C for 30 min. The reaction mixture was then quenched with water (100 mL), extracted with EtOAc (3x100 mL). The combined EtOAc extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 60-120 mesh, EtOAc/$CHCl_3$: 15/85) gave **3** (1.3 g, 45 %) as a dark brown solid.

[00320] **Step-2**

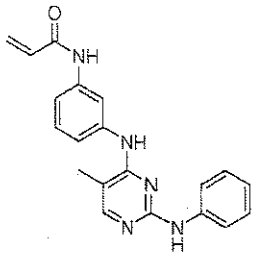


5

[00321] A solution of **3** (1.0 g, 4.27 mmol), **4** (1.5 g, 16.12 mmol) in NMP (10.0 mL) was subjected to microwave irradiation (200 ^{0}C, 10 min). The reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined ethyl acetate extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under

reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH : 98/2) gave **5** (0.5 g, 40.3%) as a light brown solid.

[00322] **Step-3**

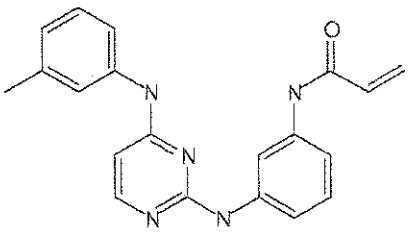


I-7

[00323] To a stirred solution of **5** (200 mg, 0.68 mmol) in NMP (2.0 mL) at 0 ^{0}C was added acryloyl chloride (248 mg, 0.2.74 mmol) and the reaction mixture was stirred at 0 ^{0}C for 60 min.. The reaction mixture was then stirred with hexane for ½ h and then hexane was removed by decantation from the mixture and the residue was quenched with water (10 mL). The aqueous solution was basified with sat. $NaHCO_3$ solution and then extracted with EtOAc (3x10 mL). The combined EtOAc extract was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 230-400, MeOH/ $CHCl_3$: 10/90) gave **I-7** (110 mg, 46.4%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.10 (s, 3H), 5.73 (dd, 1.88 & 10.42 Hz, 1H), 6.24 (dd, *J* = 1.88 & 17 Hz, 1H), 6.44 (dd, J = 10.08 & 16.92 Hz, 1H), 6.78 (t, *J* = 7.36 Hz, 1H), 7.06-7.11 (m, 2H), 7.26 (t, *J* = 8.08 Hz, 1H), 7.38-7.40 (bm, 2H), 7.65 (d, *J* = 8.52 Hz, 2H), 7.88 (s, 1H), 7.92 (s, 1H), 8.37 (s, 1H), 8.91 (s, 1H), 10.09 (s, 1H); LCMS: *m/e* 346.8 (M+1).

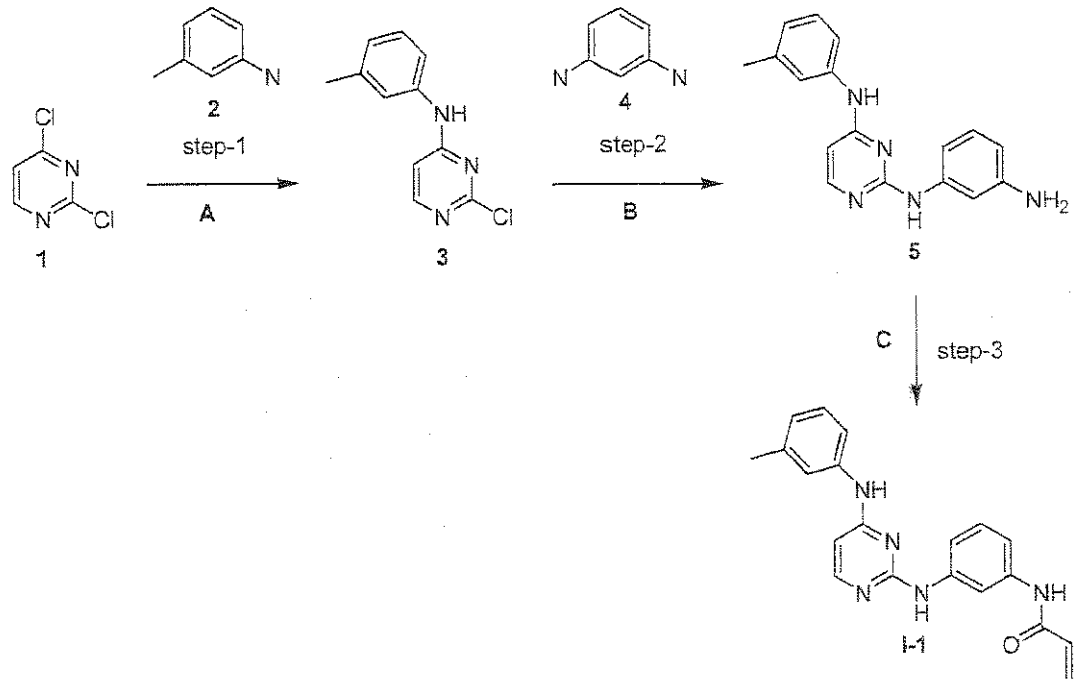
EXAMPLE 2

[00324] Preparation of N-(3-(4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)acrylamide **I-1**



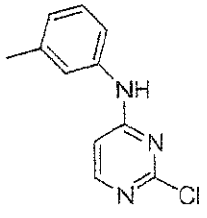
I-1

[00325] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIEA, n-BuOH, 110 ^{0}C, 30 min, microwave; B) NMP, 200 ^{0}C, 10 min, microwave; C) acryloyl chloride, NMP, 0 ^{0}C-30 min, rt-30 min.

[00326] Step-1

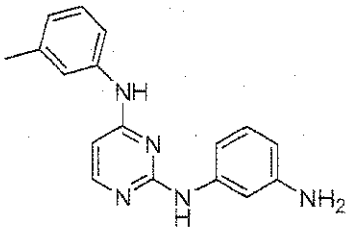


3

[00327] A solution of **1** (0.5 g, 3.35 mmol), *m*-toluidine (0.36 g, 3.35 mmol), DIEA (0.65 g, 5.0 mmol) in n-BuOH (2.0 mL) was subjected to microwave irradiation at 110 ^{0}C for 30 min. The reaction mixture was then concentrated under reduced pressure, quenched with water (5 mL), extracted with EtOAc (3x20 mL). The combined EtOAc extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue

obtained was further purified column chromatography (SiO_2, 60-120 mesh, $CHCl_3$/MeOH : 99/1) gave **3** (0.4 g, 54.2%) as a yellow solid.

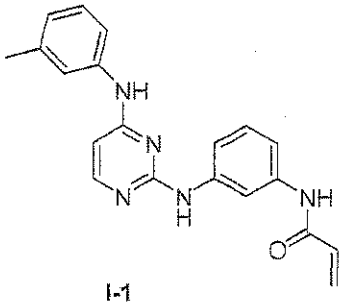
[00328] **Step-2**



5

[00329] A solution of **3** (0.2 g, 0.91 mmol), **4** (0.2 g, 1.8 mmol) in NMP (2.0 mL) was subjected to microwave irradiation (200 ^{0}C, 10 min). Then the reaction mixture was cooled, diluted with water (10 mL) and extracted with CH_2Cl_2 (3x15 mL). The combined CH_2Cl_2 extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get a residue. The crude residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH : 98/2) and gave **5** (0.14 g, 53%) as a light yellow solid.

[00330] **Step-3**

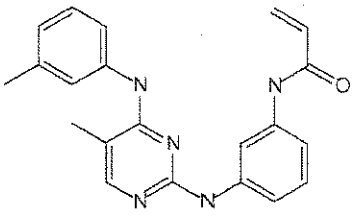


I-1

[00331] To a stirred solution of **5** (0.075 g, 0.25 mmol) in NMP (1.0 mL) at 0 ^{0}C was added acryloyl chloride (0.19 g, 2.0 mmoL) and the reaction mixture was stirred at 0 ^{0}C for 30 min followed by stirring at rt for 30 min. The neat reaction mixture was subjected to purification by column chromatography (neutral Al_2O_3, $CHCl_3$/MeOH : 98/2) gave **I-1** (0.04 g, 45%) as a white solid. ^{1}H NMR (DMSO-d6) δ ppm: 2.56 (s, 3H), 5.71 (dd, *J* = 2.0 & 10.08 Hz, 1H), 6.20-6.25 (m, 2H), 6.45 (dd, *J* = 10.12 & 17.00 Hz, 1H), 6.78 (d, *J* = 7.52 Hz, 1H), 7.12-7.19 (m, 2H), 7.31 (d, *J* = 8.44 Hz, 1H), 7.46-7.53 (m, 3H), 7.87 (s, 1H), 7.99 (d, *J* = 5.76 Hz, 1H), 9.15 (s, 1H), 9.24 (s, 1H), 10.03 (s, 1H); LCMS : *m/e* 346.4 (M+1).

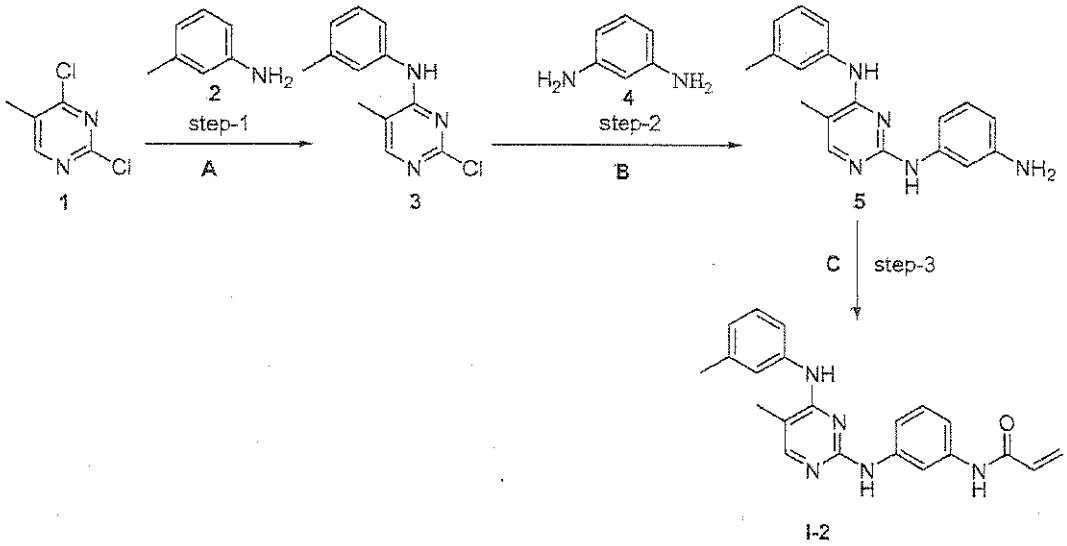
EXAMPLE 3

[00332] Preparation of N-(3-(5-methyl-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl) acrylamide **I-2**



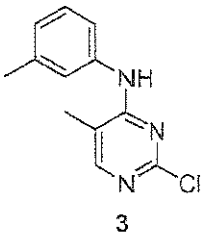
I-2

[00333] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 110 ^{0}C, 30 min, MW; B) NMP, 200 ^{0}C, 15 min, MW; C) acryloyl chloride, NMP, 0 ^{0}C-30 min, rt-30 min.

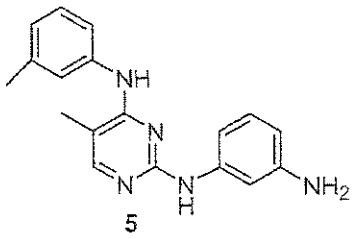
[00334] <u>Step-1</u>



3

[00335] A solution of **1** (0.1 g, 0.613 mmol), **2** (0.066 g, 0.613 mmol), DIPEA (0.118 g, 0.919 mmol) in n-BuOH (2.0 mL) was subjected to microwave irradiation at 110 ^{0}C for 90 min. The reaction mixture was cooled, concentrated under reduced pressure and the residue obtained was further purified by column chromatography (SiO_2, Methanol/chloroform mixtures) gave **3** (0.05 g, 34 %) as an off white solid.

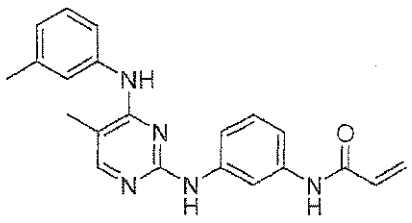
[00336] Step-2



5

[00337] A solution of **3** (0.05 g, 0.213 mmol), **4** (0.046 g, 0.427 mmol) in NMP (2.0 mL) was subjected to microwave irradiation (200 ^{0}C, 15 min). Then the reaction mixture was cooled, diluted with water (15 mL) and extracted with EtOAc (3x15 mL). The combined EtOAc extract was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH: 98/2) gave **5** (0.03 g, 46%) as a grey solid.

[00338] Step-3



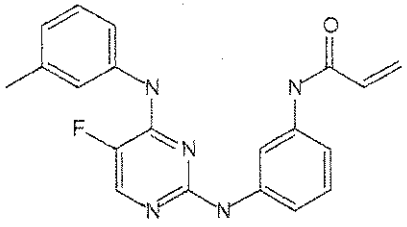
I-2

[00339] To a stirred solution of **5** (0.025 g, 0.082 mmol) in NMP (0.5 mL) at 0 ^{0}C was added acryloyl chloride (0.073 g, 0.821 mmol) and the reaction mixture was stirred at 0 ^{0}C for 30 min followed by stirring at rt for 30 min. The crude reaction mixture was passed through an alumina column (neutral Al_2O_3, chloroform/methanol mixtures) gave **I-2** (0.012 g, 41%) as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.10 (s, 3H), 2.27 (s, 3H), 5.72 (dd, J = 2 & 10.04 Hz, 1H), 6.22 (dd, J = 1.96 & 16.92 Hz, 1H), 6.45 (dd, J = 10.08 & 16.92 Hz, 1H), 6.83 (d, J = 7.36 Hz, 1H), 7.09 (t, J = 8.06 Hz, 1H), 7.17 (t, J = 7.78 Hz, 1H), 7.26 (d, J = 7.80 Hz, 1H), 7.47 (d, J =

1.08 Hz, 1H), 7.53 (s, 1H), 7.58 (d, J = 8.60 Hz, 1H), 7.78 (s, 1H), 7.88 (s, 1H), 8.15 (s, 1H), 9.01 (s, 1H), 9.99 (s, 1H); LCMS: *m/e* 360.1 (M+1).

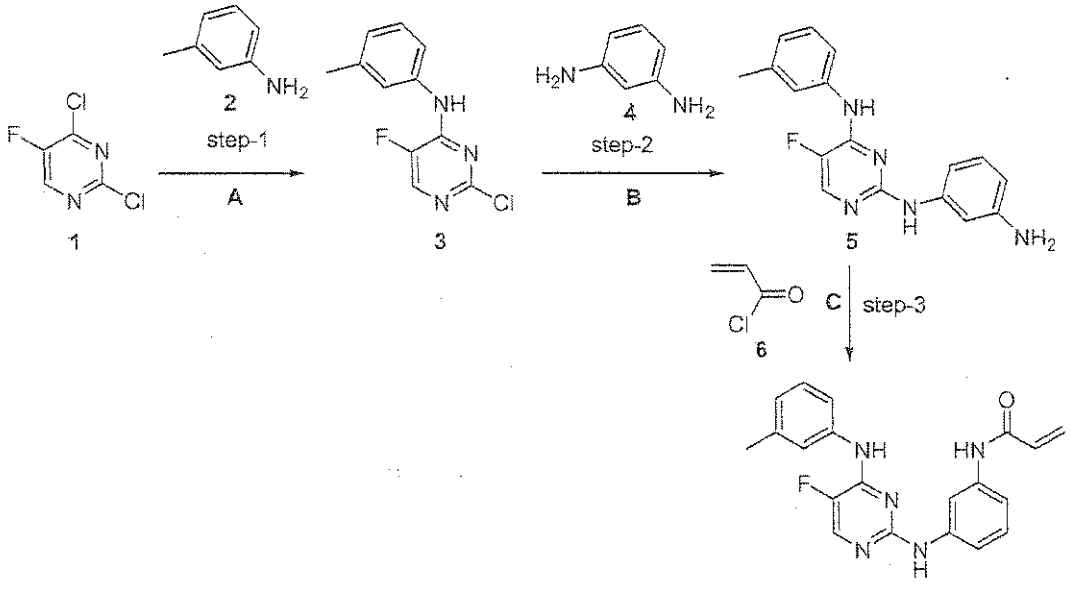
EXAMPLE 4

[00340] Preparation of N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl) acrylamide **I-3**



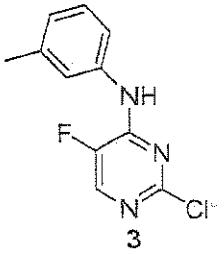
I-3

[00341] The title compound was prepared according to the schemes, steps and intermediates described below.



A) n-butanol, DIPEA, 110 ^{0}C, 45 min, MW; B) NMP, 200 ^{0}C, 10 min, MW; C) NMP, DMAP, 0 ^{0}C, 30 min.

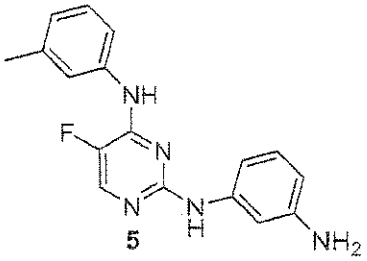
[00342] Step-1



3

[00343] To a solution of **1** (0.5 g, 3 mmol) in n-butanol (5.0 mL) was added **2** (0.64 g, 0.6 mmol), DIPEA (0.116 g, 0.8 mmol) and the reaction mixture was irradiated under microwave at 110 ^{0}C for 45 min. It was cooled, quenched with water (50 mL) and extracted with EtOAc (2x25 mL). The combined EtOAc extract was washed with water (25 mL), brine (25mL), dried over Na_2SO_4 and concentrated under reduced pressure gave **3** (0.45 g, 63%) which was taken for the next step without further purification.

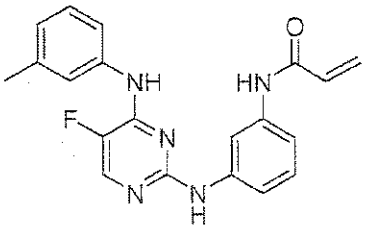
[00344] Step-2



5

[00345] A solution of **3** (0.45 g, 1.8 mmol) and **4** (0.41 g, 3.7 mmol) in NMP (4.5 mL) was subjected to microwave irradiation at 200 ^{0}C for 10 min. It was cooled, diluted with water (25 mL) and extracted with EtOAc (3x25 mL). The combined EtOAc extract was washed with water (2x25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, 60-120, Chloroform/Ethyl acetate: 90/10) gave **5** (0.23 g, 41%) as a light yellow solid.

[00346] Step-3

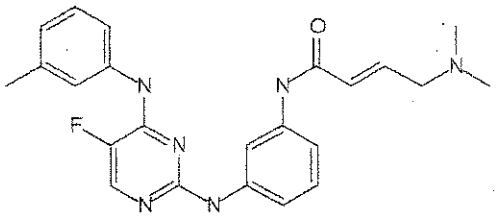


I-3

[00347] To a stirred solution of **5** (0.075 g, 0.24 mmol), in NMP(1.5 mL) at 0 ^{0}C under N2 atmosphere was added DMAP (0.059 g, 0.48 mmol) and Acryloyl chloride (0.064 g, 0.725 mmol) and the reaction mixture was kept at this temperature for 30 min. It was quenched with water (7.5 mL) and extracted with EtOAc (3x25 mL). The combined EtOAc extract was washed with 5% Citric acid (10 mL), water (2x10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was further purified by column chromatography (Al_2O_3, Chloroform/Methanol: 98/2) gave **I-3** (0.01 g, 11.3%) as an off white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.27 (s, 3H), 5.72 (d, J = 9.84 Hz, 1H), 6.22 (d, J = 16.92 Hz, 1H), 6.44 (dd, J = 10.2 & 17.02 Hz, 1H), 6.85 (d, J = 7.12 Hz, 1H), 7.12-7.19 (m, 2H), 7.29 (d, J = 7.68 Hz, 1H), 7.43 (d, J = 7.92 Hz, 1H), 7.61-7.63 (m, 2H), 7.82 (s, 1H), 8.08 (s, 1H), 9.23 (bs, 2H), 10.03 (s, 1H); LCMS: *m/e* 364.2 (M+1).

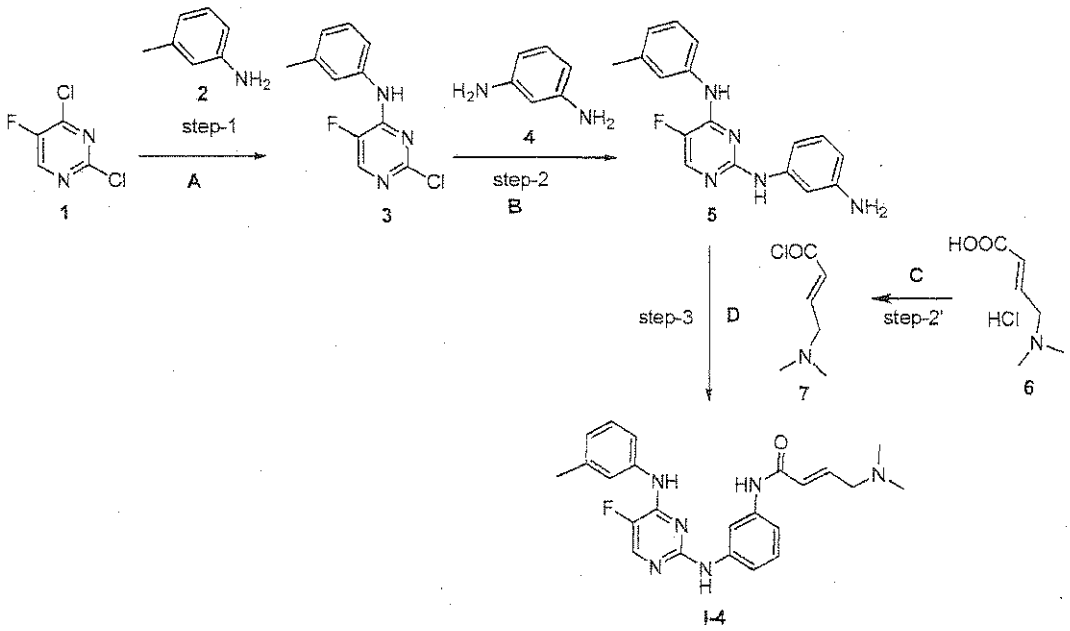
EXAMPLE 5

[00348] Preparation of (E)-4-(dimethylamino)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)but-2-enamide **I-4**



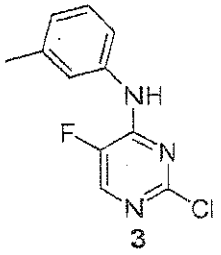
I-4

[00349] The title compound was prepared according to the schemes, steps and intermediates described below.



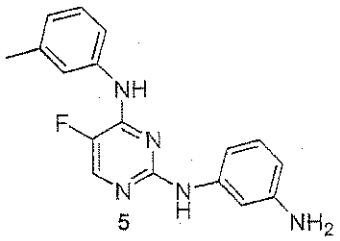
A) n-butanol, DIPEA, 110 ^{0}C, 45 min., MW; B) NMP, 200 ^{0}C, 10 min., MW; C) oxalyl chloride, CH_3CN, ½ h at 0 ^{0}C, 2 h at 25 ^{0}C, 5 min at 45 ^{0}C; D) NMP, 0 ^{0}C to10 ^{0}C, 30 min.

[00350] Step-1



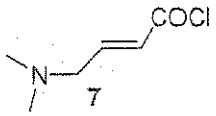
[00351] A solution of **1** (0.5 g, 3.0 mmol), **2** (0.32 g, 3.0 mmol) in n-butanol (5.0 mL) was subjected to microwave irradiation (110 ^{0}C, 45 min). It was cooled, quenched with water (50 mL) and extracted with EtOAc (2x25 mL). The combined EtOAc extract was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave **3** (0.45 g, 63%) which was taken for next step without further purification.

[00352] Step-2



[00353] A solution of **3** (0.45 g, 1.8 mmol), 4 (0.41 g, 3.7 mmol) in NMP (4.5 mL) was subjected to microwave irradiation (200 ^{0}C, 10 min). It was cooled, diluted with water (25 mL) and extracted with EtOAc (3x25 mL). The combined ethyl acetate extract was washed with water (2x25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, Chloroform/Ethyl acetate: 90/10) gave **5** (0.23 g, 41%) as a light yellow solid.

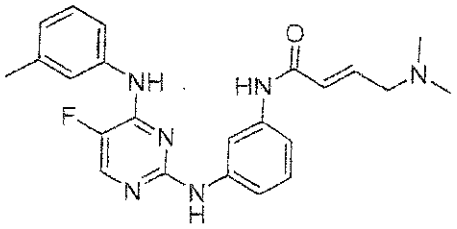
[00354] Step-3a



7

[00355] To a stirred solution of **6** (0.13 g, 0.80 mmol) in CH_3CN (1.0 mL) was added oxalyl chloride (0.122 g, 0.96 mmol) at 0 ^{0}C. The reaction mixture was allowed to stir at 0 ^{0}C for ½ h and then at RT for 2 h. Finally it was heated at 45 ^{0}C for 5 min, cooled and the reaction mixture was taken for next step without further purification.

[00356] Step-3

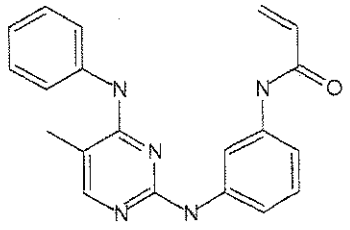


I-4

[00357] To a stirred solution of **5** (0.05 g, 0.16 mmol) in NMP (1.0 mL) was added 7 at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C for 30 min and at 10 ^{0}C for 30 min. It was quenched with sat. Sodium bicarbonate soln. (5 mL) and extracted with CH_2Cl_2 (3x5 mL). The combined organic extract was washed with water (1 mL), brine (1 mL) and dried over Na_2SO_4. Concentration under reduced pressure followed by purification by column chromatography (SiO_2, 230-400, $CHCl_3$/MeOH, 95/5) gave **I-4** (0.02 g, 29.4%) as a white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.21 (s, 6H), 2.28 (s, 3H), 3.08 (bd, *J* = 5.6 Hz, 2H), 6.29 (d, *J* = 15.60 Hz, 1H), 6.67-6.74 (m, 1H), 6.86 (d, *J* = 7.20 Hz, 1H), 7.12-7.20 (m, 2H), 7.27 (d, *J* = 8.00 Hz, 1H), 7.43 (d, *J* = 8.00 Hz, 1H), 7.62-7.64 (m, 2H), 7.82 (s, 1H), 8.08 (d, *J* = 3.6 Hz, 1H), 9.23 (s, 1H), 9.24 (s, 1H), 9.96 (s, 1H); LCMS: *m/e* 421.2 (M+1).

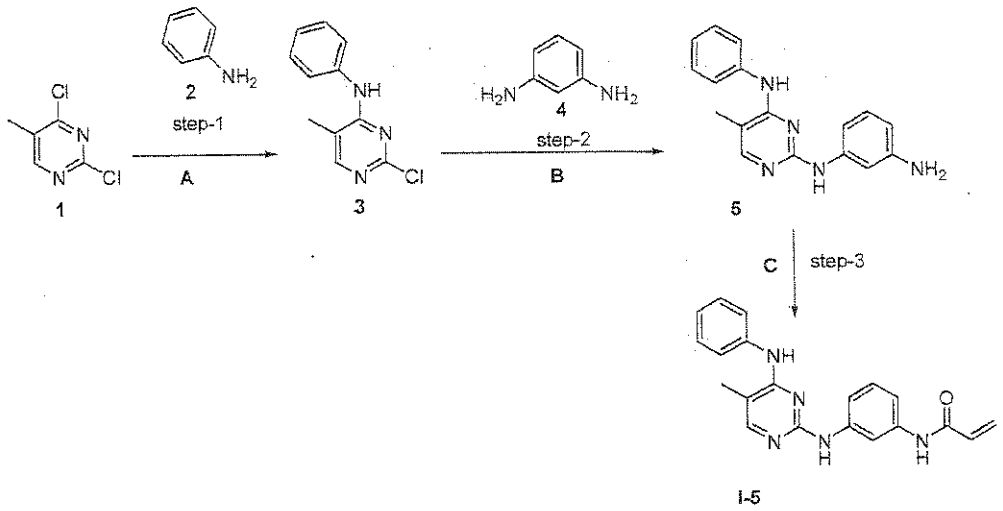
EXAMPLE 6

[00358] Preparation of N-(3-(5-methyl-4-(phenylamino)pyrimidin-2-ylamino)phenyl) acrylamide **I-5**



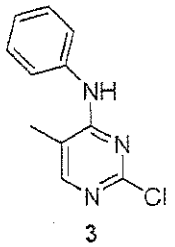
I-5

[00359] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 110 ^{0}C, 30 min, MW; B) NMP, 200 ^{0}C, 15 min, MW; C) acryloyl chloride, NMP, 0 ^{0}C-30 min, rt-30 min.

[00360] <u>Step-1</u>

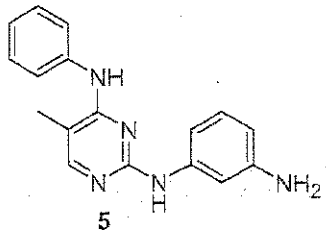


3

[00361] A solution of **1** (0.1 g, 0.613 mmol), **2** (0.114 g, 1.226 mmol), DIPEA (0.118 g, 0.919 mmol) in n-BuOH (2.0 mL) was subjected to microwave irradiation at 110 ^{0}C for 90 min. The

reaction mixture was cooled, concentrated under reduced pressure and the residue was further purified by column chromatography (SiO_2, 60-120, Methanol/chloroform: 1/9) gave **3** (0.08 g, 59 %) as a white solid

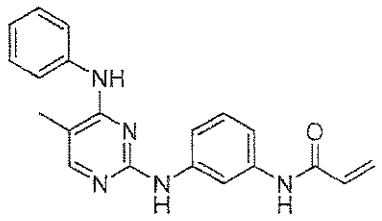
[00362] **Step-2**



5

[00363] A solution of **3** (0.08 g, 0.364 mmol), **4** (0.059 g, 0.546 mmol) in NMP (2.0 ml) was subjected to microwave irradiation (200 ^{0}C, 15 min). The reaction mixture was cooled, diluted with water (15 mL) and extracted with EtOAc (3x15 mL). The combined ethyl acetate extract was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH: 98/2) gave **5**(0.06 g, 60%) as a light grey solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.09 (s, 3H), 4.74 (s, 2H), 6.09-6.11 (m, 1H), 6.77-6.85 (m, 2H), 6.91 (t, *J* = 1.72 Hz, 1H), 7.02 (t, *J* = 7.36 Hz, 1H), 7.31 (t, *J* = 7.52 Hz, 2H), 7.75 (d, *J* = 7.68 Hz, 2H), 7.84 (s, 1H), 8.18 (s, 1H), 8.65 (s, 1H); LCMS: *m/e* 293.2 (M+1).

[00364] **Step-3**



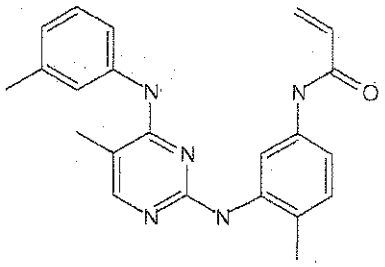
I-5

[00365] To a stirred solution of **5** (60 mg, 0.205 mmol) in NMP (2.0 mL) at 0 ^{0}C was added acryloyl chloride (0.148 g, 1.64 mmol) and the reaction mixture was stirred at 0 ^{0}C for 30 min.. The neat reaction mixture was passed through an alumina column (neutral Al_2O_3, chloroform/methanol, 99/1) gave **I-5** (0.013 g, 18.5%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H), 5.72 (dd, *J* = 1.92 & 10.04 Hz, 1H), 6.22 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, *J* = 9.32 & 16.92 Hz, 1H), 7.00 (t, *J* = 7.28 Hz, 1H), 7.09 (t, *J* = 8.04 Hz, 1H), 7.23-

7.30 (m, 3H), 7.43 (d, J = 8.04 Hz, 1H), 7.75-7.77 (m, 2H), 7.83 (s, 1H), 7.88 (s, 1H), 8.22 (s, 1H), 9.00 (s, 1H), 9.99 (s, 1H); LCMS: *m/e* 346 (M+1).

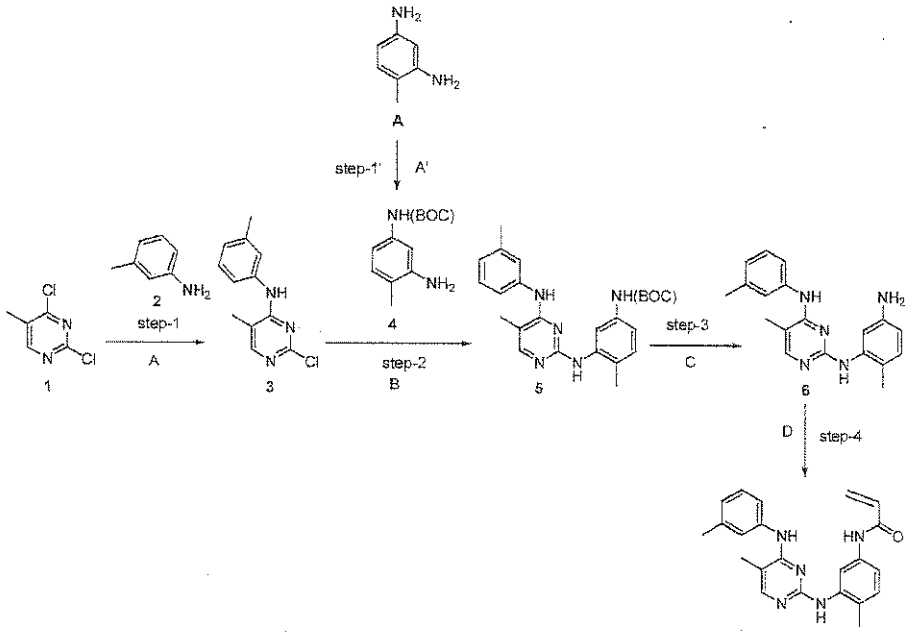
EXAMPLE 7

[00366] Preparation of N-(4-methyl-3-(5-methyl-4-(m-tolylamino)pyrimidin-2-ylamino) phenyl)acrylamide **I-8**



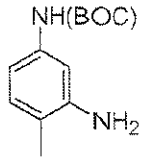
I-8

[00367] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 120 ^{0}C, 60 min., MW; **A'**) $(BOC)_2O$, MeOH, -10 ^{0}C, 4 h; **B**) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 ^{0}C, 12 h; **C**) TFA, CH_2Cl_2, 0 ^{0}C-30 min, rt-2 h; **D**) acryloyl chloride, NMP, 0 ^{0}C-30 min, rt-30 min.

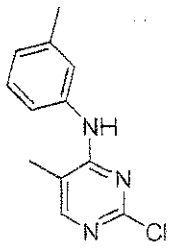
[00368] Step 1'



4

[00369] To a stirred solution of **A** (5 g, 0.04 mmol) in MeOH (75 mL) was added $(BOC)_2O$ (11.59 g, 0.050 mmol), slowly at -10 ^{0}C. The reaction was stirred at this temperature for 4 h and then reaction mixture was concentrated under reduced pressure. The residue obtained was taken in EtOAc (300 mL). It was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered **4** (2.5 g, 27%) as an off-white solid.

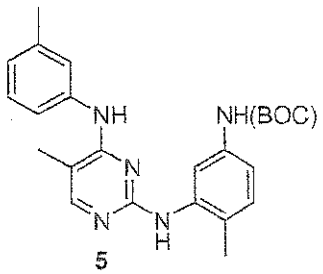
[00370] Step 1



3

[00371] A solution of **1** (0.5 g, 3.06 mmol), **2** (0.39 g, 3.06 mmol), DIPEA (0.59 g, 4.5 mmol) in n-BuOH (5 mL) was subjected to microwave irradiation (120 ^{0}C, 30 min). The reaction mixture was cooled, solvents removed under reduced pressure and the residue obtained was quenched with water (5 mL). It was extracted with EtOAc (3x20 mL) and the combined EtOAc layer was washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH : 9/1) gave **3** (0.35 g, 49%) as an off-white solid.

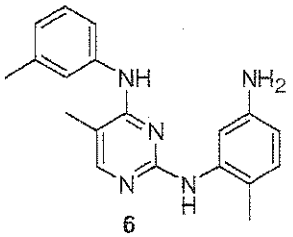
[00372] Step 2



5

[00373] A solution of **3** (0.1 g, 0.43 mmol), **4** (0.14 g, 0.64 mmol), $Pd(OAc)_2$ (10 mg, 0.043 mmol), BINAP (0.013 g, 0.021 mmol) and Cs_2CO_3 (0.2 g, 1.06 mmol) in degassed toluene (toluene was purged with N_2 for 15 min) was refluxed for 12 h under N_2 atmosphere. The reaction mixture was cooled and passed through a short bed of celite®. The filtrate was diluted with EtOAc (25 mL) and washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH : 9/1) gave **5** (40 mg, 22%) as an off-white solid.

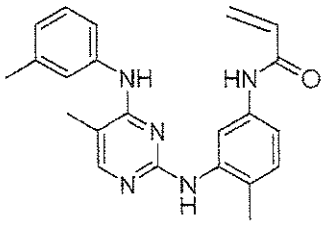
[00374] **Step-3**



6

[00375] To a stirred solution of **5** (0.04 g, 0.095 mmol) in dry CH_2Cl_2 (2 mL) at 0 ^{0}C was added CF_3COOH (0.2 mL, 5 vol) and the reaction mixture was kept at this temperature for 30 min. It was allowed to come to rt and stir at this temperature for 2 h. It was quenched with ice-cooled water (2 mL), basified with sodium carbonate solution and extracted with EtOAc (2x10 mL). The combined EtOAc extract was washed with water (2 mL), brine (2 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered **6** (22 mg, 73%) as a light brown solid.

[00376] **Step-4**



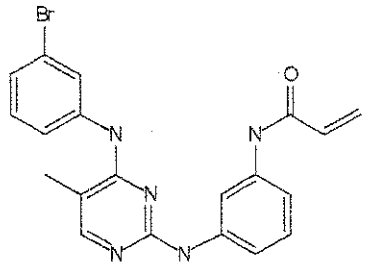
I-8

[00377] To a stirred solution of **6** (0.2 g, 0.63 mmol) in NMP (4 mL) at 0 ^{0}C was added acryloyl chloride (0.12 g, 1.25 mmol). The reaction was kept at this temperature for 30 min and then at rt for 30 min. It was quenched with ice-cooled water (2 mL) and extracted with EtOAc (2x10 mL). The combined EtOAc extract was washed with water (2 mL), brine (2 mL) and dried

over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 230-400, $CHCl_3$/MeOH : 9/1) gave **I-8** (10 mg, 4%) as a white solid. ^1H NMR (DMSO-d_6) δ ppm: 2.07 (s, 3H), 2.13 (s, 6H), 5.70 (dd, J = 1.92 & 10.08 Hz, 1H), 6.20 (dd, J = 1.96 & 16.88 Hz, 1H), 6.41 (dd, J = 10.16 & 16.96 Hz, 1H), 6.69 (d, J = 7.36 Hz, 1H), 6.98 (t, J = 7.76 Hz, 1H), 7.11 (d, J = 8.24 Hz, 1H), 7.41 (q, J = 9.92 Hz, 1H), 7.49-7.51 (m, 2H), 7.73 (s, 1H), 7.80 (s, 1H), 7.97 (s, 1H), 8.16 (s, 1H), 10.00 (s, 1H); LCMS : *m/e* 374 (M+1).

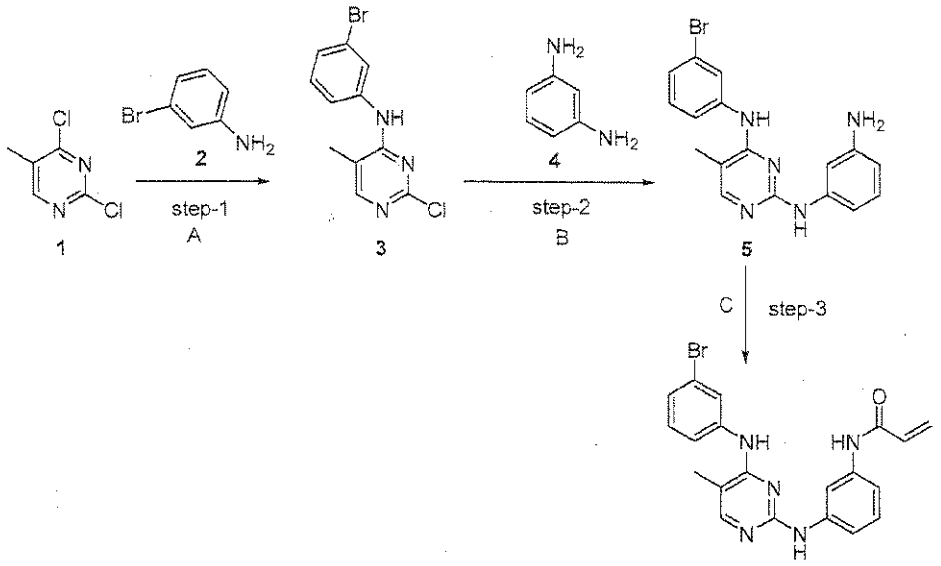
EXAMPLE 8

[00378] Preparation of N-(3-(4-(3-bromophenylamino)-5-methylpyrimidin-2-ylamino)phenyl) acrylamide **I-9**



I-9

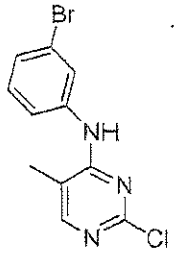
[00379] The title compound was prepared according to the schemes, steps and intermediates described below.



I-9

A) DIPEA, n-butanol, 110 ^{0}C, 1 h, MW; **B)** 1.5 N HCl, ethanol, 90 ^{0}C, 30 min., MW; C) acryloyl chloride, NMP, 0 ^{0}C, 30 min.

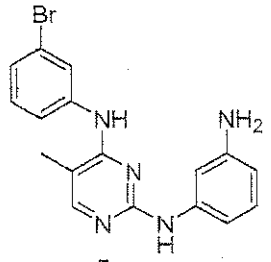
[00380] **Step 1**



3

[00381] A solution of **1** (0.5 g, 3.06 mmol), **2** (0.53 g, 3.06 mmol) and DIPEA (0.80 mL, 4.06 mmol) in n-butanol (5 mL) was subjected to microwave irradiation (110 ^{0}C, 1 h). The reaction mixture was cooled and concentrated under reduced pressure gave a residue. The residue taken in EtOAc (5 mL) and washed with $NaHCO_3$ solution (2 mL), water (2 mL) and with brine solution (2 mL). Drying over Na_2SO_4 followed by concentration under reduced pressure offered crude 3 which was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **3** (0.125 g, 13%) as a brown solid.

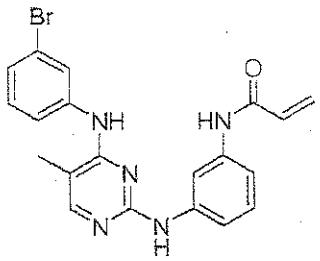
[00382] Step 2



5

[00383] To a solution of 3 (0.15 g, 0.5 mmol) in EtOH (3 mL)was added 4 (0.081 g, 0.75 mmol) followed by 1.5 N HCl (0.055 g, 1.5 mmol). The reaction mixture was subjected to microwave irradiation (90 ^{0}C, 30 min), cooled and concentrated under reduced pressure. The residue obtained was taken in EtOAc (5 mL) and washed with $NaHCO_3$ solution (2 mL), water (2 mL), and brine (2 mL). It was dried over Na_2SO_4, filtered and concentrated under reduced pressure gave crude 5. It was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave 5 (0.06 g, 32%) as a light brown solid.

[00384] Step 3

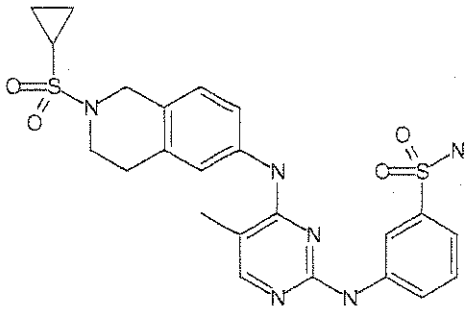


I-9

[00385] To a stirred solution of 5 (0.06 g, 0.16 mmol) in NMP (1 mL) was added acryloyl chloride (0.117 g, 1.29 mmol) at 0 ^{0}C. The reaction mixture was allowed to stir at this temperature for 30 min and then taken in dichloromethane (2 mL). It was washed with $NaHCO_3$ solution (1 mL), water (1 mL) and with brine solution (1 mL). It was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave I-9 (0.016 g, 23%) as a pale brown solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.16 (s, 3H), 5.75 (dd, J = 1.72 & 10 Hz, 1H), 6.23 (dd, J = 1.76 & 16.88, Hz, 1H), 6.45 (dd, J = 10.08 & 16.92 Hz, 1H), 7.22-7.34 (m, 4H), 7.38 (d, J = 8.00 Hz, 1H), 7.63 (d, J = 8.08 Hz, 1H), 7.77 (s, 1H), 7.82 (s, 1H), 7.93 (s, 1H), 9.68 (s, 1H), 10.26 (s, 1H), 10.34 (s, 1H); LCMS: *m/e* 426 (M−1).

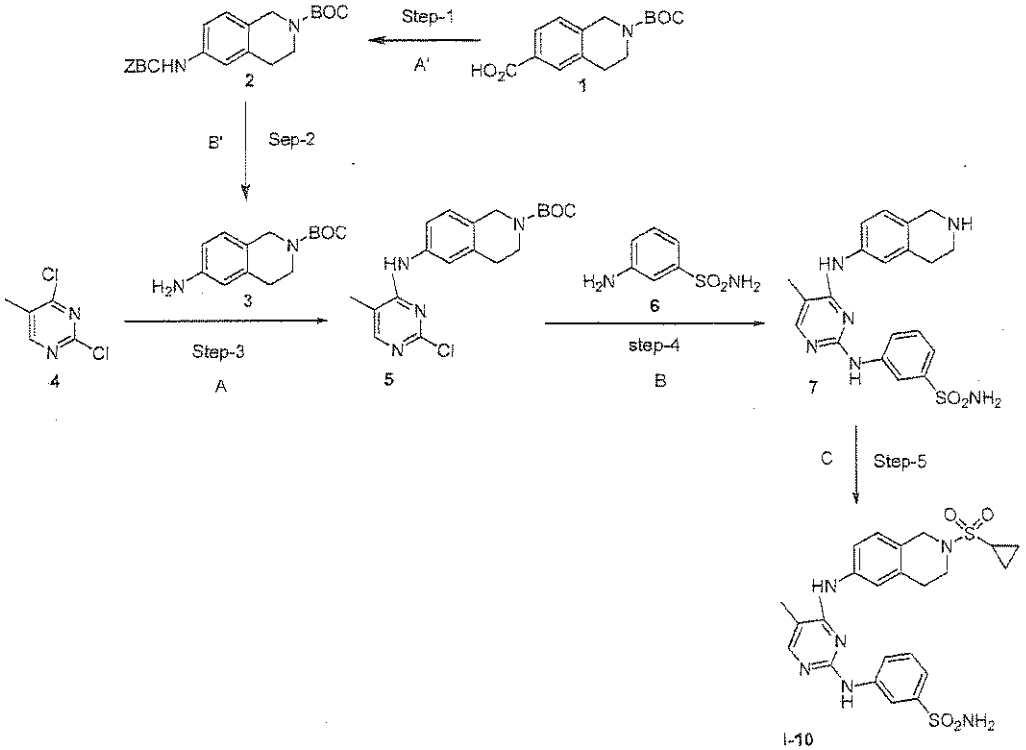
EXAMPLE 9

[00386] Preparation of 3-(4-(2-(cyclopropylsulfonyl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-5-methylpyrimidin-2-ylamino)benzenesulfonamide **I-10**



I-10

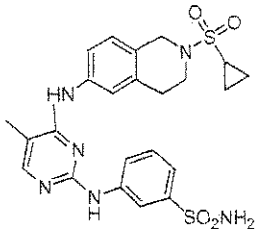
[00387] The title compound was prepared according to the schemes, steps and intermediates described below.



A') DPPA, Benzyl alcohol, Et_3N, toluene, 110 ^{0}C, 12 h.; **B'**) $Pd(OH)_2$, Ammonium formate, EtOH, reflux, 6 h; **A**) DIPEA, n-BuOH, 120 ^{0}C, 1 h., MW; **B**) 1.5 N HCl, EtOH, reflux 12 h.; C) Cyclopropylsulphonyl chloride, DIPEA, THF, rt, 12 h.

[00388] Steps 1-4 The procedure for synthesizing scaffold 7 is described in the experimental for Compound I-11 herein.

[00389] Step 5

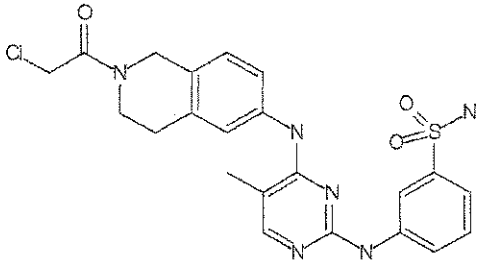


I-10

[00390] To a stirred solution of 7 (0.05 g, 0.0121 mmol) in THF (4 mL) at 0 ^{0}C, was added DIPEA (0.023 g, 0.182 mmol) followed by cyclopropylsulphonyl chloride (0.031 g, 0.182 mmol) under N_2 atmosphere. The reaction mixture was allowed to come to rt and maintained at this temperature for 12 h. It was taken in EtOAc (10 mL), washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 6/4) gave **I-10** (0.035 g, 56%) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm: 0.97-0.1.00 (m, 4H), 2.12 (s, 3H), 2.60-2.66 (m, 1H), 2.90 (t, *J* = 5.2 Hz, 2H), 3.52 (t, *J* = 6 Hz, 2H), 4.42 (s, 2H), 7.16 (d, *J* = 8.4 Hz, 1H), 7.27 (s, 2H), 7.31-7.35 (m, 2H), 7.53 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.92 (s, 1H), 8.03-8.04 (m, 2H), 8.45 (s, 1H), 9.40 (s, 1H); LCMS: *m/e* 515 (M+1).

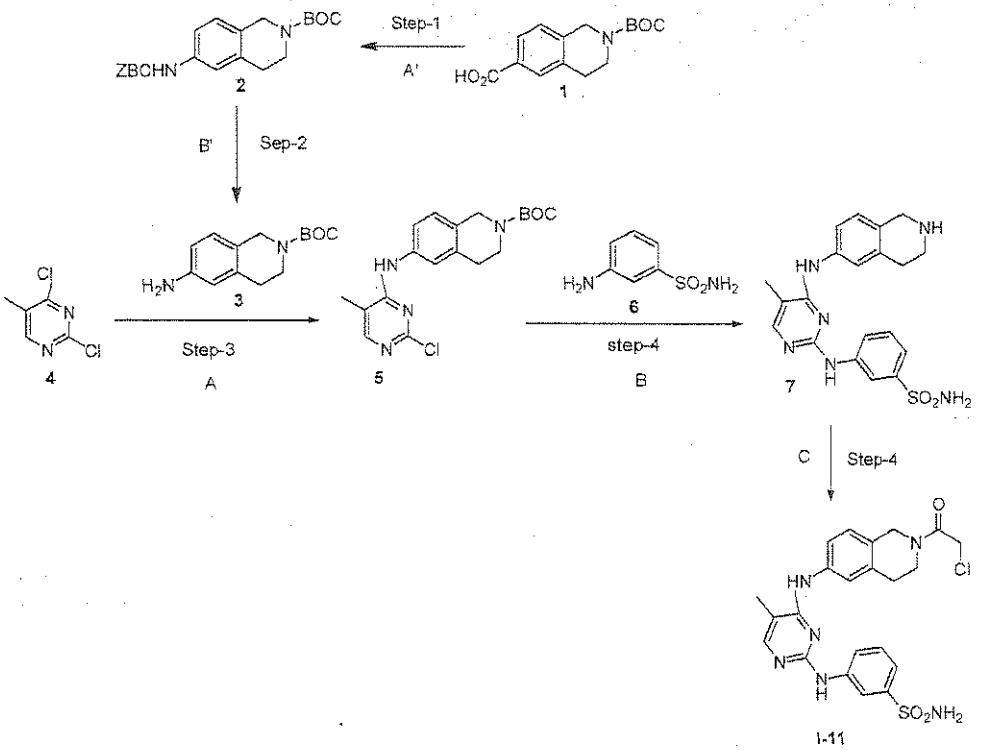
EXAMPLE 10

[00391] Preparation of 3-(4-(2-(2-chloroacetyl)-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-5-methylpyrimidin-2-ylamino)benzenesulfonamide I-11



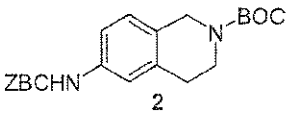
I-11

[00392] The title compound was prepared according to the schemes, steps and intermediates described below.



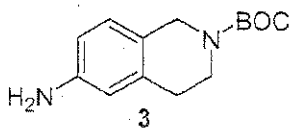
A') DPPA, Benzyl alcohol, Et_3N, toluene, 110 ^{0}C, 12 h.; **B'**) $Pd(OH)_2$, Ammonium formate, EtOH, reflux, 6 h; **A**) DIPEA, n-BuOH, 120 ^{0}C, 1 h., MW; **B**) 1.5 N HCl, EtOH, reflux 12 h.; C) Cl-CH_2-COCl, Et_3N, THF, rt, 12 h.

[00393] <u>Step-1</u>



[00394] To a stirred solution of 1 (1.5 g, 5.4 mmol) in toluene (15 mL) was added DPPA (2.17 g, 8.11 mmol), Et_3N (1.05 mL, 8.11 mmol) and benzyl alcohol (0.876 g, 8.11 mmol) under N_2. The reaction mixture was allowed to reflux for 12 h, cooled and diluted with ethyl acetate (100 mL). It was washed with water (5 mL), brine solution (5 mL) and dried over Na_2SO4. It was filtered and concentrated under reduced pressure and the residue was purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **2** (2.0 g, 97%) as a white solid.

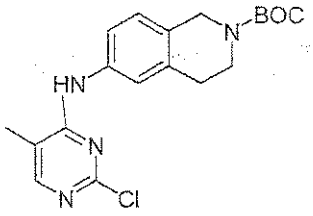
[00395] Step-2



3

[00396] To a stirred solution of **2** (2.2 g, 5.75 mmol) in EtOH (25 mL) was added ammonium formate (3.68 g, 57.5 mmol) and the reaction mixture was refluxed for 6 h. It was cooled, filtered though a celite® bed and filtrate was concentrated under reduced pressure gave **3** (1.3 g, 91%) as a dark brown oil which was used without further purification.

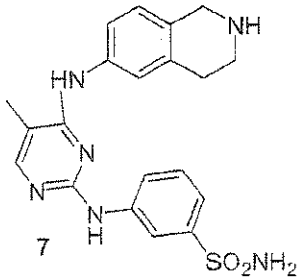
[00397] Step-3



5

[00398] A solution of **3** (1.4 g, 5.56 mmol), **4** (0.912 g, 5.56 mmol) and DIPEA (1.077 g, 8.3 mmol) in n-BuOH (15 mL) was subjected to microwave irradiation at 120 ^{0}C for 45 min. The reaction mixture was cooled and concentrated under reduced pressure. The residue was taken in ethyl acetate (20 mL) and washed with water (5 mL) and brine (5 mL). Drying over Na_2SO_4 followed by concentration under reduced pressure offered a residue which was purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **5** (1.1 g, 52%) as a cream colored solid.

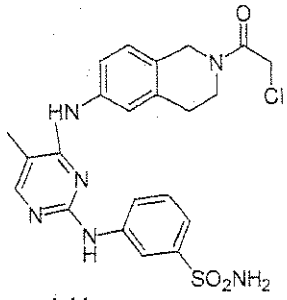
[00399] Step-4



7

[00400] To a stirred solution of **5** (0.25 g, 0.66 mmol) in ethanol (5 mL) was added **6** (0.126 g, 0.73 mmol) and catalytic amount of aq.HCl and the reaction mixture was refluxed for 12 h at 100 ^{0}C. It was cooled, the solid precipitated was filtered and washed with diethyl ether and dried under high vacuum gave 7 (0.24 g, 82%) as a light yellow solid.

[00401] **Step-5**

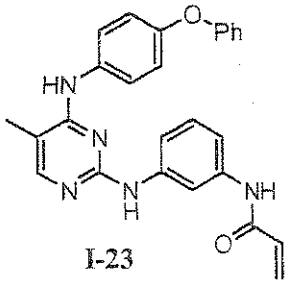


I-11

[00402] To a stirred solution of 7 (0.2 g, 0.487 mmol) in NMP (5 mL) was added Et_3N (0.094 g, 0.731 mmol). The solution was cooled to 0 ^{0}C and chloroacetylchloride (0.082 g, 0.731 mmol) was added to it. The reaction mixture was allowed to come to rt and stir at this temperature for 12 h. It was quenched with ice cooled water (2 mL) and extracted with ethyl acetate (3x5 mL). The combined ethyl acetate extract was washed with brine solution (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave I-11 (0.038 g, 16%) as a light yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H), 2.77-2.89 (m, 2H), 3.70-3.72 (m, 2H), 4.49 (d, J = 2.92 Hz, 2H), 4.63 (d, J = 23.56 Hz, 2H), 7.15-7.17 (m, 1H), 7.24 (s, 2H), 7.30-7.32 (m, 2H), 7.50-7.65 (m, 2H), 7.91 (s, 1H), 8.04-8.05 (m, 2H), 8.27 (s, 1H), 9.31 (s, 1H), .LCMS: *m/e* 486.8 (MH^+).

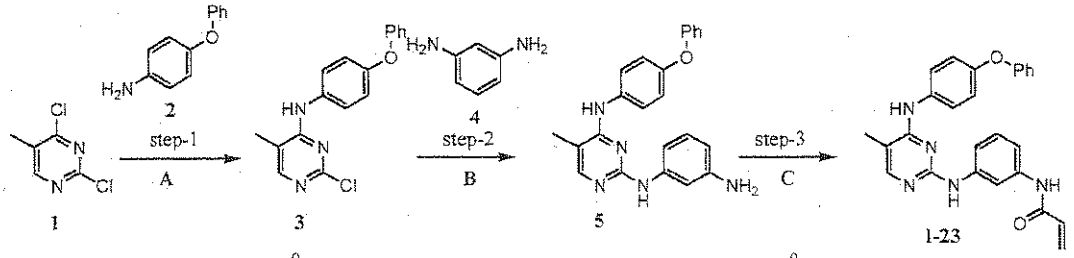
EXAMPLE 11

[00403] Preparation of N-(3-(5-methyl-4-(4-phenoxyphenylamino)pyrimidin-2-ylamino) phenyl)acrylamide I-23



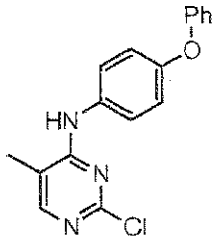
I-23

[00404] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-butanol, 100 ^{0}C, 1 h, MW; **B**) conc.HCl, n-BuOH, 160 ^{0}C, 20 min., MW; **C**) Acryloyl chloride 0 ^{0}C, rt, 1 h.

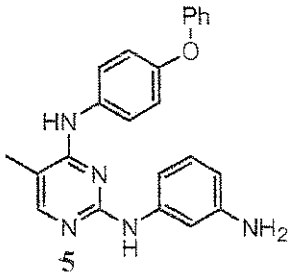
[00405] **Step-1**



3

[00406] A solution of **1** (0.2 g, 1.2 mmol), **2** (0.12 g, 0.95 mmol) and DIPEA (0.23 g, 1.78 mmol) in n-BuOH (2 mL) was subjected to microwave irradiation (100 ^{0}C for 1 h). Then the reaction mixture was cooled, concentrated under reduced pressure and the residue was taken in EtOAc (5 mL). It was washed with $NaHCO_3$ solution (2 mL), water (2 mL), brine (2 mL) and then dried over anhydrous Na_2SO_4. Concentrated under reduced pressure followed with purification by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **3** (0.11 g, 28.9%) as a light brown solid.

[00407] **Step-2**

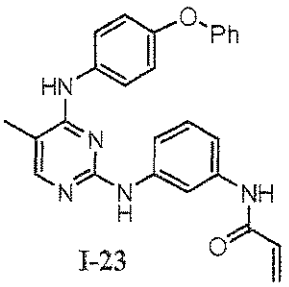


5

[00408] To a solution **3** (0.11 g, 0.3 mmol), **4** (0.114 g, 1.05 mmol) in n-butanol (1 mL) was added conc. HCl (1 drop) and the mixture was subjected to microwave irradiation (165 ^{0}C for 10 min). The reaction mixture was cooled, concentrated under reduced pressure and the residue was taken in EtOAc (5 mL). It was washed with $NaHCO_3$ solution (2 mL), water (2 mL) and brine (2

mL). Drying over Na_2SO_4 followed by concentration under reduced pressure offered residue which was purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **5** (0.08 g, 65%) as a brown solid.

[00409] Step-3

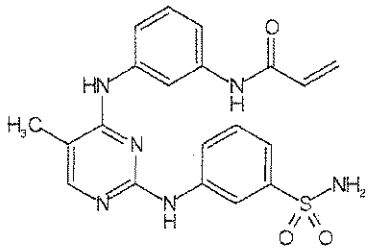


I-23

[00410] To a stirred solution **5** (0.015 g, 0.03 mmol) in NMP (1 mL) was added acryloyl chloride (0.005 g, 0.05 mmol) at 0 ^{0}C. The reaction mixture was allowed to come to rt and kept at this temperature for 1 h. It was diluted with dichloromethane (2 mL) and washed with $NaHCO_3$ solution (1 mL), water (1 mL) and brine (1 mL). Drying over Na_2SO_4 followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) gave **I-23** (0.004 g, 23%) as a brown solid. 400 MHz, MeOD: δ 2.14 (s, 3H), 5.71 (d, J = 11.20 Hz, 1H), 6.30-6.44 (m, 2H), 6.94-6.99 (m, 4H), 7.07-7.15 (m, 2H), 7.22 (d, J = 7.2 Hz, 1H), 7.34-7.36 (m, 3H), 7.63 (d, J = 8.8 Hz, 2H), 7.79 (s, 2H); LCMS: *m/e* 437 (M+1).

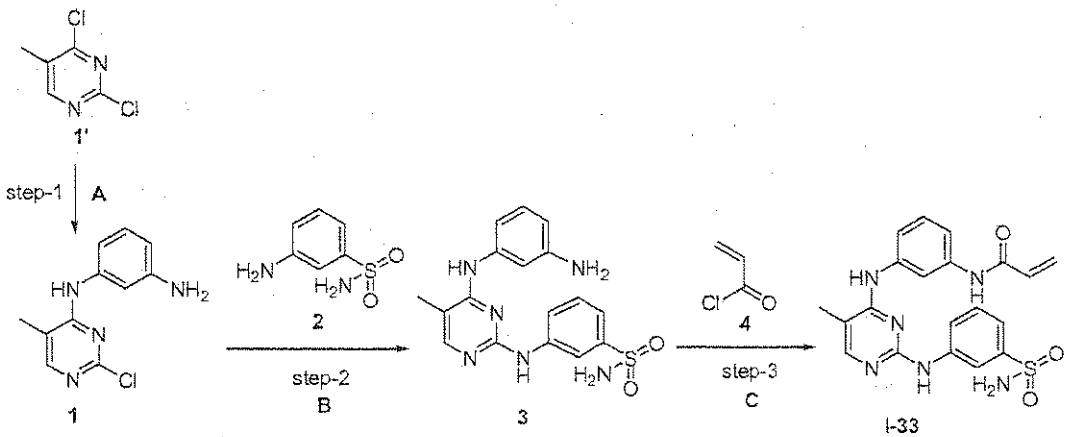
EXAMPLE 12

[00411] Preparation of N-(3-(5-methyl-2-(3-sulfamoylphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-33**



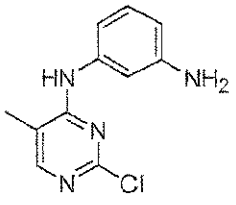
I-33

[00412] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 120 ^{0}C, 30 min., MW; **B**) 1.5 N HCl, Ethanol, 100 ^{0}C, 12 h; **C**) NMP, 0 ^{0}C to rt, 1 h.

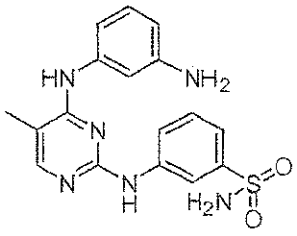
[00413] **Step-1**



1

[00414] A solution of **1** (0.5 g, 3.06 mmol), **1** (0.49 g, 4.59 mmol) and DIPEA (0.59 g, 4.59 mmol) in n-butanol (8 mL) was subjected to microwave irradiation (120 ^{0}C, 30 min). It was cooled, quenched with water (5 mL) and extracted with ethyl acetate (3x20 mL). The combined ethyl acetate layer was washed with brine solution (5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, 60-120, chloroform/ethyl acetate, 9/1) gave **1** (0.25 g, 34.77%) as a light brown solid.

[00415] **Step-2**

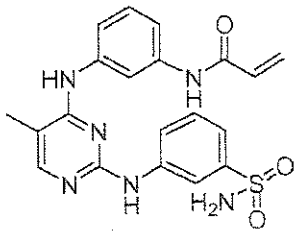


3

[00416] To a stirred solution of **3** (0.1 g, 0.48 mmol), in ethanol (2 mL) was added **4** (0.070 g, 0.42 mmol) and catalytic amount of 1.5 N HCl (3 drops), then heated to 100 ^{0}C, for 12 h.

Reaction mixture then cooled, solid separated, which was filtered and washed with ether **5** (0.1 g as crude), which was taken to next step as such.

[00417] **Step-3**

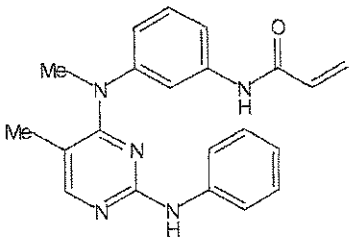


I-33

[00418] To a stirred solution of **5** (0.1 g, 0.27 mmol) in NMP (2 mL) was added acryloyl chloride (0.037 g, 0.425 mmol) at 0 ^{0}C, this was then stirred at room temperature for 1 h, then the reaction mixture was quenched with water (4 mL) and basified with NaHCO3, this was then extracted with ethyl acetate (5 mL), combined organic layer washed with brine solution (1 mL), dried over anhydrous Na_2SO_4, filtered then concentrated, Crude then purified using preparative HPLC yields **I-33** (0.07 g, 6%) as an off white solid. ^{1}H NMR (MeOD) δ ppm: 2.17 (s, 3H), 5.78 (dd, J = 2.36 & 9.52 Hz, 1H), 6.34-6.48 (m, 2H), 7.26-7.43 (m, 5H), 7.87 (s, 1H), 7.96-8.03 (m, 3H); LCMS: *m/e* 425 (M+1).

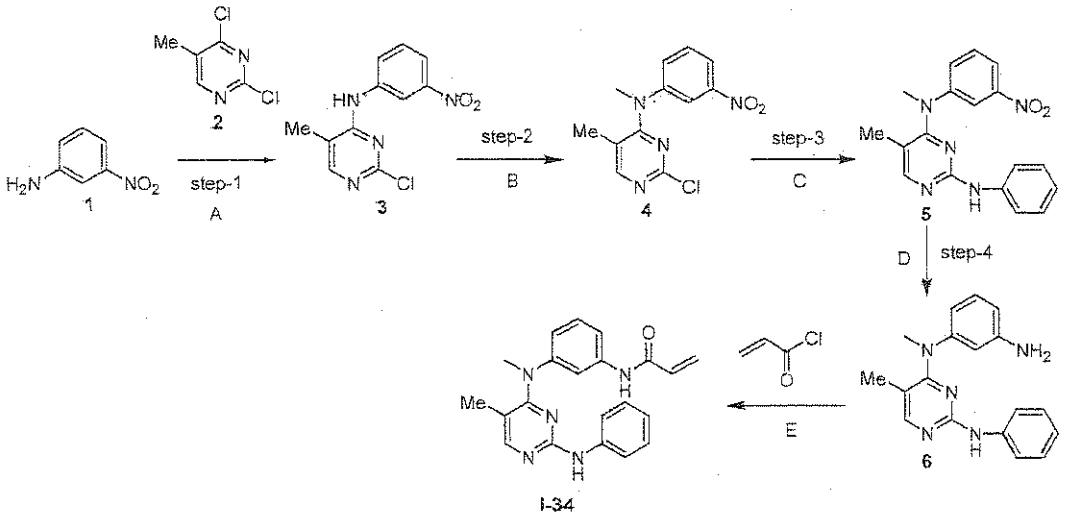
EXAMPLE 13

[00419] Preparation of N-(3-(methyl(5-methyl-2-(phenylamino)pyrimidin-4-yl)amino) phenyl)acrylamide **I-34**



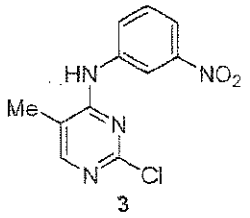
I-34

[00420] The title compound was prepared according to the schemes, steps and intermediates described below.



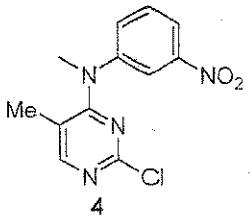
A) $Pd(OAC)_2$, BINAP, Cs_2CO_3, Toluene, 100 ^{0}C, 16 h; **B**) NaH, CH_3I, THF, 0 ^{0}C-30 min, rt-16 h.; **C**) Aniline, conc.HCl, Ethanol, 90 ^{0}C, 60 min; **D**) H_2, Pd/C, Ethanol, 16 h; **E**) acryloyl chloride, NMP, 0 ^{0}C, 1 h.

[00421] **Step-1**



[00422] To a stirred solution of **2** (1.0 g, 6.0 mmol), in Toluene (30.0 mL) was added **1** (0.84 g, 6.0 mmol), BINAP (0.186 g, 0.3 mmol), Cs_2CO_3 (4.87 g, 15.0 mmol). The reaction mixture was degassed by purging N_2 for 15 min. $Pd(OAc)_2$ (0.134 g, 0.6 mmol) was then added to the reaction mixture and the reaction mixture was heated at 100 ^{0}C for 16 h under N_2 atmosphere. It was then cooled, diluted with Ethyl acetate (30 mL) and filtered through celite®. Filtrate was washed with water (2x25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 60-120 mesh, Ethylacetete/hexane: 10/90) gave a solid which was washed with ether gave **3** (0.6 g, 37%) as a light yellow solid.

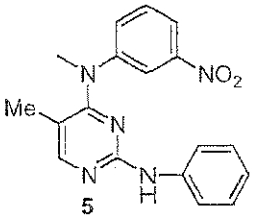
[00423] Step-2



4

[00424] To a stirred mixture of NaH (0.1 g, 2.5 mmol, 60% dispersion in paraffin oil) in dry THF (10.0 mL) was added **3** (0.5 g, 1.89 mmol) at 0 ^{0}C, and the reaction mixture was stirred at this temperature for 30 min. CH_3I (0.305 g, 2.15 mmol) was added to it and the reaction was allowed to come to rt and stir at this temperature for 16 h. The reaction mixture was diluted with water (25 mL) and extracted with EtOAc (3x25 mL). The combined EtOAc extract was washed with water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH: 99/1) gave **4** (0.12 g, 22.7%) as a light yellow solid.

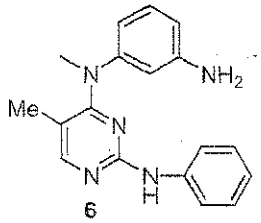
[00425] Step-3



5

[00426] To a solution of **4** (120 mg, 0.431 mmol) in EtOH (2 mL) was added Conc.HCl (0.044 g, 1.2 mmol) and Aniline (0.16 g, 1.72 mmol) and the reaction mixture was heated in a sealed pressure tube at 90 ^{0}C for 1 h. The reaction mixture was cooled, solvents removed by concentration under reduced pressure and the residue obtained was diluted with 10% $NaHCO_3$ (10.0 mL). It was extracted with EtOAc (3x15 mL) and the combined EtOAc extract was washed with water (15 mL), brine (15 mL), dried over Na_2SO_4. Concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH: 99/1) gave **5** (0.11 g, 76%) as a light yellow solid.

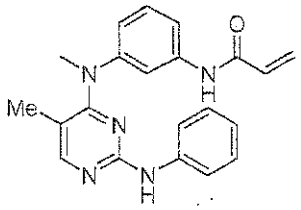
[00427] Step-4



6

[00428] A solution of **5** (0.110 g, 0.328 mmol), in Ethanol (50 mL)) was added 10% Palladium on charcoal (0.022 g) and the reaction mixture was stirred under H2 atmosphere (1.5 Kg) at rt for 16 h. It was filtered through celite® and concentrated under reduced pressure gave a residue. The residue was purified by column chromatography (SiO_2, 60-120, methanol/chloroform: 1/99) gave **6** (0.07 g, 69.9%) as a colorless viscous liquid.

[00429] Step-5

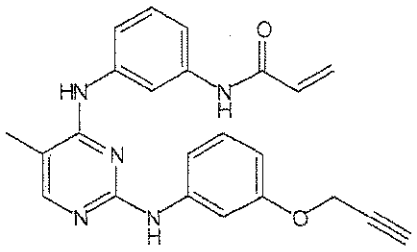


I-34

[00430] To a stirred solution of **6** (0.070 g, 0.23 mmol) in NMP (1.5 mL) at 0 ^{0}C was added acryloyl chloride (0.083 g, 0.916 mmol) and the reaction mixture was stirred at 0 ^{0}C for 1 h. It was quenched with 10% sodium bicarbonate solution (15 mL) and the solid precipitated out was filtered, washed with cold water (5 mL), hexane (5 mL). The solid was dried for 2 h under reduced pressure gave **I-34** (0.033 g, 40%) as a pale yellow sold. ^{1}H NMR (DMSO-d_6) δ ppm: δ 1.47 (s, 3H), 3.45 (s, 3H), 5.74 (dd, *J* = Hz, 1H), 6.22 (dd, *J* = 2.0 & 16.98 Hz, 1H), 6.38 (dd, J = 10 & 16.94 Hz, 1H), 6.85-6.91 (m, 2H), 7.21-7.25 (m, 2H), 7.32 (t, *J* = 8.02 Hz, 1H), 7.43-7.47 (m, 2H), 7.77-7.79 (m, 2H), 7.90 (s, 1H), 9.22 (s, 1H), 10.18 (s, 1H); LCMS: *m/e* 360.8 (M+1).

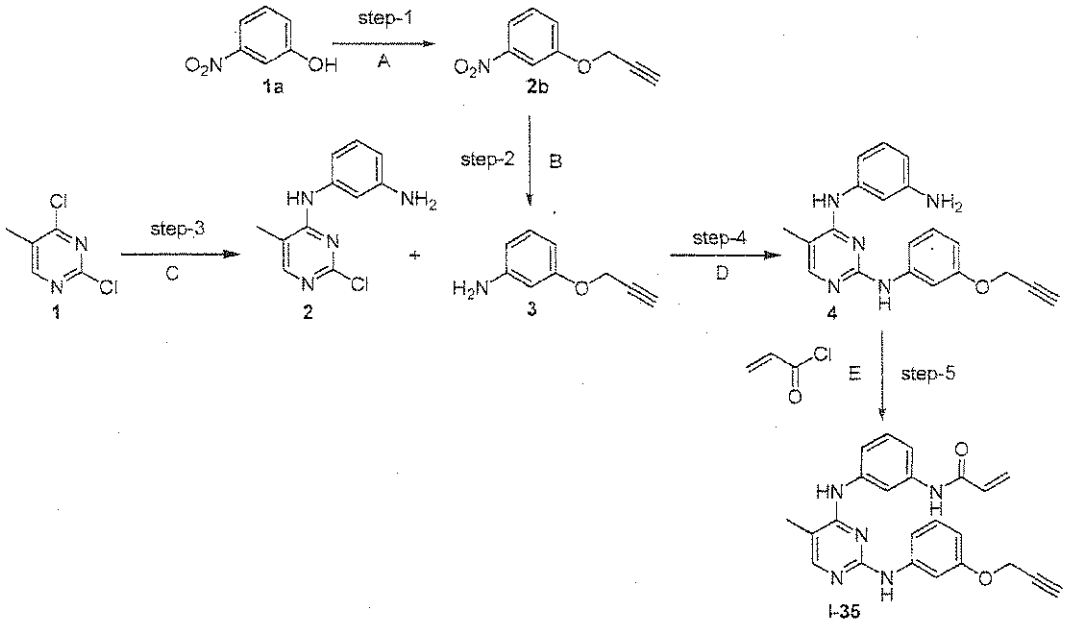
EXAMPLE 14

[00431] Preparation of N-(3-(5-methyl-2-(3-(prop-2-ynyloxy)phenylamino)pyrimidin-4-ylamino)phenyl) acrylamide **I-35**



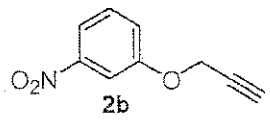
I-35

[00432] The title compound was prepared according to the schemes, steps and intermediates described below.



A) K_2CO_3, CH_3CN, 65 ^{0}C, 8 h; **B**) Fe powder, NH_4Cl, MeOH, H_2O, 80 ^{0}C, 4 h; **C**) 1,3-pheneylendiamine, DIPEA, n-BuOH, 120 ^{0}C, 30 min, MW; **D**) Con.HCl, absolute ethanol, 110 ^{0}C, 2 h; **E**) NMP, 0 ^{0}C, 1 h.

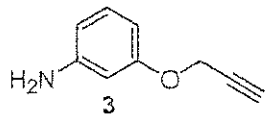
[00433] <u>Step-1</u>



2b

[00434] To a stirred solution of **1a** (4 g, 0.0287 mol) and K_2CO_3 (5.6 g, 0.0574 mol) in CH_3CN (15 mL) was added propargyl bromide (4.1 g, 0.0345 mol) and the resulting mixture was allowed to reflux for 8 h. The reaction mixture was then cooled, quenched with water and extracted with EtOAc (3x50 mL). The combined EtOAc extract was washed with water (20 mL), brine (20 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure furnished **2b** as a brownish solid which was used without further purification.

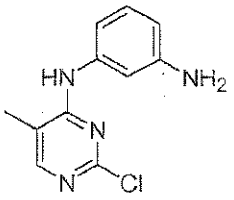
[00435] Step-2



3

[00436] To a stirred solution of **2b** in a mixture of methanol (30 mL) and water (30 mL) was added, NH_4Cl (10.3 g, 0.194 mol) and iron powder (6.8 g, 0.121 mol) respectively. Resulting mixture was refluxed at 80 ^{0}C for 4 h. Reaction mixture was cooled, diluted with methanol and filtered through a pad of celite®. The filtrate was concentrated under reduced pressure and the residue was taken in EtOAc. It was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The residue was further purified by column chromatography (SiO2, 60-120, gravity column chromatography, the expected product was eluted with $CHCl_3$/MeOH : 96/4) gave **3** (3.2 g, 91%) as a brownish solid.

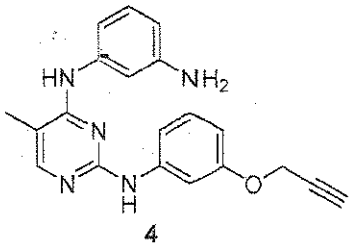
[00437] Step-3



2

[00438] A solution of 2, 4-dichloro-5-methyl pyrimidine **1** (0.3 g, 0.0018 mol), 1,3-phenylene diamine (0.24 g, 0022 mol), DIPEA (0.35 g, 0.0027 mol) in n-BuOH (3 mL) was subjected to microwave irradiation (120 ^{0}C, 30 min). The reaction mixture was cooled, quenched with water (15 mL) and extracted with EtOAc (3x15 mL). The combined EtOAc extract was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO2, 60-120) gave **2** (0.15 g, 35%) as a brownish solid.

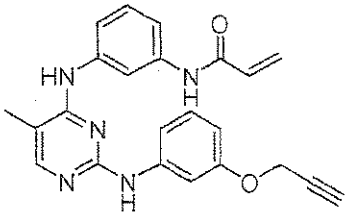
[00439] Step-4



4

2 (0.15 g, 0.006 mol) and 3 (0.37 g, 0.0025 mol) were taken in a pressure tube and to it were added abs. EtOH (3 mL) followed by conc. HCl (0.04 g, 0.0012 mol). The tube was tightly screw fitted and was heated at 120 ^{0}C for 2 h. The reaction mixture was then cooled, solvents removed under reduced pressure and residue obtained was taken in EtOAc (10 mL). It was washed with water (4 mL), $NaHCO_3$ (4 mL) and brine (5 mL). Drying over Na2SO4 followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, gravity column chromatography, expected compound getting eluted in $CHCl_3$/MeOH : 94/6) gave 4 (125 mg, 56%) as a light brown solid.

[00440] Step-5

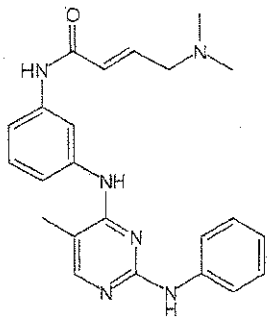


I-35

[00441] To a stirred solution of 4 (0.1 g, 0.002 mol) in NMP (8 mL) was added acryloyl chloride (0.1 g, 0.001 mol) drop wise at 0 °C. The reaction was kept at this temperature for 10 min and then allowed to come to rt and stir at this temperature for 1.5 h. It was then quenched with 10% sodium bicarbonate solution (8 mL) and extracted with EtOAc (2×15 mL). The combined EtOAc extract was washed with water (10 mL), brine (10 mL) dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was purified by column chromatography (SiO2, 60-120, gravity column chromatography, expected compound getting eluted in $CHCl_3$/MeOH : 90/10) gave I-35 (20 mg, 18%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.11 (s, 3H), 3.51 (s, 1H), 4.61 (s, 2H), 5.74 (d, J = 9.08 Hz, 1H), 6.25 (d, J = 15.84 Hz, 1H), 6.45 (s, 2H), 7.02 (s, 1H), 7.27-7.45 (m, 5H), 7.91 (d, J = 8.84 Hz, 2H), 8.36 (s, 1H), 8.93 (s, 1H), 10.09 (s, 1H), LCMS: *m/e* 400 (M+1).

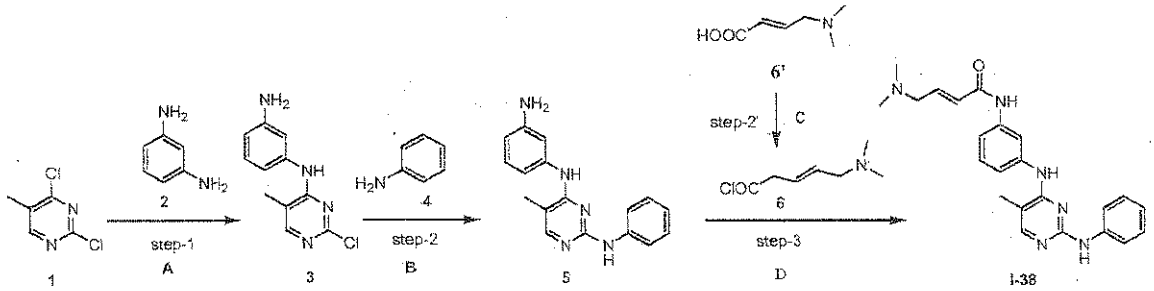
EXAMPLE 15

[00442] Preparation of (E)-4-(dimethylamino)-N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino) phenyl)but-2-enamide **I-38**



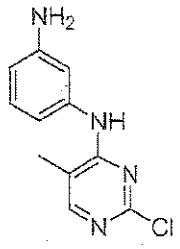
I-38

[00443] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIEA, n-BuOH, 120 ^{0}C, 30 min, MW; **B)** NMP, 200 ^{0}C, 10 min, MW; C)) oxalyl chloride, CH_3CN, 30 min at 0 ^{0}C, 2 h at 25 ^{0}C, 5 min at 45 ^{0}C, **D)** NMP, 0 ^{0}C, 1 h.

[00444] <u>Step-1</u>

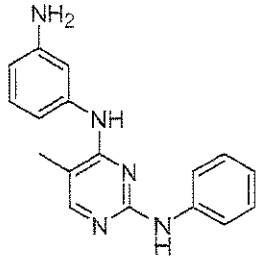


3

[00445] A solution of **1** (2.0 g, 12 mmol), **2** (2.0 g, 18 mmol), DIPEA (2.33 g, 18 mmol) in n-BuOH (20.0 mL) was subjected to microwave irradiation at 120 ^{0}C for 30 min. The reaction mixture was then quenched with water (100 mL), extracted with EtOAc (3x100 mL). The

combined EtOAc extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 60-120 mesh, EtOAc/$CHCl_3$:15/85) gave **3** (1.3 g, 45 %) as a dark brown solid.

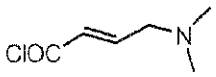
[00446] Step-2



5

[00447] A solution of **3** (1.0 g, 4.27 mmol), **4** (1.5 g, 16.12 mmol) in NMP (10 mL) was subjected to microwave irradiation (200 ^{0}C, 10 min). Then the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined EtOAc extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH : 98/2) gave **5** (0.5 g, 40.3%) as a light brown solid.

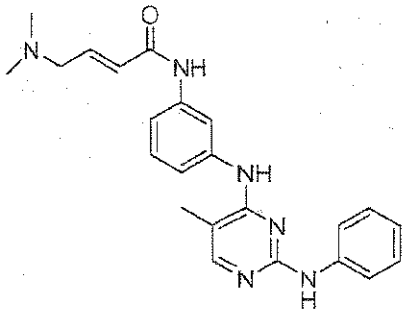
[00448] Step-2'



6

[00449] To a stirred solution of **6'** (70 mg, 0.42 mmol) in CH_3CN (1.0 mL) was added oxalyl chloride (80 mg, 0.62 mmol) at 0 ^{0}C. The reaction mixture was allowed to stir at 0 ^{0}C for ½ h and then at rt for 2 h. Finally it was heated at 45 ^{0}C for 5 min, cooled and the reaction mixture was taken for the next step without further purification.

[00450] Step-3

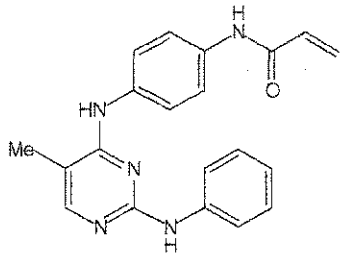


I-38

[00451] To a stirred solution of **5** (75 mg, 0.12 mmol) in NMP (1 mL) was added **6** at 0 ^{0}C. The reaction mixture was stirred at 0 ^{0}C for 1 h, quenched with cold water (5 mL), basified with Et_3N and extracted with CH_2Cl_2 (3x10 mL). The combined organic extract was washed with water (5 mL), brine (5 mL) and dried over Na_2SO_4. Concentration under reduced pressure followed by purification over silica gel (60-120) using 5% methanol in chloroform gave crude compound (20 mg) as a brown gummy solid, which was again taken into dichloromethane and stirred with 10% bicarbonate solution for 30 min, dichloromethane layer separated, dried over Na_2SO_4 and concentrated to give **I-38** (8 mg, 17%) as a brown solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.15 (s, 3H), 2.32 (s, 6H), 3.21 (d, *J* = 5.76 Hz, 2H), 6.27 (d, *J* = 15.36 Hz, 1H), 6.84-6.93 (m, 2H), 7.14 (t, *J* = 7.52 Hz, 2H), 7.27-7.33 (m, 2H), 7.44 (dd, *J* = 2.04 Hz & 5.08 Hz, 1H), 7.53 (d, *J* = 7.72 Hz, 2H), 7.80 (s, 1H), 8.00 (s, 1H); LCMS: *m/e* 402.8 (M+1).

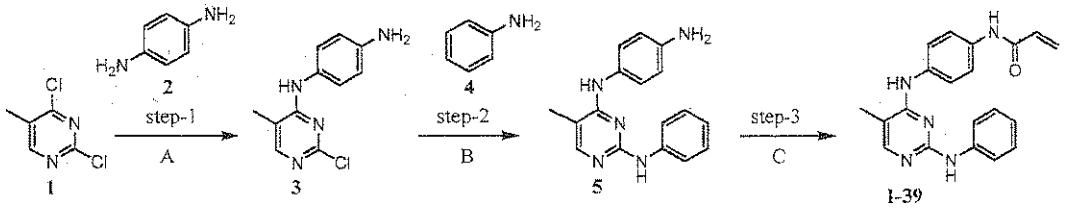
EXAMPLE 16

[00452] Preparation of N-(4-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl) acrylamide **I-39**



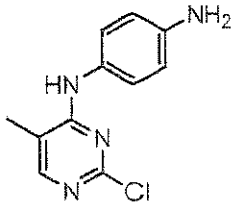
I-39

[00453] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 110 ^{0}C, 45 min, MW; **B**) Conc. HCl, n-BuOH, 150^{0}C, 10 min, MW; C) Acryloyl chloride, NMP, 0 ^{0}C-30 min, rt-2 h.

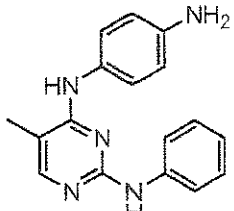
[00454] **Step-1**



3

[00455] A solution of **1** (0.4 g, 2.4 mmol), **2** (0.3 g, 2.6 mmol), DIPEA (0.46 g, 3.6 mmol) in n-BuOH (10 mL) was subjected to microwave irradiation (110 ^{0}C, 45 min). The reaction mixture was cooled, quenched with water (20 mL) and extracted with EtOAc (3x15 mL). The combined EtOAc extract was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH : 99/1) gave **3** (350 mg, 62%) as an off-white solid.

[00456] **Step-2**

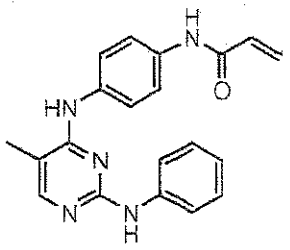


5

[00457] A solution of **3** (0.2 g, 0.8 mmol), **4** (0.63 g, 6.8 mmol) and con.HCl (0.03 g, 0.8 mmol) in n-BuOH (10 mL) was subjected to microwave irradiation (150 ^{0}C, 10 min). Then the reaction mixture was cooled, diluted with water (10 mL), basified with 10% sodium bicarbonate solution and extracted with EtOAc (3x15 mL). The combined EtOAc extract was washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The

crude residue was purified by column chromatography (SiO_2, 60-120, $CHCl_3$/MeOH : 97/3) gave **5** (110 mg, 47%) as a brown colored gummy solid.

[00458] Step-3

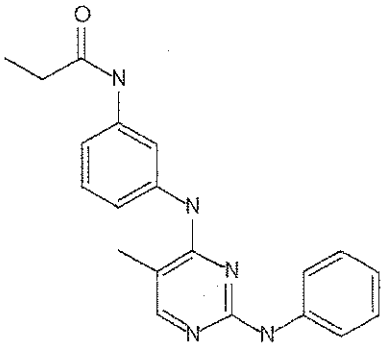


I-39

[00459] To a stirred solution of **5** (0.06 g, 0.2 mmol) in NMP (2 mL) was added acryloyl chloride (0.03 g, 0.3 mmol) at 0 ^{0}C. It was allowed to stir at the same temperature for 20 min and then at rt for 2 h. The reaction mixture was quenched with water, basified with 10% sodium bicarbonate solution and extracted with EtOAc (3x10 mL). The combined EtOAc layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 60-120) and finally by preparative HPLC gave **I-39** (10 mg, 16%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.10 (s, 3H), 5.71-5.76 (m, 1H), 6.25 (dd, J 2.04 & 16.96 Hz, 1H), 6.45 (dd, J = 10.08 & 16.92 Hz, 1H), 6.84 (t, J = 7.30 Hz, 1H), 7.14-7.18 (m, 2H), 7.62-7.68 (m, 6H), 7.86 (s, 1H), 8.26 (s, 1H), 8.94 (s, 1H), 10.11 (s, 1H), LCMS: *m/e* 346 (M+1).

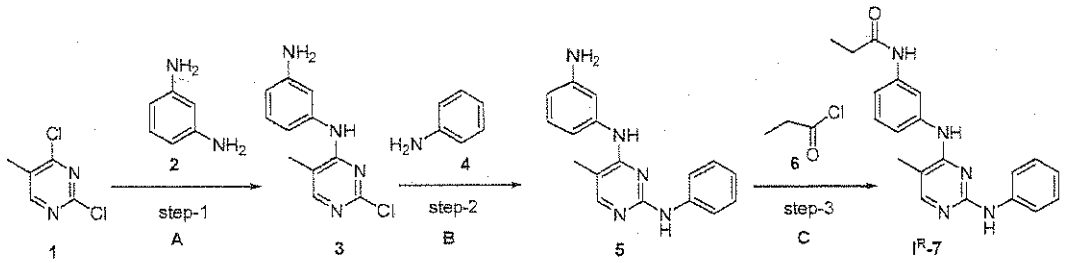
EXAMPLE 17

[00460] Preparation of N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl) propionamide I^R-7



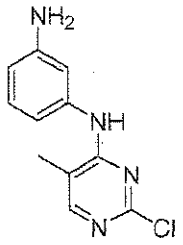
I^R-7

[00461] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 120 ^{0}C, 30 min, MW; **B**) NMP, 200 ^{0}C, 10 min, MW; **C**) **6**, NMP, 0 ^{0}C, 60 min.

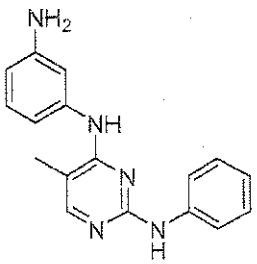
[00462] <u>Step-1</u>



3

[00463] A solution of **1** (2.0 g, 12 mmol), **2** (2.0 g, 18 mmol), DIPEA (2.33 g, 18 mmol) in n-BuOH (20.0 mL) was subjected to microwave irradiation at 120 ^{0}C for 30 min. The reaction mixture was then quenched with water (100 mL), extracted with EtOAc (3x100 mL). The combined EtOAc extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 60-120 mesh, EtOAc/$CHCl_3$: 15/85) gave **3** (1.3 g, 45%) as a dark brown solid.

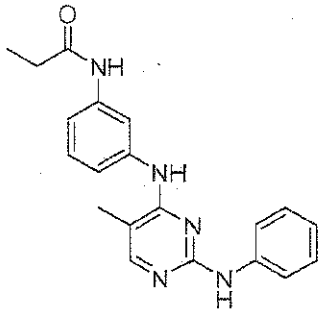
[00464] <u>Step-2</u>



5

[00465] A solution of **3** (1.0 g, 4.27 mmol), **4** (1.5 g, 16.12 mmol) in NMP (10 mL) was subjected to microwave irradiation (200 ^{0}C, 10 min). Then the reaction mixture was cooled, diluted with water (100 mL) and extracted with EtOAc (3x100 mL). The combined EtOAc extract was washed with water (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure gave a residue. The crude residue was further purified by column chromatography (SiO_2, $CHCl_3$/MeOH : 98/2) gave **5** (0.5 g, 40.3%) as a light brown solid.

[00466] **Step-3**

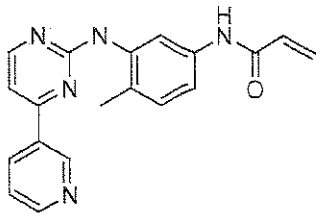


I^R-7

[00467] To a stirred solution of **5** (75 mg, 0.25 mmol) in NMP (1.0 mL) at 0 ^{0}C was added propanoyl chloride (**6**) (72 mg, 0.75 mmol) and the reaction mixture was stirred at 0 ^{0}C for 60 min. The reaction mixture was then quenched with water (5 mL), basified with Et_3N and extracted with EtOAc (3x10 mL). The combined EtOAc extract was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 230-400, methanol/chloroform : 2/98) gave I^R-7 (0.025 g, 28.73%) as an off white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 1.08 (t, *J* = 7.6 Hz, 3H), 2.11 (s, 3H), 2.31 (q, *J* = 7.6 Hz, 2H), 6.81 (t, *J* = 7.2 Hz, 1H), 7.11 (t, *J* = 8 Hz, 2H), 7.21-7.25 (m, 1H), 7.31 (d, *J* = 8.40 Hz, 1H), 7.36 (d, *J* = 8.00 Hz, 1H), 7.66 (d, *J* = 8.40 Hz, 2H), 7.86 (s, 1H), 7.89 (s, 1H), 8.35 (s, 1H), 8.93 (s, 1H), 9.81 (s, 1H); LCMS: *m/e* 348.3 (M+1).

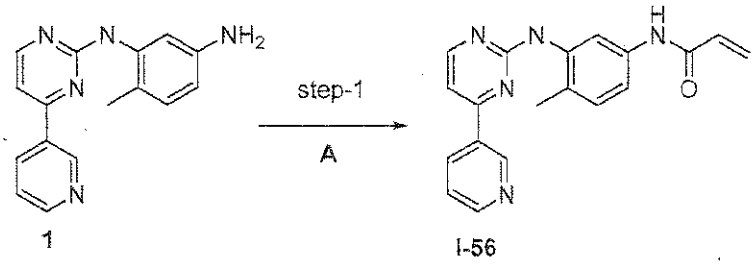
EXAMPLE 18

[00468] Preparation of N-(4-methyl-3-(4-(pyridin-3-yl)pyrimidin-2-ylamino)phenyl) acrylamide **I-56**



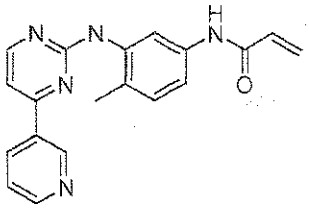
I-56

[00469] The title compound was prepared according to the schemes, steps and intermediates described below.



A) acryloyl chloride, Et_3N, DMF, rt, 12 h

[00470] <u>Step-1</u>



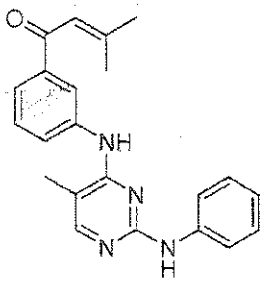
I-56

[00471] To a stirred solution of 1 (0.15 g, 0.54 mmol) and Et_3N (0.11 g, 1.08 mmol) in DMF (1 mL) at 0 ^{0}C was added acryloyl chloride (0.09 g, 1.08 mmol), drop-wise, under N_2 atmosphere. The reaction mixture was allowed to come to rt and stirred further 12 h. It was then quenched with ice-cold water (2 mL) and extracted with EtOAc (2x15 mL). The combined EtOAc extract was washed with brine (2 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get a crude residue. The residue was further purified by preparative HPLC and gave **I-56** (0.060 g, 33%) as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.19 (s, 3H), 5.72 (dd, J = 2 & 10.08 Hz, 1H), 6.22 (dd, J = 2 & 16.92 Hz, 1H), 6.45 (dd, J = 10 & 17 Hz, 1H),

7.16 (d, J = 8.36 Hz, 1H), 7.32 (dd, J = 1.92 & 8.16 Hz, 1H), 7.42 (d, J = 5.12 Hz, 1H), 7.50-7.53 (m, 1H), 7.95 (d, J = 1.68 Hz, 1H), 8.45 (dd, J = 6.16 & 8.16 Hz, 1H), 8.49 (d, J = 5.16 Hz, 1H), 8.68 (dd, J = 1.56 & 4.76 Hz, 1H), 8.95 (s, 1H), 9.25 (d, J = 1.56 Hz, 1H), 10.08 (s, 1H); LCMS: *m/e* 332.4 (M+1).

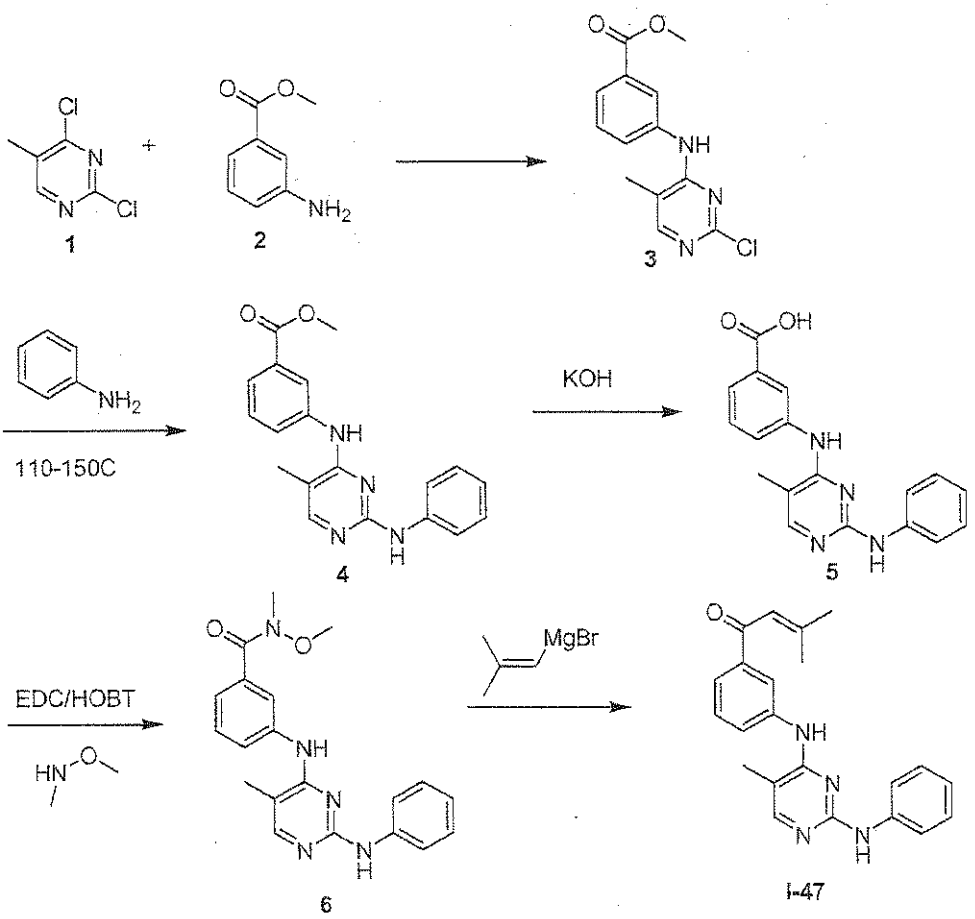
EXAMPLE 19

[00472] General method for preparing compounds having an enone-containing warhead, e.g., 3-methyl-1-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl)but-2-en-1-one I-47



I-47

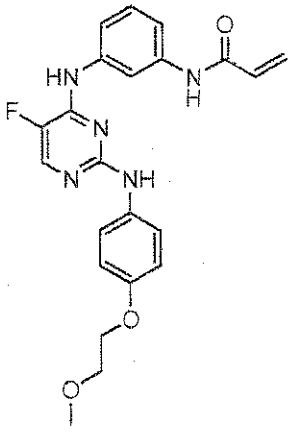
[00473] The title compound is prepared according to the schemes, steps and intermediates described below. It is also appreciated by one skilled in the art that I-47 is an exemplary compounds having enone-containing warheads, and that other compounds having enone-containing warheads can be synthesized in a substantially similar manner according to the schemes, steps and corresponding intermediates described below.



[00474] Compounds 1 and 2 are coupled in the presence of triethylamine to yield compound 3. Compound 3 is treated with analine at elevated temperature to yield compound 4. Saponification of Compound 4 with potassium hydroxide yields acid compound 5, which is coupled to N-O-dimethylhydroxylamine using EDC to yield compound 6. Treatment of Compound 6 at low temperature yields exemplary compound I-47.

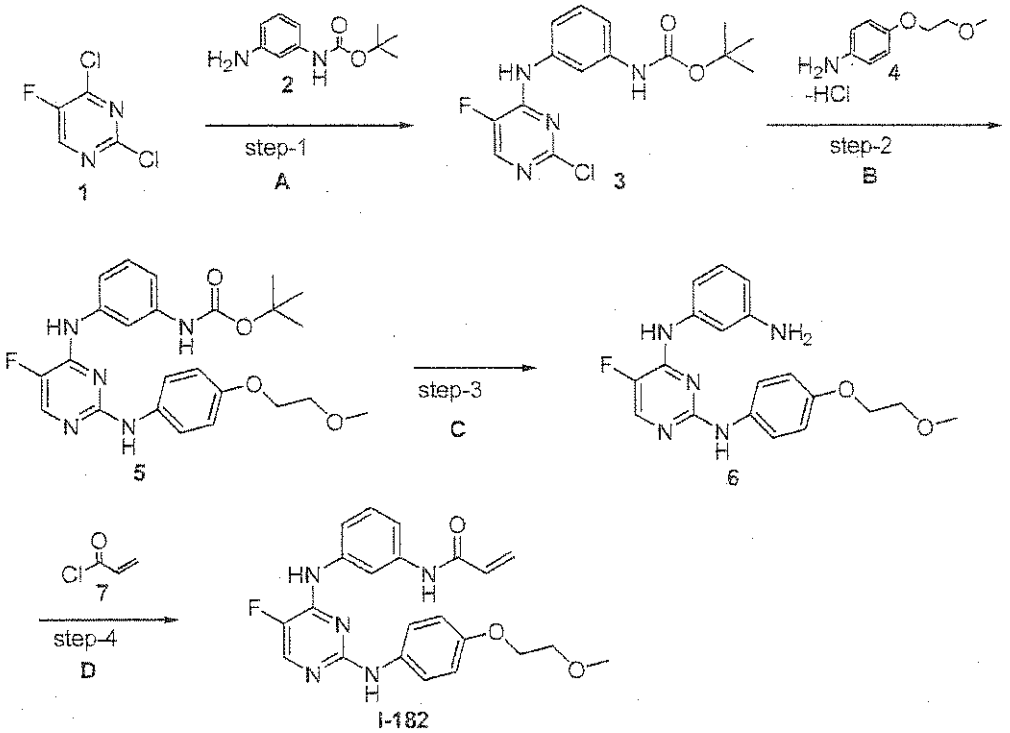
EXAMPLE 20

[00475] Preparation of *N*-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-182**



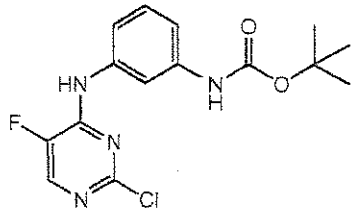
I-182

[00476] The title compound was prepared according to the schemes, steps and intermediates described below.



A) 2, DIPEA, THF, reflux; **B**) 4, t-amyl alcohol, HOAc, reflux; C) TFA, DCM; **D**) 7, DIPEA, THF, -10 °C.

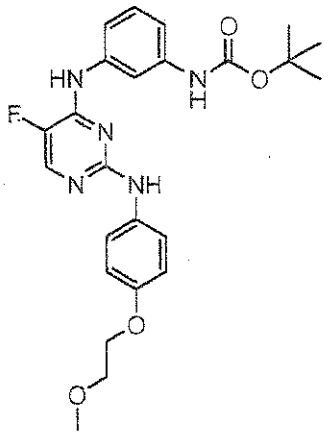
[00477] Step-1



3

[00478] 1 (800mg, 4.8mmoL), 2 (996mg, 4.8mmoL) and Hunig's base (948uL, 5.75mmoL) were dissolved in THF (20mL). The reaction mixture was heated at reflux overnight. After cooling, partitioned between water/brine (10 mL), agitated and separated the layers. Dried organic phase over sodium sulfate, and the solvent was removed via rotary evaporation. Titration with EtOAc and Heptane gave after filtration a white solid, 1g. LC/MS (RT = 2.03/(M+1)) 339.1.

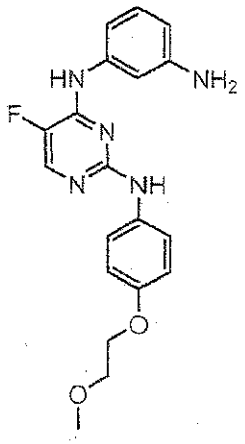
[00479] Step-2



5

[00480] 3 (800mg, 2.37mmoL) and 4 (576mg, 2.84mmoL) were suspended in tert-amyl alcohol (14 mL) and acetic acid (5 drops). Heated to reflux for 4h. After cooling, solvent was removed via rotary evaporation. The dark oil was partitioned between water/brine and THF (10 mL each), agitated, and separated layers and dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to afford a purple solid, 0.55 g. LC/MS (RT = 2.997/(M+1)) 470.2. Additional 150 mg of product minus the (BOC) protecting group crystallized from the aqueous layer.

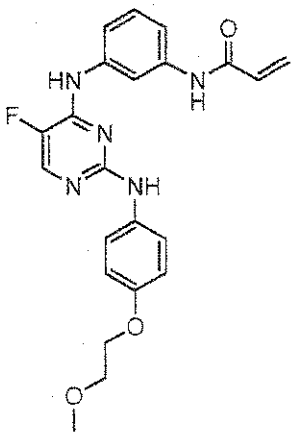
[00481] Step-3



6

[00482] To a solution of 6 (550 mg, 1.17 mmol) in DCM (20 mL) was added TFA (2 mL). Stirred for 30 min at rt for 4h; removed solvent via rotary evaporation and partitioned oil with cold (0 °C) saturated sodium bicarbonate (10 mL) and EtOAc (10 mL), agitated and separated layers. Organic phase was dried over sodium sulfate and the solvent was removed via rotary evaporation to give a dark oil. Flash chromatography using 20%-100% Heptane/EtOAc gradient using combiflash system gave 309 mg of a light pink solid. LC/MS (RT = 2.78/(M+1)) 370.2.

[00483] Step-4



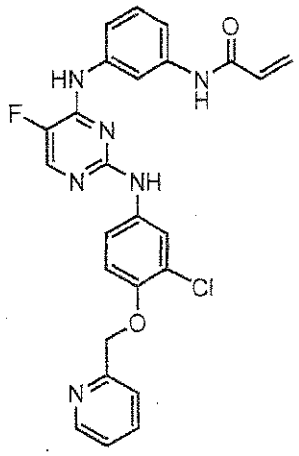
I-182

[00484] A solution of 6 (309 mg, 0.84 mmol) in THF (10 mL) was cooled in a water/ice-MeOH bath (-10 °C). To this was added 7 (71 µL, 0.88 mmoL), stirred for 10 min, then added Hunig's base (145uL, 0.88mmoL), and stirred for 10 min. Partitioned between water/brine (10

mL), agitated and separated the layers. Dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation and triturated with diethyl ether to afford after filtration 285 mg (80%) of an off-white solid. LC/MS (RT = 2.79/(M + H)) 424.2.

EXAMPLE 21

[00485] Preparation of *N*-(3-(2-(3-chloro-4-(pyridin-2-ylmethoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-86**

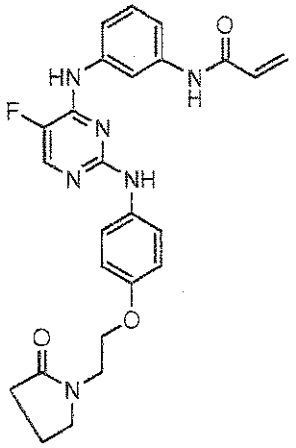


I-86

[00486] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-chloro-4-(pyridine-2-ylmethoxy)aniline in the place of **4** in Step 2. LC/MS (RT = 2.87/(M + H)) 491.1.

EXAMPLE 22

[00487] Preparation of *N*-(3-(5-fluoro-2-(4-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-92**

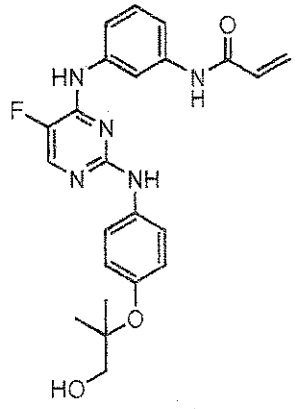


I-92

[00488] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 1-(2-(4-aminophenoxy)ethyl)pyrrolidin-2-one in the place of 4 in Step 2. LC/MS (RT = 2.718/(M + H)) 477.1.

EXAMPLE 23

[00489] Preparation of *N*-(3-(5-fluoro-2-(4-(1-hydroxy-2-methylpropan-2-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-93**

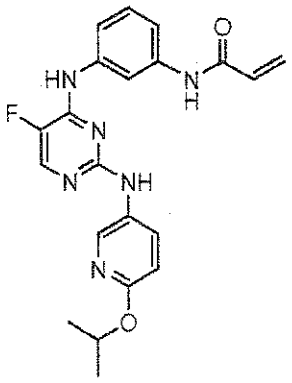


I-93

[00490] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 2-(4-aminophenoxy)-2-methylpropan-1-ol in the place of **4** in Step 2. LC/MS (RT = 2.724/(M + H)) 438.1.

EXAMPLE 24

[00491] Preparation of *N*-(3-(5-fluoro-2-(6-isopropoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-172**

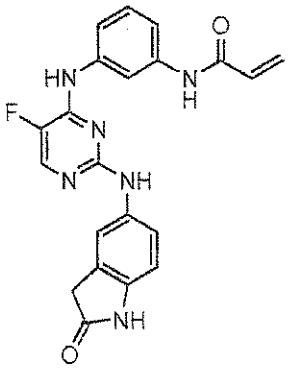


I-172

[00492] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 6-isopropoxypyridin-3-amine in the place of **4** in Step 2. LC/MS (RT = 2.878/(M + H)) 409.2.

EXAMPLE 25

[00493] Preparation of *N*-(3-(5-fluoro-2-(2-oxoindolin-5-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-181**

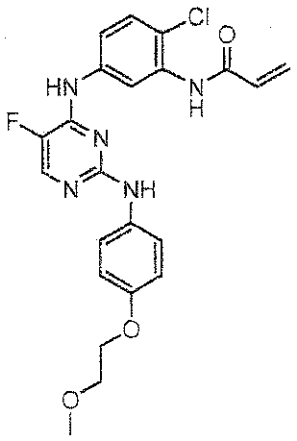


I-181

[00494] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 5-aminoindolin-2-one in the place of **4** in Step 2. LC/MS (RT = 2.617/(M + H)) 405.1.

EXAMPLE 26

[00495] Preparation of *N*-(2-chloro-5-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-108**

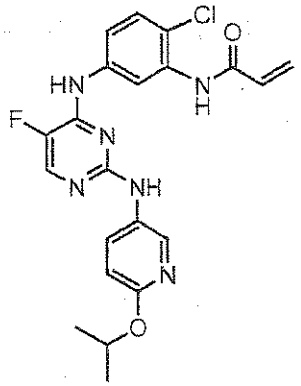


I-108

[00496] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butyl 5-amino-2-chlorophenylcarbamate in the place of **2** in Step 1. LC/MS (RT = 2.852/(M + H)) 458.1.

EXAMPLE 27

[00497] Preparation of *N*-(2-chloro-5-(5-fluoro-2-(6-isopropoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-107**

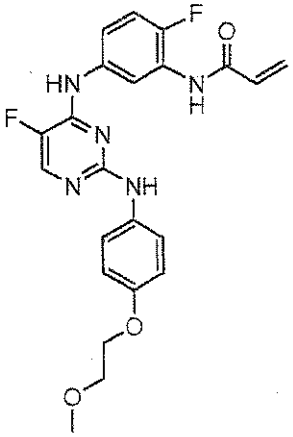


I-107

[00498] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butyl 5-amino-2-fluorophenylcarbamate in the place of **2** in Step 1 and 6-isopropoxypyridin-3-amine in the place of **4** in Step 2. LC/MS (RT = 2.938/(M + H)) 443.1.

EXAMPLE 28

[00499] Preparation of *N*-(2-fluoro-5-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-87**

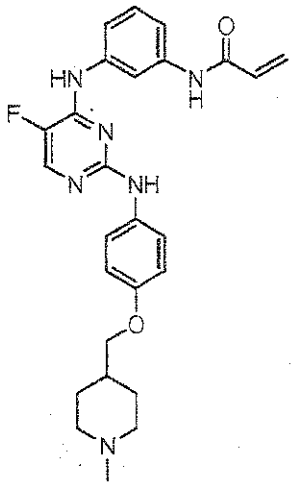


I-87

[00500] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butyl 5-amino-2-fluorophenylcarbamate in the place of **2** in Step 1. LC/MS (RT = 2.797/(M + H)) 442.0.

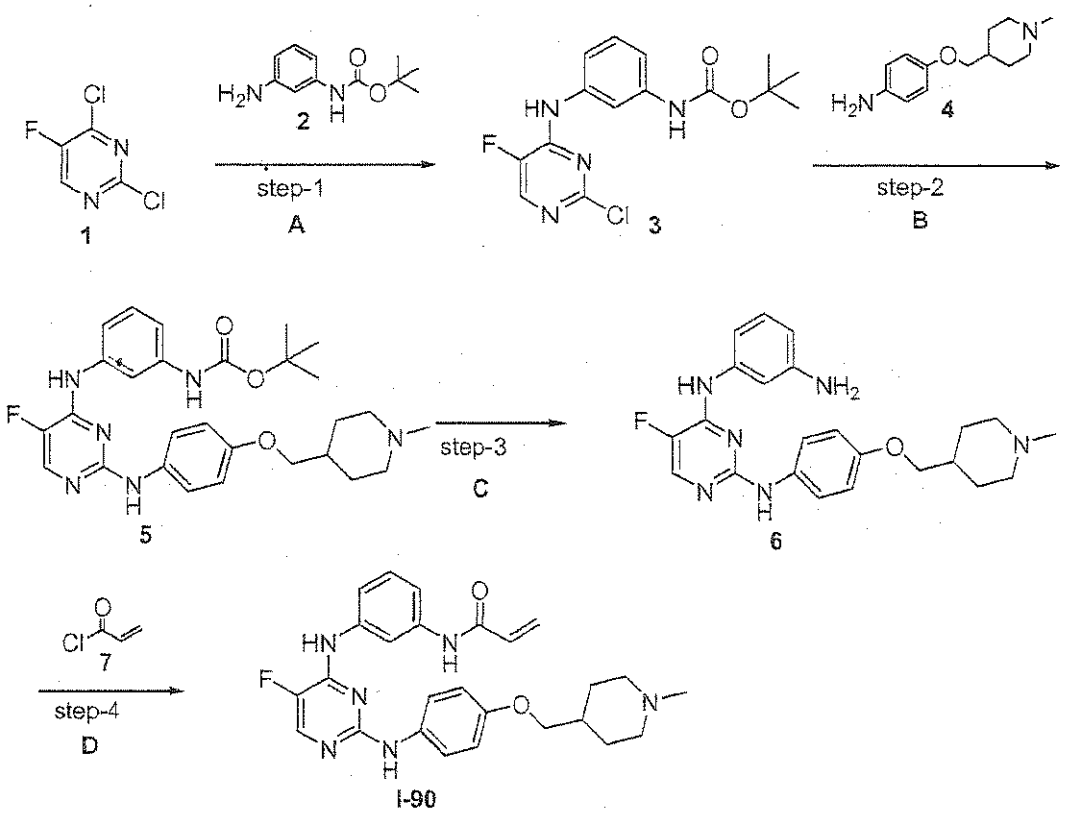
EXAMPLE 29

[00501] Preparation of *N*-(3-(5-fluoro-2-(4-((1-methylpiperidin-4-yl)methoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-90**



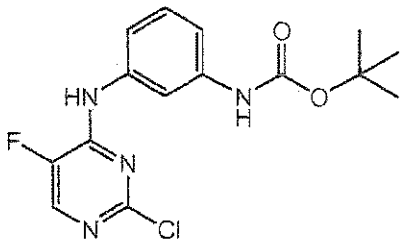
I-90

[00502] The title compound was prepared according to the schemes, steps and intermediates described below.



A) 2, DIPEA, THF, reflux; B) 4, $Pd(OAc)_2$, X-Phos, $CsCO_3$, dioxane, reflux, 12 h; C) TFA, DCM; D) 7, DIPEA, THF, -10 °C.

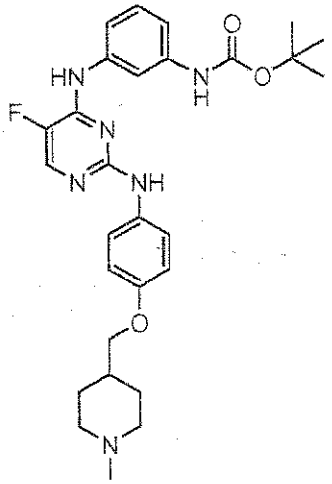
[00503] Step-1



3

[00504] 1 (800mg, 4.8mmoL), 2 (996mg, 4.8mmoL) and Hunig's base (948uL, 5.75mmoL) were dissolved in THF (20mL). The reaction mixture was heated at reflux overnight. After cooling, partitioned with water/brine (10 mL), agitated and separated the layers. Dried organic phase over sodium sulfate and the solvent was removed via rotary evaporation. Titration with EtOAc and Heptane gave after filtration a white solid, 1 g. LC/MS (RT = 2.03/(M+1)) 339.1.

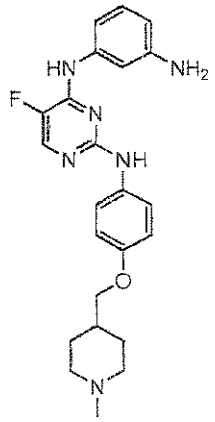
[00505] Step-2



5

[00506] 3 (205 mg, 0.61 mmoL) and 4 (150 mg, 0.73 mmoL) was dissolved in dioxane (4 mL). Degassed the solution for 1 min. Palladium acetate (20mg, 5 moL%), X-Phos ligand (35 mg, 10 moL%) and $CsCO_3$ (325 mg, 1.2 mmoL) were added in that order. Degassed the suspension for 1 min and under argon atmosphere the mixture was heated to reflux for 12 h. After cooling, solvent was removed via rotary evaporation. The dark oil was partitioned between water/brine and EtOAc (5 mL each), agitated, filtered off precipitate and separated layers of the filtrate. Dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to give a dark oil. Flash chromatography using 0-30% gradient of Heptane/EtOAc afforded light yellow oil. LC/MS (RT = 3.043/(M+1)) 523.2.

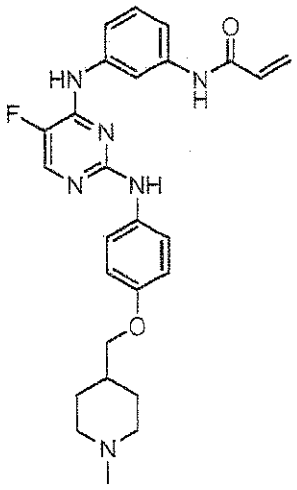
[00507] Step-3



6

[00508] To a solution of **5** (144 mg, 0.27 mmol) in DCM (10 mL) was added TFA (1 mL). Stirred for 30 min at rt for 12 h; removed solvent via rotary evaporation and partitioned oil with cold (0 °C) saturated sodium bicarbonate (5 mL) and EtOAc (5 mL), agitated and separated layers. Organic phase was dried over sodium sulfate and the solvent was removed via rotary evaporation to give light yellow foam. LC/MS (RT = 2.723/(M+1)) 423.1.

[00509] Step-4

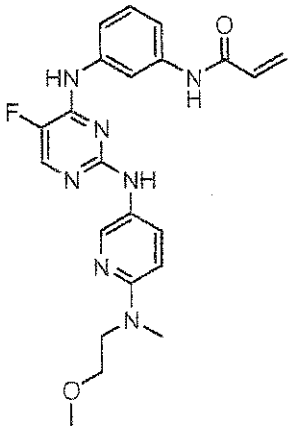


I-90

[00510] A solution of **6** (105 mg, 0.25 mmol) in THF (3 mL) was cooled in water/ice-MeOH bath (-10 °C). To this was added 7 (21 μL, 0.26 mmoL), stirred for 10 min, then added Hunig's base (51 μL, 0.26 mmoL), and stirred for 10 min. Partitioned with water/brine (5 mL), agitated and separated the layers. Dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation afford a light yellow foam. LC/MS (RT = 2.726/(M + H)) 477.1.

EXAMPLE 30

[00511] Preparation of *N*-(3-(5-fluoro-2-(6-((2-methoxyethyl)(methyl)amino)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-77**

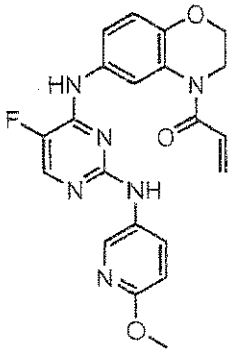


I-77

[00512] The title compound was prepared according to the schemes, steps and intermediates described in Example 29, by using N^2-(2-methoxyethyl)-N^2-methylpyridine-2,5-diamine in the place of 4 in Step 2. LC/MS (RT = 2.739/(M + H)) 438.1.

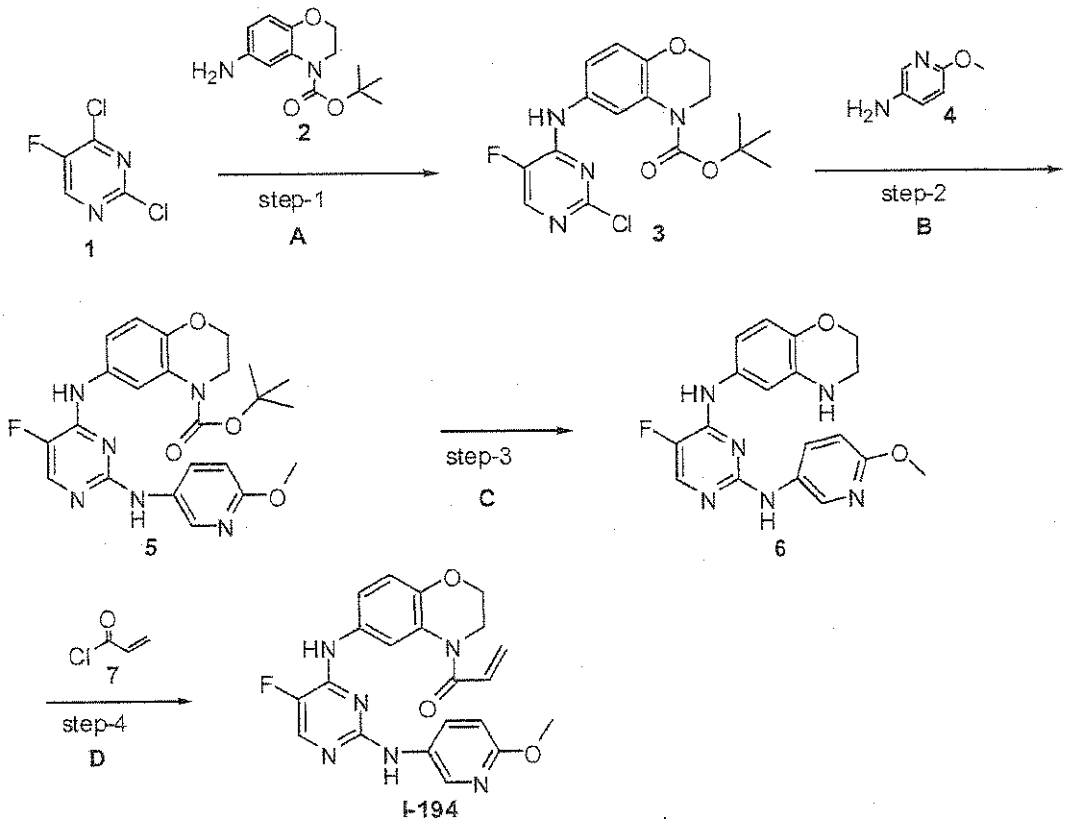
EXAMPLE 31

[00513] Preparation of 1-(6-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one **I-194**



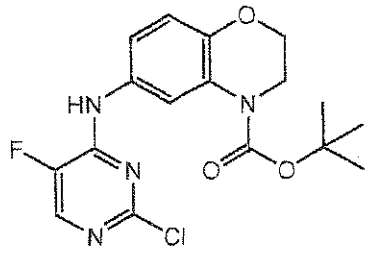
I-194

[00514] The title compound was prepared according to the schemes, steps and intermediates described below.



A) **2**, DIPEA, THF, reflux; **B**) **4**, HOAc, tert-amyl alcohol, reflux, 12 h; **C**) TFA, DCM; **D**) **7**, DIPEA, DCM, NMP, -10 °C.

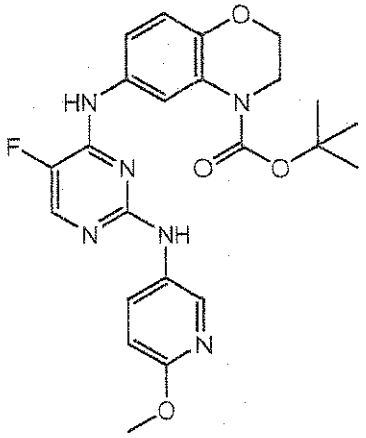
[00515] Step-1



3

[00516] **1** (186 mg, 1.1 mmoL), **2** (280mg, 1.1mmoL) and Hunig's base (220 µL, 1.3 mmoL) were dissolved in THF (6 mL). The reaction mixture was heated at reflux overnight. After cooling, partitioned with water/brine (6mL), agitated and separated the layers. Dried organic phase over sodium sulfate and the solvent was removed via rotary evaporation to give a tan solid. LC/MS (RT = 3.008/(M+1)) 381.1.

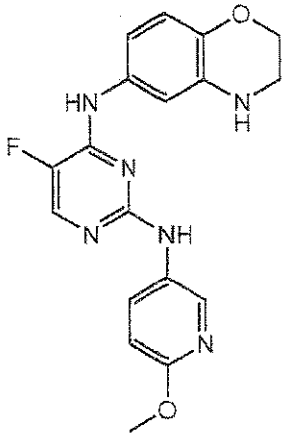
[00517] Step-2



5

[00518] 3 (215 mg, 0.56 mmoL) and 4 (83 mg, 0.66 mmoL) was suspended in tert-amyl alcohol (6 mL) and acetic acid (3 drops). Heated to reflux for 12 h. After cooling, solvent was removed via rotary evaporation. The dark oil was partitioned between water/brine and EtOAc (5 mL each), agitated, and separated layers and dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to afford an oil. Flash chromatography using 30-70% gradient of heptane/ethyl acetate on combiflash system gave a tan solid. LC/MS (RT = 2.011/(M+1)) 469.2.

[00519] Step-3

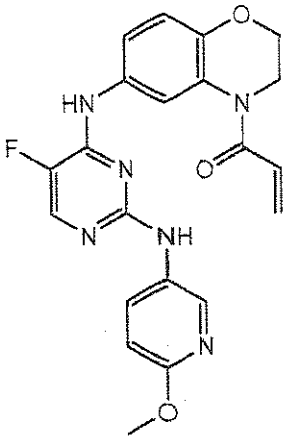


6

[00520] To a solution of 5 (200 mg, 0.43 mmol) in DCM (10 mL) was added TFA (1 mL). Stir for 30 min at rt for 12 h; removed solvent via rotary evaporation and partitioned oil between

cold (0 °C) saturated sodium bicarbonate (5 mL) and EtOAc (5 mL), agitated and separated layers. Organic phase was dried over sodium sulfate and the solvent was removed via rotary evaporation to give a pink solid. LC/MS (RT = 2.782/(M+1)) 369.1.

[00521] Step-4

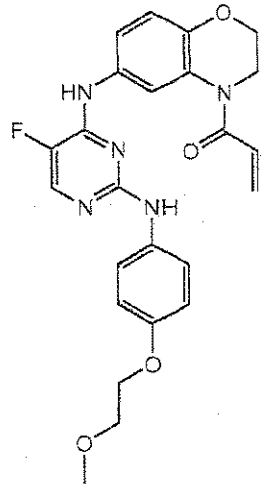


I-194

[00522] A solution of **6** (150 mg, 0.41 mmol) in DCM (2 mL) and NMP (0.5 mL) was cooled in water/ice-MeOH bath (-10 °C). To this was added 7 (34 μL, 0.43 mmoL), stirred for 10min, then added Hunig's base (70 μL, 0.43 mmoL), and stirred for 10 min. Partitioned between water/brine (5 mL), agitated and separated the layers. Dried organic phase over sodium sulfate. Purified directly via flash chromatography using 20-80% gradient of heptane/ethyl acetate to give a pink solid. LC/MS (RT = 2.8/(M + H)) 423.1.

EXAMPLE 32

[00523] Preparation of 1-(6-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one **I-141**

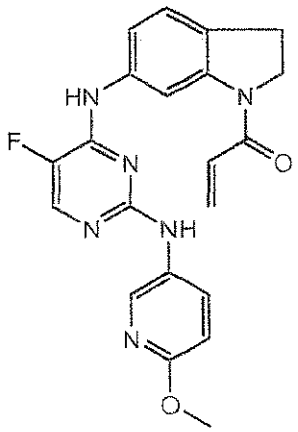


I-141

[00524] The title compound was prepared according to the schemes, steps and intermediates described in Example 31, by using 4-(2-methoxyethoxy)aniline in the place of **4** in Step 2. LC/MS (RT = 2.845/(M + H)) 466.2.

EXAMPLE 33

[00525] Preparation of 1-(6-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)indolin-1-yl)prop-2-en-1-one **I-166**

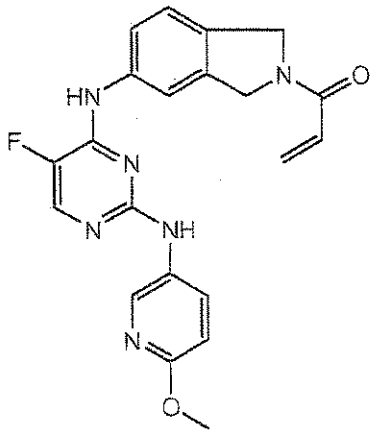


I-166

[00526] The title compound was prepared according to the schemes, steps and intermediates described in Example 31, by using tert-butyl 6-aminoindoline-1-carboxylate in the place of **2** in Step 1. LC/MS (RT = 2.825/(M + H)) 407.1.

EXAMPLE 34

[00527] Preparation of 1-(5-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)isoindolin-2-yl)prop-2-en-1-one **I-165**

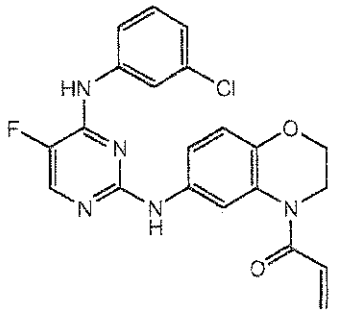


I-165

[00528] The title compound was prepared according to the schemes, steps and intermediates described in Example 31, by using tert-butyl 5-aminoisoindoline-1-carboxylate in the place of **2** in Step 1. LC/MS (RT = 2.751/(M + H)) 407.1.

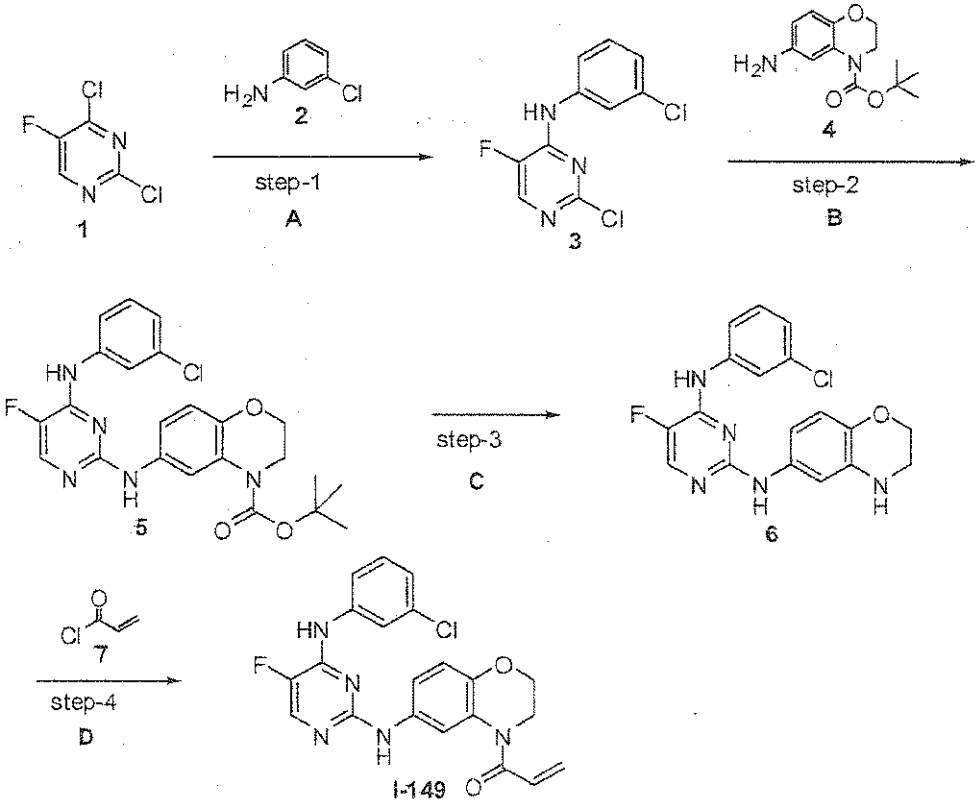
EXAMPLE 35

[00529] Preparation of 1-(6-(4-(3-chlorophenylamino)-5-fluoropyrimidin-2-ylamino)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one **I-149**



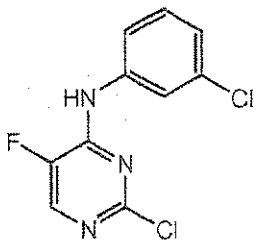
I-149

[00530] The title compound was prepared according to the schemes, steps and intermediates described below.



A) 2, DIPEA, THF, reflux; B) 4, HOAc, tert-amyl alcohol, reflux, 12 h; C) TFA, DCM; D) 7, DIPEA, THF, -10 °C.

[00531] Step-1

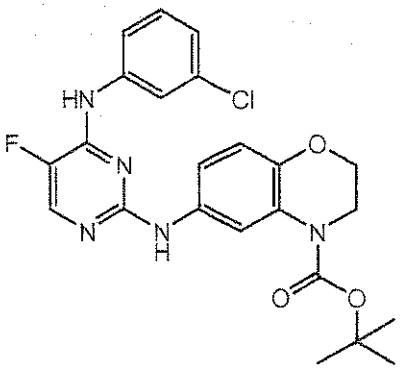


3

[00532] 1 (484 mg, 2.9 mmoL), 2 (305 mg, 2.9 mmoL) and Hunig's base (526 µL, 3.5 mmoL) were dissolved in THF (10 mL). The reaction mixture was heated at reflux overnight. After cooling, partitioned between water/brine (10 mL), agitated and separated the layers. Dried organic phase over sodium sulfate and the solvent was removed via rotary evaporation. Flash

chromatography using a gradient of 0-30% heptane/ethyl acetate on combiflash system gave a white solid. LC/MS (RT = 2.03/(M+1)) 339.1.

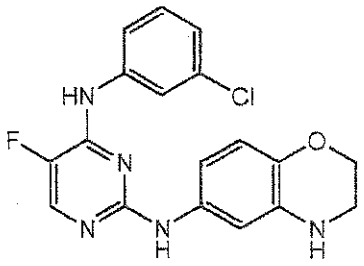
[00533] Step-2



5

[00534] 3 (150 mg, 0.58 mmoL) and 4 (175 mg, 0.7 mmoL) were suspended in tert-amyl alcohol (8 mL) and acetic acid (3 drops). Heated to reflux for 12h. After cooling, solvent was removed via rotary evaporation. The dark oil was partitioned between water/brine and EtOAC (5 mL each), agitated, and separated layers and dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to afford a dark oil. Flash chromatography using a gradient of 0-25% heptane/ethyl acetate on combiflash system gave a white solid. LC/MS (RT = 2.997/(M+1)) 470.2.

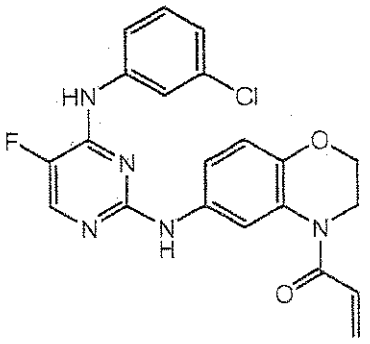
[00535] Step-3



6

[00536] To a solution of 5 (180 mg, 0.38 mmol) in DCM (10 mL) was added TFA (1 mL). Stirred for 30 min at rt for 4h; removed solvent via rotary evaporation and partitioned oil between cold (0 °C) saturated sodium bicarbonate (5 mL) and EtOAc (5 mL), agitated and separated layers. Organic phase was dried over sodium sulfate and the solvent was removed via rotary evaporation to give light yellow solid. LC/MS (RT = 2.723/(M+1)) 423.1.

[00537] Step-4

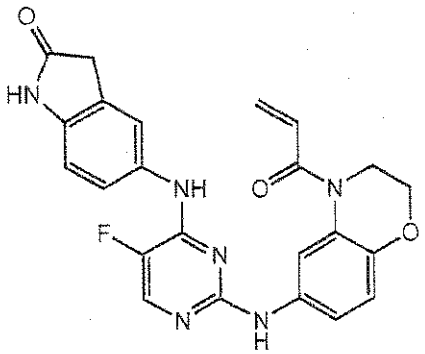


I-149

[00538] A solution of **6** (150 mg, 0.4 mmol) in THF (3 mL) was cooled in water/ice-MeOH bath (-10 °C). To this was added 7 (34 µL, 0.42 mmoL), stirred for 10 min, then added Hunig's base (70 µL, 0.42 mmoL), and stirred for 10min. Partitioned between water/brine (5mL), agitated and separated the layers. Dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to afford a light yellow solid. Flash chromatography using gradient of 10-50% heptane/ethyl acetate on combiflash system gave a white solid. LC/MS (RT = 2.945/(M + H)) 426.

EXAMPLE 36

[00539] Preparation of 5-(2-(4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)-5-fluoropyrimidin-4-ylamino)indolin-2-one **I-130**

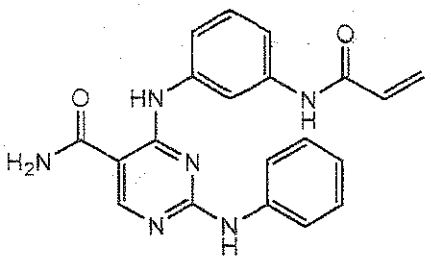


I-130

[00540] The title compound was prepared according to the schemes, steps and intermediates described in Example 35, by using 5-aminoindolin-2-one in the place of **2** in Step 1. LC/MS (RT = 2.673/(M + H)) 447.1.

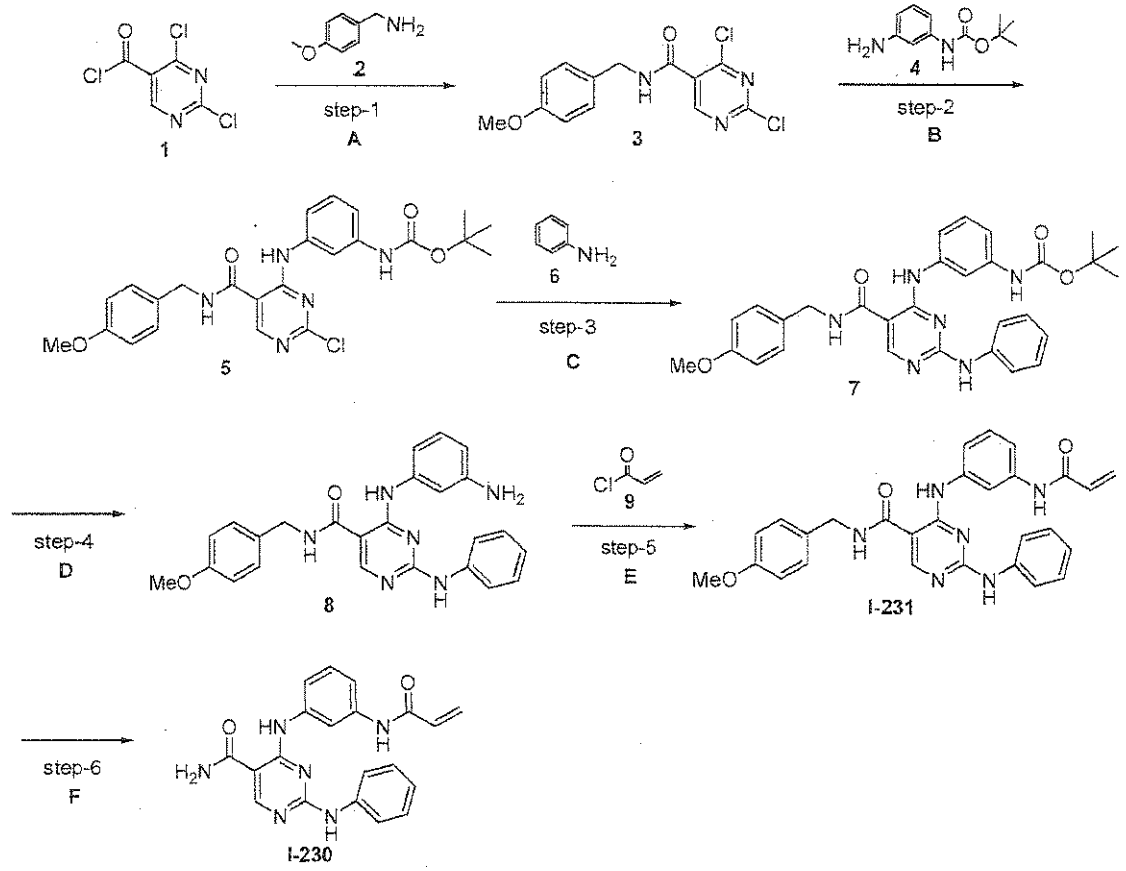
EXAMPLE 37

[00541] Preparation of 4-(3-acrylamidophenylamino)-2-(phenylamino)pyrimidine-5-carboxamide **I-230**



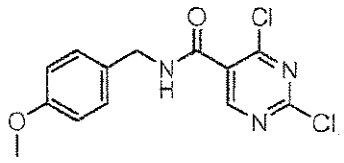
I-230

[00542] The title compound was prepared according to the schemes, steps and intermediates described below.



A) **2**, NEt_3, DCM, 0 °C to rt; B) **4**, DIPEA, THF, rt, 12 h; C) **6**, DIPEA, t-amyl alcohol, reflux, 4 h; D) TFA, DCM, rt; E) **7**, NEt_3, THF, 0 °C; F) TFA, TfOH, DCM, rt.

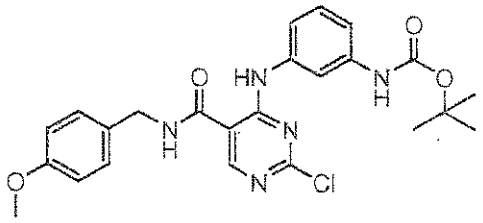
[00543] Step-1



3

[00544] 1 (500 mg, 2.4 mmoL, prepared from 2,4-dihydroxypyrimidine-5-carboxylic acid according to *J. Med. Chem.* 50: 591 (2007) and US 2007/0072851) was dissolved in DCM (10 mL) and chilled in an ice/water bath (0 °C). 2 (309 μL, 2.4 mmoL) was added and the mixture stirred for 10 min. Triethylamine (365 μL, 2.6 mmol) was added and the mixture was allowed to warm to rt and stir for 30min. The solvent was reduced in volume via rotary evaporation and directly purified by flash chromatography using a gradient of 0-30% heptane/ethyl acetate on combiflash system to give a white solid. LC/MS (RT = 2.789/(M+1)) 312.

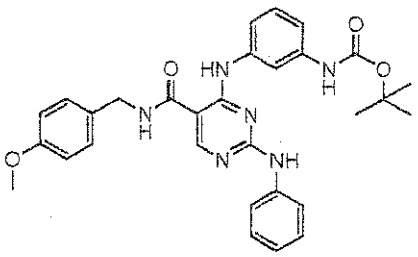
[00545] Step-2



5

[00546] 3 (170 mg, 0.55 mmoL), 4 (113 mg, 0.55 mmoL) and Hunig's base (108 μL, 0.65 mmoL) were dissolved in THF (6 mL). Stirred at rt for 12 h. Partitioned between water/brine, agitated, and separated layers and dried organic phase over sodium sulfate. The solvent was removed via rotary evaporation to afford after titration with EtOAc a white solid. LC/MS (RT = 3.123/(M+1)) 484.

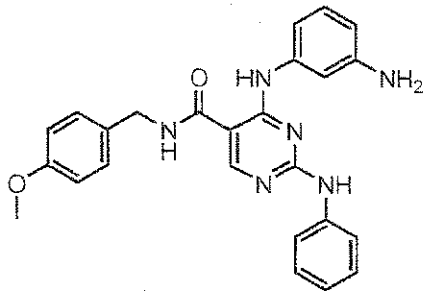
[00547] Step-3



7

[00548] **5** (230 mg, 0.48 mmol), **6** (126 μL, 1.4 mmoL) and Hunig's base (94 μL, 0.57 mmoL) is dissolved in t-amyl alcohol (6 mL). Heat to reflux for 4 h, cool and water was added to the solid mass. Agitated, filtered and dried to give a white solid. LC/MS (RT = 3.182/(M+1)) 541.2.

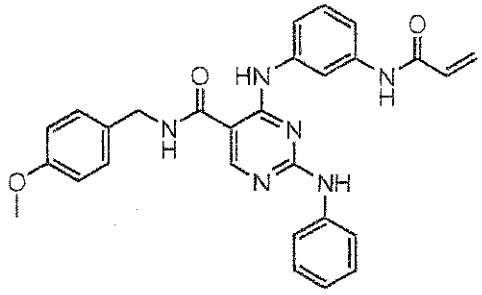
[00549] Step-4



8

[00550] 7 (180 mg, 0.33 mmol) was suspended in DCM (10 mL) and treated with TFA (1 mL). Stirred overnight at rt. Diluted with DCM (40 mL) and washed with NaOH (1N, 25mL). Agitated, precipitate formed, filtered and dry to give a white solid. LC/MS (RT = 2.934/(M+1)) 441.1.

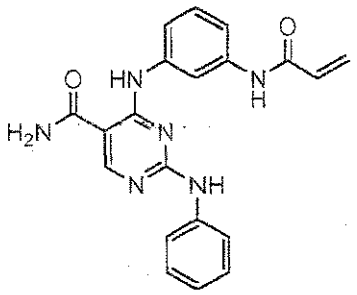
[00551] Step-5



I-231

[00552] A suspension of **8** (130 mg, 0.29 mmol) in THF (6 mL) was cooled in water/ice (0 °C). To this was added **9** (25 μL (plus additional 5 μL), 0.38 mmoL (total)), then added triethyl amine (43 μL (plus additional 11 μL), 0.38 mmoL(total)), and stirred for a total time of 1 h. Water was added, agitated, filtered off remaining precipitate and discarded. The filtrate was dried over sodium sulfate. The solvent was removed via rotary evaporation to afford a yellow solid. Flash chromatography using a gradient of 0-25% heptane/ethyl acetate on combiflash system gave a white solid. LC/MS (RT = 2.964/(M + H)) 495.1.

[00553] Step-6

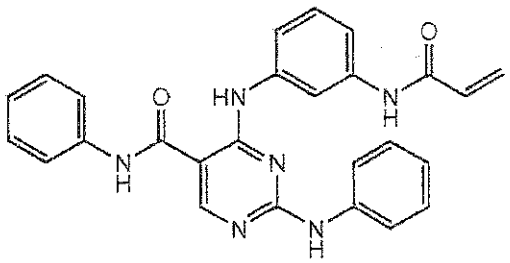


I-230

[00554] To a suspension of I-231 (30 mg, 0.061 mmol) in DCM (4 mL) was added TFA (200 μL) and triflic acid (68 μL, 0.61mmoL). Stirred at rt 1 h. Removed solvent under reduce pressure via rotary evaporation and partitioned with cold (0 °C) saturated sodium bicarbonate (10 mL) and EtOAc (10 mL), agitated and separated layers. Dried organic layer over sodium sulfate and the solvent was removed via rotary evaporation to afford after titration with diethyl ether a white solid. LC/MS (RT = 2.715/(M + H)) 375.1.

EXAMPLE 38

[00555] Preparation of 4-(3-acrylamidophenylamino)-N-phenyl-2-(phenylamino)pyrimidine-5-carboxamide I-222

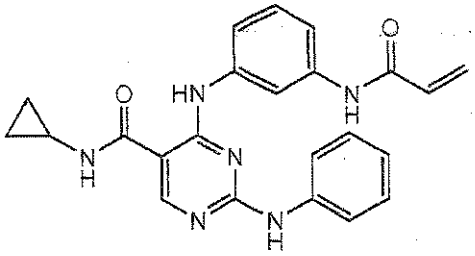


I-222

[00556] The title compound was prepared according to the schemes, steps and intermediates described in Example 37, by using aniline in the place of 2 in Step 1 and omitting Step 6. LC/MS (RT = 2.991/(M + H)) 451.2.

EXAMPLE 39

[00557] Preparation of 4-(3-acrylamidophenylamino)-N-cyclopropyl-2-(phenylamino)pyrimidine-5-carboxamide **I-221**

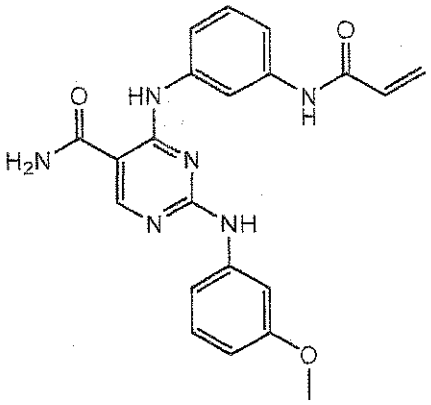


I-221

[00558] The title compound was prepared according to the schemes, steps and intermediates described in Example 37, by using cyclopropylamine in the place of **2** in Step 1 and omitting Step 6. LC/MS (RT = 2.838/(M + H)) 415.2.

EXAMPLE 40

[00559] Preparation of 4-(3-acrylamidophenylamino)-2-(3-methoxyphenylamino)pyrimidine-5-carboxamide **I-210**

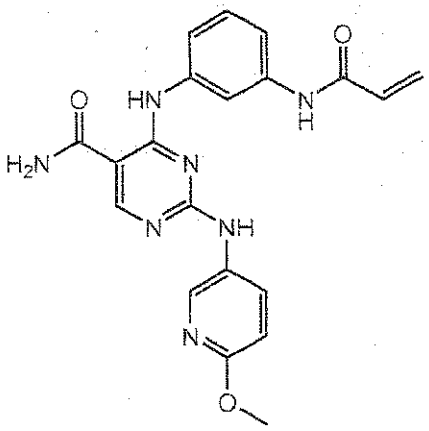


I-210

[00560] The title compound was prepared according to the schemes, steps and intermediates described in Example 37, by using 3-methoxyaniline in the place of **6** in Step 3. LC/MS (RT = 2.743/(M + H)) 405.1.

EXAMPLE 41

[00561] Preparation of 4-(3-acrylamidophenylamino)-2-(6-methoxypyridin-3-ylamino)pyrimidine-5-carboxamide **I-209**

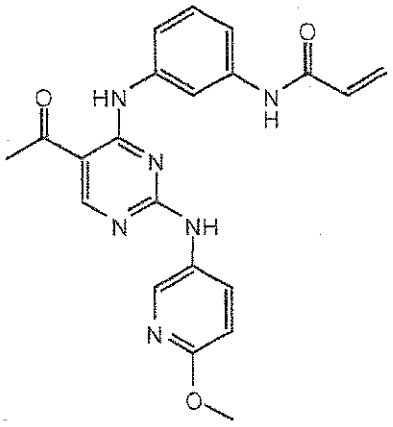


I-209

[00562] The title compound was prepared according to the schemes, steps and intermediates described in Example 37, by using 6-methoxypyridin-3-amine in the place of **6** in Step 3. LC/MS (RT = 2.657/(M + H)) 406.2.

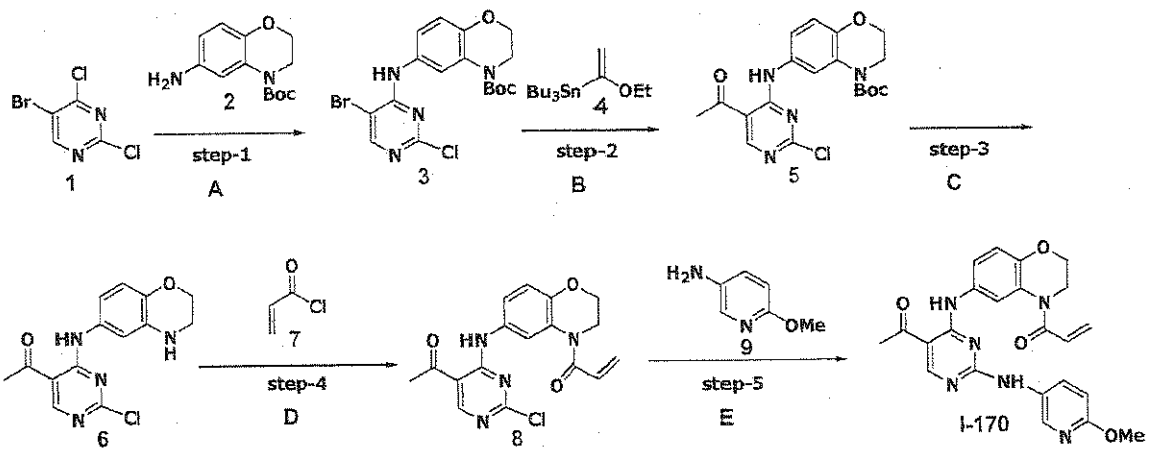
EXAMPLE 42

[00563] Preparation of 1-{6-[5-Acetyl-2-(6-methoxy-pyridin-3-ylamino)-pyrimidin-4-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-propenone **I-170**



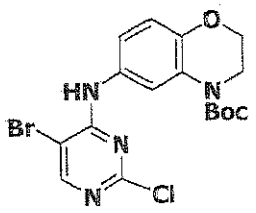
I-170

[00564] The title compound was prepared according to the schemes, steps and intermediates described below.



A) **2**, DIPEA, THF, 70 °C, 16 h; **B**) (a) **4**, $PdCl_2(PPh_3)_2$, DMF, 70 °C; (b) 1N HCl, acetone, 60 °C, 15 min; **C**) HCl/dioxane, DCM; **D**) **7**, DIPEA, NMP, DCM, -20 °C to rt; **E**) **9**, pTsOH, dioxane, 100 °C, 15 min.

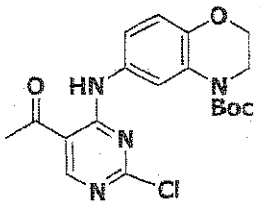
[00565] **Step-1**



3

[00566] A mixture of 499 mg of **1** (2.19 mmol), 547 mg of **2** (2.19 mmol), and 500 uL of N,N-diisopropylethylamine in 20 mL of anhydrous tetrahydrofuran was heated at 70 °C overnight. After cooling down, the reaction mixture was concentrated, and subject to aqueous workup with 50 mL of EtOAc, 20 mL of sodium bicarbonate solution, brine, and dried over anhydrous sodium sulfate. After filtration and concentration, the residue was passed through a short silica cartridge, eluted with heptanes/EtOAc (v/v 3/1), giving 815 mg of a slight yellow solid (84%). LC-MS: m/z 441.0 (ES+), 439.0 (ES-).

[00567] Step-2

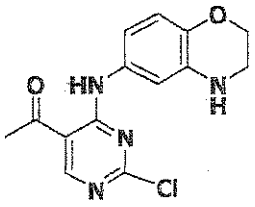


5

[00568] A mixture of intermediate **3** (815 mg, 1.85 mmol), **4** (740 mg, 1.1 equiv.), 27 mg of dichlorobis(triphenylphosphine)palladium (II) (2% mol) in 6 mL of anhydrous DMF was purged with nitrogen for 30 min. The reaction mixture was then heated at 70 °C overnight. LC-MS showed 70% conversion. After cooling down, 30 mL of ethyl acetate and 760 mg of potassium fluoride in 5 mL of water was added, and the mixture was stirred at rt for at least 2 hr. The white precipitate was filtered out, and the organic layer was separated, washed with water, brine, and dried over anhydrous sodium sulfate.

[00569] After filtration and concentration, the residue was dissolved in 20 mL of acetone, followed by additon of 3 mL of 1.0 N aqueous HCl solution. The mixture was heated at 60 °C for 15 min, and concentrated under reduced pressure. Normal workup was done using 50 mL of EtOAc, 10 mL of saturated sodium bicarbonate solution, brine, anhydrous sodium sulfate. After concentration, the residue was purified by flash column chromatography on silica gel, giving 405 mg of yellow solid (70% based on consumed starting material), also recovering intermediate 3 183 mg. LC-MS: m/z 405.1 (ES+), 403.1 (ES-).

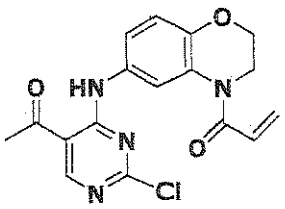
[00570] Step-3



6

[00571] To a mixture of 1.28 g of intermediate **I-2** in 10 mL of dichloromethane, was added 10 mL of 4.0 N HCl in dioxane. After stirring at rt overnight, the solvent was removed, and the residue was dried in vacuum. LC-MS: m/z 305.1 (ES+), 303.1 (ES-).

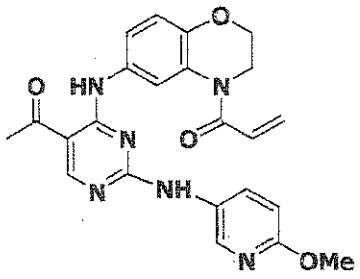
[00572] Step-4



8

[00573] Under N_2, to a mixture of the intermediate **6** obtained above, 1 mL of DIPEA in 10 mL of NMP and 10 mL of dichloromethane at -20 °C, was added 275 uL of 7 (1.1 equiv). The reaction was continued for 5 min, then quenched with 1 mL of isopropyl alcohol. The reaction mixture was warmed up to rt, and extracted with 100 mL of EtOAc, washed with water 10 mL x 2, brine, dried over sodium sulfate. After filtration and concentration, the residue was purified by flash column chromatography with eluent heptanes/EtOAc (v/v 2/3), giving yellow solid **I-3** 450 mg (40 %). LC-MS: m/z 359.1 (ES+), 357.1 (ES-).

[00574] Step-5

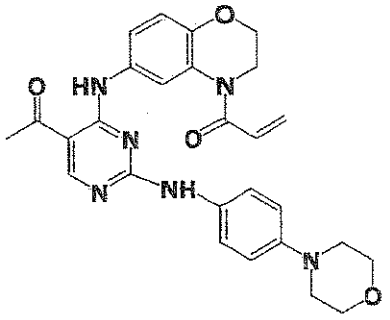


I-170

[00575] The mixture of 30 mg intermediate **8** (84 μmol) and 13 mg of **9** (1.2 equiv) in 1 mL of 0.08 M p-TsOH dioxane solution was heated at 100 °C for 15 min. After cooling down, the reaction mixture was subject to regular work up with 50 mL of EtOAc, aqueous sodium bicarbonate, brine, and dried over anhydrous sodium sulfate. After concentration, the residue was purified by column chromatography on silica gel with heptane/EtOAc (v/v 1/4) as eluent, giving 22.8 mg pale white solid (61%). LC-MS: m/z = 447.1 (ES+), 445.2 (ES-).

EXAMPLE 43

[00576] Preparation of 1-{6-[5-Acetyl-2-(4-morpholin-4-yl-phenylamino)-pyrimidin-4-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-propenone **I-169**

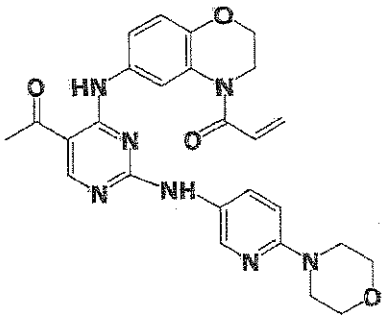


I-169

[00577] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 4-morpholin-4-yl-phenylamine in the place of **9** in Step 5. LC-MS: m/z 501.1 (ES+), 499.2 (ES-).

EXAMPLE 44

[00578] Preparation of 1-{6-[5-Acetyl-2-(6-morpholin-4-yl-pyridin-3-ylamino)-pyrimidin-4-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-propenone **I-168**

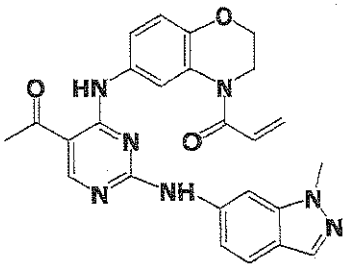


I-168

[00579] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 3-amino-[6-morpholin-4-yl]-pyridine in the place of **9** in Step 5. LC-MS: m/z 502.2 (ES+), 500.3 (ES-).

EXAMPLE 45

[00580] Preparation of 1-{6-[5-Acetyl-2-(1-methyl-1H-indazol-6-ylamino)-pyrimidin-4-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-propenone **I-154**

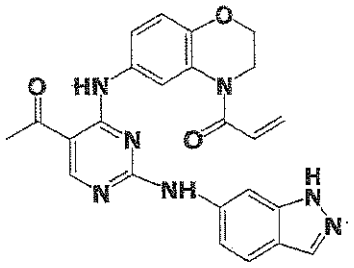


I-154

[00581] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 1-methyl-1H-indazol-6-ylamine in the place of **9** in Step 5. LC-MS: m/z 470.1 (ES+), 468.1 (ES-).

EXAMPLE 46

[00582] Preparation of 1-{6-[5-Acetyl-2-(1H-indazol-6-ylamino)-pyrimidin-4-ylamino]-2,3-dihydro-benzo[1,4]oxazin-4-yl}-propenone **I-153**

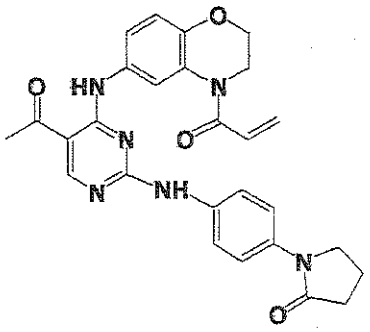


I-153

[00583] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 1H-indazole-6-ylamine in the place of **9** in Step 5. LC-MS: m/z 456.1 (ES+), 454.2 (ES-).

EXAMPLE 47

[00584] Preparation of 1-{4-[5-Acetyl-4-(4-acryloyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamino)-pyrimidin-2-ylamino]-phenyl}-pyrrolidin-2-one **I-152**

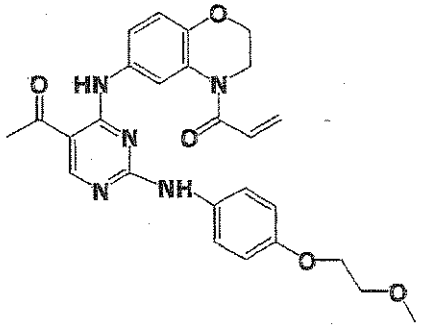


I-152

[00585] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 1-(4-amino-phenyl)-pyrrolidin-2-one in the place of **9** in Step 5. LC-MS: m/z 456.1 (ES+), 454.2 (ES-).

EXAMPLE 48

[00586] Preparation of 1-(6-{5-Acetyl-2-[4-(2-methoxy-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propenone **I-150**

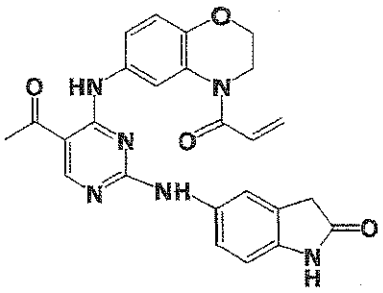


I-150

[00587] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 4-(2-methoxy-ethoxy)-phenylamine in the place of **9** in Step 5. LC-MS: m/z 490.2 (ES+), 488.3 (ES-).

EXAMPLE 49

[00588] Preparation of 5-[5-Acetyl-4-(4-acryloyl-3,4-dihydro-2H-benzo[1,4]oxazin-6-ylamino)-pyrimidin-2-ylamino]-1,3-dihydro-indol-2-one **I-129**

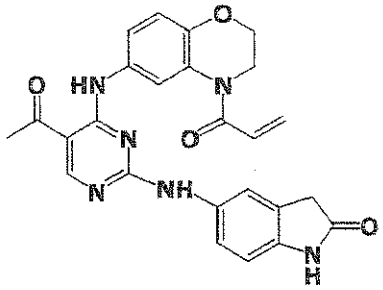


I-129

[00589] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 5-amino-1,3-dihydro-indol-2-one in the place of **9** in Step 5. LC-MS: m/z 471.1 (ES+), 469.2 (ES-).

EXAMPLE 50

[00590] Preparation of 1-(6-{5-Acetyl-2-[6-(2-hydroxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-ylamino}-2,3-dihydro-benzo[1,4]oxazin-4-yl)-propenone **I-128**

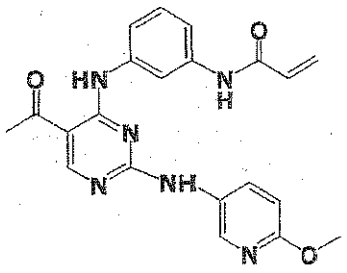


I-128

[00591] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 2-(5-amino-pyridin-2-yloxy)-ethanol in the place of **9** in Step 5. LC-MS: m/z 477.1 (ES+), 475.2 (ES-).

EXAMPLE 51

[00592] Preparation of N-{3-[5-Acetyl-2-(6-methoxy-pyridin-3-ylamino)-pyrimidin-4-ylamino]-phenyl}-acrylamide **I-189**

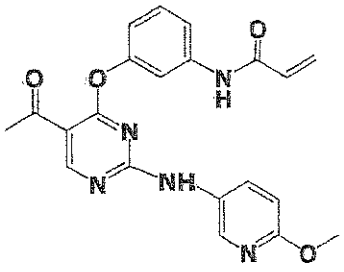


I-189

[00593] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using tert-butyl 3-aminophenylcarbamate in the place of **2** in Step 1 and 5-amino-2-methoxypyridine in the place of **9** in Step 5. LC-MS: m/z 405.1 (ES+), 403.2 (ES-).

EXAMPLE 52

[00594] Preparation of N-{3-[5-Acetyl-2-(6-methoxy-pyridin-3-ylamino)-pyrimidin-4-yloxy]-phenyl}-acrylamide **I-188**

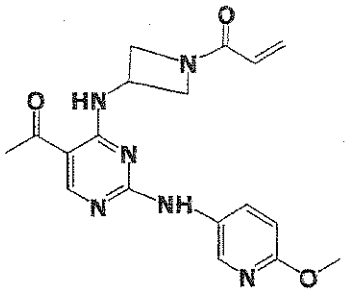


I-188

[00595] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using tert-butyl 3-hydroxyphenylcarbamate in the place of **2** in Step 1 and 5-amino-2-methoxypyridine in the place of **9** in Step 5. LC-MS: m/z 406.2 (ES+), 404.1 (ES-).

EXAMPLE 53

[00596] Preparation of 1-{3-[5-Acetyl-2-(6-methoxy-pyridin-3-ylamino)-pyrimidin-4-ylamino]-azetidin-1-yl}-propenone **I-187**

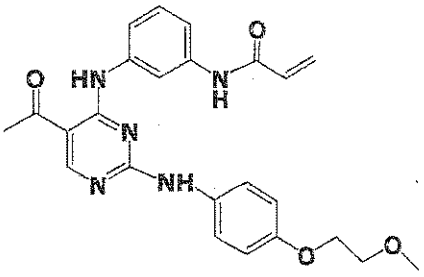


I-187

[00597] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using 3-amino-N-Boc-azetidine in the place of **2** in Step 1 and 5-amino-2-methoxypyridine in the place of **9** in Step 5. LC-MS: m/z 369.1 (ES+), 367.2 (ES-).

EXAMPLE 54

[00598] Preparation of N-(3-{5-Acetyl-2-[4-(2-methoxy-ethoxy)-phenylamino]-pyrimidin-4-ylamino}-phenyl)-acrylamide **I-124**

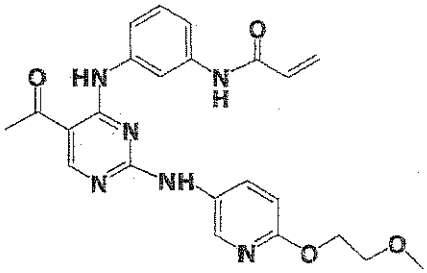


I-124

[00599] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using tert-butyl 3-aminophenylcarbamate in the place of **2** in Step 1 and 4-(2-methoxy-ethoxy)-phenylamine in the place of **9** in Step 5. LC-MS: m/z 448.2 (ES+), 446.3 (ES-).

EXAMPLE 55

[00600] Preparation of N-(3-{5-Acetyl-2-[6-(2-methoxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-ylamino}-phenyl)-acrylamide I-122

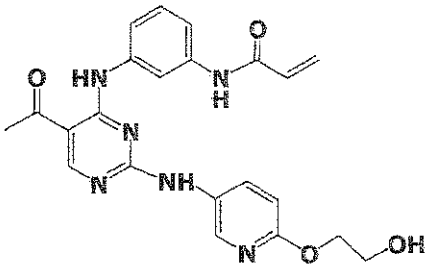


I-122

[00601] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using tert-butyl 3-aminophenylcarbamate in the place of 2 in Step 1 and 6-(2-Methoxy-ethoxy)-pyridin-3-ylamine in the place of 9 in Step 5. LC-MS: m/z 449.2 (ES+), 447.1 (ES-).

EXAMPLE 56

[00602] Preparation of N-(3-{5-Acetyl-2-[6-(2-hydroxy-ethoxy)-pyridin-3-ylamino]-pyrimidin-4-ylamino}-phenyl)-acrylamide I-121

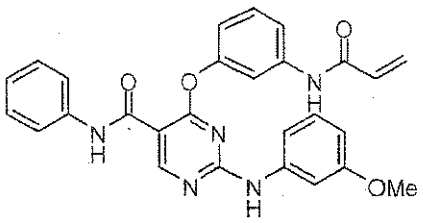


I-121

[00603] The title compound was prepared according to the schemes, steps and intermediates described in Example 42, by using tert-butyl 3-aminophenylcarbamate in the place of 2 in Step 1 and 2-(5-Amino-pyridin-2-yloxy)-ethanol in the place of 9 in Step 5. LC-MS: m/z 435.1 (ES+), 433.2 (ES-).

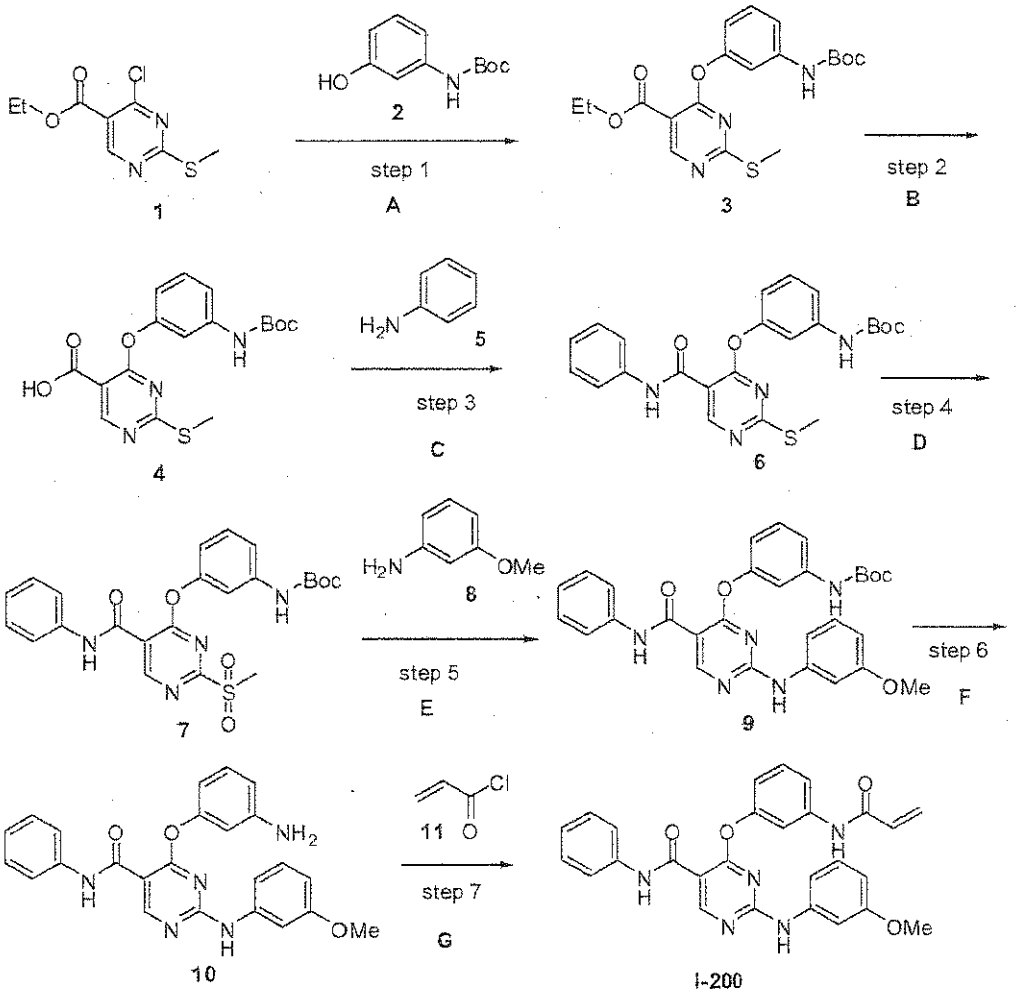
EXAMPLE 57

[00604] Preparation of 4-(3-acrylamidophenoxy)-2-(3-methoxyphenylamino)-pyrimidine-5-carboxylic acid phenylamide **I-200**



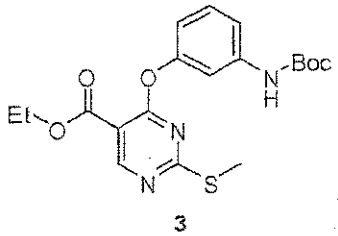
I-200

[00605] The title compound was prepared according to the schemes, steps and intermediates described below.



A) **2**, NaH, THF, 0 °C; B) NaOH, THF, MeOH; C) **5**, TBTU, DIPEA, CH_3CN, 0 °C; D) MCPBA, CH_2Cl_2, 0 °C; E) **8**, 50 °C, 3 h; F) TFA, CH_2Cl_2; G) **11**, DIPEA, CH_2Cl_2

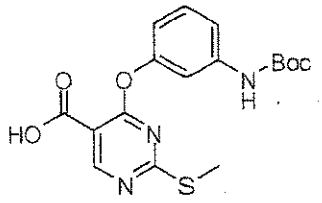
[00606] **Step 1**



[00607] To a stirred solution of (3-hydroxyphenyl)carbamic acid *tert*-butyl ester **2** (1.79 g, 8.59 mmol) at 0 °C was added a suspension of sodium hydride (60% dispersion in mineral oil) (0.34 g, 8.9 mmol) in anhdyrous THF (30 mL). The mixture was stirred at 0 °C for 20 minutes.

The phenoxide solution was then added dropwise at 0 °C to a solution of 4-chloro-(2-methylsulfanyl)pyrimidine-5-carboxylic acid ethyl ester **1** (2 g, 8.59 mmol) in THF (20 mL). The reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was diluted with ethyl acetate (150 mL) and washed with water (50 mL) and then brine (50 mL). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude product was washed with CH_2Cl_2:hexane (1:9) to afford the title compound **3** as a white solid (2.43 g, 70%).

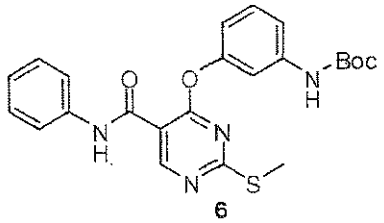
[00608] Step-2



4

[00609] To a stirred solution of 4-(3-*tert*-butoxycarbonylaminophenoxy)-2-(methylsulfanyl-pyrimidine)-5-carboxylic acid ethyl ester **3** (2 g, 4.93 mmol) in THF (60 mL), was added methanol (60 mL) at -10 °C, followed by aqueous sodium hydroxide (0.3 g, 30 mL water, 7.5 mmol). The reaction mixture was allowed warm to room temperature and was stirred for 1 hour. The reaction mixture was diluted with water (50 mL), acidified with citric acid and the resulting solid was collected by filtration and washed with ice cold water (50 mL) to yield **4** as a white solid. (1.52 g, 82%).

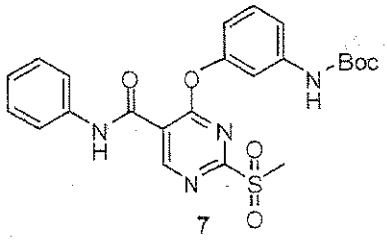
[00610] Step-3



6

[00611] To a stirred solution of 4-(3-*tert*-butoxycarbonylaminophenoxy)-2-(methylsulfanyl)pyrimidine-5-carboxylic acid **4** (2.0 g, 5.29 mmol) and TBTU (2.55 g, 7.94 mmol) in acetonitrile (30 mL) at 0°C was added DIPEA (1.36g, 10.6 mmol) followed by aniline **5** (0.60 g, 6.35 mmol). The reaction was stirred at room temperature for 2 hours. After completion of the reaction the reaction mixture was poured into ice cold water (100 mL) and the white solid obtained was collected by filtration and washed with ice cold water (20 mL), dried under *in vacuo* to afford the title compound **6** (1.79 g, 75%).

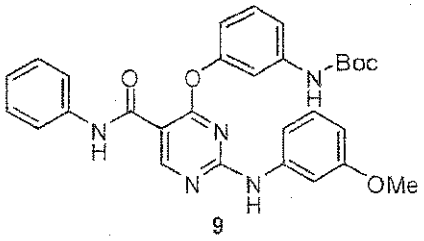
[00612] Step-4



7

[00613] To a stirred solution of [3-(2-methylsulfanyl-5-phenylcarbamoylpyrimidin-4-yloxy)-phenyl]-carbamic acid *tert*-butyl ester **6** (1.5 g, 3.31 mmol) in CH_2Cl_2 at 0 °C was added a solution *m*-CPBA (70%, 1.62 g, 2 eq) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ and the whole was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was washed with CH_2Cl_2:hexane (1:9) to afford the title compound **7** as a white solid (1.16 g, 73%).

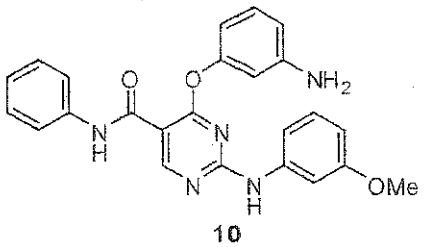
[00614] Step-5



9

[00615] Excess 3-methoxyaniline (**8**) (2 mL) was added to solid [3-(2-methanesulfonyl-5-phenylcarbamoyl-pyrimidin-4-yloxy)-phenyl]-carbamic acid *tert*-butyl ester **7** (0.5 g, 1.03 mmol) and the resulting mixture was heated to 50 °C under an argon atmosphere for 3 hours. The reaction mixture was cooled to room temperature and diluted with ethyl acetate/hexane (1:1, 20 mL) and the resulting precipitate filtered and washed with ethyl acetate/hexane (1:1, 10 mLl) to afford the desired product **9** as a white solid (0.40 g, 75% yield).

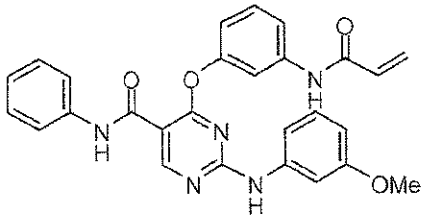
[00616] Step-6



10

[00617] To a solution of {3-[2-(3-methoxy-phenylamino)-5-phenylcarbamoyl-pyrimidin-4-yloxy]-phenyl}-carbamic acid *tert*-butyl ester **9** (0.3 g, 0.56 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL) and the mixture was stirred at room temperature for 1 hour. Solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with 10% aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide the free amine **10** as white solid.

[00618] Step-7

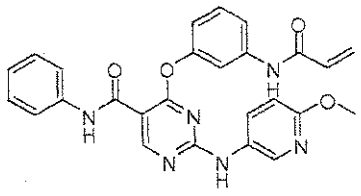


I-200

[00619] To a stirred solution of amine **10** (0.24 g, 0.56 mmol) in dichloromethane (20mL) under argon atmosphere cooled to -70 °C was added DIPEA (0.072 g, 0.56 mmol) followed by drop wise addition of acryloyl chloride (0.050 g, 0.56 mmol). The resulting mixture was stirred at -70 °C for 5 minutes, and the reaction mixture diluted with CH_2Cl_2 (50 mL) and then was washed with saturated aqueous NaCl solution (10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using (MeOH-$CHCl_3$ 5:95) as eluent to provide the target compound **11** (0.094 g, 35%) as white solid: ^{1}H NMR (200 MHz, DMF-d7) δ 8.9 (s, 1H), 8.10–7.70 (m, 6H), 7.60-7.10 (m, 6H),6.60 (m, 2H) 6.40 (dd, 1H, J = 8.0, 2.0 Hz), 5.80 (m, 2H), 3.70 (s, 3H).

EXAMPLE 58

[00620] Preparation of 4-(3-acrylamidophenoxy)-2-(6-methoxypyridin-3-ylamino)-pyrimidine-5-carboxylic acid phenylamide **I-159**

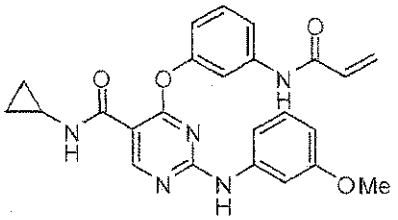


I-159

[00621] The title compound was prepared according to the schemes, steps and intermediates described in Example 57 by using 6-methoxy-3-aminopyridine in place of **8** in Step 5. ^{1}H NMR (200 MHz, DMSO-d_6 δ 8.90 (s, 1H), 8.20 (brs, 1H), 7.90-7.60 (m, 4H), 7.45(m, 4H), 7.10 (m, 2H), 6.50 (m, 1H), 6.20 (m, 2H), 5.90 (dd, J = 8.0, 2.0 Hz, 1H), 3.90 (s, 3H).

EXAMPLE 59

[00622] Preparation of 4-(3-acrylamidophenoxy)-2-(3-methoxyphenylamino)-pyrimidine-5-carboxylic acid cyclopropylamide **I-177**

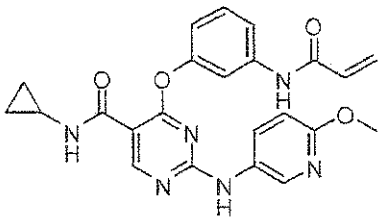


I-177

[00623] The title compound was prepared according to the schemes, steps and intermediates described in Example 57 by using cyclopropylamine in place of **5** in Step 3. ^{1}H NMR (200 MHz, CD_3OD) δ 9.0 (s, 1H), 7.90 (brs, 1H), 7.50 (m, 3H), 7.0 (m, 4H), 6.50 (m, 1H), 6.40 (d, J = 8.0 Hz, 2H), 5.80 (dd, J = 8.2, 3.0 Hz, 1H), 3.60 (s, 3H), 0.90 (m, 2H), 0.62 (m, 2H).

EXAMPLE 60

[00624] Preparation of 4-(3-acrylamidophenoxy)-2-(6-methoxypyridin-3-ylamino)-pyrimidine-5-carboxylic acid cyclopropylamide **I-176**



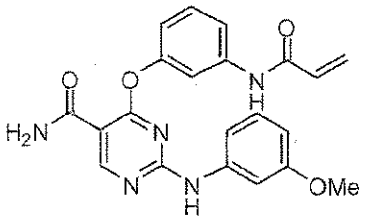
I-176

[00625] The title compound was prepared according to the schemes, steps and intermediates described in Example 57 by using cyclopropylamine in place of **5** in Step 3 and 6-methoxy-3-aminopyridine in place of **8** in Step 5. ^{1}H NMR (200 MHz, CD_3OD) δ 8.90 (s, 1H), 7.95 (brs,

1H), 7.90-7.82 (m, 3H), 7.40 (m, 3H), 6.98 (d, J = 6.0 Hz, 1H), 6.42 (m, 2H), 5.90 (dd, J = 8.0, 2.0 Hz, 1H), 3.90 (s, 3H), 0.95 (m, 2H), 0.83 (m, 2H).

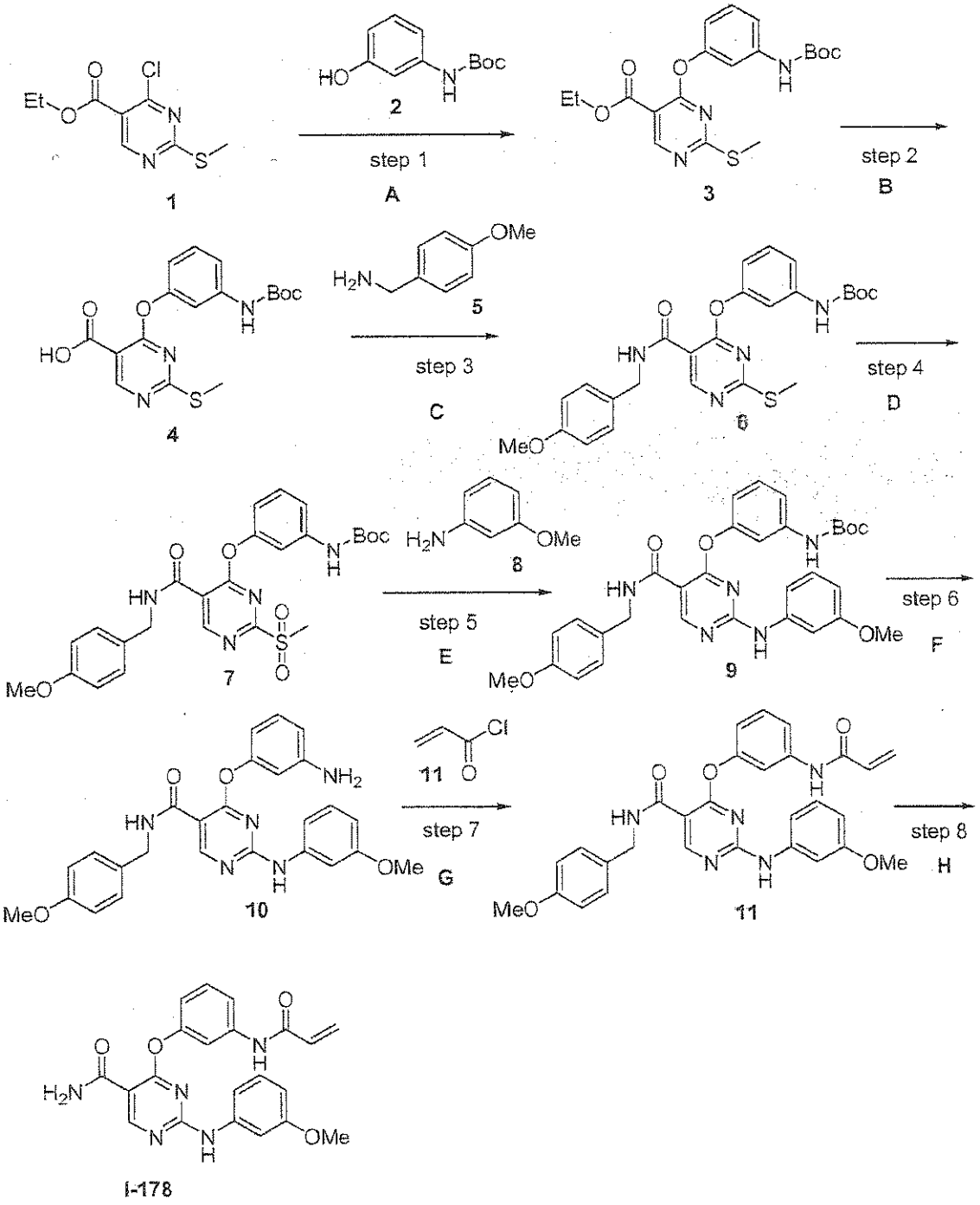
EXAMPLE 61

[00626] Preparation of 4-(3-acrylamidophenoxy)-2-(3-methoxyphenylamino)pyrimidine-5-carboxylic acid amide **I-178**



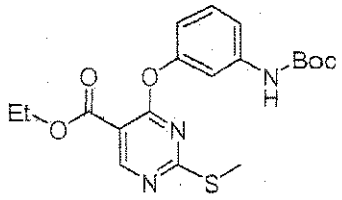
I-178

[00627] The title compound was prepared according to the schemes, steps and intermediates described below.



A) **2**, NaH, THF, 0 °C; B) LiOH, THF, H_2O; C) **5**, TBTU, DIPEA, CH_3CN; D) MCPBA, $CHCl_3$, 0 °C; E) **8**, DMA, 90 °C, 24 h; F) 4N HCl, dioxane; G) **11**, CH_2Cl_2; H) triflic acid, TFA, CH_2Cl_2

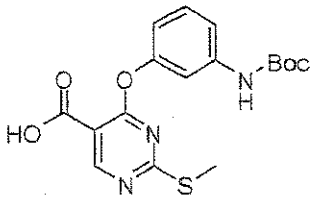
[00628] Step-1



3

[00629] Step 1 was carried out in a manner similar to Step 1 in Example 57.

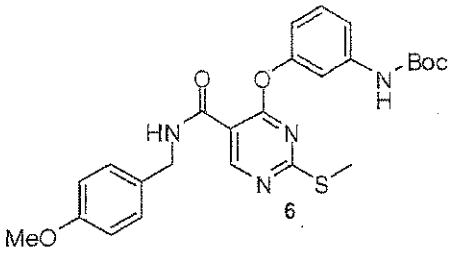
[00630] Step-2



4

[00631] Saponification of 3 (4.58 g, 11.3 mmol) by LiOH (500 mg, 20 mmol) in 80 mL THF/H2O (1:1) and usual workup with 1 N HCl gave free acid 4.

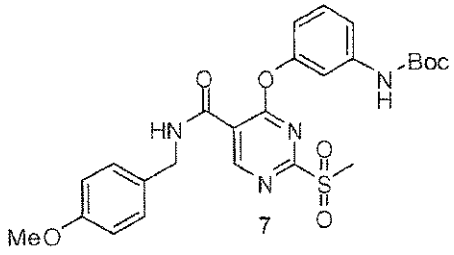
[00632] Step-3



6

[00633] Acid 4 was directly mixed with 4-methoxybenzylamine (1.55 g, 11.3 mmol), TBTU (5.4 g, 16.8 mmol) and DIEA (2.4 mL, 13.4 mmol) in 100 mL MeCN at room temperature. The reaction mixture was run overnight to give 6 as a white solid (4.2 g, 8.5 mmol) after flash chromatography (EtOAc-hexane).

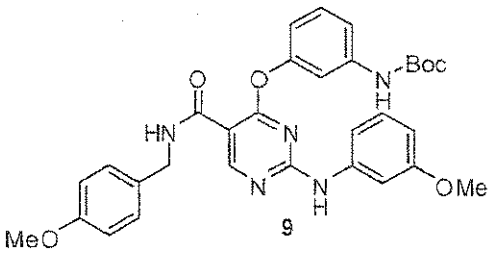
[00634] Step-4



7

[00635] Step 4 was run in a manner similar to Step 4 in Example 57 with $CHCl_3$ being substituted for CH_2Cl_2 as the solvent.

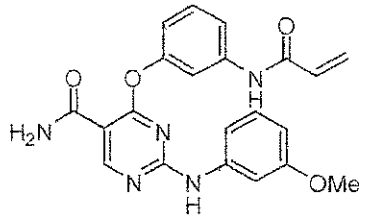
[00636] **Step-5**



9

[00637] The 2-methylsulfone of 7 (1.0 g, 1.9 mmol) was mixed with 3-methoxyaniline (420 mg, 3.4 mmol) in DMA and the mixture was heated at 90 ^{0}C for 24 hours. Workup was done in a manner similar to that for Step-5 in Example 57 to give **9** (300 mg, 0.52 mmol).

[00638] **Steps-6, 7, and 8**

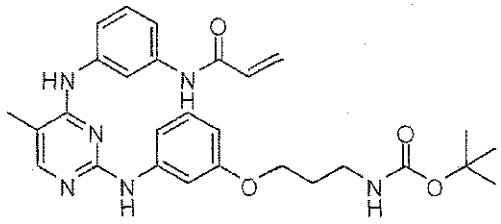


I-178

[00639] The Boc group was removed from **9** by treatment with 4 N HCl in dioxane. The product (300 mg, 0.52 mmol) was treated immediately with acryloyl chloride (43 µL, 0.52 mmol) in 15 mL DCM at -40 °C. This intermediate was purified by flash chromatography (MeOH-DCM) and was reacted with triflic acid and TFA in DCM to provide the crude benzylamine 11 (120 mg, 0.228 mmol). This intermediate(120 mg, 0.228 mmol) was converted to **I-178** using triflic acid (305 µL, 3.44 mmol) in TFA/DCM (5 mL, 1:1) at room temperature to provide ~ 35 mg final compound **I-178** as grey powder after purification via column chromatography (16% yield for three steps). MS: m/z = 405.

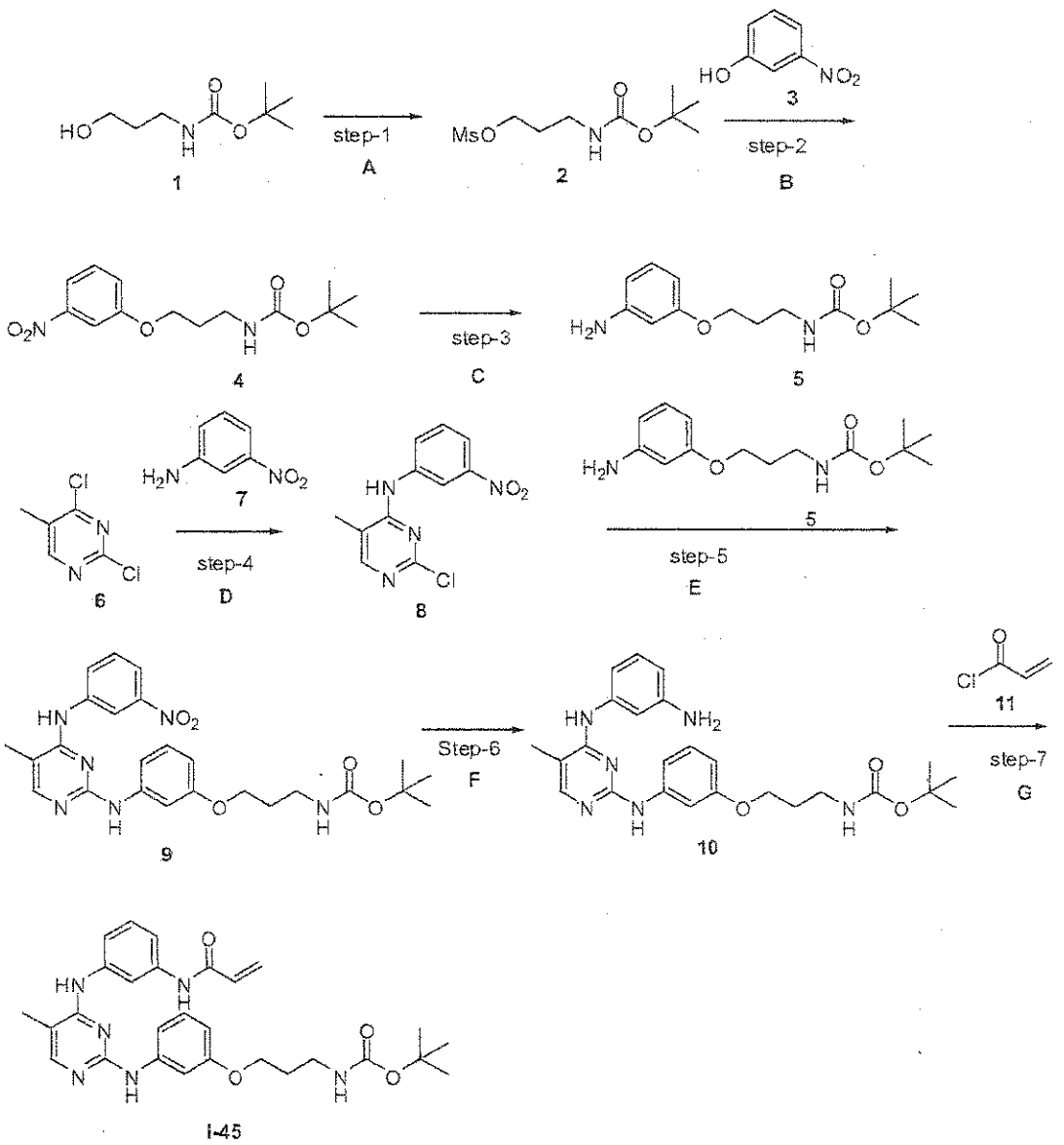
EXAMPLE 62

[00640] Preparation of tert-butyl 3-(3-(4-(3-acrylamidophenylamino)-5-methylpyrimidin-2-ylamino)phenoxy)propylcarbamate **I-45**



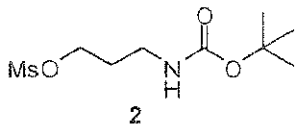
I-45

[00641] The title compound was prepared according to the schemes, steps and intermediates described below.



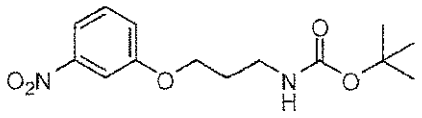
A) **1**, methanesulfonyl chloride, CH_2Cl_2, Et3N, rt, 1 h; B) **3**, K_2CO_3, DMF, 60 °C; C) H_2, Pd/C, EtOH, rt, 16 hr; D) **6**, **7**, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 °C, 16 hr; E) 5, AcOH, EtOH, 90 °C, 16 hr; F) H_2, Pd/C, EtOH, rt, 16 hr; G) **11**, NMP, 0 °C, 15 min

[00642] Step-1



[00643] To a stirring solution of **1** (1.0 g, 5.7 mmol) in dichloromethane (20.0 mL) was added Et_3N (1.15 g, 11.41 mmol) and methanesulfonyl chloride (0.98 g, 8.56 mmol). The reaction mixture was stirred under nitrogen atmosphere at rt for 60 min. It was quenched with water (20 mL) and extracted with EtOAc (2 x 50 mL). The combined EtOAc extract was washed with 10% $NaHCO_3$ soln. (25 mL), water (25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **2** (1.36 g, 94%) as a colorless viscous liquid. It was used in the next step without further purification.

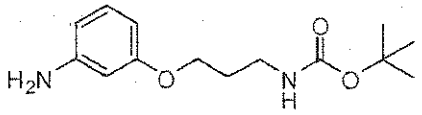
[00644] Step-2



4

[00645] To a stirring solution of **2** (0.749 g, 5.39 mmol) and K_2CO_3 (0.99 g, 7.19 mmol) in dry DMF (20 mL) was added **3** (1.36 g, 5.39 mmol) and the reaction mixture was heated at 60 ^{0}C for 16 h under nitrogen atmosphere. It was cooled, concentrated under reduced pressure and the residue was taken in ethyl acetate (25 mL). The ethyl acetate soln. was washed with water (2x10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **4** (1.2 g, 75%) as a yellowish viscous liquid. It was used in the next step without further purification.

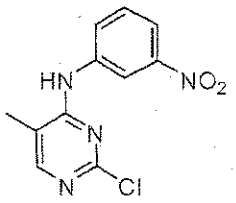
[00646] Step-3



5

[00647] To a solution of **4** (1.20 g, 4.05 mmol) in ethanol (25 mL)) was added Pd/C (0.12 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to get **5** (0.95 g, 88%) as a brownish viscous oil. It was used in the next step without further purification.

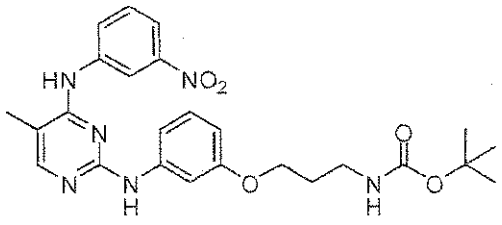
[00648] Step-4



8

[00649] To a solution of **6** (1.69 g, 12.26 mmol), in toluene (50.0 mL) was added **7** (2.0 g, 12.26 mmol), BINAP (0.3 g, 0.49 mmol), cesium carbonate (7.9 g, 24.5 mmol). The solution was degassed (by purging N_2 for 15 min) and to it was added $Pd(OAc)_2$ (0.054 g, 0.25 mmol). The reaction mixture was stirred at 100 ^{0}C for 16 h under nitrogen atmosphere. It was cooled, diluted with ethyl acetate (100 mL) and filtered through Celite®. The filtrate was washed with water (2 x 25 mL), brine (25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, 60-120 mesh, Ethylacetete/hexane: 15/85). The solid obtained after evaporating the required fractions was washed with diethyl ether and dried under high vacuum to get **8** (1.2 g, 37%) as a light yellow solid.

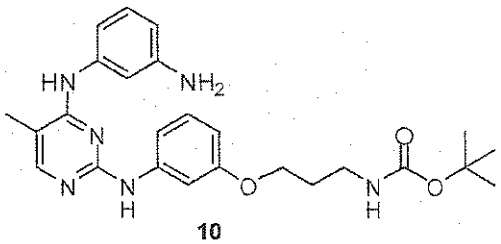
[00650] Step-5



9

[00651] To a solution of **8** (0.5 g, 1.89 mmol) and **5** (0.805 g, 3.0 mmol) in ethanol (10.0 mL) was added glacial acetic acid (0.056 g, 0.95 mmol), and the reaction mixture was stirred in a sealed tube for 16 h at 90 ^{0}C. The reaction mixture was cooled, concentrated under reduced pressure. The residue was quenched with 10% sodium bicarbonate soln. (10.0 mL) and extracted with ethyl acetate (3x15 mL). The combined ethyl acetate extract was washed with water (15 mL), brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get a residue. The crude residue was further purified by column chromatography (SiO_2, EtOAc/Hexane: 50/50) to get **9** (0.57 g, 61%) as a light yellow solid.

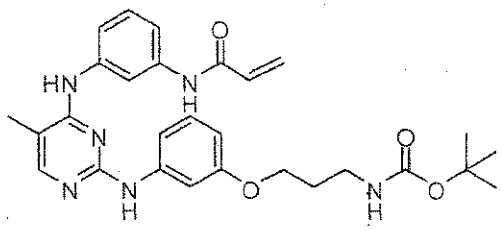
[00652] Step-6



10

[00653] To a solution of **9** (0.56 g, 1.13 mmol) in ethanol (25 mL)) was added 10% Pd/C (0.068 g) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to get **10** (0.45 g, 85%) as a brownish solid. It was used in the next step without further purification.

[00654] Step-7



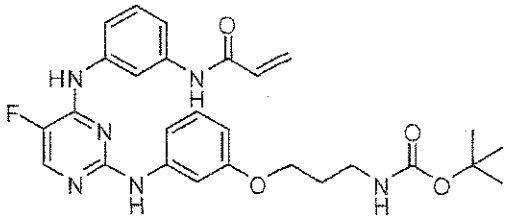
I-45

[00655] To a stirred solution of **10** (0.25 g, 0.5382 mmol) in NMP (2.5 mL) at 0 ^{0}C was added acryloyl chloride (0.073 g, 0.807 mmol) and the reaction mixture was stirred at 0 ^{0}C for 15 min The reaction mixture was added drop wise to a cold, stirring solution of 10% $NaHCO_3$. After complete addition the solution was stirred for another 30 min at 0 ^{0}C, and then filtered through a Buchner funnel to isolate the precipitated solid. The solid was washed with cold water and hexane. It was dissolved in methanol: dichloromethane (50:50, 10 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (50 mL), Et_3N was added to it and it was extracted with ethyl acetate (2 x 100 mL). The combined ethyl acetate extract was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **I-45** (0.100 g, 35.8%) as an off-white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 1.37 (s, 9H), 1.70-1.80 (m, 2H), 2.10 (s, 3H), 3.00-3.06 (m, 2H), 3.79 (t, J = 6.24 Hz, 2H), 5.74 (d, J = 11.92 Hz, 1H), 6.24 (dd, J = 1.84 & 15.16 Hz, 1H), 6.35-6.47 (m, 2H), 6.80-6.90 (bs, 1H), 6.97 (t, J = 8.28 Hz, 1H), 7.23-7.27 (m, 2H), 7.31 (s, 1H), 7.37 (d, J = 8.2 Hz, 1H), 7.46 (d, J = 7.48

Hz, 1H), 7.90-7.90-7.91 (m, 2H), 8.36 (s, 1H), 8.87 (s, 1H), 10.07 (s, 1H); LCMS: *m/e* 519 (M+1).

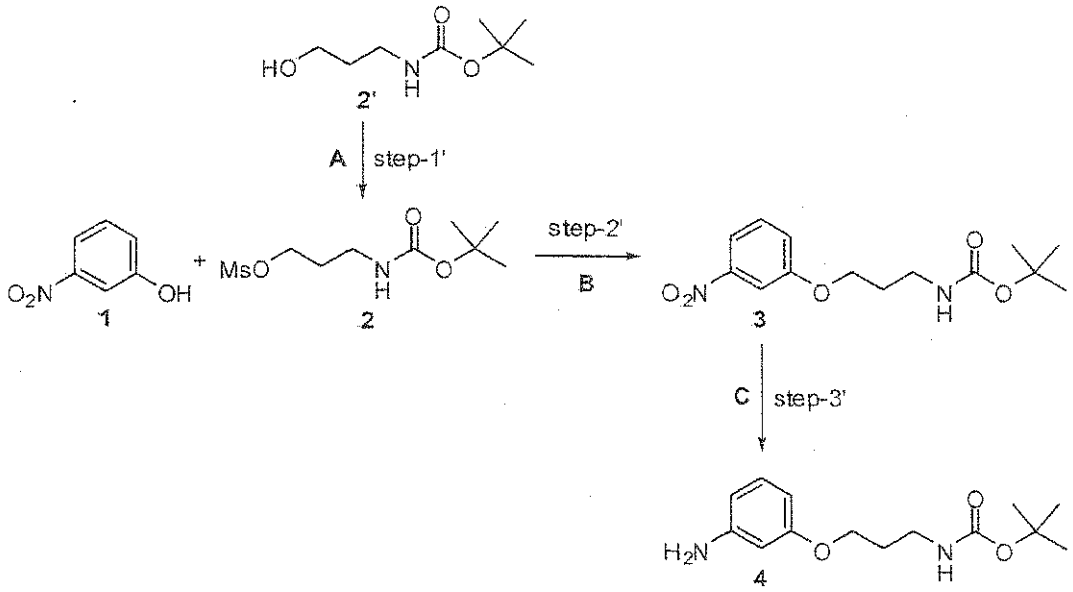
EXAMPLE 63

[00656] Preparation of tert-butyl 3-(3-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)phenoxy)propylcarbamate **I-183**



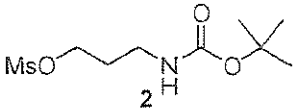
I-183

[00657] The title compound was prepared according to the schemes, steps and intermediates described below.



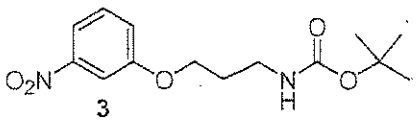
A) methanesulfonyl chloride, CH_2Cl_2, Et_3N, rt, 1 h; B) K_2CO_3, DMF, 60 °C, 16 h; C) Pd-C, H_2, ethanol, rt, 16 h.

[00658] <u>Step 1'</u>



[00659] To a stired solution of **2'** (4.0 g, 22.8 mmol) in dichloromethane (80.0 mL) was added Et_3N (4.6 g, 45.5 mmol) and methanesulfonyl chloride (3.92 g, 34.2 mmol), and the reaction mixture was stirred under nitrogen atmosphere at RT for 60 min. The reaction was quenched with water (50 mL) and extracted with EtOAc (2x100 mL). The combined extracts were washed with 10% $NaHCO_3$ solution (50 mL), water (50 mL), and brine (50 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **2** (5.5 g, 95.2%) as a light yellow viscous liquid. Compound **2** was used in the next step without further purification.

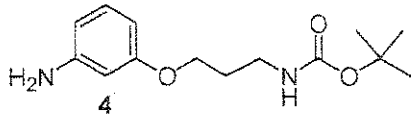
[00660] <u>Step 2'</u>



3

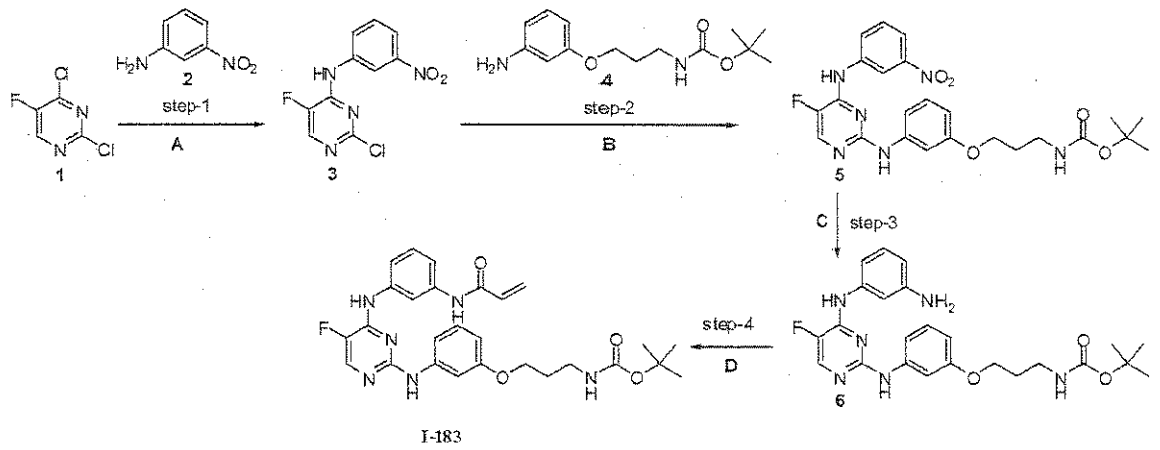
[00661] To a stirred solution of **1** (2.3 g, 16.5 mmol) and K_2CO_3 (4.6 g, 33.3 mmol) in dry DMF (100 mL) was added **2** (5.5 g, 21.7 mmol), and the reaction mixture was heated at 60 °C for 16 h under nitrogen atmosphere. The reaction was cooled, quenched with water (250ml), and extracted with EtOAc (2x100 mL). The combined extracts were washed with 10% $NaHCO_3$ solution(100 mL), water (3x100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give **3** (4.0 g, 81.6%) as a light yellow viscous liquid. Compound **3** was used in the next step without further purification.

[00662] <u>Step 3'</u>

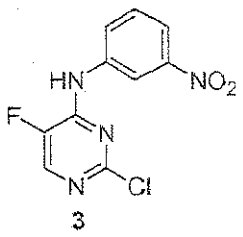


4

[00663] To a solution of **3** (4.0 g, 13.4 mmol) in ethanol (50 mL) was added Pd/C (0.8 g, 10% w/w), and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give **4** (3.3 g, 91.9%) as a brownish viscous oil. Compound **4** was used in the next step without further purification.

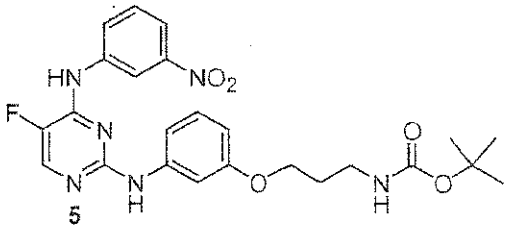


[00664] **Step 1**



[00665] A pressure tube was charged with 2 (10.0 g, 0.072 mol), 1 (24.1 g; 0.145 mol), n-BuOH (100 mL) and DIPEA (13.9 g, 0.108 mol), and the contents were stirred at 120 °C for 2 h. The reaction mixture was cooled, and the precipitated solid was isolated by filtration through a Buchner funnel, washed with cold hexane and dried to give 3 (12.5 g, 64%) as a yellow solid. Compound 3 was used in the next step without further purifications.

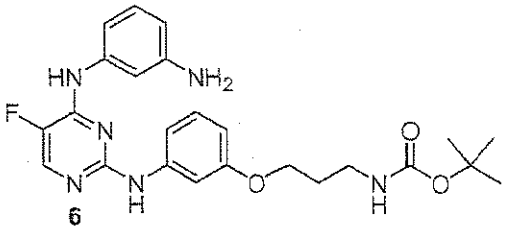
[00666] **Step 2**



[00667] To a solution of 3 (1.5 g, 5.58 mmol) and 4 (1.48 g, 5.58 mmol) in ethanol (30.0 mL) was added glacial acetic acid (0.167 g, 2.79 mmol), and the reaction mixture was stirred in a pressure tube at 90 °C for 48 h. The reaction mixture was cooled and concentrated under reduced

pressure; the residue was quenched with 10% sodium bicarbonate solution (20.0 mL) and extracted with ethyl acetate (2x50 mL). The combined extracts were washed with water (25 mL) and brine (25 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give crude **5**. The crude residue was purified by column chromatography (neutral Al_2O_3, MeOH/Chloroform: 0.5/99.5) to give **5** (1.4 g, 50.3%) as a brown solid.

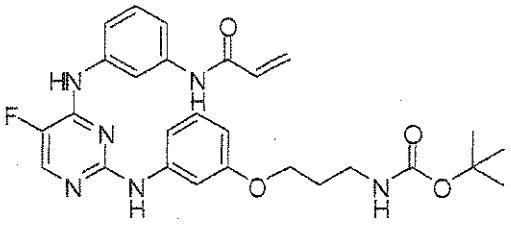
[00668] **Step 3**



6

[00669] To a solution of **5** (1.4 g, 2.8 mmol) in ethanol (50 mL)) was added 10% Pd/C (0.28 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give a residue. The crude residue was further purified by column chromatography (neutral Al_2O_3, MeOH/Chloroform: 0.5/99.5) to give a solid which was washed with dichloromethane/hexane mixtures to give **6** (0.7 g, 53.4%) as a pale brown solid.

[00670] **Step 4**



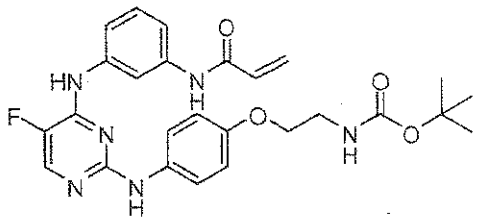
I-183

[00671] **tert-Butyl 3-(3-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)phenoxy)propylcarbamate.** To a stirred solution of **6** (0.25 g, 0.533 mmol) and potassium carbonate (0.138 g, 1.02 mmol) in NMP (2.5 mL) at 0 °C was added acryloyl chloride (0.060 g, 0.665 mmol), and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was added dropwise to a cold, stirring solution of 10% $NaHCO_3$ and stirred at the same temperature (0 °C) for 30 min. A white solid precipitated out and was isolated by filtration through a Buchner funnel. The solid was washed with cold water and hexane and dissolved in mixture of methanol/dichloromethane (50:50, 10 mL) and concentrated under reduced pressure.

The residue obtained was suspended in cold water (25 mL), Et_3N was added, and it was extracted with ethyl acetate (2x50 mL). The combined extracts were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **I-183** (0.255 g, 91.4%) as light yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm: 1.36 (s, 9H), 1.78 (quin, *J* = 6.4 Hz, 2H), 3.01-3.06 (m, 2H), 3.83 (t, *J* = 6.12 Hz, 2H), 5.74 (dd, *J* = 1.4 & 10.04 Hz, 1H), 6.24 (d, *J* = 16.84 Hz, 1H), 6.41-6.48 (m, 2H), 6.88 (s, 1H), 7.03 (t, *J* = 8.24 Hz, 1H), 7.23-7.31 (m, 3H), 7.41 (d, *J* = 8.28 Hz, 1H), 7.56 (d, *J* = 7.96 Hz, 1H), 7.90 (s, 1H), 8.11 (d, *J* = 3.56 Hz, 1H), 9.11 (s, 1H), 9.43 (s, 1H), 10.10 (s, 1H); LCMS : *m/e* 523.1 (M+1).

EXAMPLE 64

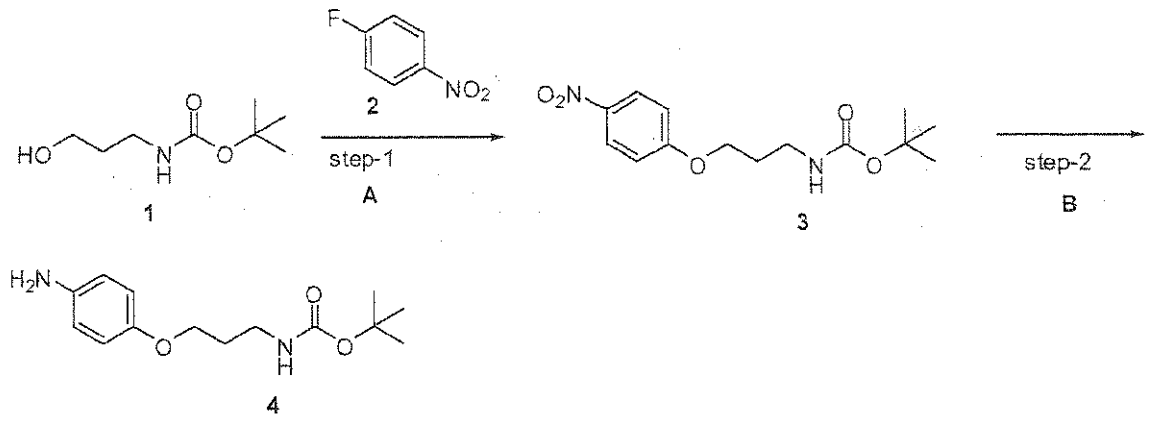
[00672] Preparation of tert-butyl 3-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)phenoxy)propylcarbamate **I-198**



I-198

[00673] The title compound was prepared according to the schemes, steps and intermediates described in Example 63 by using tert-butyl 3-(4aminophenoxy)propylcarbamate in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.37 (s, 9H), 1.78 (quin, *J* = 6.36 Hz, 2H), 3.05 (q, *J* = 6.24 Hz, 2H), 3.86 (t, *J* = 6.2 Hz, 2H), 5.75 (dd, *J* = 1.92 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, J = 10.08 & 16.92 Hz, 1H), 6.72 (d, J = 9 Hz, 2H), 6.89 (t, *J* = 5.4 Hz, 1H), 7.26 (t, *J* = 8.08 Hz, 1H), 7.40 (d, *J* = 8.12 Hz, 1H), 7.48-7.52 (m, 3H), 7.92 (s, 1H), 8.05 (d, *J* = 3.72 Hz,1H), 8.95 (s, 1H), 9.36 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 523.2 (M+1).

[00674] The intermediate tert-butyl 3-(4aminophenoxy)propylcarbamate was prepared by the scheme shown below.



A) NaH, THF, rt, 16 h; B) H_2, Pd/C, EtOH, rt, 16 hr

[00675] Step-1

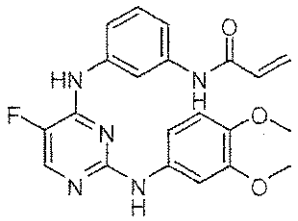
[00676] To a stirring solution of **1** (1.7 g, 9.7 mmol) in dry THF (40 mL) was added NaH (0.72 g, 18.0 mmol, 60% dispersion in paraffin oil) at 0 ^{0}C and the reaction mixture was stirred at rt for 15 min under nitrogen atmosphere. To it was added **2** (2.0 g, 13.87 mmol) and the reaction mixture was stirred at rt for 16 h. It was quenched with cold water (20 mL), and extracted with ethyl acetate (25 mL). The ethyl acetate extract was washed with water (2x10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get an oily liquid which was triturated with hexane to get **3** (2.0g, 69.5%) as a yellow crystalline solid.

[00677] Step-2

[00678] To a solution of **3** (2.0 g, 6.749 mmol) in ethanol (30 mL)) was added 10% Pd/C (0.4 g, 20% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to get **4** (1.6 g, 89.3%) as a pinkish viscous oil. It was used in the next step without further purification.

EXAMPLE 65

[00679] Preparation of 4-(3acrylamidophenylamino)-5-fluoro-2-(3,4-dimethoxyphenylamino)-pyrimidine **I-134**

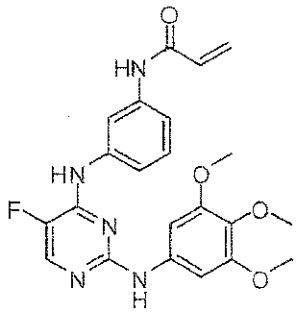


I-134

[00680] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3,4-dimethoxyaniline in place of 4 in Step-2. ^{1}H NMR (200 MHz, CD_3OD) δ 8.50 (s, 1H), 7.80 (d, J = 6.5 Hz, 1H), 7.70-7.66 (m, 2H), 7.20 (m, 1H), 7.0 (m, 2H), 6.41 (m, 2H), 5.92 (dd, J = 8.0, 2.0 Hz, 1H), 3.89 (s, 6H).

EXAMPLE 66

[00681] Preparation of 4-(3-acrylamidophenylamino)-5-fluoro-2-(3,4,5-trimethoxyphenylamino)-pyrimidine **I-133**

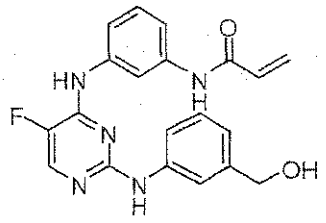


I-133

[00682] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3,4,5-trimethoxyaniline in place of 4 in Step-2. ^{1}H NMR (200 MHz, CD_3OD) δ 8.10 (s, 1H), 8.0 (d, J = 6.0 Hz, 1H), 7.50 (m, 2H), 7.30 (m, 1H), 7.0 (m, 2H), 6.45 (m, 2H), 5.90 (dd, J = 8.0, 2.0 Hz, 1H), 3.90 (s, 3H), 3.89 (s, 9H).

EXAMPLE 67

[00683] Preparation of 4-(3-acrylamidophenylamino)-5-fluoro-2-(3-(hydroxymethyl)phenylamino)-pyrimidine **I-145**

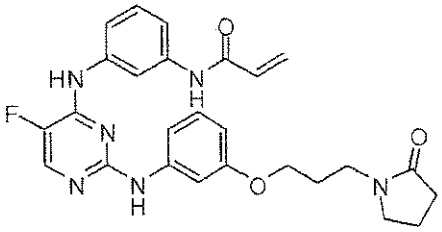


I-145

[00684] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-hydroxymethylaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 4.38 (d, J = 5.6 Hz, 2H), 5.07 (t, J = 5.68 Hz, 1H), 5.75 (d, J = 10.84 Hz, 1H), 6.24 (dd, J = 16.96 Hz, 1H), 6.44 (dt, J = 10.04 & 17.0 Hz, 1H), 6.83 (d, J = 7.4 Hz, 1H), 7.10 (t, J = 7.72 Hz, 1H), 7.28 (t, J = 8.16 Hz, 1H), 7.40 (d, J = 8.08 Hz, 1H), 7.55-7.59 (m, 3H), 7.92 (s, 1H), 8.09 (d, J = 3.6 Hz, 1H), 9.11 (s, 1H), 9.40 (s, 1H), 10.1 (s, 1H); LCMS : *m/e* 378.0 (M+1).

EXAMPLE 68

[00685] Preparation of 4-(3-acrylamidophenylamino)-5-fluoro-2-(3-(3-(2-oxopyrrolidin-1-yl)propoxy)phenylamino)-pyrimidine **I-144**



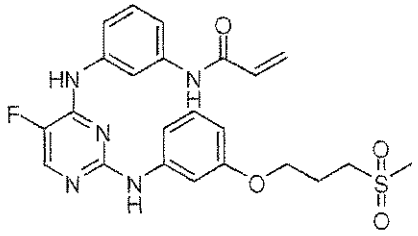
I-144

[00686] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-(2-oxopyrrolidin-1-yl)propoxyaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.8-1.94 (m, 4H), 2.18 (q, J = 8.08 Hz, 2H), 3.26-3.40 (m, 4H), 3.80 (t, J = 6 Hz, 2H), 5.74 (d, J = 10.72 Hz, 1H), 6.24 (d, J = 15.64 Hz, 1H), 6.41-6.80 (m, 2H), 7.04 (t, J = 8.16 Hz, 1H), 7.22-7.29 (m, 2H), 7.33 (s, 1H), 7.42 (d, J = 8.08 Hz, 1H), 7.55 (d, J =

7.52 Hz, 1H), 7.91 (s, 1H), 8.11 (d, J = 3.48 Hz, 1H), 9.13 (s, 1H), 9.43 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 491 (M+1).

EXAMPLE 69

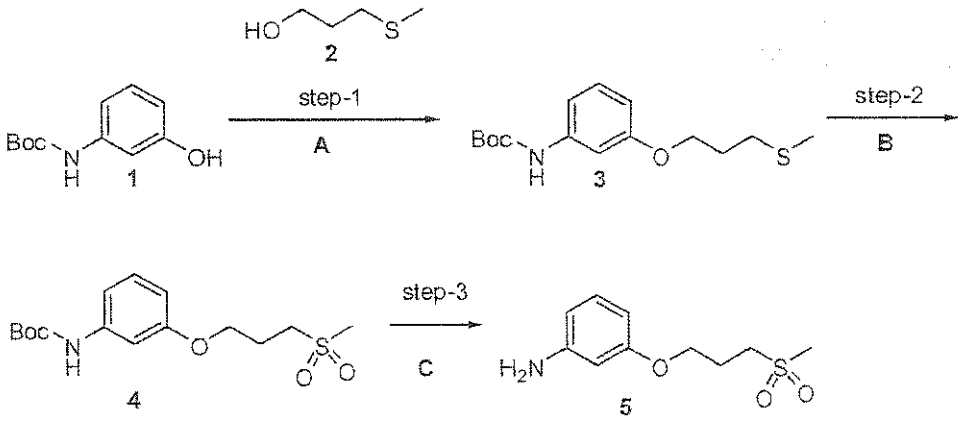
[00687] Preparation of 4-(3-acrylamidophenylamino)-5-fluoro-2-(3-(3-(methylsulfonyl)propoxy)phenylamino)-pyrimidine **I-138**



I-138

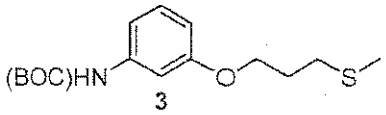
[00688] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-(3-(methylsulfonyl)propoxyaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.05-2.15 (m, 2H), 3.0 (s, 3H), 3.22 (t, J = 7.76 Hz, 2H), 3.93 (t, J = 6.08 Hz, 2H), 5.74 (dd, J = 1.88 & 10 Hz, 1H), 6.25 (dd, J = 1.8 & 16.88 Hz, 1H), 6.44 (dd, J = 10.16 & 16.84 Hz, 2H), 7.05 (t, J = 8.16 Hz, 1H), 7.24-7.30 (m, 2H), 7.35 (s, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8 Hz, 1H), 7.90 (s, 1H), 8.11 (d, J = 3.6 Hz, 1H), 9.14 (s, 1H), 9.43 (s, 1H), 10.10 (s, 1H); LCMS : *m/e* 484 (M+1).

[00689] The intermediate 3-(3-(methylsulfonyl)propoxyaniline was prepared by the scheme shown below.



A) DEAD, Ph_3P, Et_3N, THF, rt, 1 hr; B) MCPBA, CH_2Cl_2, rt, 30 min; C) TFA, CH_2Cl_2, rt, 1 hr

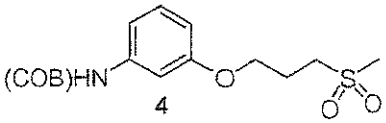
[00690] Step-1



3

[00691] To a stirred solution of **2** (1.1 g, 10.3 mmol) in THF (20 mL) were added **1** (2.18 g, 10.3 mmol), PPh_3 (2.98 g, 11.3 mmol) and Et_3N (1.68 g, 15 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 ^{0}C and to it was added DEAD (1.98 g, 11.3 mmol). The reaction mixture was allowed to come to rt and stirred for 1 h. It was quenched with water, extracted with ethyl aceate (3x25 mL) and the combined EtOAc extract was washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 8/2) to get **3** (2 g 60.6%) as a white solid.

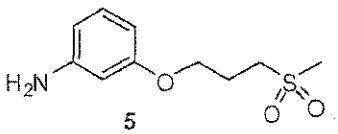
[00692] Step-2



4

[00693] To a stirred solution of **3** (2 g, 6.7 mmol) in CH_2Cl_2 (25 mL) was added m-CPBA (4.13 g, 26.7 mmol) at -10 ^{0}C. The reaction mixture was allowed to come to rt and stirred for 30 min. It was quenched with Na_2CO_3 solution (10 mL), extracted with CH_2Cl_2 (10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol 9/1) to get **4** (1.05 g, 68.8%) as a yellow oil.

[00694] Step-3

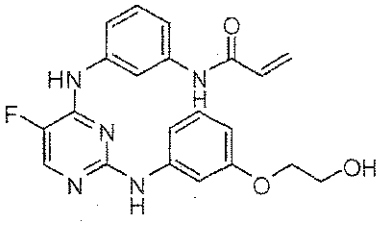


5

[00695] To a stirred solution of 4 (0.75 g, 2.2 mmol) in CH_2Cl_2 (7.5 mL) was added TFA (3 vol.) at 0 ^{0}C. The reaction mixture was allowed to come to rt and stirred further at it for 1 h. It was concentrated under reduced pressure, basified with $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic extract was washed with water (2 mL) and brine solution (2 mL). Drying over Na_2SO_4 followed by filtration and concentration under reduced pressure offered **5** (500 mg, 96%) as brown solid.

EXAMPLE 70

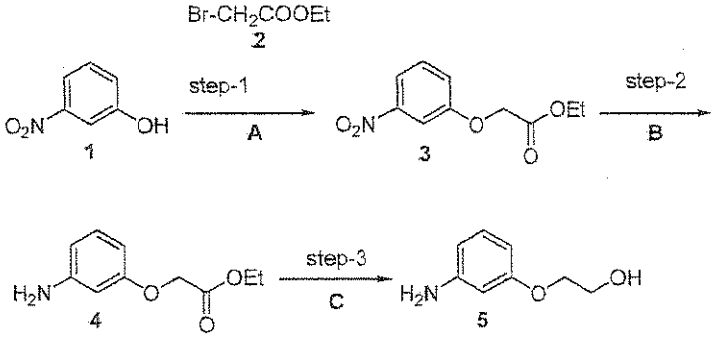
[00696] Preparation of N-(3-(5-fluoro-2-(3-(2-hydroxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-105**



I-105

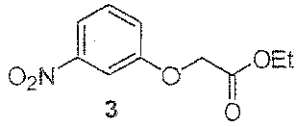
[00697] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-(2-hydroxy)ethoxyaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.67 (dd, J = 4.5 & 10 Hz, 2H), 3.85-3.87 (m, 2H), 4.83 (t, J = 5.6 Hz, 1H), 5.75 (bd, J = 10 Hz, 1H), 6.25 (d, J = 15.6 Hz, 1H), 6.42-6.46 (m, 2H), 7.05 (t, J = 8.4 Hz, 1H), 7.26 (d, J = 8 Hz, 1H), 7.30 (d, J = 8 Hz, 1H), 7.33 (s, 1H), 7.41 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 8.11 (d, J = 3.6 Hz, 1H), 9.11 (s, 1H), 9.42 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 409.9 (M+1).

[00698] The intermediate 3-(2-hydroxy)ethoxyaniline was prepared by the scheme shown below.



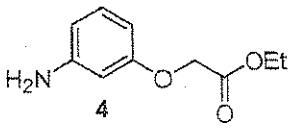
A) K_2CO_3, DMF, 70 ^{0}C, 12 h; **B**) Pd-C, H_2, ethanol, rt, 10 h; C) 1M LAH solution, THF, -15 ^{0}C, 45 min.

[00699] <u>Step-1</u>



[00700] To a stirring solution of **1** (2.0 g, 14.37 mmol) and K_2CO_3 (3.95 g, 28.6 mmol) in dry DMF (15 mL) was added **2** (2.88 g, 17.25 mmol) and the reaction was stirred at rt 70 ^{0}C for 12 h under nitrogen atmosphere. The reaction mixture was cooled, concentrated under reduced pressure and the residue was diluted with ethyl acetate (50 mL). It was washed with water (2x10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **3** (2.5g, 78%) as a light brown liquid. It was used in the next step without further purification.

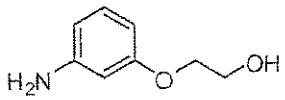
[00701] Step-2



4

[00702] To a solution of **3** (2.0 g, 8.88 mmol) in ethanol (20 mL)) was added Pd/C (0.2 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.0 Kg hydrogen pressure) at rt for 10 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to get **4** (1.6 g, 94%) as a light brown liquid. It was used in the next step without further purification.

[00703] Step-3

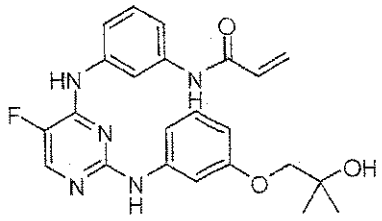


5

[00704] To a stirring solution of **4** (1.2 g, 6.14 mmol) in dry THF (12 mL)) was added lithium aluminum hydride (9.2 mL, 9.20 mmol, 1.0 M soln. in THF) at -15 ^{0}C, under N_2 atmosphere. The reaction mixture was allowed to come to rt and stirred at it for 45 min. The reaction mixture was quenched with saturated ammonium chloride solution and was filtered through a pad of celite® and extracted with EtOAc (2 x 20 mL).The combined organic layer was washed with brine (10 mL) and concentrated under reduced pressure to get **A** (0.9 g, 95%) as a dark brown liquid. It was used in the next step without further purification.

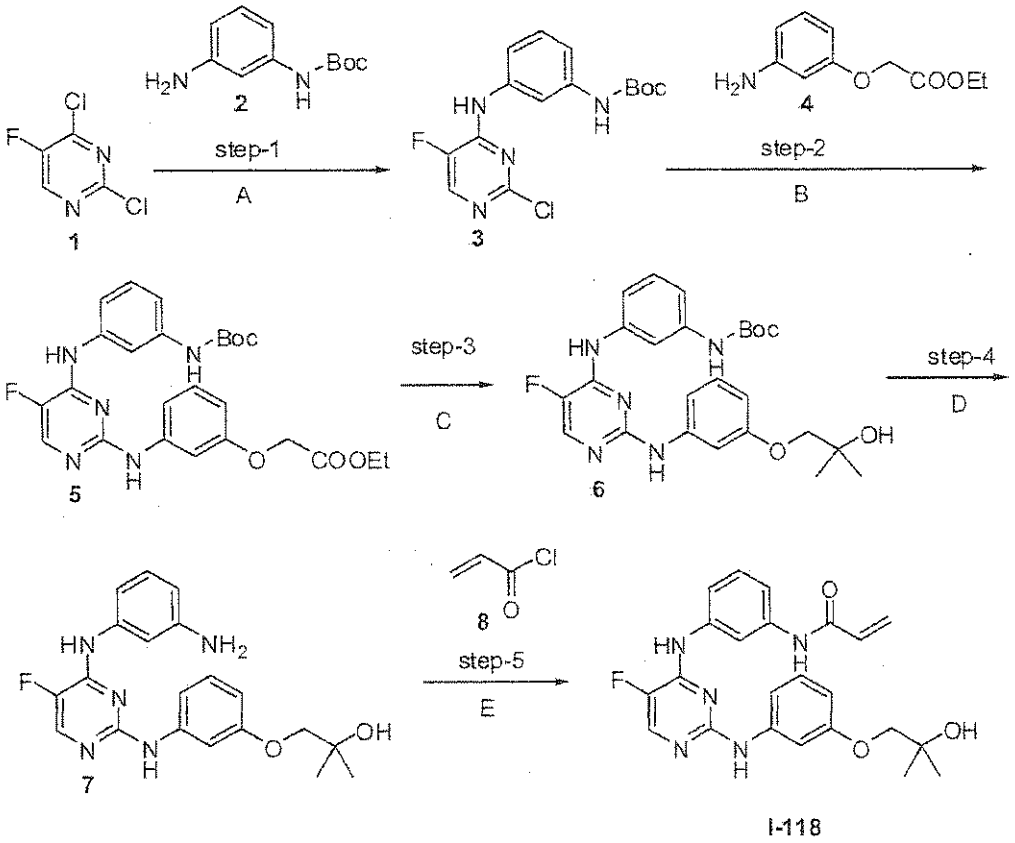
EXAMPLE 71

[00705] Preparation of N-(3-(5-fluoro-2-(3-(2-hydroxy-2-methylpropoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-118



I-118

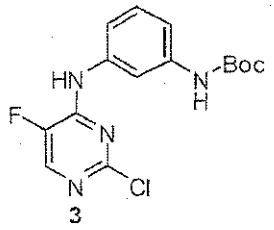
[00706] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 110 ^{0}C, 16 h; B) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 ^{0}C, 16 h; C) MeMgBr (3M solution in ether), THF, -78 ^{0}C, 3 h; D) TFA, CH_2Cl_2, rt, 3 h.

E) K_2CO_3, NMP, rt, 45 min.

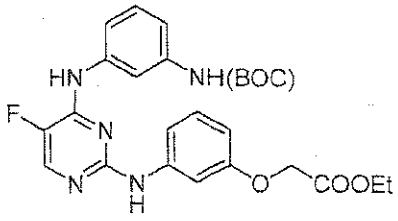
[00707] Step-1



3

[00708] Compound **3** was prepared according to the schemes, steps and intermediates described in Example 20.

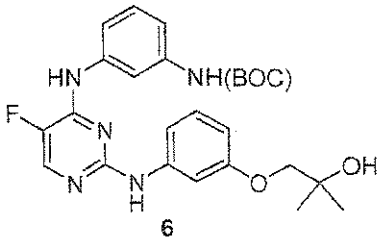
[00709] Step-2



5

[00710] A solution of **4** (0.7 g, 3.5 mmol), **3** (1.45g, 4.3 mmol), $Pd(OAc)_2$ (0.03 g, 0.14 mmol), BINAP (0.13 g, 0..21 mmol) and Cs_2CO_3 (2.8 g, 8.7 mmol) in degassed toluene (30 mL) (toluene was purged with N_2 for 30 min) was heated at 100 ^{0}C for 16 h under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (15 mL) and washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 6/4) to get **5** (700 mg, 40%) as a white solid.

[00711] Step-3

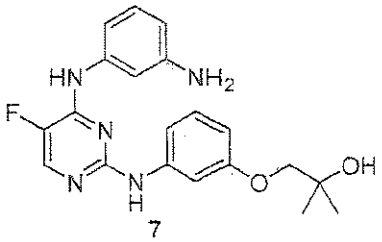


6

[00712] To a stirred solution of **5** (0.4 g, 0.8 mmol) in THF (10 mL) was added Methyl magnesium bromide ((3 M solution in ether, 1.6 mL, 4.8 mmol) at -78 ^{0}C. The reaction mixture was allowed to warm to -30 ^{0}C over 3 h, cooled again to -78 ^{0}C and quenched with saturated

ammonium chloride solution (5 mL). The mixture was filtered through Celite® and filtrate was concentrated under reduced pressure to afford **6** as a pale yellow solid (300 mg, 78%) which was taken for next step without further purification.

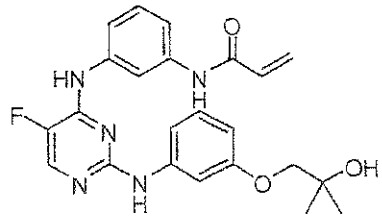
[00713] **Step-4**



7

[00714] To a stirred solution of **6** (0.2 g, 0.4 mmol) in CH_2Cl_2 (7.5 mL) was added TFA (3 vol.) at 0 ^{0}C. The reaction mixture was allowed to come to rt and stirred further at it for 3 h. It was concentrated under reduced pressure, basified with $NaHCO_3$ solution (5 mL) and extracted with CH_2Cl_2 (3x10 mL). The combined organic extract was washed with water (2 mL) and brine solution (2 mL). Drying over Na_2SO_4 followed by filtration and concentration under reduced pressure afforded a residue which was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 6/4) to get 7 (130 mg, 86%) as a white solid.

[00715] **Step-5**



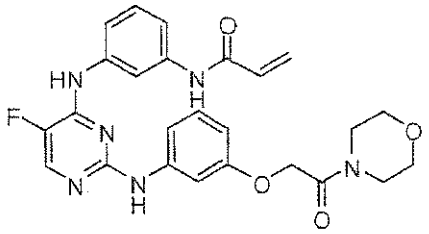
I-118

[00716] To a stirred solution of 7 (0.08 g, 0.2 mmol) and potassium carbonate (0.11 g, 0.8 mmol) in NMP (1 mL) at 0 ^{0}C was added **8** (0.023 g, 0.22 mmol) and the reaction mixture was stirred at 0 ^{0}C for 45 min The reaction mixture was added drop wise to a cold, stirring solution of 10% $NaHCO_3$ and stirred at the same temperature (0 ^{0}C) for 30 min. A solid precipitated out which was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and dissolved in a mixture of methanol/dichloromethane (50:50, 5 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (10 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x5 mL). The combined ethyl

acetate extract was washed with water (2 mL), brine (2 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 5/5) to get **I-118** (35 mg, 38%) as a white solid. ^{1}H NMR (CD_3OD) δ ppm: 1.27 (s, 6H), 3.67 (s, 2H), 5.76 (dd, J = 2.4 & 9.6 Hz, 1H), 6.34 (dd, J = 2 & 16.8 Hz, 1H), 6.42 (dd, J = 9.6 & 16.8 Hz, 1H), 6.54 (td, J = 2 & 7.2 Hz, 1H), 7.07-7.12 (m, 2H), 7.27-7.31 (m, 2H), 7.40 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.92 (d, J = 4 Hz, 1H), 8.07 (d, J = 2 Hz, 1H); LCMS : *m/e* 436.2 (M-1).

EXAMPLE 72

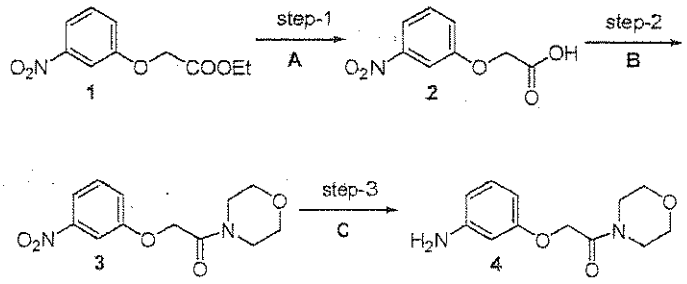
[00717] Preparation of N-(3-(5-fluoro-2-(3-(2-morpholino-2-oxoethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-110**



I-110

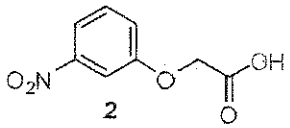
[00718] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 4-[(3-aminophenoxy)acetyl]-morpholine in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.4-3.5 (bm, 4H), 3.5-3.6 (bm, 4H), 4.69 (s, 2H), 5.75 (dd, J = 2 & 10 Hz, 1H), 6.25 (dd, J = 2 & 17.2 Hz, 1H), 6.42-6.49 (m, 2H), 7.05 (t, J = 8 Hz, 1H), 7.29 (t, J = 8 Hz, 3H), 7.41 (d, J = 8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.91 (s, 1H), 8.12 (d, J = 3.6 Hz, 1H), 9.15 (s, 1H), 9.45 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 491.0 (M-2).

[00719] The intermediate 4-[(3-aminophenoxy)acetyl]-morpholine was prepared by the scheme shown below.



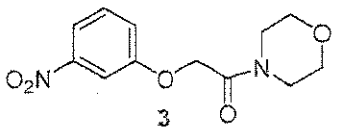
A) LiOH, THF, MeOH, H_2O, rt, 4 h; **B**) $SOCl_2$, 85 ^{0}C, morpholine, 0 ^{0}C, 30 min; C) Pd-C, H_2, ethyl acetate, rt, 2 h.

[00720] **Step-1**



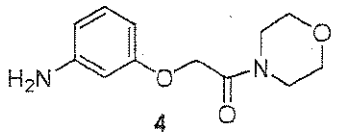
[00721] To a stirred solution of **1** (1.0 g, 4.44 mmol) in methanol/THF/water : 5 mL/ 5 mL/5 mL was added LiOH monohydrate (0.75 g, 17.76 mmol) and the reaction mixture was stirred at rt for 4 h. It was concentrated under reduced pressure, the residue was diluted with water (10 mL), acidified with 1.0 N HCl (PH ~5-6) and extracted with ether (2x20 mL). The combined ether extract was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **2** (0.8 g, 91.43%) as an off-white solid.

[00722] **Step-2**



[00723] Thionyl chloride (2.0 ml, 27.56 mmol) was added to **2** (0.2 g, 1.014 mmol) under nitrogen atmosphere. A drop of N,N Dimethylformamide was added to the mixture and the contents were stirred at 85 ^{0}C for 2 h. After cooling to rt thionyl chloride was removed by concentration under reduced pressure. The residue was cooled to 0 ^{0}C, morpholine (0.5 g, 5.74 mmol) was added to it in small portions and the reaction mixture was stirred at 0 ^{0}C for 30 min. The reaction mixture was allowed to come to rt and stirred at it for 30 min, cooled and quenched with water (10 mL). The contents were extracted with ether (2x10 mL) and the combined ether extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **3** (0.180 g, 66.67%) as a yellow solid.

[00724] Step-3

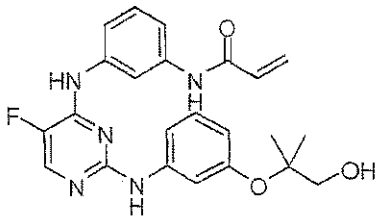


4

[00725] To a solution of **3** (0.180 g, 0.676 mmol) in ethyl acetate (10 mL)) was added Pd/C (0.036 g, 20% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.0 Kg hydrogen pressure) at rt for 2 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to get **A** (0.14 g, 87.67%) as an off-white solid. It was used in the next step without further purifications.

EXAMPLE 73

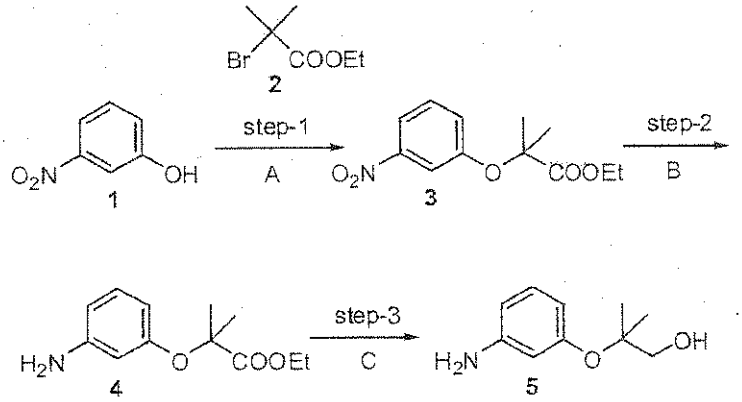
[00726] Preparation of N-(3-(5-fluoro-2-(3-(1-hydroxy-2-methylpropan-2-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-91**



I-91

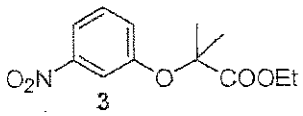
[00727] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-(1-hydroxy-2-methylpropan-2-yloxy)aniline in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.16 (s, 6H), 3.32-3.35 (m, 2H), 4.81 (t, *J* = 5.74 Hz, 1H), 5.74 (dd, *J* = 1.84 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.88 & 16.96 Hz, 1H), 6.44 (dd, *J* = 10.12 & 16.96 Hz, 1H), 6.50 (dd, *J* = 2.12 & 7.96 Hz, 1H), 7.02 (t, *J* = 8.12 Hz, 1H), 7.26-7.30 (m, 2H), 7.41 (d, *J* = 8.16 Hz, 1H), 7.48 (d, *J* = 8.24 Hz, 1H), 7.57 (d, *J* = 8.12 Hz, 1H), 7.92 (s, 1H), 8.09 (d, *J* = 3.6 Hz, 1H), 9.07 (s, 1H), 9.41 (s, 1H), 10.09 (s, 1H); LCMS : *m/e* 438.0 (M+1).

[00728] The intermediate 3-(1-hydroxy-2-methylpropan-2-yloxy)aniline was prepared by the scheme shown below.



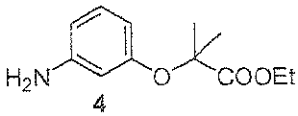
A) K_2CO_3, DMF, 16 h, rt; B) Pd/C, ethanol, 5 h, rt; C) LAH (1M in THF solution), 0 ^{0}C to rt, 2 h.

[00729] **Step-1**



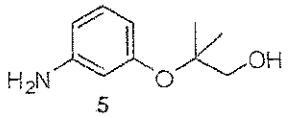
[00730] To a solution of **1** (0.5 g 3.59 mmol) and **2** (0.84 g 4.316 mmol) in DMF was added K_2CO_3 (0.99 g, 7.194 mmol). After stirring at rt for 16 h, reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (10 mL) and washed with 10% NaOH solution (5 mL), water (5 mL) and brine solution (5 mL). Drying over Na_2SO_4, followed by concentration under reduced pressure gave **3** as red brown liquid (0.5 g, 52%).

[00731] **Step-2**



[00732] To a stirred solution of **3** (0.45 g, 1.77 mmol) in ethanol (5 mL) was added Pd/C (45 mg) and the reaction mixture was hydrogenated (bladder pressure, ~1.5 Kg) for 5 h. The reaction mixture was passed through a celite® bed and concentrated under vacuum to get **4** (0.35 g, 88%) as a colorless liquid.

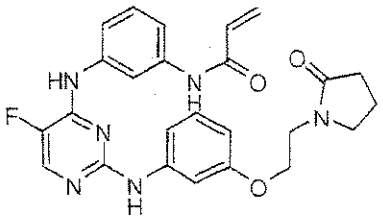
[00733] **Step-3**



[00734] To a stirred solution of 4 (0.25 g, 1.15 mmol) in THF (5 mL) under N_2 was added LAH (3.45 mL, 3.35 mmol, 1M solution in THF,) at 0 ^{0}C. The reaction mixture was allowed to come to rt and stirred at it for 2 h. It was carefully quenched with saturated Na_2SO_4 solution (2 mL), filtered and concentrated. The residue was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 6/4) to give **5** as a light brown liquid (0.15 g, 71%).

EXAMPLE 74

[00735] Preparation of N-(3-(5-fluoro-2-(3-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-164**

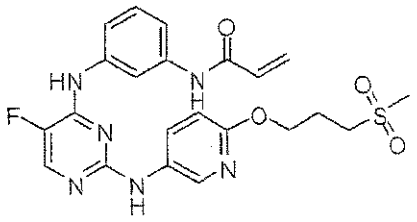


I-164

[00736] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-(2-(2-oxopyrrolidin-1-yl)ethoxy)aniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.89 (quin, J = 7.6 Hz, 2H), 2.21 (t, J = 8 Hz, 2H), 3.40 (t, J = 6.8 Hz, 2H), 3.50 (t, J = 5.6 Hz, 2H), 3.93 (t, J = 5.2 Hz, 2H), 5.75 (dd, J = 2 & 10 Hz, 1H), 6.25 (dd, J = 2 & 16.84 Hz, 1H), 6.42-6.49 (m, 2H), 7.05 (t, J = 8.4 Hz, 1H), 7.28 (t, J = 8 Hz, 2H), 7.33 (s, 1H), 7.43 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 8.12 (d, J = 3.6 Hz, 1H), 9.15 (s, 1H), 9.45 (s, 1H), 10.13 (s, 1H); LCMS : *m/e* 475 (M-2).

EXAMPLE 75

[00737] Preparation of N-(3-(5-fluoro-2-(6-(3-(methylsulfonyl)propoxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-80**

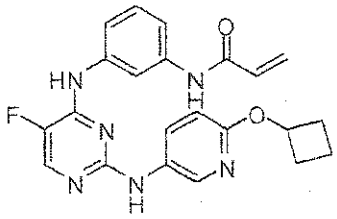


I-80

[00738] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-(3-(methylsulfonyl)propoxy)pyridine in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.05-2.20 (m, 2H), 3.00 (s, 3H), 3.24 (t, *J* = 7.46 Hz, 2H), 4.27 (t, *J* = 6.32 Hz, 2H), 5.75 (dd, *J* = 1.76 & 10 Hz, 1H), 6.25 (dd, *J* = 1.8 & 16.96 Hz, 1H), 6.45 (dd, *J* = 10.04 & 16.92 Hz, 1H), 6.65 (d, *J* = 8.88 Hz, 1H), 7.27 (t, *J* = 8.08 Hz, 1H), 7.39 (d, *J* = 8.08 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 7.92 (s, 1H), 7.99 (dd, *J* = 2.6 & 8.76 Hz, 1H), 8.07 (d, *J* = 3.64 Hz, 1H), 8.31 (d, *J* = 2.28 Hz, 1H), 9.10 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 486.9 (M+1).

EXAMPLE 76

[00739] Preparation of N-(3-(2-(6-cyclobutoxypyridin-3-ylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-79**

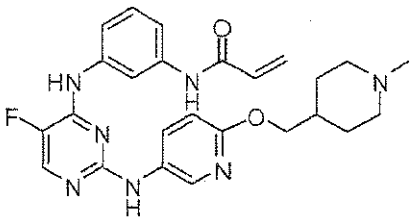


I-79

[00740] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-cyclobutoxypyridine in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.57-1.66 (m, 1H), 1.71-1.78 (m, 1H), 1.94-2.04 (m, 2H), 2.32-2.38 (m, 2H), 4.95-5.05 (m, 1H), 5.73-5.76 (m, 1H), 6.25 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.92 Hz, 1H), 6.58 (d, *J* = 8.84 Hz, 1H), 7.25 (t, *J* = 8.04 Hz, 1H), 7.39 (d, *J* = 7.84 Hz, 1H), 7.45-7.55 (m, 1H), 7.90 (s, 1H), 7.94 (dd, *J* = 2.72 & 8.88 Hz, 1H), 8.06 (d, *J* = 3.68 Hz, 1H), 8.27 (d, *J* = 2.6 Hz, 1H), 9.04 (s, 1H), 9.41 (s, 1H), 10.1 (s, 1H); LCMS : *m/e* 421.2 (M+1).

EXAMPLE 77

[00741] Preparation of N-(3-(5-fluoro-2-(6-((1-methylpiperidin-4-yl)methoxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-78**

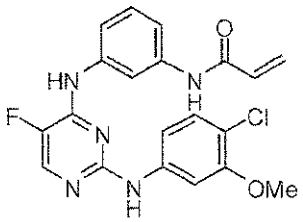


I-78

[00742] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-(1-methylpiperidin-4-yl)methoxypyridine in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.23-1.27 (m, 3H), 1.65-1.69 (m, 2H), 1.83 (t, *J* = 11.72 Hz, 2H), 2.14 (s, 3H), 2.75 (d, *J* = 11.24 Hz, 2H), 4.0 (d, *J* = 6.2 Hz, 2H), 5.74 (dd, *J* = 2 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.96 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.92 Hz, 1H), 6.62 (d, *J* = 8.88 Hz, 1H), 7.27 (t, *J* = 8.08 Hz, 1H), 7.40 (d, *J* = 8.88 Hz, 1H), 7.47 (d, *J* = 7.6 Hz, 1H), 7.92 (s, 1H), 7.97 (dd, *J* = 2.76 & 8.92 Hz, 1H), 8.07 (d, *J* = 3.72 Hz, 1H), 8.28 (d, *J* = 2.64 Hz, 1H), 9.07 (s, 1H), 9.41 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 478.0 (M+1).

EXAMPLE 77

[00743] Preparation of N-(3-(5-fluoro-2-(4-chloro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-74**



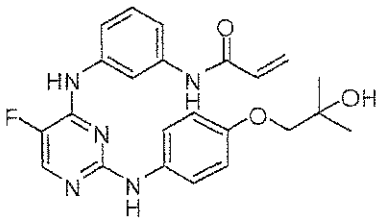
I-74

[00744] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 4-chloro-3-methoxyaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.64 (s, 3H), 5.74 (dd, *J* = 2.12 & 9.96 Hz, 1H), 6.24 (dd, *J* = 1.84 & 17 Hz, 1H), 6.44 (dd, *J* = 10 & 16.84 Hz, 1H), 7.13 (s, 1H), 7.28 (t, *J* = 8.08 Hz, 1H), 7.36 (dd, *J* = 2.12

& 8.68 Hz, 1H), 7.40 (d, J = 7.64 Hz, 1H), 7.45 (d, J = 2.04 Hz, 1H), 7.50 (d, J = 8.12 Hz, 1H), 7.91 (s, 1H), 8.13 (d, J = 3.52 Hz, 1H), 9.28 (s, 1H), 9.48 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 414.0 (M+1).

EXAMPLE 78

[00745] Preparation of N-(3-(5-fluoro-2-(4-(2-hydroxy-2-methylpropoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-73**

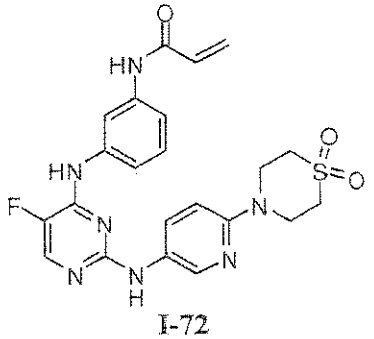


I-73

[00746] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 4-(2-hydroxy-2-methylpropoxy)aniline in place of 4 in Step-2. ^{1}H NMR (MeOD) δ ppm: 1.33 (s, 6H), 3.75 (s, 2H), 5.80 (dd, J = 3.28 & 10.64 Hz, 1H), 6.39 (dd, J = 2.24 & 16.96 Hz, 1H), 6.47 (dd, J = 9.6 & 16.96 Hz, 1H), 6.84 (td, J = 3.48 & 9.0 Hz, 2H), 7.30 (t, J = 7.72 Hz, 1H), 7.41-7.50 (m, 4H), 7.89 (d, J = 3.88 Hz, 1H), 8.09 (s, 1H); LCMS : *m/e* 438 (M+1).

EXAMPLE 79

[00747] Preparation of N-(3-(5-fluoro-2-(6-(1,1-dioxidothiomorpholin-4-yl) pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-72**



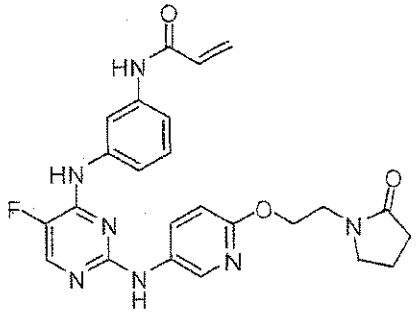
I-72

[00748] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-(1,1-dioxidothiomorpholin-4-yl) pyridine in place

of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.00-3.15 (bm, 4H), 3.90-4.10 (bm, 4H), 5.76 (dd, *J* = 1.64 & 10.04 Hz, 1H), 6.26 (dd, *J* = 1.72 & 16.92 Hz, 1H), 6.46 (dd, *J* = 10.04 & 16.88 Hz, 1H), 6.87 (d, *J* = 9.04 Hz, 1H), 7.20 (t, *J* = 8.04 Hz, 1H), 7.39 (d, *J* = 8.24 Hz, 1H), 7.50 (d, *J* = 7.68 Hz, 1H), 7.90-7.93 (m, 2H), 8.06 (d, *J* = 3.6 Hz, 1H), 8.35 (d, *J* = 2.4 Hz, 1H), 9.0 (s, 1H), 9.40 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 484 (M+1).

EXAMPLE 80

[00749] Preparation of N-(3-(5-fluoro-2-(6-(2-(2-oxopyrrolidin-1-yl)ethoxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-70**

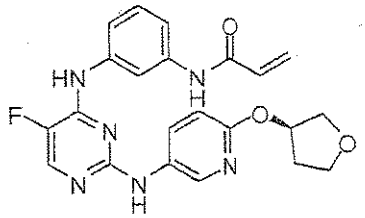


I-70

[00750] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-(2-(2-oxopyrrolidin-1-yl)ethoxy)pyridine in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.90 (quintet, *J* = 7.6 Hz, 2H), 2.19 (t, *J* = 8.04 Hz, 2H), 3.41 (t, *J* = 6.88 Hz, 2H), 3.50 (t, *J* = 5.36 Hz, 2H), 4.27 (t, *J* = 5.48 Hz, 2H), 5.75 (d, *J* = 10.92 Hz, 1H), 6.25 (d, *J* = 17.04 Hz, 1H), 6.45 (dd, *J* = 10.12 & 16.84 Hz, 1H), 6.63 (d, *J* = 8.96 Hz, 1H), 7.27 (t, *J* = 8.04 Hz, 1H), 7.39 (d, *J* = 7.56 Hz, 1H), 7.47 (d, *J* = 7.32 Hz, 1H), 7.92 (s, 1H), 7.98 (dd, *J* = 2.36 & 8.84 Hz, 1H), 8.08 (d, *J* = 3.3 Hz, 1H), 8.31 (d, *J* = 2.24 Hz, 1H), 9.10 (s, 1H), 9.44 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 478.0 (M+1).

EXAMPLE 81

[00751] Preparation of (R)-N-(3-(5-fluoro-2-(6-(tetrahydrofuran-3-yloxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-69**

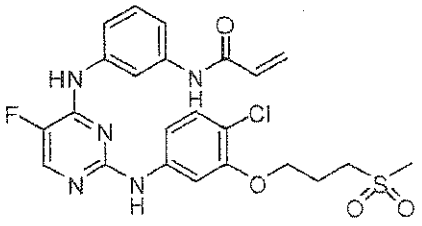


I-69

[00752] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using (R)-3-amino-6-(tetrahydrofuran-3-yloxy)pyridine in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.91-1.99 (m, 1H), 2.14-2.23 (m, 1H), 3.70-3.77 (m, 2H), 3.81 (dd, *J* = 7.90 & 15.48 Hz, 1H), 3.88 (dd, *J* = 4.76 & 10.16 Hz, 1H), 5.38 (t, *J* = 4.68 Hz, 1H), 5.75 (dd, *J* = 1.72 & 10.08 Hz, 1H), 6.24 (d, *J* = 16.92 Hz, 1H), 6.45 (dd, *J* = 10.16 & 16.88 Hz, 1H), 6.63 (d, *J* = 8.84 Hz, 1H), 7.26 (d, *J* = 7.64 Hz, 1H), 7.39 (d, J= 7.92 Hz, 1H), 7.46 (d, *J* = 7.64 Hz, 1H), 7.92 (s, 1H), 7.97 (dd, *J* = 2.6 & 8.83 Hz, 1H), 8.07 (d, *J* = 3.6 Hz, 1H), 8.32 (d, *J* = 2.48 Hz, 1H), 9.08 (s, 1H), 9.42 (s, 1H), 10.10 (s, 1H); LCMS : *m/e* 437.2 (M+1).

EXAMPLE 82

[00753] Preparation of N-(3-(2-(4-chloro-3-(3-(methylsulfonyl)propoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-55**



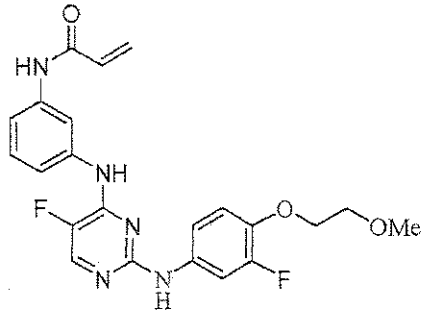
I-55

[00754] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 4-chloro-3-(3-(methylsulfonyl)propoxy)aniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.07-2.14 (m, 2H), 3.0 (s, 3H), 3.22 (t, *J* = 7.72 Hz, 2H), 3.90 (t, *J* = 6.08 Hz, 2H), 5.75 (dd, *J* = 1.88 & 10.08 Hz, 1H), 6.24 (dd, *J* = 1.84 & 16.92 Hz,

1H), 6.44 (dd, J = 10.12 & 16.96 Hz, 1H), 7.15 (d, J = 8.72 Hz, 1H), 7.30 (t, J = 8.08 Hz, 1H), 7.35 (dd, J = 2.2 & 8.8 Hz, 1H), 7.43 (d, J = 8 Hz, 1H), 7.45-7.55 (m, 2H), 7.91 (s, 1H), 8.14 (d, J = 3.56 Hz, 1H), 9.31 (s, 1H), 9.49 (s, 1H), 10.14 (s, 1H); LCMS : *m/e* 520.0 (M+1).

EXAMPLE 83

[00755] Preparation of N-(3-(2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-96**

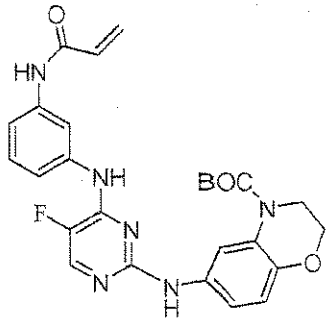


I-96

[00756] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in Step-2. ^{1}H NMR (DMSO, 400 MHz) δ 10.13 (s, 1H), 9.43 (s, 1H), 9.18 (s, 1H), 8.09 (d, 1H, J = 3.68 Hz), 7.92 (s, 1H), 7.65 (dd, 1H, J = 2.3, 14.2 Hz), 7.47 (d, 1H, J = 8.24 Hz), 7.41 (d, 1H, J = 8.28 Hz), 7.27 (t, 2H, J = 8.0 Hz), 6.94 (t, 1H, J = 9.4 Hz), 6.44 (dd, 1H, J = 16.96, 10.1 Hz), 6.23 (dd, 1H, J =1.84, 16.96 Hz), 5.73 (dd, 1H, J=1.4, 10.1 Hz), 4.04 (m, 2H), 3.61 (m, 2H), 3.29 (s, 3H). MS m/z: 442.0 ($M+H^+$).

EXAMPLE 84

[00757] Preparation of N-(3-(2-(4-tert-butoxycarbonyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide I-175

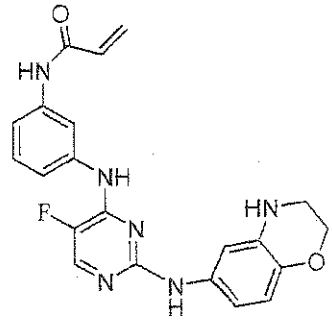


I-175

[00758] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 6-amino-4-tert-butoxycarbonyl-2,3-dihydrobenzo[1,4]oxaxine in place of 4 in Step-2. MS m/z: 507.1 ($M+H^+$).

EXAMPLE 85

[00759] Preparation of N-(3-(2-(4-tert-butoxycarbonyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide I-174

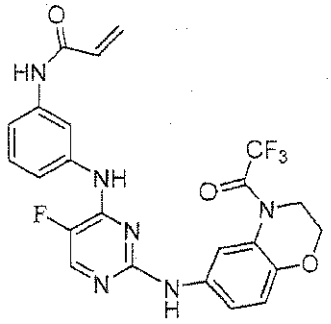


I-174

[00760] The title compound was prepared by treating the product of Example 84 with 4N HCl in dioxane at rt for 1 hr followed by removal of solvents in vacuo. MS m/z: 407.1 ($M+H^+$).

EXAMPLE 86

[00761] Preparation of N-(3-(2-(4-trifluoroacetyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-143**

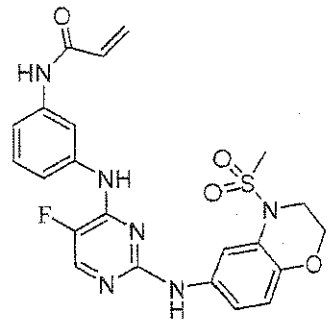


I-143

[00762] The title compound was prepared by treating the product of Example 85 with trifluoroacetic anhydride at rt for 1 hr followed by removal of solvents in vacuo. MS m/z: 503.1 ($M+H^+$).

EXAMPLE 87

[00763] Preparation of N-(3-(2-(4-methylsulfonyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-140**

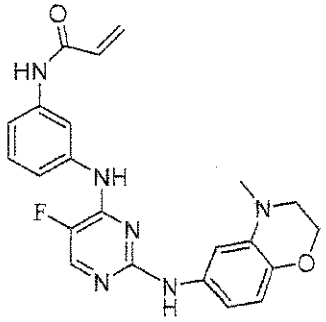


I-140

[00764] The title compound was prepared by treating the product of Example 85 with mesyl chloride Et_3N in CH_2Cl_2 at 0 °C for 30 min, followed by washing with aqueous $NaHCO_3$, drying over Na_2SO_4 and removal of solvents in vacuo. MS m/z: 485.1 ($M+H^+$).

EXAMPLE 88

[00765] Preparation of N-(3-(2-(4-methyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-126**

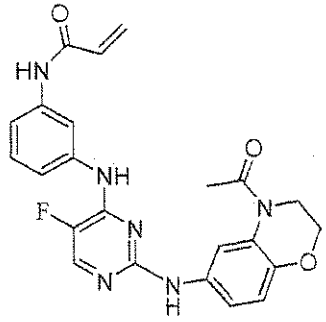


I-126

[00766] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 6-amino-4-methyl-2,3-dihydrobenzo[1,4]oxazine in place of **4** in Step-2. MS m/z: 421.1 ($M+H^+$).

EXAMPLE 89

[00767] Preparation of N-(3-(2-(4-acetyl-2,3-dihydrobenzo[1,4]oxazin-6-yl)amino-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-112**

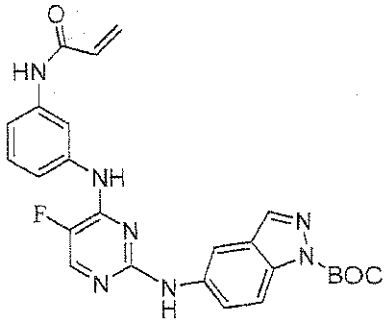


I-112

[00768] The title compound was prepared by treating the product of Example 85 with acetic anhydride and pyridine in CH_2Cl_2 at rt for 1 hr, followed by washing with 1N HCl, then with aqueous $NaHCO_3$, drying over Na_2SO_4 and removal of solvents in vacuo. MS m/z: 449.1 ($M+H^+$).

EXAMPLE 90

[00769] Preparation of N-(3-(2-(1-tert-butoxycarbonyl-1H-indazol-5-yl)amino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-151**

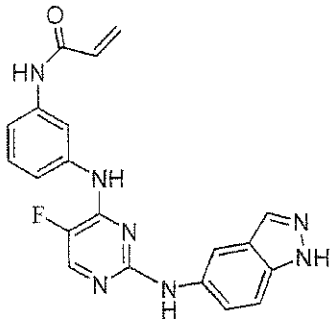


I-151

[00770] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 5-amino-N-(tert-butoxycarbonyl)-1H-indazole in place of **4** in Step-2. MS m/z: 490.2 ($M+H^+$).

EXAMPLE 91

[00771] Preparation of N-(3-(2-(1H-indazol-5-yl)amino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-156**

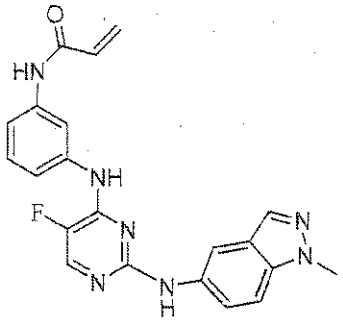


I-156

[00772] The title compound was prepared by treating the product of Example 90 with 4N HCl in dioxane at rt for 1 hr followed by removal of solvents in vacuo. MS m/z: 390.1 ($M+H^+$).

EXAMPLE 92

[00773] Preparation of N-(3-(2-(1-methyl-1H-indazol-5-yl)amino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-155**

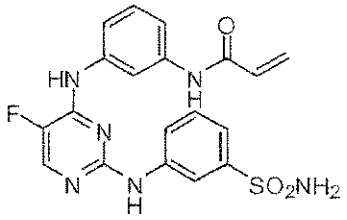


I-155

[00774] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 5-amino-1-methyl-1H-indazole in place of 4 in Step-2. MS m/z: 404.2 ($M+H^+$).

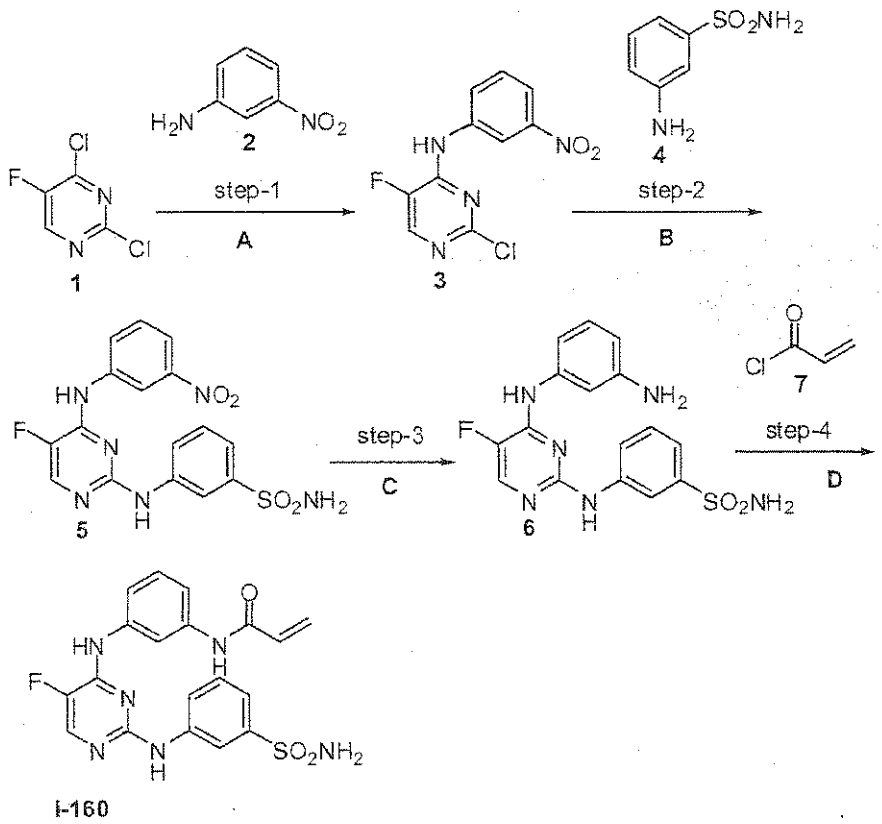
EXAMPLE 93

[00775] Preparation of N-(3-(5-fluoro-2-(3-sulfamoylphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-160**



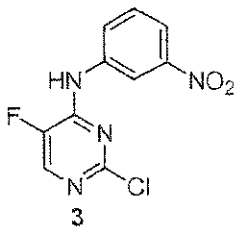
I-160

[00776] The title compound was prepared according to the schemes, steps and intermediates described below.



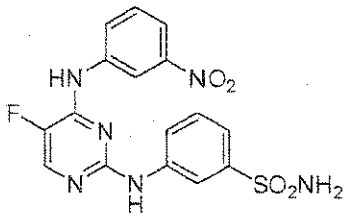
A) DIPEA, n-butanol, 120 ^{0}C, 2 h, pressure tube; **B**) AcOH, ethanol, 90 ^{0}C, 16 h; **C**) Pd-C, H_2, ethanol, rt, 3 h; **D**) acryloyl chloride, K_2CO_3, NMP, 0 ^{0}C, 60 min.

[00777] Step-1



[00778] A pressure tube was charged with **2** (10.0 g, 0.072 mol), **1** (24.1 g, 0.145 mol), n-BuOH (100 mL) and DIPEA (13.9 g, 0.108 mol) and the contents were stirred at 120 ^{0}C for 2 h. The reaction mixture was cooled, the precipitated solid was isolated by filtration through a Buchner funnel, washed with cold hexane and dried to get **3** (12.5 g, 64%) as a yellow solid. It was used in the next step without further purification.

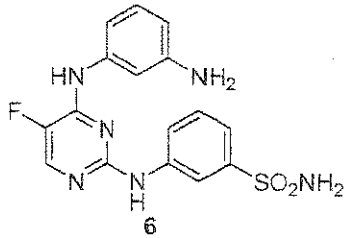
[00779] Step-2



5

[00780] To a solution of 3 (0.25 g, 0.93 mmol) and 4 (0.16 g, 0.93 mmol) in ethanol (2.5 mL) was added glacial acetic acid (0.083 g, 1.39 mmol), and the reaction mixture was stirred in a pressure tube at 90 ^{0}C for 16 h. It was cooled, the precipitated solid was isolated by filtration through a Buchner funnel, washed with cold ether and dried to get 5 (0.245 g, 65%) as brown solid. It was used in the next step without further purification.

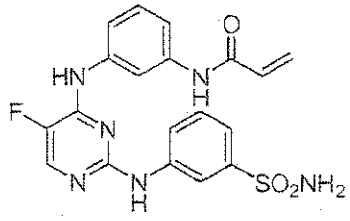
[00781] Step-3



6

[00782] To a solution of 5 (0.1 g, 0.24 mmol in methanol (4 mL)) was added 10% Pd/C (0.2 g, 20% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 3 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to get 6 (0.076 g, 82%) as a brown solid. It was used in the next step without further purification.

[00783] Step-4



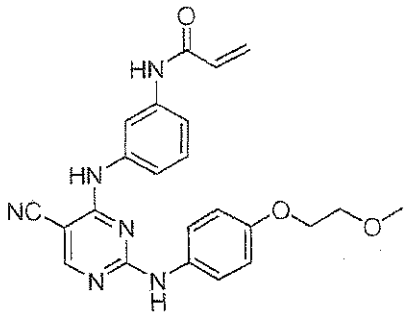
I-160

[00784] To a stirred solution of 6 (0.07 g, 0.18 mmol) and potassium carbonate (0.051 g, 0.37 mmol) in NMP (0.7 mL) at 0 ^{0}C was added acryloyl chloride (0.021 g, 0.23 mmol) and the

reaction mixture was stirred at 0 ^{0}C for 60 min The reaction mixture was added drop wise to a cold, stirring solution of 10% $NaHCO_3$ and kept at the same temperature (0 ^{0}C) for 30 min. A solid precipitated out which was isolated by filtration through a Buchner funnel. The solid was washed with cold water and hexane and dissolved in mixture of methanol/dichloromethane (50:50, 5 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (10 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x10 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure get a residue. The crude residue was further purified by column chromatography (neutral Al_2O_3, MeOH/chloroform: 3/97) to get **I-160** (0.028 g, 35%) as light brown solid. ^{1}H NMR (DMSO-d_6) δ ppm: 5.75 (dd, J = 1.68 & 10.24 Hz, 1H), 6.25 (dd, J = 1.8 & 17 Hz, 1H), 6.43 (dd, J = 10 & 16.92 Hz, 1H), 7.27-7.35 (m, 5H), 7.40 (d, J = 8 Hz, 1H), 7.60 (d, J = 8.16 Hz, 1H), 7.92 (s, 1H), 7.95-8.05 (m, 1H), 8.07 (s, 1H), 8.14 (d, J = 3.52 Hz, 1H), 9.50 (s, 2H), 10.12 (s, 1H); LCMS : *m/e* 428.9 (M+1).

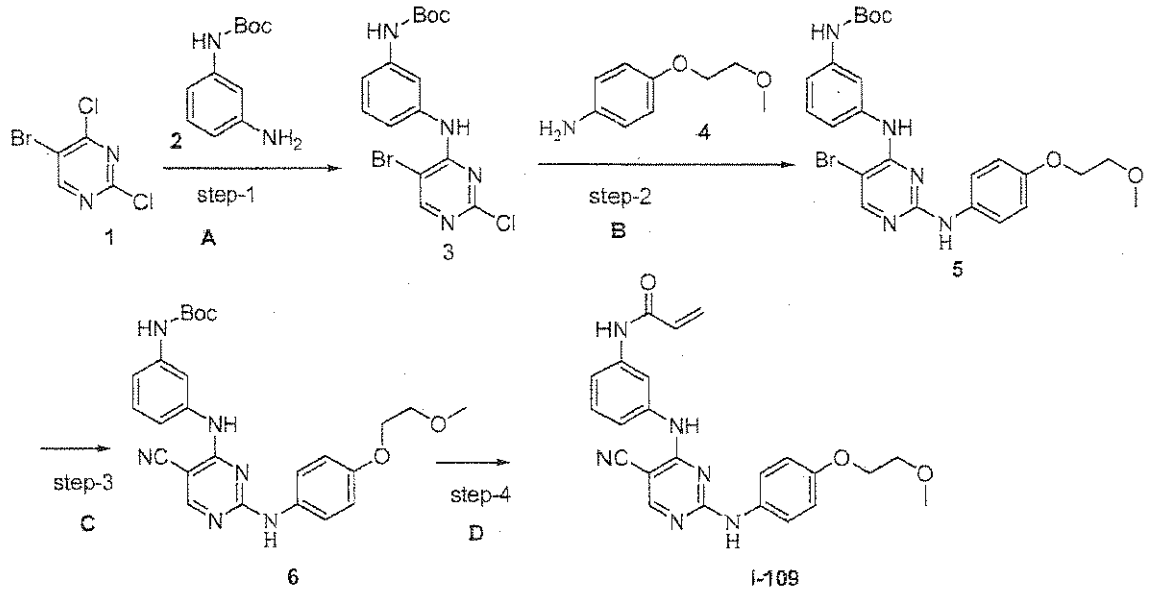
EXAMPLE 94

[00785] Preparation of N-(3-(5-cyano-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-109**



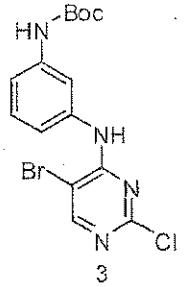
I-109

[00786] The title compound was prepared according to the steps and intermediates as described below.



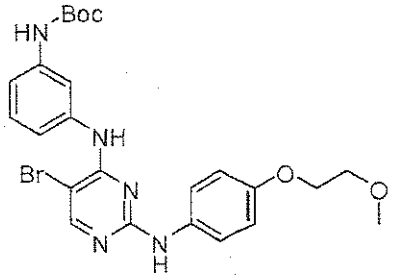
A) DMA, K_2CO_3, rt, 10 h, pressure tube; B) PTSA, dioxane, 100 ^{0}C, 2 h; C) $Zn(CN)_2$, Ph_3P, DMF, 120 ^{o}C, 12 h; D) 4N HCl, dioxane, rt, 1 hr; then acryloyl chloride, Et_3N, DCM, -10 ^{0}C, 10 min.

[00787] **Step-1**



[00788] To a solution of 5-bromo-2,4-dichloropyrimidine (0.45 g, 2.0 mmol) and tert-butyl 3-aminophenylcarbamate (0.44 g, 2.1 mmol) in DMA (3 mL) was added K_2CO_3 (0.55 g, 4.0 mmol). The suspention was stirred for 10 hours. Water (10 mL) was added and the precipitate was collected by filtration. The solid was washed with ether and dried to yield 0.8 g of compound **3**. MS: m/e=399.1, 401.2 (M+1).

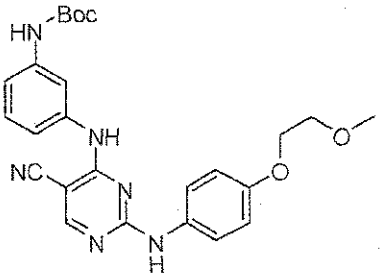
[00789] Step-2



5

[00790] To a solution of compound 3 (400 mg, 1.0 mmol) and 4-(2-methoxyethoxy)aniline (0.2 g, 1.2 mmol) in 8 ml dioxane was added 4-methylbenzenesulfonic acid monohydrate (0.15g, 0.8 mmol). The mixture was stirred at 100 °C for two hours. The solvent was evaporated. The residue was dissolved in 30 ml ethyl acetate and washed with $NaHCO_3$ aqueous solution, water and brine. The organic layer was separated and dried over Na_2SO_4. After removal of solvent, the crude product was subject to chromatography on silica gel (hexane:EtOAc = 1:1). 0.40 g of the title compound 5 was obtained: MS m/z: 530.1, 532.1($M+H^+$).

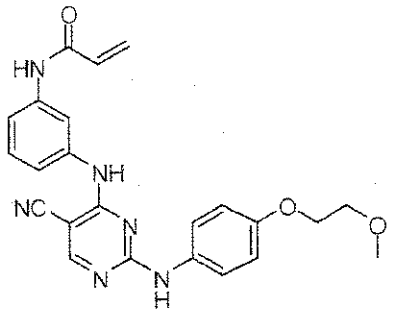
[00791] Step-3



6

[00792] To a suspension of $Zn(CN)_2$ (0.24g, 2.0 mmol), $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) in 3 ml DMF was added to 5 (0.25 g, 0.5 mmol). The mixture was degassed and sealed under argon, and heated at 120 °C for 12 hours. Water (10 ml) was added and the precipitate was collected by filtration. The solid was washed with ether and dried to yield 0.2 g of compound 6. MS: m/e=477.1 (M+1).

[00793] **Step-4**



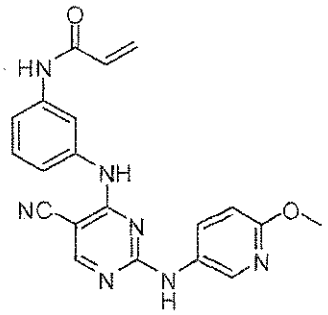
I-109

[00794] Compound **6** (0.10 g, 0.21 mmol) was dissolved in 4 N HCl (2 mL) in dioxane. The mixture was stirred at rt for 1 hour. After removal of solvents, a 5-mL portion of DCM was poured in followed by evaporation to dryness. This process of DCM addition followed by evaporation was repeated three times to give a residue solid which was used directly for the next step: MS m/z: 377.0 ($M+H^+$).

[00795] To a solution of the intermediate obtained above, triethylamine (0.1 ml, 0.8 mmol) in 2 ml dichloromethane was added acryloyl chloride (19 mg, 0.21 mmol) at -10 °C. The reaction was stirred for 10 minutes at -10 °C and was quenched by $NaHCO_3$ aqueous solution. Ethyl acetate (10 mL) was added and washed with $NaHCO_3$ aqueous solution, water and brine. The organic layer was separated and dried over Na_2SO_4. After removal of solvent, the crude product was subject to chromatography on silica gel (hexane:EtOAc = 1:2) to give 30 mg of the title compound. MS m/z: 431.1 ($M+H^+$).

EXAMPLE 95

[00796] Preparation of N-(3-(5-cyano-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-173**

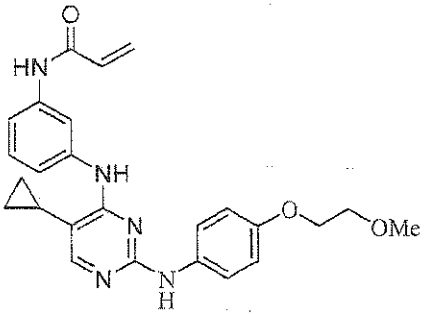


I-173

[00797] The title compound was prepared according to the schemes, steps and intermediates described in Example 94 by using 3-amino-6-methoxypyridine in place of **4** in Step-2. MS m/z: 388.2 ($M+H^+$).

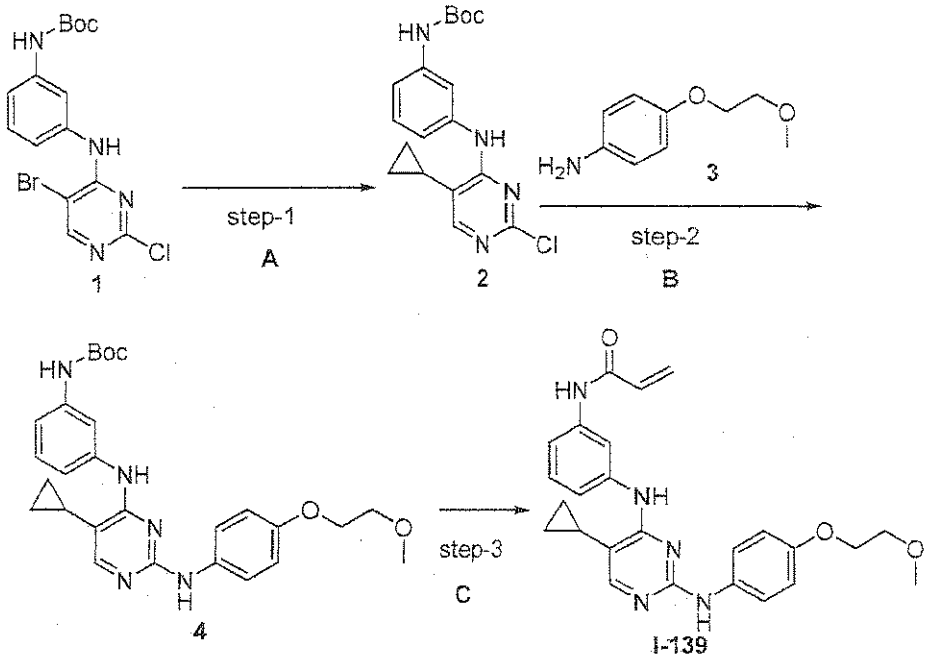
EXAMPLE 96

[00798] Preparation of N-(3-(5-cyclopropyl-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-139**



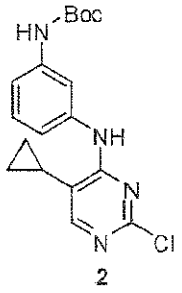
I-139

[00799] The title compound was prepared according to the steps and intermediates as described below.



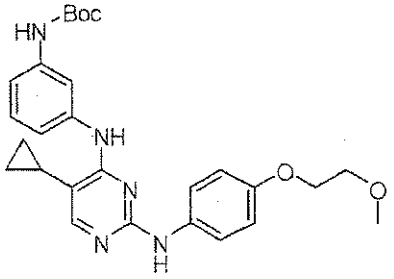
A) Potassium cyclopropyltrifluoroborate, $Pd(OAc)_2$, Xanphos, $Cs_2(CO_3)$, toluene, 100 °C, 12 h; B) PTSA, dioxane, 100 °C, 2 h; C) $Zn(CN)_2$, Ph_3P, DMF, 120 °C, 12 h; D) 4N HCl, dioxane, rt, 1 hr; then acryloyl chloride, Et_3N, DCM, -10 °C, 10 min.

[00800] Step-1



[00801] Potassium cyclopropyltrifluoroborate (0.4g, 3.0 mmol), compound 1 (1.0g, 2.5 mmol), palladium acetate (34 mg, 0.15 mmol), Xanphos (0.17 g, 0.3 mmol) and Cs_2CO_3 (2.4g, 7.5 mmol) were suspended in 25 ml toluene and 5ml water. The mixture was degassed, sealed under argon and heated at 100 °C for 12 hours. 50 ml ethyl acetate was added and washed with $NaHCO_3$ aqueous solution, water and brine. The organic layer was separated and dried over Na_2SO_4. After removal of solvent, the crude product was subject to chromatography on silica gel (hexane:EtOAc = 3:2). 0.54 g of the title compound 2 was obtained: MS m/z: 361.2 ($M+H^+$).

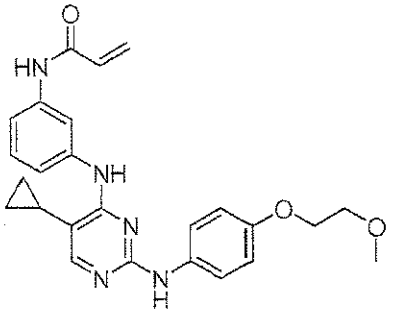
[00802] Step-2



4

[00803] Compound 4 was prepared from compound **2** and **3** following the procedure described in Step-2 of Example 94. MS m/z: 492.2 ($M+H^+$).

[00804] Step-3

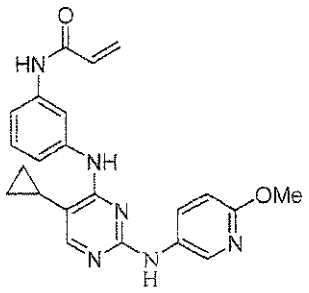


I-139

[00805] The title compound **I-139** was prepared from compound **4** following the procedure described in Step-4 of Example 94. MS m/z: 446.1 ($M+H^+$).

EXAMPLE 97

[00806] Preparation of N-(3-(5-cyclopropyl-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-167**

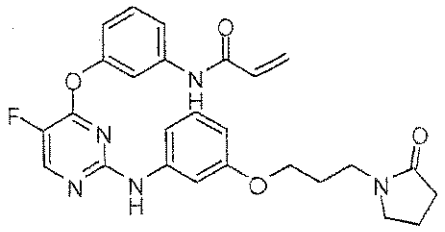


I-167

[00807] The title compound was prepared according to the schemes, steps and intermediates described in Example 96 by using 3-amino-6-methoxypyridine in place of **3** in Step-2. MS m/z: 403.2 ($M+H^+$).

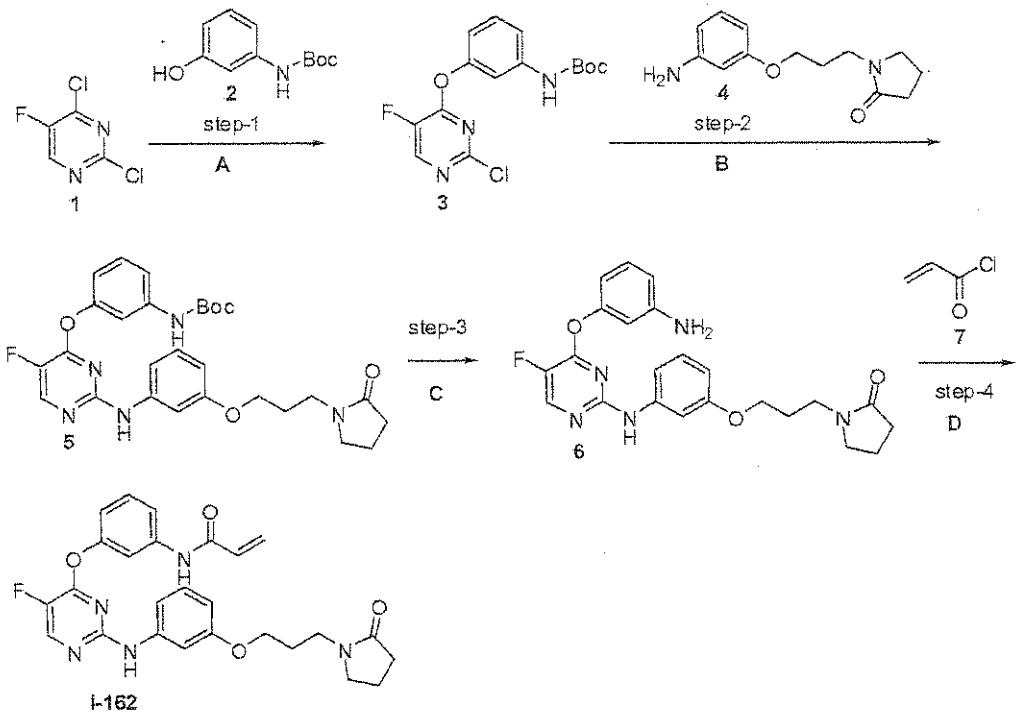
EXAMPLE 98

[00808] Preparation of N-(3-(5-fluoro-2-(3-(3-(2-oxopyrrolidin-1-yl)propoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-162**



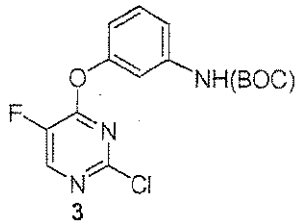
I-162

[00809] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIPEA, n-BuOH, 110 ^{0}C, 16 h; **B**) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 ^{0}C, 16 h; **C**) TFA, CH_2Cl_2, rt. 2 h; **D**) K_2CO_3, NMP, rt, 45 min.

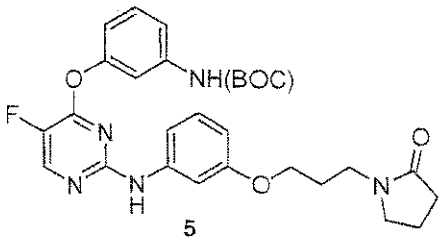
[00810] Step-1



3

[00811] A pressure tube was charged with **2** (2.0 g, 9.61 mmol), **1** (3.21 g, 19.23 mmol), n-BuOH (30 mL) and DIPEA (1.86 g, 14.42 mmol) and the contents were stirred at 110 ^{0}C for 16 h. The reaction mixture was cooled, concentrated under reduced pressure, quenched with water (30 mL) and extracted with ethyl acetate (2 x 30 mL). The combined ethyl acetate extract was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get a residue. It was triturated with hexane to get **3** (2.5 g, 96%) as a yellow solid.

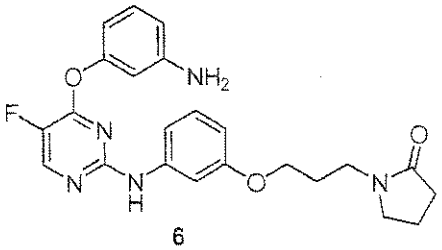
[00812] Step-2



5

[00813] To a solution of **3** (0.36 g, 1.1 mmol) in toluene (15 mL) was added 3-(3-(2-oxopyrrolidin-1-yl)propoxyaniline **4** (0.25 g, 1.1 mmol) followed by BINAP (0.031 g, 0.05 mmol), palladium acetate (0.0022 g, 0.01 mmol), and Cs_2CO_3 (0.82 g, 2.5 mmol). The reaction mixture was stirred and N_2 was bubbled into it for 15 min. It was heated at 100 ^{0}C for 8 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (30 mL), washed with water (15 mL), brine (15 mL), and dried over Na_2SO_4. Concentration under reduced pressure offered a residue which was purified by column chromatography (SiO_2, 60-120, product getting eluted in 3% methanol/chloroform: 3/97) to get **5** (0.3 g, 60%) as yellow solid.

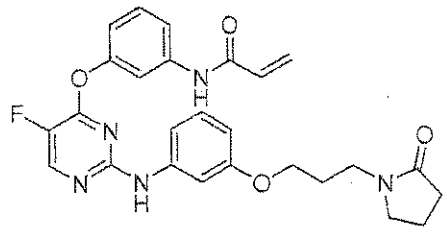
[00814] Step-3



6

[00815] To a stirred solution of **5** (0.25 g, 0.46 mmol) in CH_2Cl_2 (10 mL) was added TFA (1.0 mL) at 0 ^{0}C under nitrogen atmosphere. The reaction mixture was allowed to come to rt and stirred at this temperature for 2 h. Crude reaction mixture was poured into ice cold water (10 mL), basified with sodium bicarbonate solution and extracted with ethyl acetate (3x15 mL). The combined ethyl acetate extract was washed with water (15 mL), brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get **6** (0.130 g, 65%) as a yellow solid. It was used in the next step without further purifications

[00816] Step-4

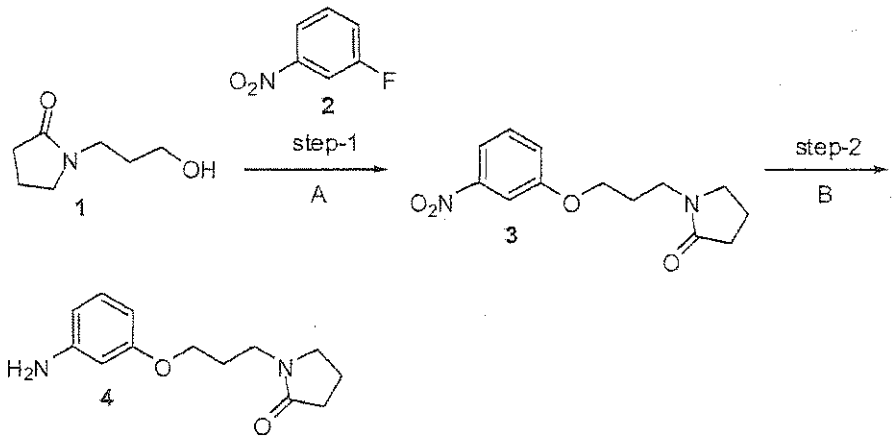


I-162

[00817] To a stirred solution of **6** (0.08 g, 0.18 mmol) and potassium carbonate (0.124 g, 0.9 mmol) in NMP (1.2 mL) at 0 ^{0}C was added acryloyl chloride (0.020 g, 0.22 mmol) and the reaction mixture was stirred at 0 ^{0}C for 45 min The reaction mixture was added drop wise to a cold, stirring solution of 10% $NaHCO_3$ and stirred at the same temperature (0 ^{0}C) for 30 min. A solid precipitated out which was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and dissolved in a mixture of methanol/dichloromethane (50:50, 5 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (10 mL), Et_3N was added to it and it was extracted with ethyl acetate (2 x 10 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **I-162** (0.050 mg, 56%). ^{1}H NMR (DMSO-d_6) δ ppm: 1.81-1.91 (m, 4H), 2.19 (t, J = 7.84 Hz, 2H), 3.26-3.35 (m, 4H), 3.73 (t, J = 6.04 Hz, 2H),

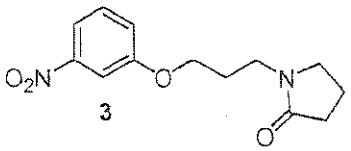
5.76 (dd, J = 1.92 & 10.04 Hz; 1H), 6.25 (dd, J = 1.88 & 16.9 Hz, 1H), 6.38-6.45 (m, 2H), 6.93 (t, J = 8.12 Hz, 1H), 7.02-7.04 (m, 2H), 7.11 (s, 1H), 7.43 (t, J = 8.16 Hz, 1H), 7.55 (d, J = 8.24 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 8.56 (d, J = 2.88 Hz, 1H), 9.56 (s, 1H), 10.34 (s, 1H); LCMS : *m/e* 490.0 (M-2).

[00818] The intermediate 3-(3-(2-oxopyrrolidin-1-yl)propoxyaniline **4** was prepared according to the scheme shown below.



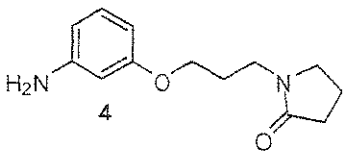
A) NaH, DMF, rt, 16 h; **B**) $SnCl_2$, Conc. HCl, 50 ^{0}C, 2 h.

[00819] <u>Step-1</u>



[00820] To a stirred solution of NaH (1.0 g, 20.94 mmol) in DMF (10 mL) was added **1** (2.0 g, 13.96 mmol) at 0 ^{0}C. The reaction mixture was allowed to come to rt and stirred at it for 30 mins. To the reaction mixture was added **2** (1.96 g, 13.96 mmol), slowly and the reaction mixture was allowed to stir at rt for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate (20 mL). It was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered crude **3** (2 g, 55.5%) which was used in the next step without further purification.

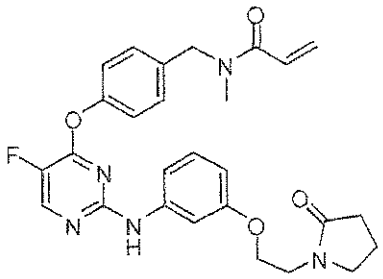
[00821] <u>Step-2</u>



[00822] To a stirred solution of **3** (2 g, 7.57 mmol) in conc. HCl (20 mL) was added $SnCl_2$ (7.5 g, 34.06 mmol) in small portions. The reaction mixture was stirred at 50 ^{0}C for 2 h, cooled and basified with $NaHCO_3$. It was extracted with ethyl acetate (3 x 25 mL), washed with water (5 mL), brine solution (5 mL) and dried over anhydrous Na_2SO_4. Filtration followed by concentration under reduced pressure gave **4** (1.65 g, 93%) as dark brown solid which was used as such in the next step.

EXAMPLE 99

[00823] Preparation of N-(4-(5-fluoro-2-(3-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yloxy)benzyl)-N-methylacrylamide **I-146**

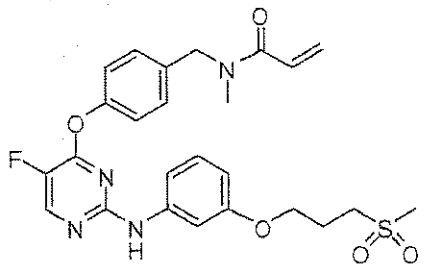


I-146

[00824] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using (4-hydroxybenzyl)(methyl)carbamic acid tert-butyl ester in place of **2** in Step-1 and 3-(2-(2-oxopyrrolidin-1-yl)ethoxyaniline in place of **4** in Step-2. ^{1}H NMR ($CDCl_3$) δ ppm: 2.03 (quin, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 8 Hz, 2H), 3.07 & 3.06 (s, together 3H), 3.57 (t, *J* = 6.96 Hz, 2H), 3.66 (t, *J* = 5.08 Hz, 2H), 4.03-4.04 (bd, *J* = 4.96 Hz, 2H), 4.67 & 4.72 (s, together 2H), 5.70-5.85 (m, 1H), 6.43 (d, *J* = 16.72 Hz, 1H), 6.50 (d, *J* = 5.72 Hz, 1H), 6.60-6.75 (m, 1H), 6.89-6.96 (m, 2H), 7.06-7.08 (m, 2H), 7.18-7.30 (m, 2H), 7.37 (d, *J* = 8.44 Hz, 1H), 8.21 (d, *J* = 2.36 Hz, 1H); LCMS : *m/e* 506.2 (M+1).

EXAMPLE 100

[00825] Preparation of N-(4-(5-fluoro-2-(3-(3-(methylsulfonyl)propoxy)phenylamino)pyrimidin-4-yloxy)benzyl)-N-methylacrylamide **I-136**

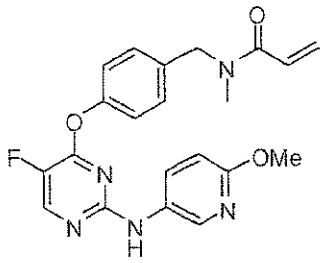


I-136

[00826] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using (4-hydroxybenzyl)(methyl)carbamic acid tert-butyl ester in place of **2** in Step-1 and 3-(3-(3-methylsulfonyl)propoxyaniline in place of **4** in Step-2. ^{1}H NMR ($CDCl_3$) δ ppm: 2.25-2.40 (m, 2H), 2.97 (s, 3H), 3.07 (s, 3H), 3.20-3.30 (m, 2H), 3.98-4.05 (m, 2H), 4.67 (s, 1H), 4.72 (s, 1H), 5.7-5.82 (m, 1H), 6.43 (dd, *J* = 1.96 & 16.96 Hz, 1H), 6.49-6.53 (m, 1H), 6.6-6.75 (m, 1H), 6.85-7.00 (m, 2H), 7.05-7.15 (m, 2H), 7.18-7.25 (m, 2H), 7.36 (d, *J* = 8.36 Hz, 1H), 8.21 (bd, *J* = 2.52 Hz, 1H); LCMS : *m/e* 515.0 (M+1).

EXAMPLE 101

[00827] Preparation of N-(4-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-yloxy)benzyl)-N-methylacrylamide **I-117**



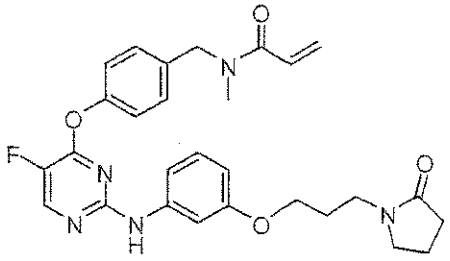
I-117

[00828] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using (4-hydroxybenzyl)(methyl)carbamic acid tert-butyl ester in place of **2** in Step-1 and 6-methoxy-3-aminopyridine in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.92 & 3.07 (s, together 3H), 3.76 (s, 3H), 4.62 & 4.74 (s, together 2H), 5.69 & 5.75

(dd, J = 1.6 & 10.4 Hz, together 1H), 6.20 (dd, J = 1.2 & 16.4 Hz, 1H), 6.56 (d, J = 8.8 Hz, 1H), 6.82-6.90 (m, 1H), 7.28-7.35 (m, 4H), 7.71 (bd, J = 7.6 Hz, 1H), 8.14 (s, 1H), 8.44 (bd, J = 2.8 Hz, 1H), 9.48 (s, 1H); LCMS : *m/e* 410 (M+1).

EXAMPLE 102

[00829] Preparation of N-(4-(5-fluoro-2-(3-(3-(2-oxopyrrolidin-1-yl)propoxy)phenylamino)pyrimidin-4-yloxy)benzyl)-N-methylacrylamide **I-111**

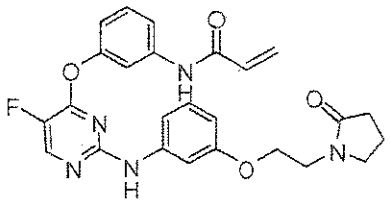


I-111

[00830] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using (4-hydroxybenzyl)(methyl)carbamic acid tert-butyl ester in place of **2** in Step-1 and 3-(3-(2-oxopyrrolidin-1-yl)propoxy)aniline in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.80-2.6 (m, 4H), 2.20 (t, J = 7.6 Hz, 2H), 2.92 & 3.06 (s, together 3H), 3.20-3.40 (m, 4H), 3.75-3.90 (m, 2H), 4.62 & 4.73 (s, together 2H), 5.65-5.77 (m, 1H), 6.20 (dd, J = 2.4 & 16.8 Hz, 1H), 6.24 (bd, J = 8 Hz, 1H), 6.86 (dd, J = 10.4 & 16.8 Hz, 1H), 6.93 (t, J = 8 Hz, 1H), 7.08 (t, J = 8 Hz, 2H), 7.28-7.36 (m, 4H), 8.48 (d, J = 2.8 Hz, 1H), 9.51 (s, 1H); LCMS : *m/e* 520.2 (M+1).

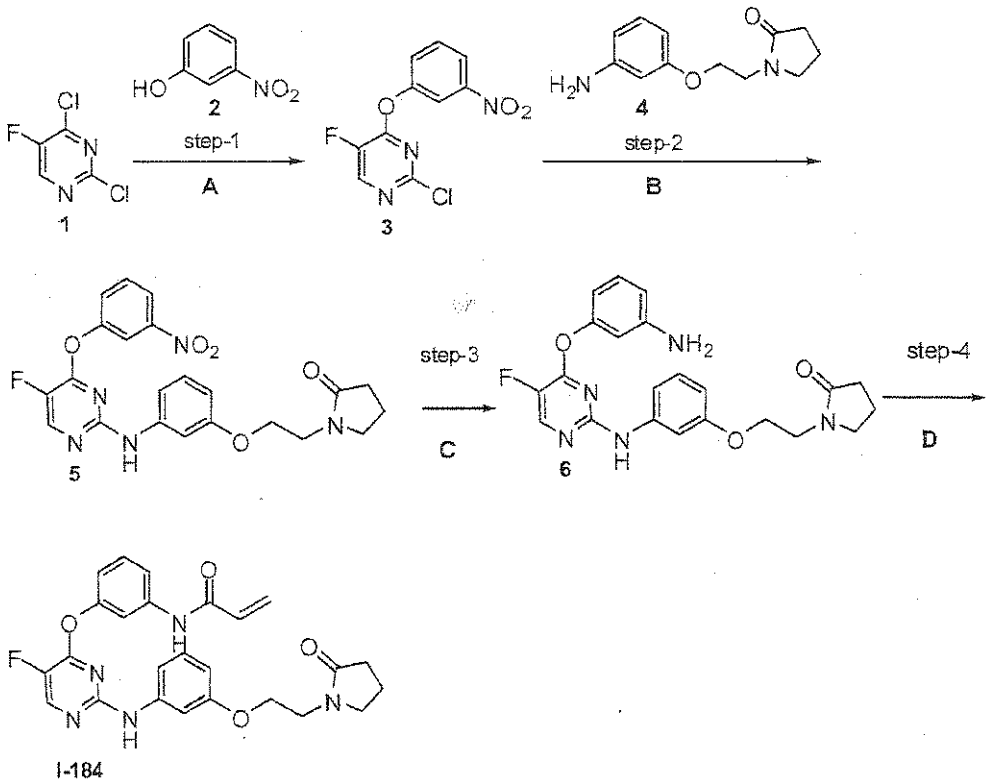
EXAMPLE 103

[00831] Preparation of N-(3-(5-fluoro-2-(3-(2-(2-oxopyrrolidin-1-yl)ethoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-184**



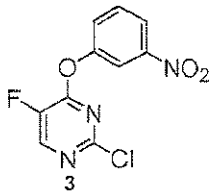
I-184

[00832] The title compound was prepared according to the schemes, steps and intermediates described below.



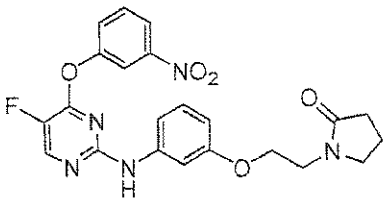
A)) K_2CO_3, DMF, rt, 16 h; **B**) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 100 ^{0}C, 8 h; **C**) Pd-C, H_2, methanol, rt, 16 h. **D**)) acryloyl chloride, K_2CO_3, NMP, 0 ^{0}C, 30 min.

[00833] **Step-1**



[00834] To a stirring solution of **1** (24 g, 143.7 mmol) and K_2CO_3 (20 g, 143.6 mmol) in dry DMF (300 mL) was added **2** (10 g, 71.8 mmol) and the reaction mixture was stirred at rt for 16 h under nitrogen atmosphere. It was cooled and quenched with water (600 mL). A white solid precipitated out which was isolated by filtration through Buchner funnel and vacuum dried to get **3** (13 g, 68%) as a white solid.

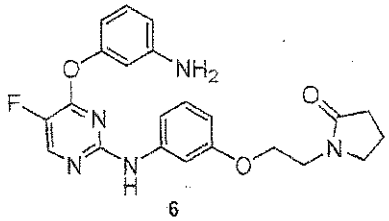
[00835] Step-2



5

[00836] To a solution of **3** (0.9 g, 3.3 mmol) in toluene (30 mL) was added **4** (950 mg, 4.3 mmol) followed by BINAP (0.12 g, 0.19 mmol), palladium acetate (0.02 g, 0.09 mmol), and Cs_2CO_3 (2.7 g, 8.2 mmol). The reaction mixture was stirred and N_2 was bubbled into it for 15 min. It was then heated at 100 ^{0}C for 8 h under N_2 atmosphere. The reaction mixture was cooled to room temperature, diluted with ethyl acetate (60 mL), washed with water (35 mL), brine (35 mL), and dried over Na_2SO_4. Concentration under reduced pressure offered a residue which was purified by column chromatography (SiO_2, 60-120, product getting eluted in methanol/chloroform: 8/92) to get **5** (0.50 g, 33%) as a white solid.

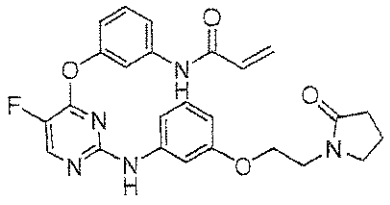
[00837] Step-3



6

[00838] To a solution of **5** (0.5 g, 1.1 mmol) in methanol (50 mL)) was added 10% Pd/C (0.05 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to get **6** (0.3 g, 65%) as a colorless viscous liquid.

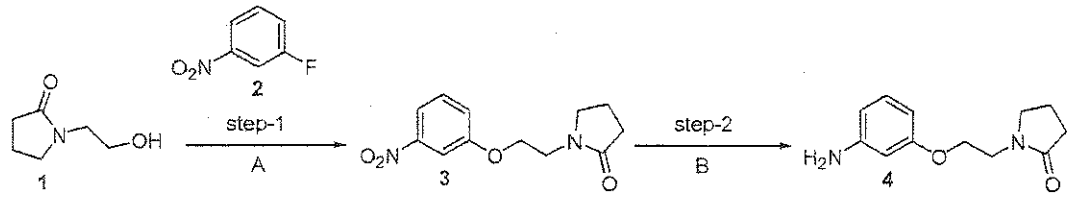
[00839] Step-4



I-184

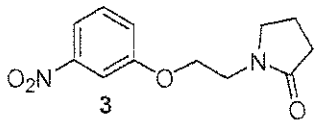
[00840] To a stirred solution of **6** (0.21 g, 0.5 mmol) and potassium carbonate (0.27 g, 2.0 mmol) in NMP (2.5 mL) at 0 ^{0}C was added acryloyl chloride (0.053 g, 0.6 mmol) and the reaction mixture was stirred at 0 ^{0}C for 30 min The reaction mixture was added drop wise to a cold, stirring solution of 10% $NaHCO_3$ and stirred at the same temperature (0 ^{0}C) for 30 min. A white solid precipitated out which was isolated by filtration through a Buchner funnel. The solid was washed with cold water and hexane and dissolved in mixture of methanol/dichloromethane (50:50, 10 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (25 mL), Et_3N was added to it and it was extracted with ethyl acetate (2 x 50 mL). The combined ethyl acetate extract was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **I-184** (0.150 g, 65%) as white solid. ^{1}H NMR (DMSO-d_6) δ ppm: 1.89 (quin, *J* = 7.2 Hz, 2H), 2.21 (t, *J* = 7.6 Hz, 2H), 3.39 (t, *J* = 7.2 Hz, 2H), 3.49 (t, *J* = 5.2 Hz, 2H), 3.87 (t, *J* = 5.6 Hz, 2H), 5.77 (dd, *J* = 1.6 & 10.4 Hz, 1H), 6.26 (dd, *J* = 1.6 & 17.2 Hz, 1H), 6.39-6.46 (m, 2H), 6.95 (t, *J* = 8.4 Hz, 1H), 7.03-7.12 (m, 3H), 7.44 (t, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.70 (s, 1H), 8.51 (d, *J* = 2.8 Hz, 1H), 9.56 (s, 1H), 10.35 (s, 1H); LCMS : *m/e* 478 (M+1).

[00841] The intermediate 3-(2-(2-oxopyrrolidin-1-yl)ethoxyaniline **4** was prepared according to the scheme shown below.



A) NaH, THF, rt,16 h; **B**) Pd-C, H_2, methanol, rt, 16 h.

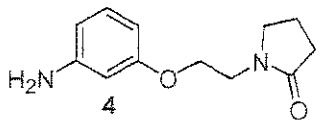
[00842] <u>Step-1</u>



[00843] To a stirring solution of NaH (3.4 g, 141.6 mmol, 60% dispersion in paraffin oil) in dry THF (50 mL) was added **1** (6 g, 46.0 mmol) at 0 ^{0}C and the reaction mixture was stirred at rt for 15 min under nitrogen atmosphere. To it was added a solution of **2** (5.0 g, 35.4 mmol) in THF (10 mL) and the reaction mixture was stirred at rt for 16 h. It was quenched with cold water (40 mL), and extracted with ethyl acetate (35 mL). The ethyl acetate extract was washed with water

(2x25 mL), brine (25 mL), dried over Na_2SO_4 and concentration under reduced pressure to get a residue which was purified by column chromatography (SiO_2, 60-120, product getting eluted in methanol/chloroform: 10/90) to get **3** (2.5 g, 30%) as a brownish liquid.

[00844] Step-2

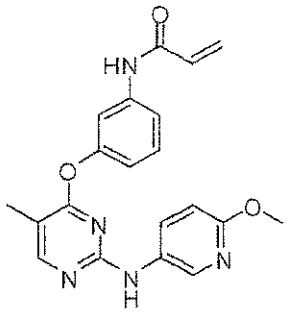


4

[00845] To a solution of **3** (2.2 g, 8.8 mmol) in methanol (50 mL)) was added 10% Pd/C (0. 22 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to get **4** (1.7 g, 89%) as a yellowish liquid. It was used in the next step without further purification.

EXAMPLE 104

[00846] Preparation of N-(3-(2-(6-methoxypyridin-3-ylamino)-5-methylpyrimidin-4-yloxy)phenyl)acrylamide **I-186**

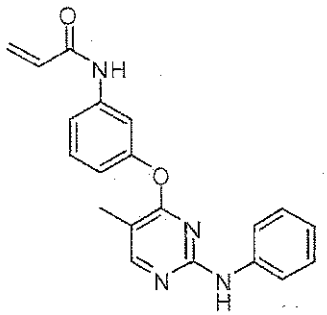


I-186

[00847] The title compound was prepared according to the schemes, steps and intermediates described in Example 103 by using 2,4-dichloro-5-methylpyrimidine in place of **1** in Step-1 and 6-methoxy-3-aminopyridine in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.16 (s, 3H), 3.73 (s, 3H), 5.76 (dd, J = 1.92 & 10.04 Hz, 1H), 6.24 (dd, J = 1.92 & 16.92 Hz, 1H), 6.39-6.49 (m, 2H), 6.92 (dd, J = 1.48 & 8 Hz, 1H), 7.40 (t, J = 8.08 Hz, 1H), 7.49 (d, J = 8.16 Hz, 1H), 7.64 (d, J = 1.84 Hz, 1H), 7.77-7.79 (m, 1H), 8.17 (bs, 1H), 8.20 (s, 1H), 9.27 (s, 1H), 10.29 (s, 1H); LCMS : *m/e* 378 (M+1).

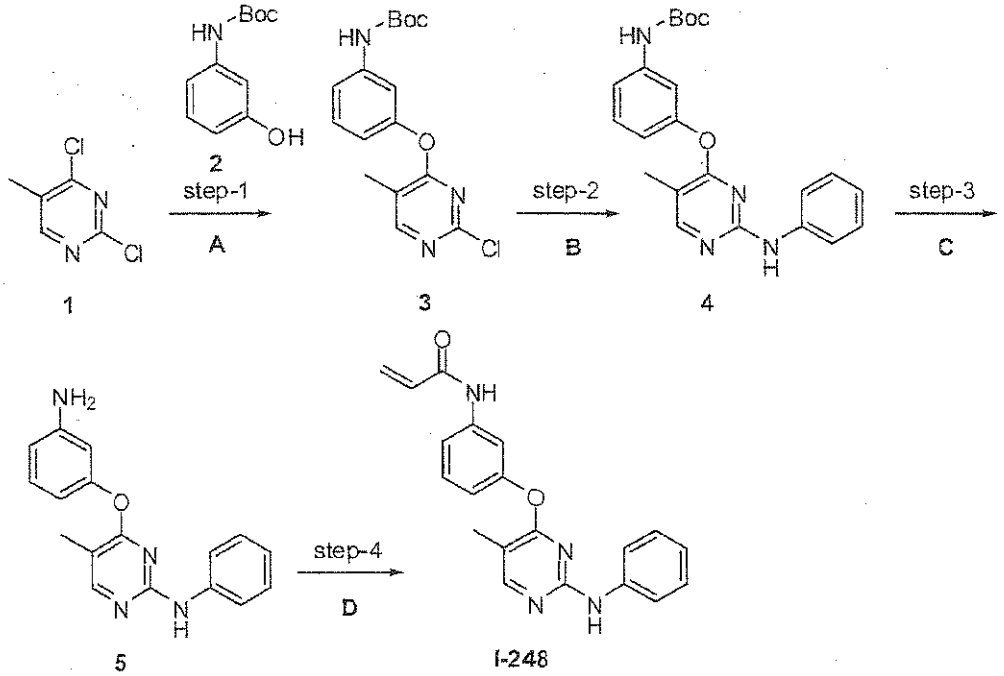
EXAMPLE 105

[00848] Preparation of N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-248**



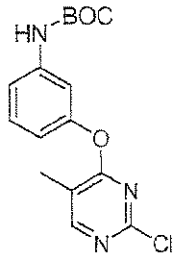
I-248

[00849] The title compound was prepared according to the schemes, steps and intermediates described below.



A) K_2CO_3, DMF, rt, 24 h; A') $(Boc)_2O$, THF, 60 ^{0}C, 2 h; B) aniline, conc. HCl, EtOH, 80 ^{0}C, 1 h; C) TFA, CH_2Cl_2, 0 ^{0}C to rt, ½ h; D) acryloyl chloride, NMP, 0 ^{0}C, 10 min.

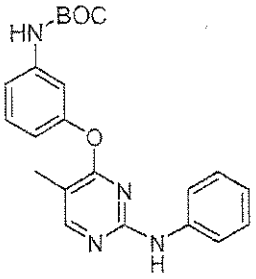
[00850] Step-1



3

[00851] To a stirring solution of 2 (100 mg, 0.48 mmol) and K_2CO_3 (99.2 mg, 0.717 mmol) in dry DMF (5 mL) was added 1 (78 mg, 0.478 mmol) and the reaction was continued at rt for 24 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure and the residue was diluted with ethyl acetate (10 mL). It was washed with water (2 x 5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get 3 (120 mg, 75%) as a white solid. It was used for next step without further purification.

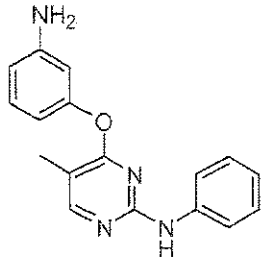
[00852] Step-2



4

[00853] A pressure tube was charged with 3 (75 mg, 0.224 mmol), conc. HCl (40 mg, 0.4 mmol), aniline (83 mg, 0.89 mmol) and ethanol (2.0 mL). The tube was screw capped and the contents were stirred at 80 ^{0}C for 60 min. The reaction mixture was cooled, concentrated under reduced pressure and the residue was quenched with water (5.0 mL). It was basified with 10% $NaHCO_3$ soln. and extracted with Ethyl acetate (3x10 mL). The combined EtOAc layer was washed with water (2x5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, 60-120 mesh, EtoAc/Hexane: 50/50) to get 4 (0.04 g, 45.9%) as an off-white sold.

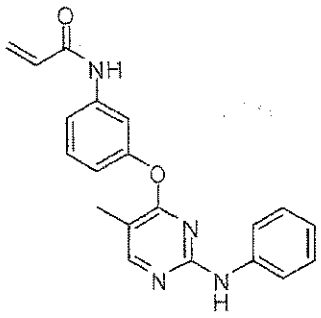
[00854] Step-3



5

[00855] To a stirring solution of **4** (160 mg, 0.40 mmol) in dichloromethane (4.0 mL) was added at 0 ^{0}C, trifluoroacetic acid (0.8 mL). Stirring was continued at the same temperature for 30 min after which the reaction mixture was concentrated under reduced pressure and the residue was dissolved in water (5.0 mL), basified with 10% $NaHCO_3$ solution and extracted with dichloromethane (2 x 5 mL). The dichloromethane extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to get **5** (110 mg, 93.2%) as an off white solid. It was used for next step without further purification.

[00856] Step-4



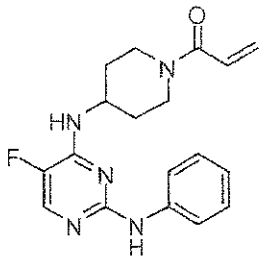
I-248

[00857] To a stirred solution of **5** (75 mg, 0.256 mmol) in NMP (0.8 mL) at 0 ^{0}C was added acryloyl chloride (34.8 mg, 0.38 mmol) and the reaction mixture was stirred at 0 ^{0}C for 10 min. The reaction mixture was quenched with water (4.0 mL), basified with 10% NaHCO3 soln. and extracted with dichloromethane (2x5 mL). The dichloromethane extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was further purified column chromatography (SiO_2, 60-120 mesh, $CHCl_3$/MeOH: 99/1) to get **I-248** (0.035 g, 39.6%) as a white colored solid. ^{1}H NMR (DMSO-d_6) δ ppm: 2.15 (s, 3H), 5.75 (dd, *J* = 1.92 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.96 & 16.96 Hz, 1H), 6.41 (dd, *J* = 10.6 & 17 Hz, 1H), 6.78-6.8 (m, 1H), 6.94 (dd, *J* = 1.44 & 8.04 Hz, 1H), 7.00 (t, *J* = 7.52 Hz, 2H), 7.40-

7.44 (m, 3H), 7.53 (d, J = 8.24 Hz, 1H), 7.6 (t, J = 2 Hz, 1H), 8.23 (d, J = 1.04 Hz, 1H), 9.36 (s, 1H), 10.30 (s, 1H); LCMS: *m/e* 346.8 (M+1).

EXAMPLE 106

[00858] Preparation of 1-(4-(5-fluoro-2-(phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-229**

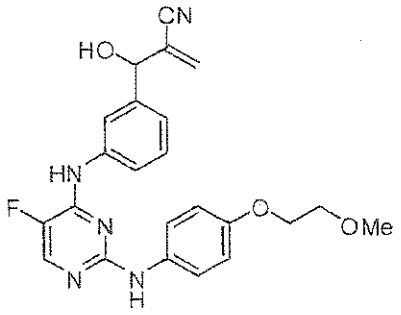


I-229

[00859] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 1-tert-butyloxycarbonyl-4-aminopiperidine in place of **2** in Step-1 and aniline in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm:1.35-1.50 (m, 2H), 1.90-2.05 (m, 2H), 2.7-2.85 (m, 1H), 3.10-3.20 (m, 1H), 4.11-4.15 (m, 2H), 4.46 (bd, J = 13.72 Hz, 1H), 5.67 (dd, J = 2.44 & 10.4 Hz, 1H), 6.10 (dd, J = 2.44 & 16.6 Hz, 1H), 6.82-6.88 (m, 2H), 7.22 (t, J = 7.44 Hz, 2H), 7.35 (d, J = 7.56 Hz, 1H), 7.70 (d, J = 7.72 Hz, 2H), 7.87 (d, i = 3.76 Hz, 1H), 9.07 (s, 1H); LCMS : *m/e* 341.383 (M+1).

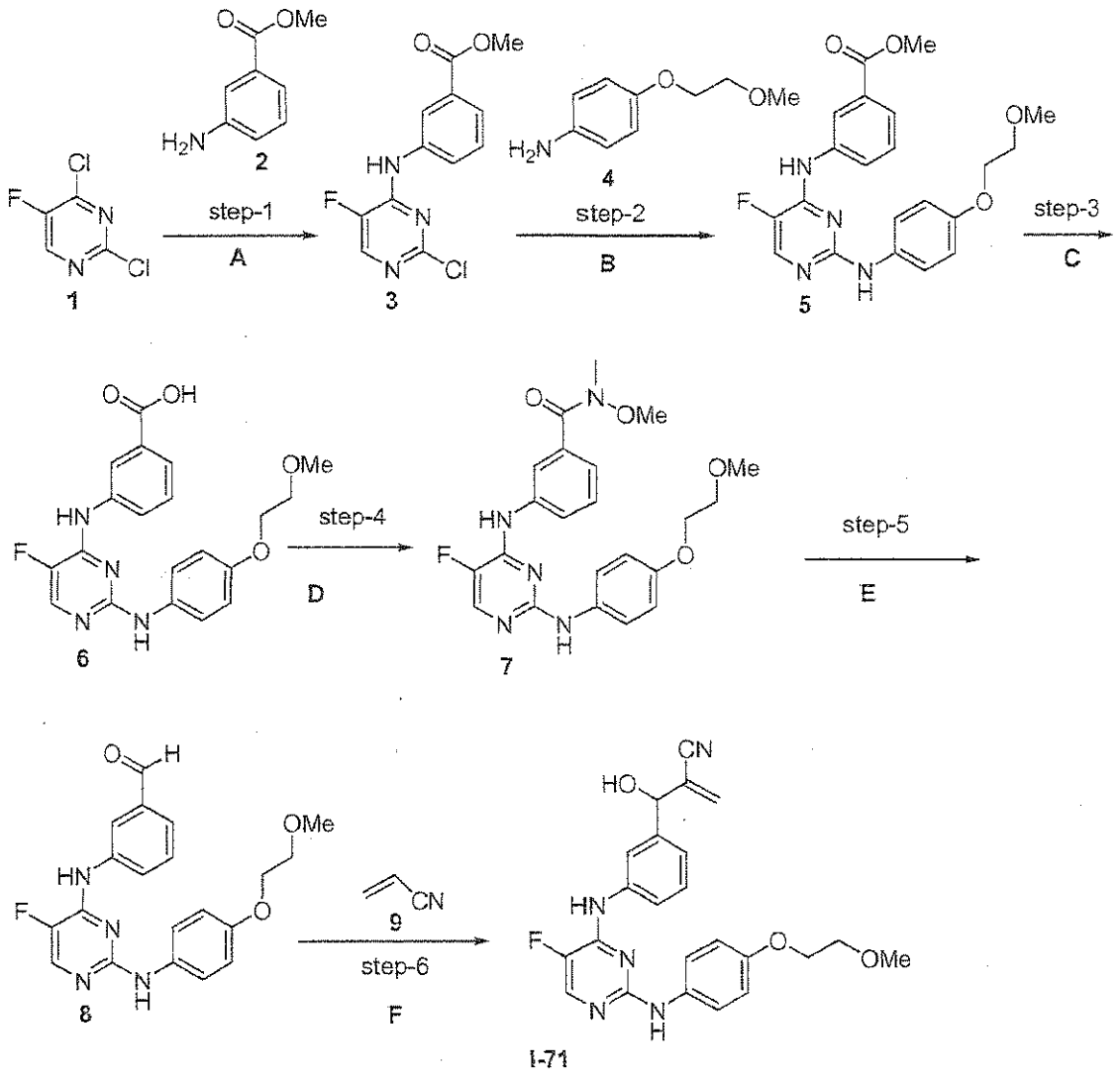
EXAMPLE 107

[00860] Preparation of 2-((3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-71**



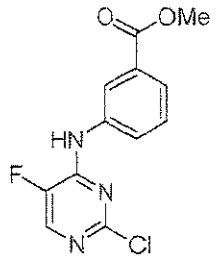
I-71

[00861] The title compound was prepared according to the schemes, steps and intermediates described below.



A) 2, DIPEA, n-BuOH, 120 ^{0}C, 12 h; B) conc. HCl, ethanol, 100 ^{0}C, 5 h; C) LiOH, MeOH/THF/H2O, rt, 6 h; D) Me-NH-OMe.HCl, EDCI.HCl, HOBT, DIPEA, DMF, rt, 8 h; E) LAH (1.0 M soln. in THF), -78 ^{0}C, 30 min; F) DABCO, 1,4-dioxan/water, rt, 48 h.

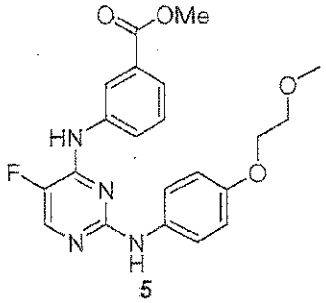
[00862] Step-1



3

[00863] A solution of 1 (0.50 g, 2.99 mmol), 2 (0.45 g, 2.99 mmol) and DIPEA (0.57 g, 4.48 mmol) in n-butanol (5.0 mL) was heated in a pressure tube (120 ^{0}C, 16 h). It was cooled, quenched with water (5 mL) and extracted with EtOAc (2x5 mL). The combined EtOAc extract was washed with water (2 mL), brine (2 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford 3 (0.70 g, 83.3%) as an off-white solid.

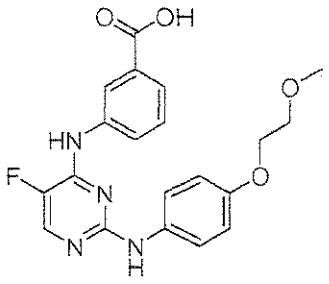
[00864] Step-2



5

[00865] A solution of 3 (0.5 g, 1.77 mmol) and 4 (0.29 g, 1.77 mmol) in ethanol (2.5 mL) was taken in a pressure tube and acetic acid (0.1 mL) was added to it. The tube was tightly closed and the contents were stirred at 100 ^{0}C for 5 h. The reaction mixture was cooled, ethanol was removed under reduced pressure and the residue was taken in ethyl acetate (50 mL). It was washed with $NaHCO_3$ solution (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The solid precipitated was isolated by filtration. It was dried under vacuum to get 5 (0.6 g, 80%).

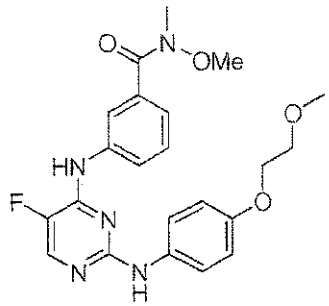
[00866] Step-3



6

[00867] To a stirred solution of **5** (0.6 g, 1.4 mmol) in methanol/THF/water: 6 mL/6 mL/3 mL was added LiOH (0.298 g, 7 mmol) and the reaction mixture was stirred at rt for 2 h. It was concentrated under reduced pressure; residue was diluted with water (2 mL) and extracted with diethyl ether (5 mL). The aqueous layer was separated and acidified with 1.5 N HCl (pH ~4-5), concentrated and dried under vacuum to get **6** (0.4 g, 70%) as a white solid which was taken for next step without further purification.

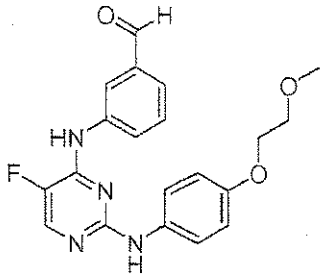
[00868] Step-4



7

[00869] To a stirred solution of **6** (0.4 g, 1 mmol) in DMF (3 mL) were added MeNH-OMe.HCl (0.102 g, 0.1 mmol), EDCI.HCl (0.003g, 1.5 mmol), HOBT (71 mg, 0.5 mmol) and DIPEA (0.204 g, 1.5mmol). The reaction mixture was stirred at room temperature for 8 h and quenched with water and extracted with EtOAc (2 x 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get **7** (0.4 g, 90.9%) as a white solid.

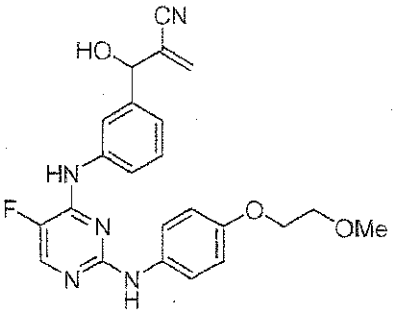
[00870] Step-5



8

[00871] To a stirred solution of 7 (0.4 g, 0.9 mmol) in THF (10 mL) was added LAH (1.8 mL, 1.8 mmol) at -78 ^{0}C. The reaction mixture was allowed to stir at the same temperature for 30 mins after which it was quenched with Na_2SO_4 solution (2 mL) and extracted with ethyl acetate (10 mL). The ethyl acetate layer was separated and washed with water (2 mL), brine solution (2 mL) and dried over anhydrous Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate 7/3) to get **8** (200 mg, 58%) as a yellow solid.

[00872] Step-6



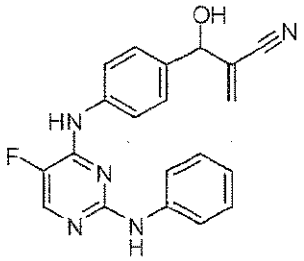
I-71

[00873] To a stirred solution of **8** (200 mg, 0.523 mmol) and **9** (69 mg, 1.3 mmol) in 1,4-dioxane/H_2O (1.4 mL/0.6 mL) was added DABCO (50 mg, 0.2523 mmol) at rt. Stirring was continued at room temperature for 48 h after which the reaction mixture was concentrated under reduced pressure. The residue obtained was further purified by column chromatography (SiO_2, pet ether/ethyl acetate, 6/4) to get **I-71** as greenish gummy material (0.05 g, 22.7%).^{1}H NMR (DMSO-d_6) δ ppm: 3.48 (s, 3H), 3.77 (t, J = 4.4 Hz, 2H), 4.11-4.16 (m, 2H), 5.11 (s, 1H), 5.99

(s, 1H), 6.06 (s, 1H), 6.85 (s, 1H), 6.91 (d, J = 8.84 Hz, 2H), 7.15 (d, J = 7.44 Hz, 1H), 7.30-7.40 (m, ; LCMS : *m/e* (M+1).

EXAMPLE 108

[00874] Preparation of 2-((4-(5-fluoro-2-(phenylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-161**

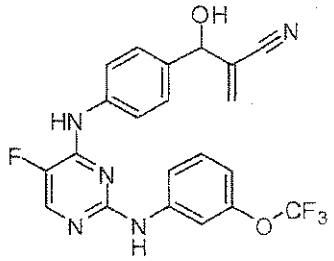


I-161

[00875] The title compound was prepared according to the schemes, steps and intermediates described in Example 107 by using aniline in place of 4 in Step-2. ^{1}H NMR ($CDCl_3$) δ ppm: 5.32 (s, 1H), 6.07 (d, J = 0.8 Hz, 1H), 6.15 (d, J = 1.6 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 7.03-7.06 (m, 2H), 7.29 (t, J = 1.6 Hz, 2H), 7.38 (d, J = 8.44 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 7.67 (dd, J = 1.6 & 6.4 Hz, 2H), 7.96 (d, J = 3.2 Hz, 1H); LCMS : *m/e* 361.8 (M+1).

EXAMPLE 109

[00876] Preparation of 2-((4-(5-fluoro-2-(3-trifluoromethoxyphenylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-163**



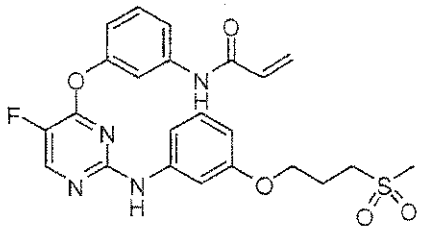
I-163

[00877] The title compound was prepared according to the schemes, steps and intermediates described in Example 107 by using 3-trifluoromethoxyaniline in place of 4 in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 5.29 (d, J = 3.8 Hz, 1H), 6.13 (s, 1H), 6.19 (s, 1H), 6.31 (dd, J = 3.8 Hz, 1H),

6.83 (d, J = 7.76 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.30-7.37 (m, 2H), 7.61-7.63 (m, 2H), 7.81 (s, 1H), 7.90 (d, J = 7.4 Hz, 1H), 8.16 (dd, J = 1.44 & 3.56 Hz, 1H), 9.45 (s, 1H), 9.53 (s, 1H); LCMS : *m/e* 446 (M+1).

EXAMPLE 110

[00878] Preparation of N-(3-(5-fluoro-2-(3-(3-(methylsulfonyl)propoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-116**

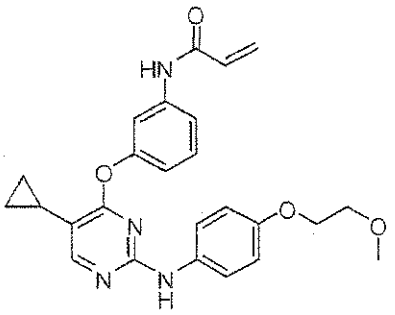


I-116

[00879] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using 3-(3-methylsulfonyl)propoxyaniline in place of **4** in Step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.02-2.15 (m, 2H), 3.01 (s, 3H), 3.22 (t, J = 7.56 Hz, 2H), 3.88 (t, J = 6.12 Hz, 2H), 5.77 (dd, J = 1.84 & 10.12 Hz, 1H), 6.25 (dd, J = 1.72 & 16.88 Hz, 1H), 6.43 (d, J = 9.96 & 16.76 Hz, 2H), 6.95 (t, J = 8.12 Hz, 1H), 7.06 (t, J = 7.48 Hz, 2H), 7.13 (s, 1H), 7.44 (t, J = 8.12 Hz, 1H), 7.56 (d, J = 8.44 Hz, 1H), 7.68 (s, 1H), 8.50 (d, J = 2.84 Hz, 1H), 9.57 (s, 1H), 10.34 (s, 1H); LCMS : *m/e* 487.0 (M+2).

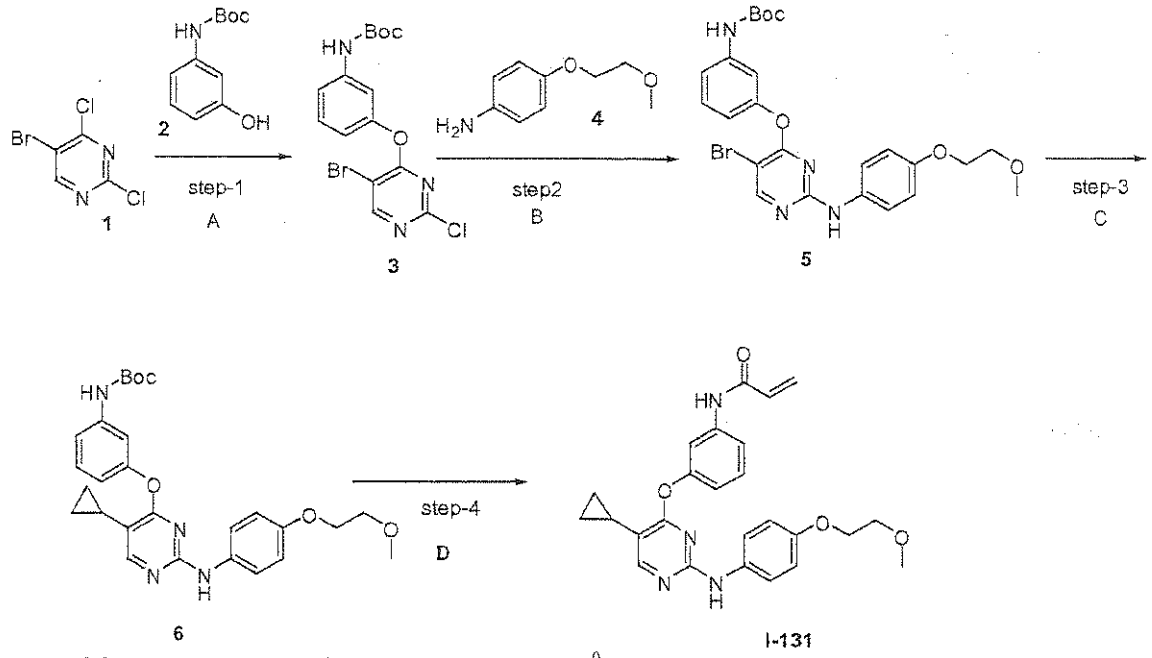
EXAMPLE 111

[00880] Preparation of N-(3-(5-cyclopropyl-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-131**



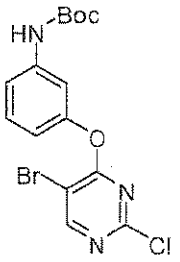
I-131

[00881] The title compound was prepared according to the steps and intermediates as described below.



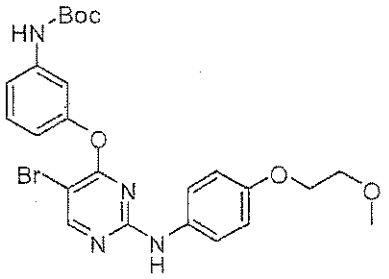
A) K_2CO_3, DMA, rt, 5 h; **B**) PTSA, dioxane, 100 ^{0}C, 2 h; **C**) potassium cyclopropyltrifluoroborate, $Pd(OAc)_2$, Xanphos, Cs_2CO_3, toluene, 100 ^{0}C, 12 h; **D**) 4N HCL, dioxane, rt, 1 hr; then acryoyl chloride, Et_3N, DCM, -10 °C, 10 min

[00882] **Step-1**



[00883] To a solution of 5-bromo-2,4-dichloropyrimidine (0.68g, 3.0 mmol) and tert-butyl 3-hydroxyphenylcarbamate (0.65g, 3.1 mmol) in DMA (4 mL) was added K_2CO_3 (0.83g, 6.0 mmol). The suspension was stirred for 5 hours. Water (15 ml) was added and the precipitate was collected by filtration. The solid was washed with ether and dried to yield 1.2 g of compound **3**. MS: m/e=400.2, 402.2 (M+1).

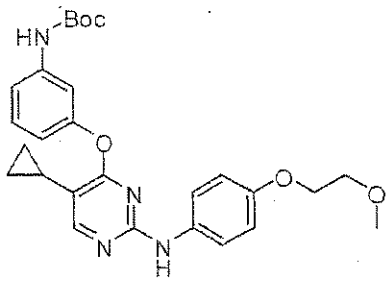
[00884] Step-2



5

[00885] To a solution of compound 3 (200 mg, 0.5 mmol) and 4-(2-methoxyethoxy)aniline (0.1 g, 0.6 mmol) in 5 ml dioxane was added 4-methylbenzenesulfonic acid monohydrate (0.08 g, 0.4 mmol). The mixture was stirred at 100°C for two hours. The solvent was evaporated. The residue was dissolved in 20 ml ethyl acetate and washed with $NaHCO_3$ aqueous solution, water and brine. The organic layer was separated and dried over Na_2SO_4. After removal of solvent, the crude product was subject to chromatography on silica gel (hexane:EtOAc = 1:1). 0.10 g of compound 5 was obtained: MS m/z: 531.1, 531.0 ($M+H^+$).

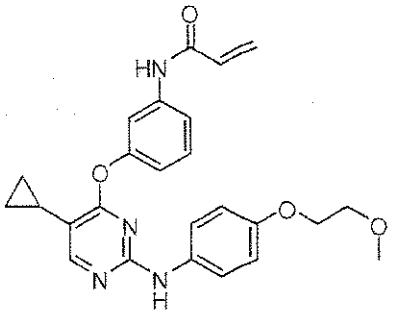
[00886] Step-3



6

[00887] Potassium cyclopropyltrifluoroborate (36 mg, 0.25 mmol), compound 5 (0.10 g, 0.19 mmol), palladium acetate (3.4 mg, 0.015 mmol), Xantphos (17.5 mg, 0.03 mmol) and Cs_2CO_3 (186 mg, 0.57 mmol) were suspended in 5 mL toluene and 1 mL water. The mixture was degassed, sealed under argon and heated at 100 °C for 12 hours. 20 mL ethyl acetate was added and washed with $NaHCO_3$ aqueous solution, water and brine. The organic layer was separated and dried over Na_2SO_4. After removal of solvent, the crude product was subject to chromatography on silica gel (hexane:EtOAc = 1:1). 50 mg of compound 6 was obtained: MS m/z: 493.2 ($M+H^+$).

[00888] Step-4

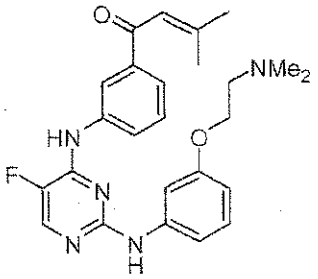


I-131

[00889] The title compound was prepared from compound **6** following the procedure described in Example 96. MS m/z: 447.1 ($M+H^+$).

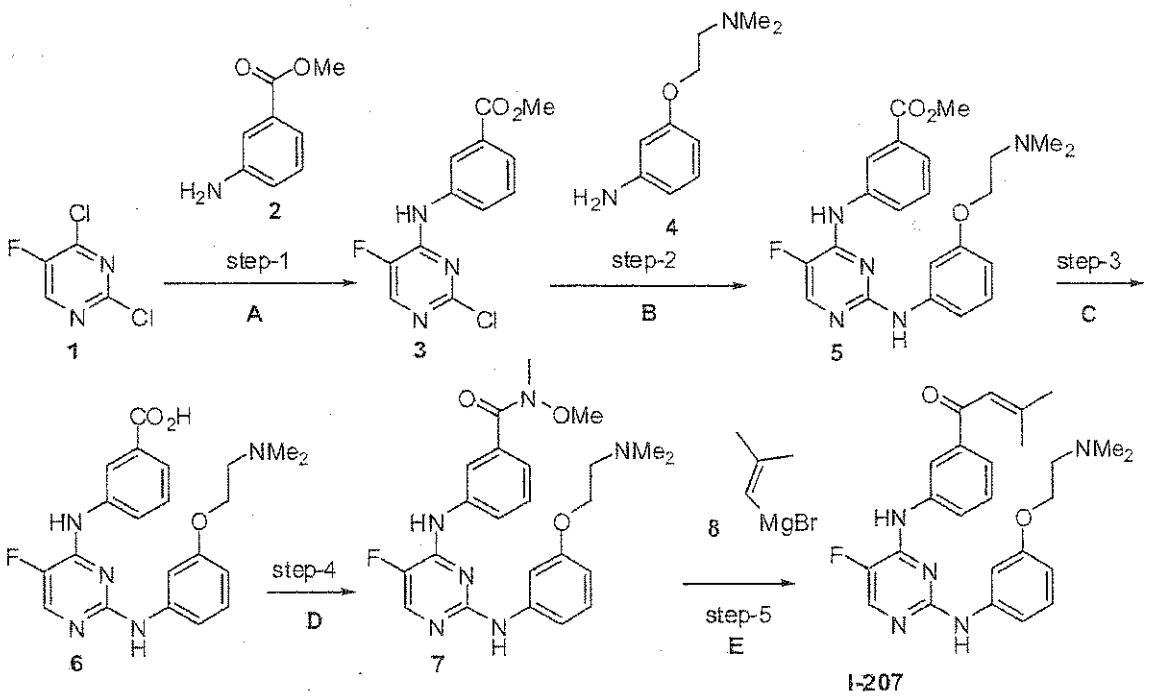
EXAMPLE 112

[00890] Preparation of 1-(4-(5-fluoro-2-(3-(2-dimethylaminoethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-2-methylprop-2-en-1-one **I-207**



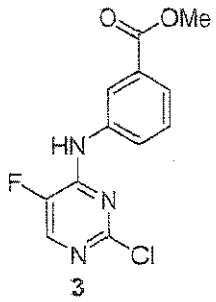
I-207

[00891] The title compound was prepared according to the schemes steps and intermediates described below.



A) **2**, DIPEA, n-BuOH, 90 ^{0}C, 12 h; **B**) **4**, $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 ^{0}C, 16 h; C) LiOH, MeOH/THF/H2O, rt, 6 h; **D**) MeNHOMe.HCl, EDCI.HCl, HOBT, DIPEA, DMF, rt, 3 h; **E**) **8**, THF, 0 ^{0}C to rt, 2 h.

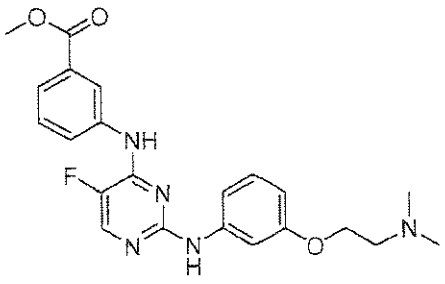
[00892] **Step-1**



3

[00893] A solution of **1** (4 g, 23.9 mmol), **2** (3.6 g, 23.7 mmol) and DIPEA (4.6 g, 35.58 mmol) in n-butanol (40 mL) was heated in a pressure tube (90 ^{0}C, 12 h). It was cooled, quenched with water (5 mL) and extracted with EtOAc (2 x 5 mL). The combined EtOAc extract was washed with water (60 mL), brine (40 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford **3** (5.5 g, 82 %) as an off-white solid.

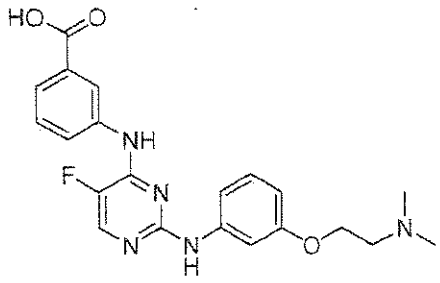
[00894] Step-2



5

[00895] A solution of **4** (0.319 g, 1.76 mmol), **3** (0.5 g, 1.76 mmol), $Pd(OAc)_2$ (0.039 g, 0.17 mmol), BINAP (0.055 g, 0.08 mmol) and Cs_2CO_3 (1.44 g, 4.42 mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated for 16 h at 110 ^{0}C under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (25 mL) and washed with water (5 mL), brine (2 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, chloroform/methanol, 9/1) to get **4** (0.63 g, 84%) as yellow solid.

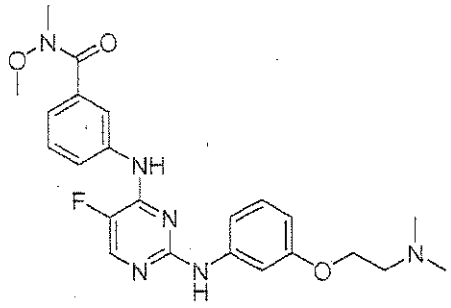
[00896] Step-3



6

[00897] To a stirred solution of **5** (0.3 g, 0.70 mmol) in methanol/THF/water : 1 mL/1 mL/0.5 mL was added LiOH (0.147 g, 3.52 mmol) and the reaction mixture was stirred at rt for 6 h. It was concentrated under reduced pressure; residue was diluted with water (2 mL) and extracted with diethyl ether (5 mL). The aqueous layer was separated and acidified with 1.5 N HCl (pH ~4-5) which was concentrated as such and dried under vacuum to get **6** (0.31 g, crude) as yellow gummy solid which was taken for next step without further purification.

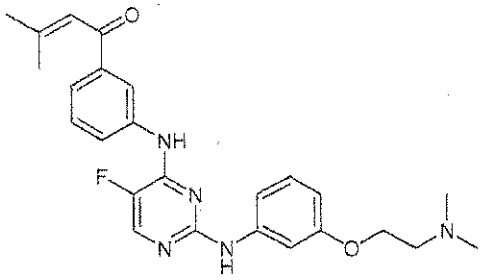
[00898] Step-4



7

[00899] To a stirred solution of **6** (0.29 g, 0.70 mmol) in DMF (3 mL) were added MeNH-OMe.HCl (0.068 g, 0.70 mmol), EDCI.HCl (0.202 g, 1.05 mmol), HOBT (0.047 g, 0.35 mmol) and DIPEA (0.136 g, 1.05 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with water and extracted with EtOAc (2x5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, 60-120, methanol/chloroform : 20/80) to get 7 (0.061 g, 19%) as gummy yellow solid.

[00900] Step-5



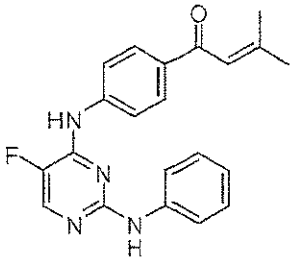
I-207

[00901] To a stirred solution of 7 (100 mg, 0.22 mmol) in THF (1 mL) at 0 ^{0}C was added **8** (17.6 mL, 8.80 mmol). The reaction mixture was allowed to stir at room temperature for 2 h. It was quenched with saturated NH_4Cl solution (0.5 mL) and extracted with EtOAc (2x3 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get a white solid. It was further purified by column chromatography (SiO_2, 60-120, product getting eluted in 20% methanol/chloroform) to get **I-207** (9 mg. 9%) as gummy yellow solid. ^{1}H NMR (DMSO-d_6) δ ppm: 1.90 (s, 3H), 2.01 (s, 3H), 2.19 (s, 6H), 2.57 (t, J = 5.64 Hz, 2H), 3.87 (t, J = 5.84 Hz, 2H), 6.45 (dd, J = 1.64 & 8.08 Hz, 1H), 6.82 (s, 1H), 7.04 (t, J = 8.16 Hz, 1H), 7.18 (d, J = 8.16 Hz, 1H), 7.33 (s, 1H), 7.47 (t, J = 7.88

Hz, 1H),7.62 (d, J = 7.72 Hz, 1H), 8.13-8.16 (m, 3H), 9.24 (s, 1H), 9.56 (s, 1H); LCMS : *m/e* 450.1 (M+1).

EXAMPLE 113

[00902] Preparation of 1-(4-(5-fluoro-2-(phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one **I-206**

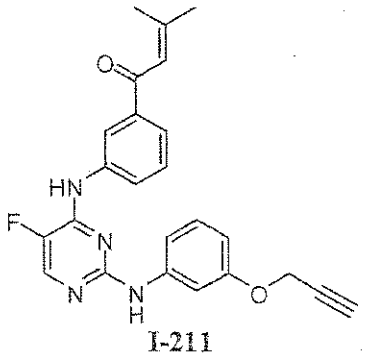


I-206

[00903] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 by using methyl 4-aminobenzoate in place of **2** in step-1 and aniline in place of **4** in step-2. ^{1}H NMR (DMSO-d_6) δ ppm : 1.98 (s, 3H), 2.12 (s, 3H), 6.90-7.00 (m, 2H), 7.20-7.30 (m, 2H), 7.65 (d, J = 8.16 Hz, 2H), 7.90 (d, J = 8.56 Hz, 2H), 7.98 (d, J = 8.68 Hz, 2H), 8.18 (bs, 1H), 9.31 (s, 1H), 9.68 (s, 1H); LCMS : *m/e* 363.0 (M+1).

EXAMPLE 114

[00904] Preparation of 1-(3-(5-fluoro-2-(3-(prop-2-ynyloxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one **I-211**



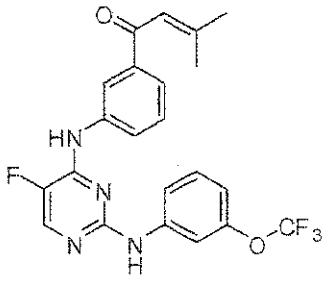
I-211

[00905] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 by using 3-prop-2-ynyloxyaniline in place of **4** in step-2. ^{1}H NMR

(CD_3OD) δ ppm: 2.0 (d, *J* = 1 Hz, 3H), 2.21 (d, *J* = 1.04 Hz, 3H), 2.94-2.96 (d, J = 2.44 Hz, 1H), 4.59 (d, J = 2.36 Hz, 2H), 6.79-6.81 (m, 2H), 7.03 (dd, *J* = 3.12 & 8.04 Hz, 1H), 7.14 (t, *J* = 2.2 Hz, 1H), 7.23 (t, *J* = 8.12 Hz, 1H), 7.54 (t, *J* = 7.92 Hz, 1H), 7.83 (d, *J* = 7.96 Hz, 1H), 7.86 (dd, *J* = 2.08 & 8.08 Hz, 1H), 8.03 (d, *J* = 4.96 Hz, 1H), 8.21 (t, *J* = 1.88 Hz, 1H); LCMS : *m/e* 417.0 (M+1).

EXAMPLE 115

[00906] Preparation of 1-(3-(5-fluoro-2-(3-(trifluoromethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one **I-223**

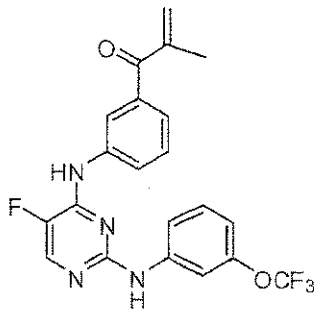


I-223

[00907] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 by using 3-trifluoromethoxyaniline in place of 4 in step-2. ^{1}H NMR ($CDCl_3$) δ ppm: 2.0 (d, *J* = 1.08 Hz, 3H), 2.24 (d, *J* = 1.04 Hz, 3H), 6.74 (t, *J* = 1.24 Hz, 1H), 6.85 (dd, *J* = 1.08 & 7.0 Hz, 1H), 6.90 (s, 1H), 7.08 (s, 1H), 7.24-7.28 (m, 1H), 7.35 (td, *J* = 1.2 & 7.44 Hz, 1H), 7.49 (t, *J* = 7.88 Hz, 1H), 7.63 (s, 1H), 7.72 (td, *J* = 1.04 & 7.76 Hz, 1H),7.90-7.92 (m, 1H), 8.00-8.05 (m, 2H); LCMS : m/e 447 (M+1).

EXAMPLE 116

[00908] Preparation of 1-(3-(5-fluoro-2-(3-(trifluoromethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-2-methylprop-2-en-1-one **I-199**

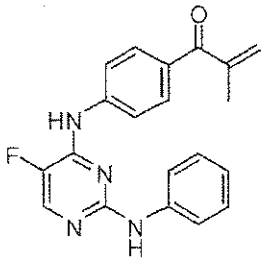


I-199

[00909] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 by using 3-trifluoromethoxyaniline in place of **4** in step-2 and isopropenylmagnesium bromide in place of **8** in step-5. ^{1}H NMR (DMSO-d_6) δ ppm: 1.97 (s, 3H), 5.6 (s, 1H), 6.0 (d, *J* = 0.96 Hz, 1H), 6.82 (d, *J* = 8.08 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 1H), 7.41 (dd, *J* = 1.12 & 7.56 Hz, 1H), 7.48 (t, *J* = 7.76 Hz, 1H), 7.60 (dd, *J* = 1.28 & 7.88 Hz, 1H), 7.78 (s, 1H), 7.90 (d, *J* = 1.64 Hz, 1H), 8.15 (d, *J* = 8 Hz, 1H), 8.19 (d, *J* = 3.64 Hz, 1H), 9.55 (s, 1H), 9.65 (s, 1H); LCMS : *m/e* 433 (M+1).

EXAMPLE 117

[00910] Preparation of 1-(4-(5-fluoro-2-(phenylamino)pyrimidin-4-ylamino)phenyl)-2-methylprop-2-en-1-one **I-185**



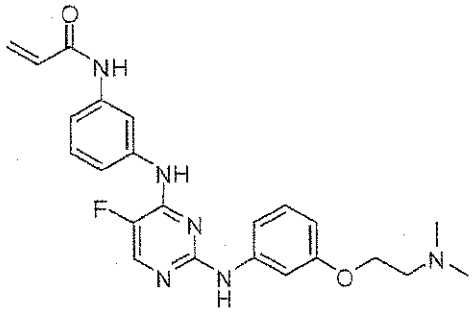
I-185

[00911] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 by using methyl 4-aminobenzoate in plave of **2** in step-1, aniline in place of **4** in step-2 and isopropenylmagnesium bromide in place of **8** in step-5. ^{1}H NMR

(DMSO-d_6) δ ppm: 1.99 (s, 3H), 5.54 (s, 1H), 1.01 (s, 1H), 6.93 (t, J = 7.36 Hz, 1H), 7.24 (t, J = 7.52 Hz, 2H), 7.66-7.72 (m, 4H), 8.01 (d, J = 8.72 Hz, 2H), 8.19 (d, J = 3.6 Hz, 1H), 9.32 (s, 1H), 9.72 (s, 1H); LCMS : *m/e* 348.8 (M+1).

EXAMPLE 118

[00912] Preparation of N-(3-(2-(3-(2-(dimethylamino)ethoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-233**

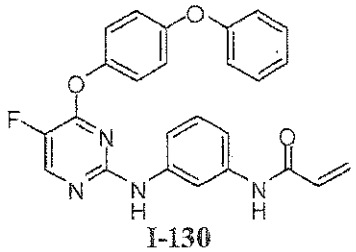


I-233

[00913] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 3-(2-dimethylaminoethoxy)aniline in place of 4 in step-2. ^{1}H NMR (CD_3OD) δ ppm: 2.31 (s, 6H), 2.76 (t, J = 5.6 Hz, 2H), 3.97 (t, J = 5.2 Hz, 2H), 5.78 (dd, J = 2 & 9.2 Hz, 1H), 6.38-6.42 (m, 2H), 6.52-6.55 (m, 1H), 7.1-7.11 (m 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.42-7.48 (m, 2H), 7.94 (d, J = 3.6 Hz, 1H), 8.05 (s, 1H); LCMS : *m/e* 437 (M+1).

EXAMPLE 119

[00914] Preparation of N-(3-(5-fluoro-4-(4-phenoxyphenoxy)pyrimidin-2-ylamino)phenyl)acrylamide **I-130**

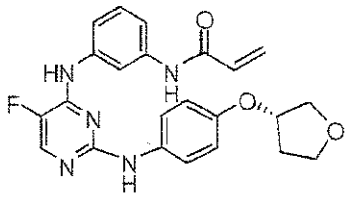


I-130

[00915] The title compound was prepared according to the steps, schemes and intermediates described in Example 11 by using 5-fluoro-2,4-dichloropyrimidine in place of **1** in step-1. ^{1}H NMR (DMSO-d_6) δ ppm: 5.71 (dd, J = 1.6 & 10 Hz, 1H), 6.22 (dd, J = 1.6 & 16.8 Hz, 1H), 6.44 (dd, J = 10.4 & 17.2 Hz, 1H), 6.98-7.05 (m, 3H), 7.1-7.12 (m, 2H), 7.17 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 2H), 7.35-7.37 (m, 2H), 7.42 (t, J = 8.4 Hz, 2H), 7.71 (s, 1H), 8.5 (s, 1H), 9.6 (s, 1H), 10.05 (s, 1H); LCMS : *m/e* 443.0 (M+1).

EXAMPLE 120

[00916] Preparation of (S)-N-(3-(5-fluoro-2-(4-(tetrahydrofuran-3-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-43**

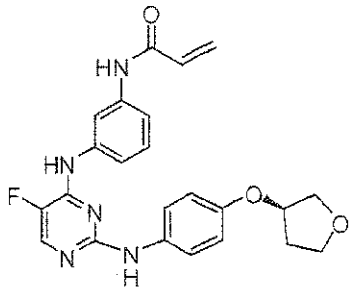


I-43

[00917] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using (S)-4-(tetrahydrofuran-3-yloxyaniline in place of **4** in step-2. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.10 (s, 1H), 9.35 (s, 1H), 8.95 (s, 1H), 8.05 (d, J = 4.0 Hz, 1H), 7.92 (s, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.45 (dd, J = 1.5, 17.0 Hz, 1H), 6.25 (dd, J = 1.1, 16.5 Hz, 1H), 5.75 (dd, J = 1.1, 10.0 Hz, 1H), 4.93 - 4.84 (m, 1H), 3.88 - 3.72 (m, 4H), 2.20 - 2.10 (m, 1H), 1.97 - 1.90 (m, 1H). MS m/e = 436 [M^++1]

EXAMPLE 121

[00918] Preparation of (R)-N-(3-(5-fluoro-2-(4-(tetrahydrofuran-3-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-46**

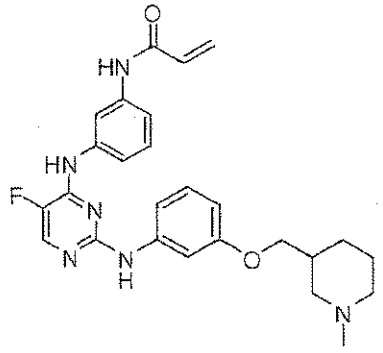


I-46

[00919] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using (R)-4-(tetrahydrofuran-3-yloxyaniline in place of 4 in step-2. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.10 (s, 1H), 9.35 (s, 1H), 8.95 (s, 1H), 8.05 (d, J = 4.0 Hz, 1H), 7.92 (s, 1H), 7.52 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 7.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 2H), 6.45 (dd, J = 1.5, 17.0 Hz, 1H), 6.25 (dd, J = 1.1, 16.5 Hz, 1H), 5.75 (dd, J = 1.1, 10.0 Hz, 1H), 4.93 - 4.84 (m, 1H), 3.88 - 3.72 (m, 4H), 2.22 – 2.14 (m, 1H), 1.97 - 1.90 (m, 1H). MS: m/e = 436 [M^++1]

EXAMPLE 122

[00920] Preparation of N-(3-(5-fluoro-2-(3-((1-methylpiperidin-3-yl)methoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-acrylamide **I- 76**)



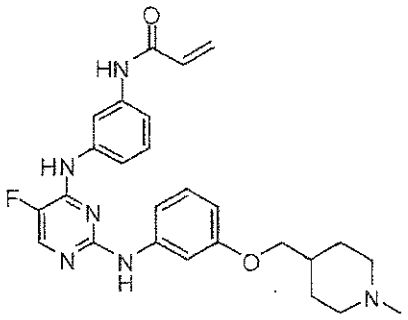
I- 76

[00921] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 3-(1-methylpiperidin-3-yl)methoxyaniline in place of 4 in

step-2. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 10.08 (s, 1H), 9.41 (s, 1H), 9.09 (s, 1H), 8.11 (d, J = 3.5 Hz, 1H), 7.90 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.30 - 7.20 (m, 2H), 7.03 (t, J = 8.0 Hz, 1H), 6.50 - 6.40 (m, 2H), 6.24 (dd, J = 1.5, 17.0 Hz, 1H), 5.74 (dd, J = 2.0, 10.5 Hz, 1H), 3.75 - 3.65 (m, 2H), 2.73 (d, J = 10 Hz, 1H), 2.60 (d, J = 10.5 Hz, 1H), 2.13 (s, 3H), 1.98 - 1.83 (m, 2H), 1.75 - 1.58 (m, 3H), 1.55 - 1.45 (m, 1H), 1.05 - 0.95 (m, 1H). MS: m/e = 477 (M^++1).

EXAMPLE 123

[00922] Preparation of N-(3-(5-fluoro-2-(3-((1-methylpiperidin-4-yl)methoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-acrylamide **I-82**

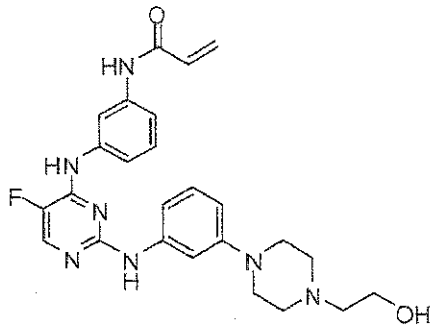


I-82

[00923] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 3-(1-methylpiperidin-4-yl)methoxyaniline in place of **4** in step-2. ^{1}H-NMR ($CDCl_3$+DMSO-D_6, 500 MHz): δ 9.04 (bs, 1H), 8.30 (s, 1H), 7.96 (s, 1H), 7.75 (s, 1H), 7.63 (s, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.38 - 7.33 (m, 2H), 7.27 (t, J = 8.5 Hz, 1H), 7.16 (t, J = 8 Hz, 1H), 7.09 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 7.0 Hz, 1H), 6.51 - 6.38 (m, 2H), 5.73 (dd, J = 2.0, 9.0 Hz, 1H), 3.77 (d, J = 6.0 Hz, 2H), 2.90 - 2.84 (m, 2H), 2.28 (s, 3H), 1.95 (t, J = 10.0 Hz, 1H), 1.85 - 1.74 (m, 2H), 1.45 - 1.32 (m, 2H), 1.28 - 1.25 (m, 2H). MS: m/e = 477 (M^++1).

EXAMPLE 124

[00924] Preparation of N-(3-(2-(3-(4-(2-hydroxyethyl)piperazin-1-yl)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-83**

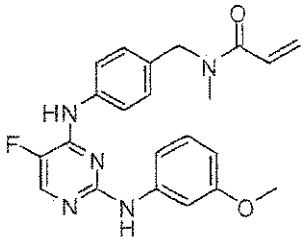


I-83

[00925] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 3-(4-(2-t-butyldimethylsilyloxyethyl)piperazin-1-ylaniline in place of **4** in step-2 and deprotecting the TBS ether with TFA in DCM as a step-5. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.99 (s, 1H), 8.85 (s, 1H), 8.04 (d, J = 4.0 Hz, 1H), 7.28 - 7.19 (m, 2H), 7.08 - 7.00 (m, 2H), 6.94 (t, J = 3.5 Hz, 2H), 6.48 (dd, J = 2.0, 8.0 Hz, 1H), 6.35 - 6.31 (m, 1H), 4.94 (s, 2H), 3.71 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 4.5 Hz, 4H), 2.57 - 2.50 (m, 4H), 2.46 (t, J = 6.0 Hz, 2H), 0.87 (s, 9H), 0.05 (s, 6H). MS: m/e = 538 (M^++1).

EXAMPLE 125

[00926] Preparation of N-(4-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)benzyl)-N-methylacrylamide **I-113**



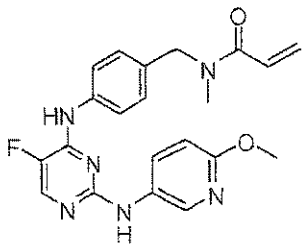
I-113

[00927] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 4-(N-methyl-N-tert-butyloxycarbonylamino)methylaniline in place of **2** in step-1 and 3-methoxyaniline in place of **4** in step-2. ^{1}H-NMR (DMSO-d_6, 200

MHz): δ 9.36 (bs, 1H), 9.16 (bs, 1H), 8.10 (d, J = 3.4 Hz, 1H), 7.83 - 7.70 (m, 2H), 7.34 (bs, 1H), 7.26 - 7.01 (m, 4H), 6.86 - 6.73 (m, 1H), 6.48 (d, J = 8.0 Hz, 1H), 6.21 (dd, J = 16.4, 2.2 Hz, 1H), 5.76- 5.64 (m, 1H), 4.64 - 4.53 (two s, 2H), 3.65 (s, 3H), 3.00 - 2.88 (two s, 3H). MS: m/e = 408.2 [M^++1].

EXAMPLE 126

[00928] Preparation of N-(4-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)benzyl)-N-methylacrylamide **I-114**

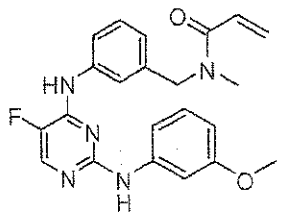


I-114

[00929] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 4-(N-methyl-N-tert-butyloxycarbonylamino)methylaniline in place of **2** in step-1 and 6-methoxy-3-aminopyridine in place of **4** in step-2. ^{1}H-NMR (DMSO-D_6, 200 MHz): δ 9.36 (bs, 1H), 9.09 (bs, 1H), 8.32 (bs, 1H), 8.06 (dd, J = 3.8 Hz, 1H), 7.97-7.92 (m, 1H), 7.76- 7.68 (m, 2H), 7.20 - 7.08 (m, 2H), 6.87 - 6.75 (m, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.22 (dd, J = 19.4, 2.6 Hz, 1H), 5.74 - 5.65 (m, 1H), 4.64 - 4.53 (two s, 2H), 3.78 (s, 3H), 3.00 - 2.88 (two s, 3H). MS: m/e = 409 (M^++1).

EXAMPLE 127

[00930] Preparation of N-(3-(5-fluoro-2-(3-methyoxyphenylamino)pyrimidin-4-ylamino)benzyl)-N-methylacrylamide **I-115**

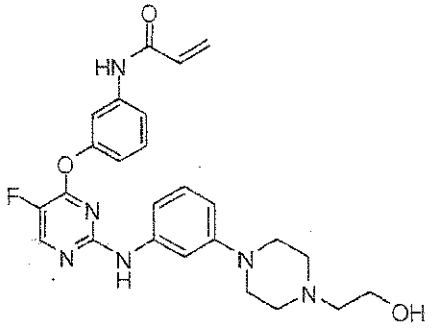


I-115

[00931] The title compound was prepared according to the steps, schemes and intermediates described in Example 20 by using 3-(N-methyl-N-tert-butyloxycarbonylamino)methylaniline in place of **2** in step-1 and 3-methoxyaniline in place of **4** in step-2. ^{1}H-NMR (DMSO-d_6, 200 MHz): δ 9.50 - 9.30 (m, 1H), 9.15 - 8.96 (m, 1H), 8.15 (bs, 1H), 7.82 - 7.59 (m, 2H), 7.45 - 7.00 (m, 4H), 6.97 - 6.65 (m, 2H), 6.55 - 6.45 (m, 1H), 6.26 - 6.12 (m, 1H), 5.78 - 5.60 (m, 1H), 4.68 (s, 1H), 4.55 & 3.75 (two s, 3H), 2.90 & 3.00 (two s, 3H). MS: m/e = 408.2 [M^++1].

EXAMPLE 128

[00932] Preparation of N-(3-(5-fluoro-2-(3-(4-(2-hydroxyethyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy) phenyl)acrylamide **I-84**

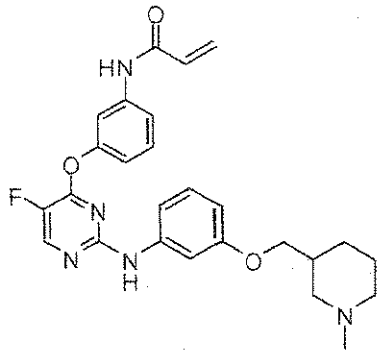


I-84

[00933] The title compound was prepared according to the steps, schemes and intermediates described in Example 98 by using 3-(4-(2-t-butyldimethylsilyloxyethyl)piperazin-1-ylaniline in place of **4** in step-2 and deprotecting the TBS ether with TFA in DCM as a step-5. ^{1}H-NMR (DMSO-D_6, 500 MHz): δ 8.19 (s, 1H), 7.75 - 7.70 (m, 2H), 7.42 - 7.35 (m, 2H), 7.12 - 7.05 (m, 2H), 6.97 (dd, J = 2.0, 10.5 Hz, 1H), 6.93 (s, 1H), 6.72 (d, J = 6.5 Hz, 1H), 6.57 - 6.54 (m, 1H), 6.44 (d, J = 17.0 Hz, 1H), 6.29 - 6. 20 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 3.68 (t, J = 5.5 Hz, 2H), 3.00 - 2.94 (m, 4H), 2.63 - 2.56 (m, 6H). MS: m/e = 479 (M^++1).

EXAMPLE 129

[00934] Preparation of N-(3-(5-fluoro-2-(3-((1-methylpiperidin-3-yl)methoxy)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-81**

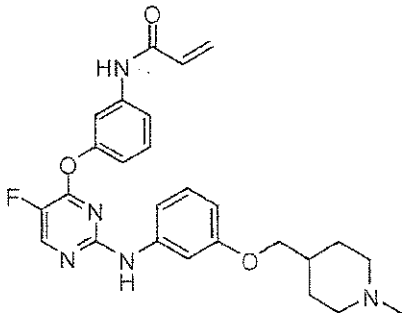


I-81

[00935] The title compound was prepared according to the steps, schemes and intermediates described in Example 98 by using 3-(1-methylpiperidin-3-yl)methoxyaniline in place of 4 in step-2. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.19 (d, J = 2.5 Hz, 1H), 7.82 - 7.75 (m, 2H), 7.42 - 7.36 (m, 2H), 7.08 - 7.02 (m, 3H), 6.99 (d, J = 7.0 Hz, 1H), 6.91 (s, 1H), 6.79 (d, J = 7.5 Hz, 1H), 6.48 - 6.44 (m, 1H), 6.42 (s, 1H), 6.29 - 6.23 (m, 1H), 5.77 (d, J = 10 Hz, 1H), 3.67 - 3.62 (m, 2H), 2.95 - 2.91 (m, 1H), 2.82 - 2.76 (m, 1H), 2.28 (s, 3H), 2.11 - 2.05 (m, 1H), 1.98 - 1.92 (m, 1H), 1.79 - 1.70 (m, 3H), 1.11 - 1.04 (m, 1H). MS: m/e = 478 (M^++1).

EXAMPLE 130

[00936] Preparation of N-(3-(5-fluoro-2-(3-((1-methylpiperidin-4-yl)methoxy)phenylamino)pyrimidin-4-yloxy)phenyl)-acrylamide **I-75**

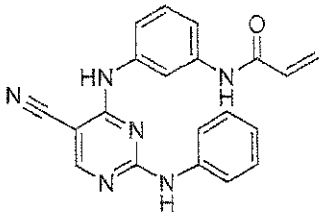


I-75

[00937] The title compound was prepared according to the steps, schemes and intermediates described in Example 98 by using 3-(1-methylpiperidin-4-yl)methoxyaniline in place of 4 in step-2. ^{1}H-NMR (DMSO-D_6, 500 MHz): δ 10.31(s, 1H), 9.50 (s, 1H), 8.50 (s, 1H), 7.67 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.10 (s, 1H), 7.04 (d, J = 7.0 Hz, 2H), 6.94 (t, J = 8.0 Hz, 1H), 6.45 - 6.39 (m, 2H), 6.27 (d, J = 15.0 Hz, 1H), 5.78 (dd, J = 2.0, 10.5 Hz, 1H), 3.64 (d, J = 6.0 Hz, 2H), 2.75 (d, J = 6.5 Hz, 2H), 2.14 (s, 3H), 1.83 (t, J = 10.5 Hz, 2H), 1.66 - 1.64 (m, 3H), 1.25 - 1.23 (m, 2H). MS: m/e = 478 (M^++1).

EXAMPLE 131

[00938] Preparation of N-(3-(5-cyano-2-(phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-157

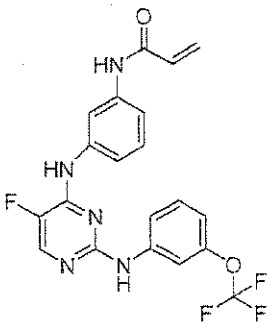


I-157

[00939] The title compound was prepared according to the schemes, steps and intermediates described in Example 94, by using 2,4-dichloro-5-cyanopyrimidine in the place of 4 in Step 2. MS 379.1 (M+Na).

EXAMPLE 132

[00940] Preparation of N-(3-(5-fluoro-2-(3-(trifluoromethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-244

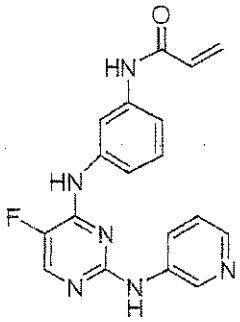


I-244

[00941] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-(trifluoromethoxy)aniline in the place of **4** in Step 2. MS 434.1 (M+1).

EXAMPLE 133

[00942] Preparation of N-(3-(5-fluoro-2-(pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-234**

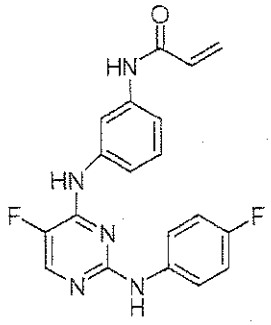


I-234

[00943] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-aminopyridine in the place of **4** in Step 2. MS 351.1 (M+1).

EXAMPLE 134

[00944] Preparation of N-(3-(5-fluoro-2-(4-fluorophenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I- 247**

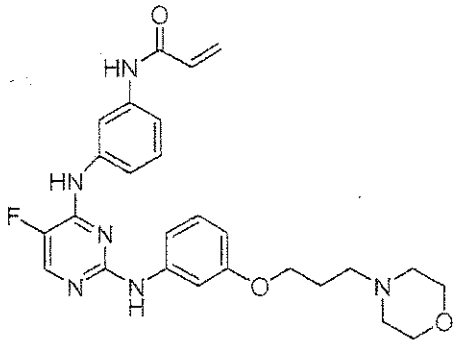


I- 247

[00945] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-fluoroaniline in the place of **4** in Step 2. MS 368.1 (M+1)

EXAMPLE 135

[00946] Preparation of N-(3-(5-fluoro-2-(3-(3-morpholinopropoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-208**

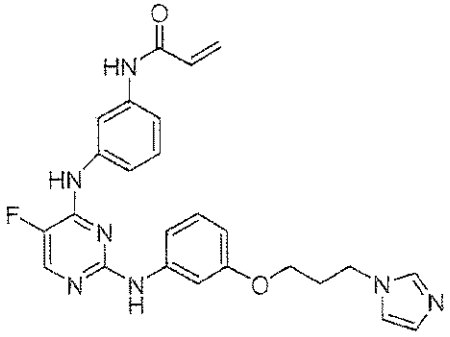


I- 208

[00947] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-(3-morpholinopropoxy)aniline in the place of 4 in Step 2. MS 515.3 (M+Na).

EXAMPLE 136

[00948] Preparation of N-(3-(2-(3-(3-(1H-imidazol-1-yl)propoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I- 204**

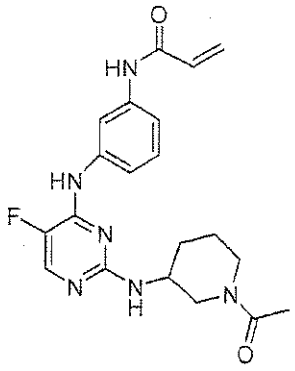


I- 204

[00949] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-(3-(1H-imidazol-1-yl)propoxy)aniline in the place of 4 in Step 2. MS 474.3 (M+Na).

EXAMPLE 137

[00950] Preparation of N-(3-(2-(1-acetylpiperidin-3-ylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-238**

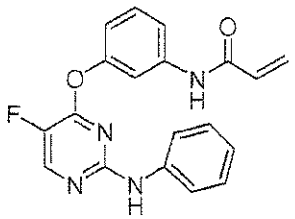


I-238

[00951] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 1-(3-aminopiperidin-1-yl)ethanone in the place of **4** in Step 2. MS 421.1 (M+Na).

EXAMPLE 138

[00952] Preparation of N-(3-(5-fluoro-2-(phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-228**

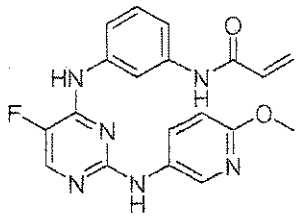


I-228

[00953] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using aniline in the place of **4** in Step 2. MS 351.3 (M+1).

EXAMPLE 139

[00954] Preparation of N-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-243**

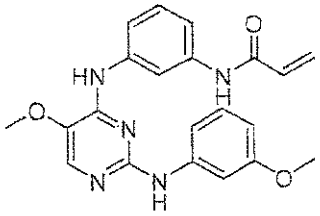


I-243

[00955] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 6-methoxypyridin-3-amine in the place of **4** in Step 2. MS 381.1 (M+1).

EXAMPLE 140

[00956] Preparation of N-(3-(5-methoxy-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide. **I-158**

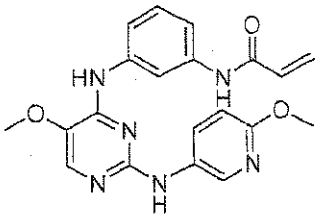


I-158

[00957] The title compound was prepared according to the schemes, steps and intermediates described in Example 1, by using 5-methoxy-2,4-dichloropyrimidine in the place of **1** in Step 1 and 3-methoxyaniline in place of 4 in step 2. MS 392.3 (M+1).

EXAMPLE 141

[00958] Preparation of N-(3-(5-methoxy-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-192

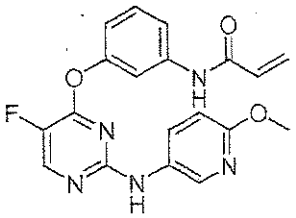


I-192

[00959] The title compound was prepared according to the schemes, steps and intermediates described in Example 1, by using 5-methoxy-2,4-dichloropyrimidine in the place of 1 in Step 1 and 5-amino-2-methoxypyridine in place of 4 in step 2. MS 393.3 (M+1).

EXAMPLE 142

[00960] Preparation of N-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-yloxy)phenyl)acrylamide I-222

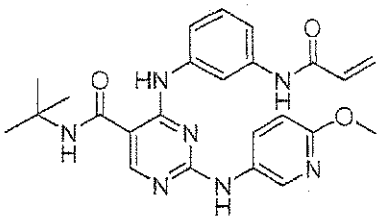


I-222

[00961] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using 3-amino-6-methoxypyridine in the place of 4 in Step 2. MS 382.3 (M+1).

EXAMPLE 143

[00962] Preparation of 4-(3-acrylamidophenylamino)-N-tert-butyl-2-(6-methoxypyridin-3-ylamino)pyrimidine-5-carboxamide **I-216**

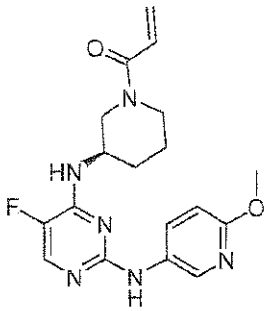


I-216

[00963] The title compound was prepared according to the schemes, steps and intermediates described in Example 37, by using tert-butylamine in the place of **2** in Step-1 and omitting Step-6. MS 484.3 (M+Na).

EXAMPLE 144

[00964] Preparation of (R)-1-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-202**

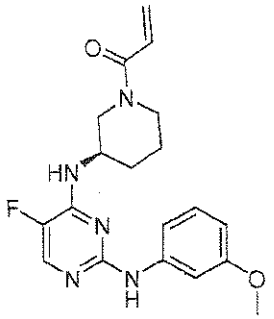


I-202

[00965] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-amino-6-methoxypyridine in place of **4** in step 2. MS 395.3 (M+Na).

EXAMPLE 145

[00966] Preparation of (R)-1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-195**

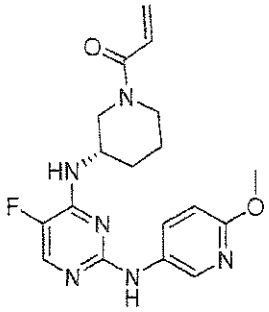


I-195

[00967] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-methoxyaniline in place of **4** in step 2. MS 394.3 (M+Na).

EXAMPLE 146

[00968] Preparation of (S)-1-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-197**

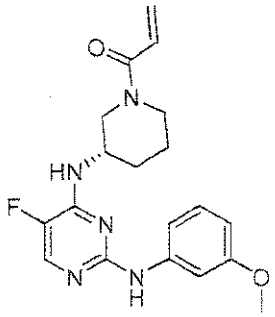


I-197

[00969] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-amino-6-methoxypyridine in place of **4** in step 2. MS 373.3 (M+1).

EXAMPLE 147

[00970] Preparation of (S)-1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-196**

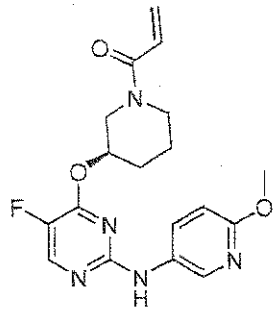


I-196

[00971] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-methoxyaniline in place of **4** in step 2. MS 372.3 (M+1).

EXAMPLE 148

[00972] Preparation of (R)-1-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-yloxy)piperidin-1-yl)prop-2-en-1-one **I-180**

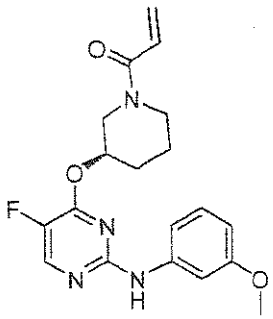


I-180

[00973] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using (R)-tert-butyl 3-hydroxypiperidine-1-carboxylate in the place of **2** in Step 1 and 3-amino-6-methoxypyridine in place of **4** in step 2. MS 374.3 (M+1).

EXAMPLE 149

[00974] Preparation of (R)-1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-yloxy)piperidin-1-yl)prop-2-en-1-one **I-190**

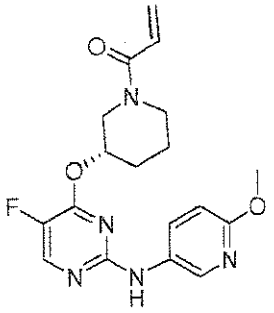


I-190

[00975] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using (R)-tert-butyl 3-hydroxypiperidine-1-carboxylate in the place of **2** in Step 1 and 3-methoxyaniline in place of **4** in step 2. MS 395.3 (M+Na).

EXAMPLE 150

[00976] Preparation of (S)-1-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-yloxy)piperidin-1-yl)prop-2-en-1-one **I-193**

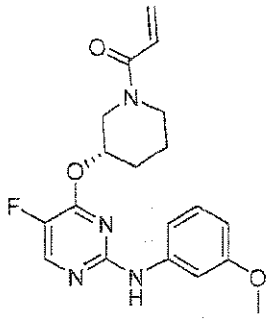


I-193

[00977] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate in the place of **2** in Step 1 and 3-amino-6-methoxypyridine in place of **4** in step 2. MS 396.3 (M+Na).

EXAMPLE 151

[00978] Preparation of (S)-1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-yloxy)piperidin-1-yl)prop-2-en-1-one I-179

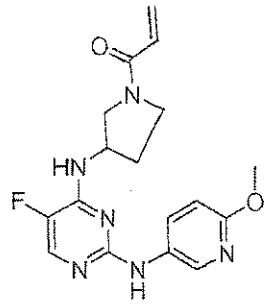


I-179

[00979] The title compound was prepared according to the schemes, steps and intermediates described in Example 98, by using (S)-tert-butyl 3-hydroxypiperidine-1-carboxylate in the place of 2 in Step 1 and 3-methoxyaniline in place of 4 in step 2. MS 395.3 (M+Na).

EXAMPLE 152

[00980] Preparation of 1-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)pyrrolidin-1-yl)prop-2-en-1-one I-203

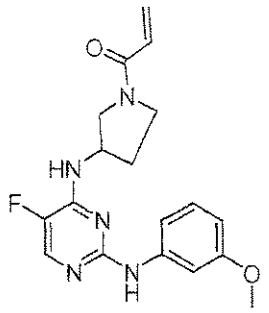


I-203

[00981] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butyl 3-aminopyrrolidine-1-carboxylatein the place of 2 in Step 1 and 3-amino-6-methoxypyridine in place of 4 in step 2. MS 381.3 (M+Na).

EXAMPLE 153

[00982] Preparation of 1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)pyrrolidin-1-yl)prop-2-en-1-one **I-201**

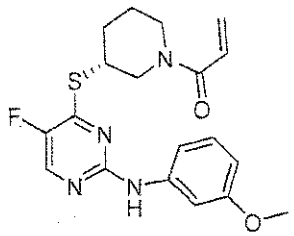


I-201

[00983] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butyl 3-aminopyrrolidine-1-carboxylate in the place of 2 in Step 1 and 3-methoxyaniline in place of 4 in step 2. MS 358.3 (M+1).

EXAMPLE 154

[00984] Preparation of (R)-1-(3-(5-fluoro-2-(3-methoxyphenylamino)pyrimidin-4-ylthio)piperidin-1-yl)prop-2-en-1-one **I-137**

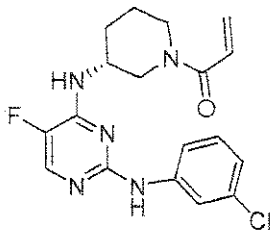


I-137

[00985] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)-tert-butyl 3-mercaptopiperidine-1-carboxylate in the place of 2 in Step 1 and 3-methoxyaniline in place of 4 in step 2. MS 411.1 (M+Na).

EXAMPLE 155

[00986] Preparation of (R)-1-(3-(2-(3-chlorophenylamino)-5-fluoropyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-147**

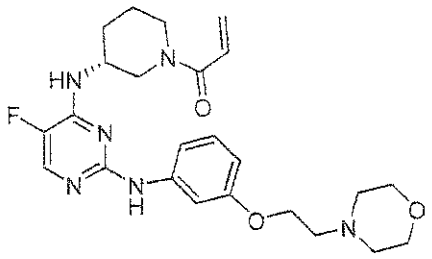


I-147

[00987] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-chloroaniline in place of **4** in step 2. MS 376.1 (M+1).

EXAMPLE 156

[00988] Preparation of (R)-1-(3-(5-fluoro-2-(3-(2-morpholinoethoxy)phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-135**

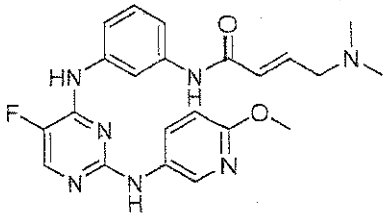


I-135

[00989] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)-tert-butyl 3-aminopiperidine-1-carboxylate in the place of **2** in Step 1 and 3-(2-morpholinoethoxy)aniline in place of **4** in step 2. MS 471.3 (M+1).

EXAMPLE 157

[00990] Preparation of (E)-4-(dimethylamino)-N-(3-(5-fluoro-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)but-2-enamide **I-125**

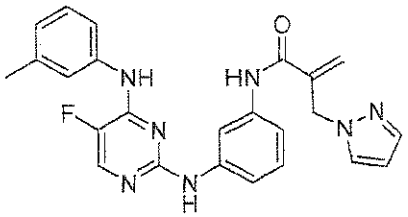


I-125

[00991] The title compound was prepared according to the schemes, steps and intermediates described in Example 139, by using (E)-4-(dimethylamino)but-2-enoyl chloride in the place of **7** in Step 4. MS 460.1 (M+Na).

EXAMPLE 158

[00992] Preparation of 2-((1H-pyrazol-1-yl)methyl)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)acrylamide. **I-98**

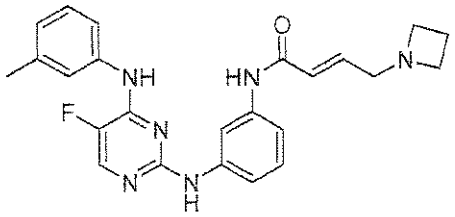


I-98

[00993] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using 2-((1H-pyrazol-1-yl)methyl)acryloyl chloride in the place of **6** in Step 3. MS 466.1 (M+Na).

EXAMPLE 159

[00994] Preparation of (E)-4-(azetidin-1-yl)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)but-2-enamide **I-123**

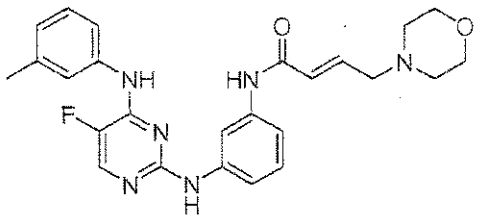


I-123

[00995] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (E)-4-(azetidin-1-yl)but-2-enoyl chloride in the place of **6** in Step 3. MS 455.1 (M+Na).

EXAMPLE 160

[00996] Preparation of (E)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)-4-morpholinobut-2-enamide **I-102**

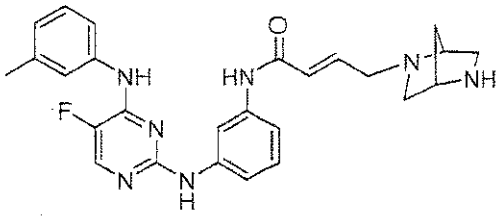


I-102

[00997] The title compound was prepared according to the schemes, steps and intermediates described in Example Example 4, by using (E)-4-(morpholin-4-yl)but-2-enoyl chloride in the place of **6** in Step 3. MS 485.3 (M+Na).

EXAMPLE 161

[00998] Preparation of (E)-4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)but-2-enamide **I-101**

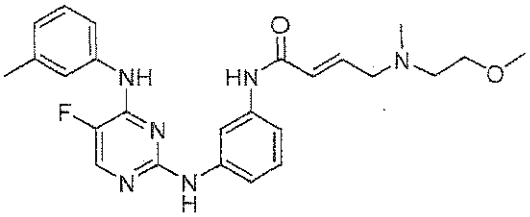


I-101

[00999] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (E)-4-((1S,4S)-2,5-diazabicyclo[2.2.1]heptan-2-yl)but-2-enoyl chloride in the place of **6** in Step 3. MS 496.1 (M+Na).

EXAMPLE 162

[001000] Preparation of (E)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)-4-((2-methoxyethyl)(methyl)amino)but-2-enamide **I-120**

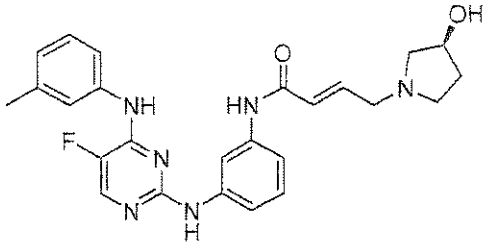


I-120

[001001] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (E)-4-((2-methoxyethyl)(methyl)amino)but-2-enoyl chloride in the place of **6** in Step 3. MS 487.3 (M+Na).

EXAMPLE 163

[001002] Preparation of (S,E)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)-4-(3-hydroxypyrrolidin-1-yl)but-2-enamide **I-99**

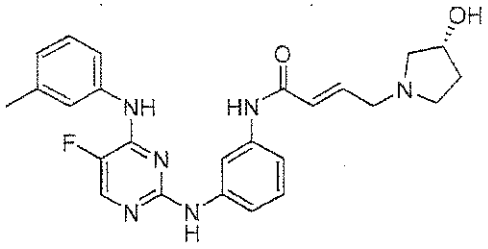


I-99

[001003] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (S,E)-4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl chloride in the place of **6** in Step 3. MS 485.3 (M+Na)

EXAMPLE 164

[001004] Preparation of (R,E)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)-4-(3-hydroxypyrrolidin-1-yl)but-2-enamide **I-104** .

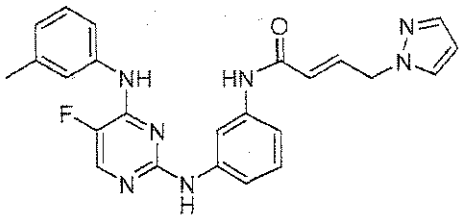


I-104

[001005] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (R,E)-4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl in the place of **6** in Step 3. MS 485.3 (M+Na).

EXAMPLE 165

[001006] Preparation of (E)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)-4-(1H-pyrazol-1-yl)but-2-enamide **I-100**

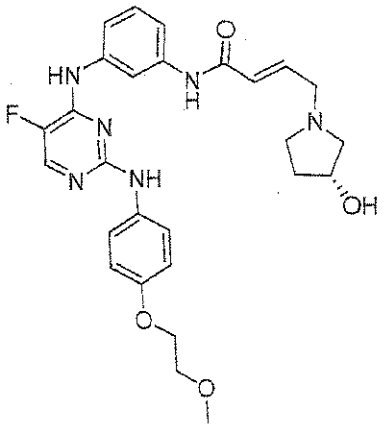


I-100

[001007] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (E)-4-(1H-imidazol-1-yl)but-2-enoyl chloride in the place of **6** in Step 3. MS 466.1 (M+Na).

EXAMPLE 166

[001008] Preparation of (R,E)-N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-4-(3-hydroxypyrrolidin-1-yl)but-2-enamide **I-89**

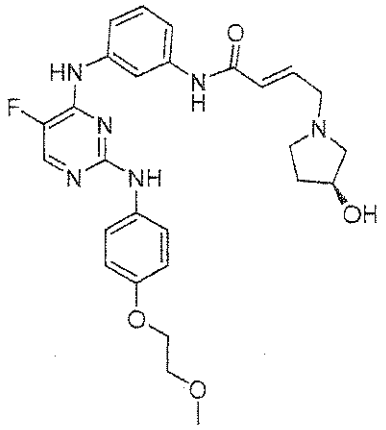


I-89

[001009] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R,E)-4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl chloride in the place of **7** in Step 4. MS 545.3 (M+Na).

EXAMPLE 167

[001010] Preparation of (S,E)-N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-4-(3-hydroxypyrrolidin-1-yl)but-2-enamide **I-88**

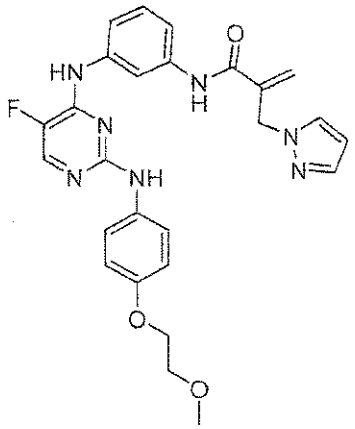


I-88

[001011] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S,E)-4-(3-hydroxypyrrolidin-1-yl)but-2-enoyl chloride in the place of 7 in Step 4. MS 545.3 (M+Na).

EXAMPLE 168

[001012] Preparation of 2-((1H-pyrazol-1-yl)methyl)-N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-85**

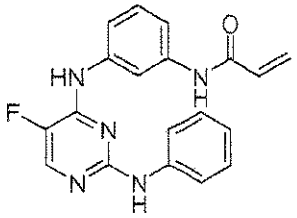


I-85

[001013] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 2-((1H-pyrazol-1-yl)methyl)acryloyl chloride in the place of 7 in Step 4. MS 526.1 (M+Na).

EXAMPLE 169

[001014] Preparation of N-(3-(5-fluoro-2-(phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-28**

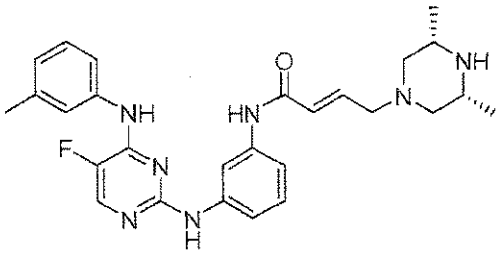


I-28

[001015] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using aniline in the place of 4 in Step 2. MS 372.1 (M+Na).

EXAMPLE 170

[001016] Preparation of (E)-4-((3R,5S)-3,5-dimethylpiperazin-1-yl)-N-(3-(5-fluoro-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)but-2-enamide **I-119**

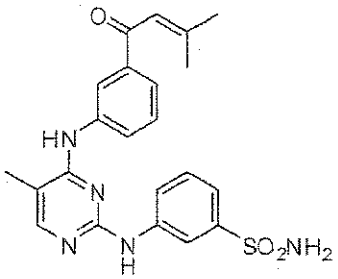


I-119

[001017] The title compound was prepared according to the schemes, steps and intermediates described in Example 4, by using (E)-4-((3R,5S)-3,5-dimethylpiperazin-1-yl)but-2-enoyl chloride in the place of 6 in Step 3. MS 512.3 (M+Na).

EXAMPLE 171

[001018] Preparation of 1-(3-(5-methyl-2-(3-aminosulfonylphenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one I-224

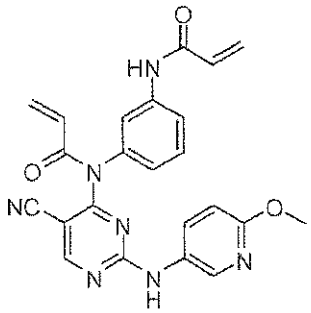


I-224

[001019] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 using 2,4-dichloro-5-methylpyrimine in place of **1** in step-1 and 3-aminobenzenesulfonamide in place of **4** in step-2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.97 (s, 3H), 2.14 (s, 6H), 6.88 (s, 1H), 7.25-7.30 (m, 4H), 7.47 (t, J = 7.92 Hz, 1H), 7.62 (d, J = 7.72 Hz. 1H), 7.96 (s, 1H), 8.0-8.07 (m, 3H), 8.20 (t, J = 7.36 Hz, 1H), 8.55 (s, 1H), 9.37 (s, 1H); LCMS : *m/e* 438 (M+1).

EXAMPLE 172

[001020] Preparation of N-(3-acrylamidophenyl)-N-(5-cyano-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-yl)acrylamide **I-171**

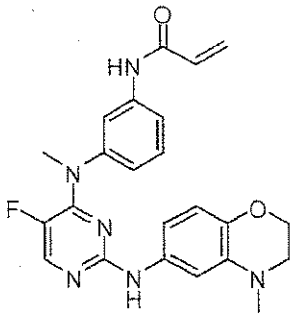


I-171

[001021] The title compound was prepared according to the schemes, steps and intermediates described in Example 95 using excess acroyl chloride in step-4. MS m/z: 442.1 ($M+H^+$).

EXAMPLE 173

[001022] Preparation of N-3-(N-methyl-N-(5-fluoro-2-(4-methyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidin-4-yl)aminophenylacrylamide **I-127**

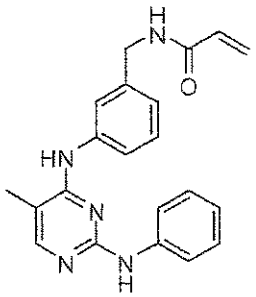


I-127

[001023] The title compound was prepared by treating the product of Example 88 with excess formaldehyde and $NaBH_3CN$ (2 equiv.) in acetonitrile and acetic acid (4:1). MS m/z: 435.1 ($M+H^+$).

EXAMPLE 174

[001024] Preparation of N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)benzyl)acrylamide **I-205**

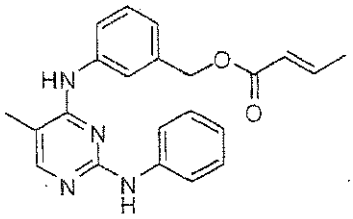


I-205

[001025] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 using 2,4-dichloro-5-methylpyrimidine in place of **1** and 3-(tert-butoxycarbonylamino)methylaniline in place of **2** in step-1, and aniline in place of **4** on step-2. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.91 (s, 1H), 7.77 (s, 1H), 7.57 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.36 - 7.26 (m, 2H), 7.13 - 6.96 (m, 4H), 6.36 - 6.25 (m, 2H), 5.97 (dd, J = 10.5, 17.0 Hz, 1H), 5.78 (bs, 1H), 5.63 (d, J = 10.5 Hz, 1H), 4.51 (d, J = 6.0 Hz, 2H), 2.12 (s, 3H). MS: m/e = 360 (M^++1).

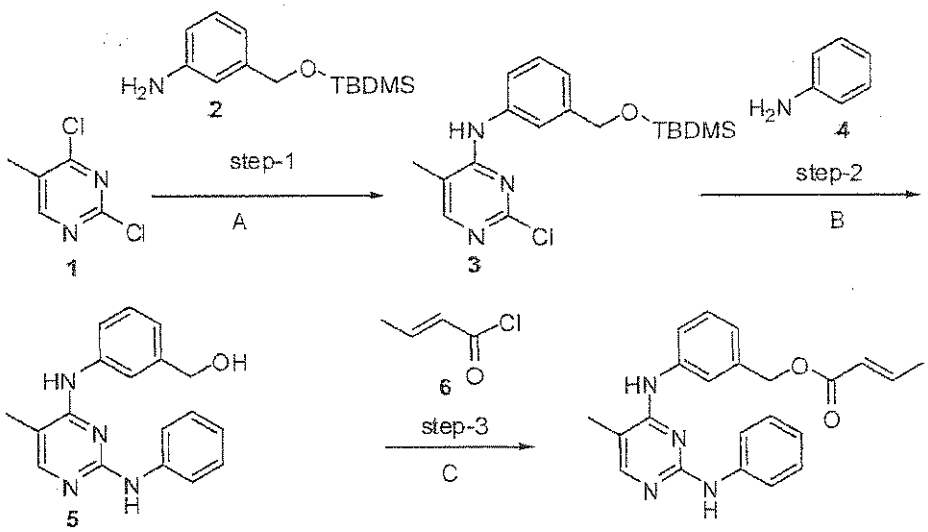
EXAMPLE 175

[001026] Preparation of (E)-3-(5-methyl-2-(phenylamino) pyrimidin-4-ylamino) benzyl but-2-enoate **I-246**



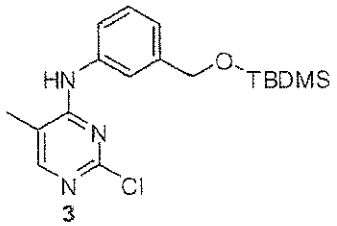
I-246

[001027] The title compound was prepared according to the schemes, steps, and intermediates described below.



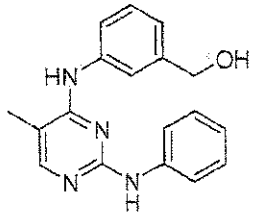
A) **2**, Xanthophos, $Pd_2(dba)_3$, Cs_2CO_3, CH_3CN, 90 °C, 12 hr; B) **4**, t-BuOH, 90 °C, 4 hr; C) **6**, TEA, DCM , -30 °C, 5 min

[001028] <u>Step-1</u>



[001029] To a stirred solution of **1** (0.34 g, 2.08 mmol) in acetonitrile (5 mL) were added Cs_2CO_3 (1.09 g, 3.35 mmol), Xanthophos (0.024 g, 0.041 mmol), $Pd_2(dba)_3$ (38 mg, 0.04 mmol) and **2** (0.5 g, 2.1 mmol) at RT under N_2 atmosphere. Argon gas was purged in to the reaction mixture for 1 h and stirred at 90 ^{0}C for 12 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography to afford **3** (0.56 g, 29.16%) as light yellow liquid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.0 (s, 1H), 7.55 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), (t, J = 7.5 Hz, 1H), (d, J = 7.5 Hz, 1H), 6.48 (s, 1H), 4.76 (s, 2H), 2.18 (s, 3H), 0.95 (s, 9H), 0.10 (s, 6H). MS: m/e = 364 [M^++1].

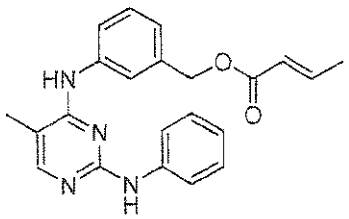
[001030] **Step-2**



5

[001031] To a stirred solution of **3** (0.07 g, 0.19 mmol) in t-BuOH (1.5 mL) was added aniline (**4**) (0.018 g, 0.19 mmol) at room temperature. The reaction mixture was heated up to 90 ^{0}C and stirred for 4 h at the same temperature. The progress of the reaction was monitored by TLC. After the completion of starting materials, the volatiles were removed under reduced pressure to give **5** (0.033 g, 55.9%) as light yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.45 (s, 1H), 9.82 (s, 1H), 7.91 (s, 1H), 7.58-7.01 (m, 9H), 4.50 (s, 2H), 2.16 (s, 3H). MS: m/e = 307 [M^++1].

[001032] **Step-3**



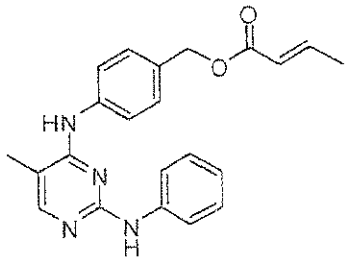
I-246

[001033] To a stirred solution of **5** (0.5 g, 1.63 mmol) in DCM (5 mL) was added **6** (0.18 g, 1.72 mmol) followed by TEA (0.66 mL, 4.78 mmol) at -30 ^{0}C under N_2 atmosphere. The

reaction mixture was stirred for 5 minutes at -30 ^{0}C and the progress of the reaction was monitored by TLC. After the completion of reaction, quenched with water and extracted with DCM (2 x 50 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by silica gel column chromatography to give 50 mg of an isomeric mixture of the title compound. This mixture in DCM (2 mL) was treated with DBU (0.02 g, 0.127 mmol) at room temperature. The reaction mixture was stirred for 2 h at room temperature, quenched with water and extracted with DCM (2 x 10 mL). The organic layer was separated, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford **I-246** (0.05 g, 10%) as light yellow solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.87 (s, 1H), 7.65 (s, 1H), 7.58-7.51 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.30-7.23 (m, 3H), 7.13 (d, *J* = 7.5 Hz, 1H), 7.08-6.96 (m, 2H), 6.40 (s, 1H), 5.87 (dd, *J* = 1.5, 15.5 Hz, 1H), 5.16 (s, 2H), 2.13 (s, 3H), 1.87 (dd, *J* = 2.0, 7.0 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 125 MHz): δ 166.3, 159.1, 158.4, 155.4, 145.3, 139.9, 138.9, 137.0, 128.9, 128.7, 123.2, 122.4, 121.9, 121.2, 121.0, 119.3, 105.2, 65.7, 17.9, 13.2. MS: m/e = 375 [M^++1].

EXAMPLE 176

[001034] Preparation of (E)-4-(5-methyl-2-(phenylamino) pyrimidin-4-ylamino) benzyl but-2-enoate **I-60**

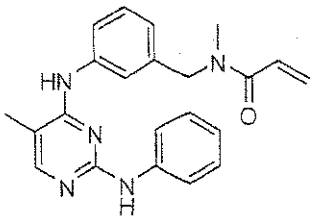


I-60

[001035] The title compound was prepared according to the schemes, steps and intermediates described in Example 175 using 4-((tert-butyldimethylsilyloxy) methyl) aniline in place of **2** in step-1. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 8.19 (bs, 1H), 7.81 (s, 1H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.42-7.36 (m, 3H), 7.28-7.22 (m, 1H), 7.08-6.98 (m, 2H), 6.54 (s, 1H), 5.89 (dd, *J* = 12.5, 14.0 Hz, 1H), 5.17 (s, 2H), 2.15 (s, 3H), 1.89 (dd, *J* = 1.5, 7.0 Hz, 3H). MS: m/e = 375 [M^++1].

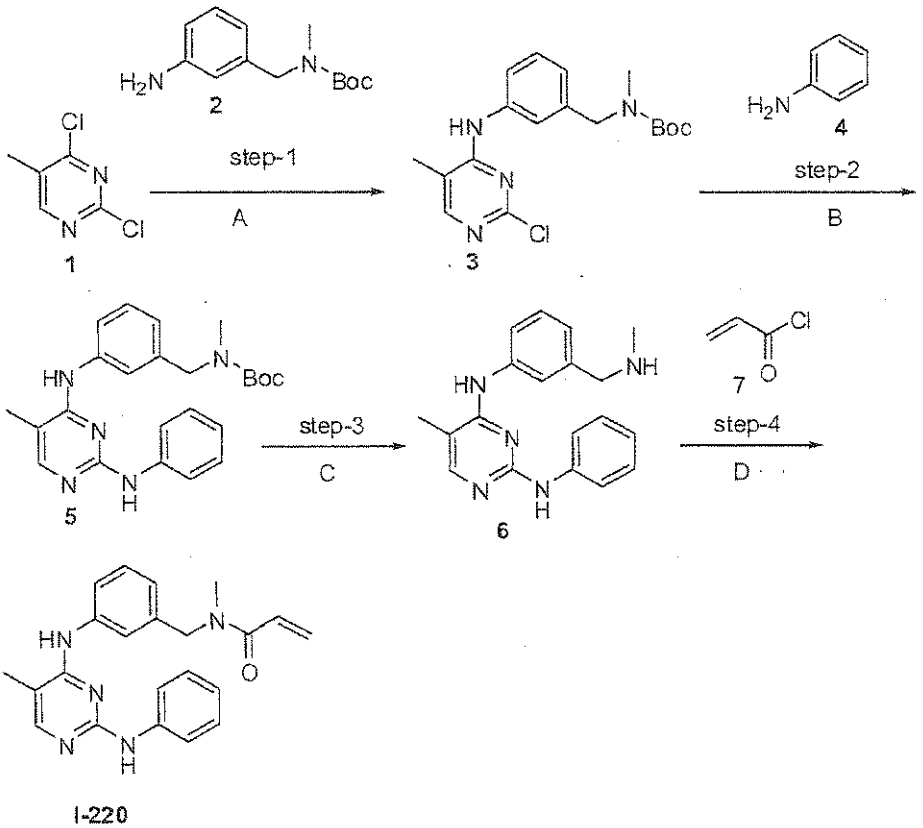
EXAMPLE 177

[001036] Preparation of N-methyl-N-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)benzyl)acrylamide **I-220**



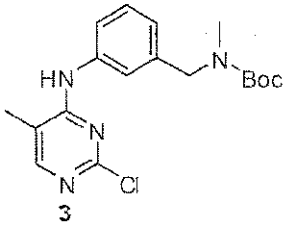
I-220

[001037] The title compound was prepared according to the schemes, steps, and intermediates described below.



A) **2**, Xanthophos, $Pd_2(dba)_3$, Cs_2CO_3, CH_3CN, 100 °C, 12 hr; B) **4**, t-BuOH, 90 °C, 4 hr; C) 10 N HCl, DCM , rt, 30 min: D) 7, TEA, DCM, -10 °C, 10 min.

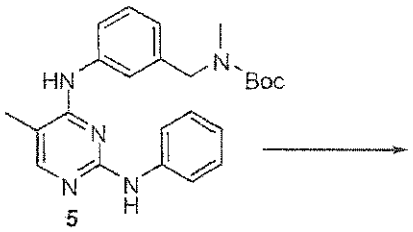
[001038] Step-1



3

[001039] To a stirred solution of 1 (2.6 g, 15.7 mmol) in acetonitrile (26.7 mL) was added 2 (2.67 g, 11.3 mmol), Pd_2 (dba)$_3$ (0.31 g, 0.33 mmol), Xanthophos (0.52 g, 0.89 mmol) and Cs_2CO_3 (6.6 g, 20.0 mmol). The reaction mixture was then degassed by purging argon for 1h and further heated to 100 ^{0}C for 12 h. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The resulting crude material was purified by column chromatography (60-120 mesh silica gel; 20% ethyl acetate/Hexane) to afford 3 (2.32 g, 56.71%) as light brown solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.01 (s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.43 (s, 1H), 7.35 (t, J = 7.0 Hz, 1H), 7.05 (s, 1H), 6.80 (bs, 1H), 4.45 (s, 2H), 2.87 (s, 3H), 2.30 (s, 3H), 1.48 (s, 9H).

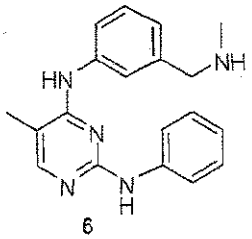
[001040] Step-2



5

[001041] To a stirred solution of 3 (2.32 g, 6.0 mmol) in t-BuOH (11.6 mL) was added 4 (0.65 g, 6.9 mmol) at RT and the reaction mixture was further heated at reflux for 48 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, t-BuOH was concentrated under reduced pressure to dryness to give 5 (2.3 g, 85.82%) as light yellow solid. ^{1}H-NMR (DMSO-d_6, 500 MHz): δ 10.32 (s, 1H), 9.78 (s, 1H), 7.91 (s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.45 - 7.30 (m, 4H), 7.24 (t, J = 7.0 Hz, 2H), 7.15 - 7.06 (m, 2H), 4.36 (s, 2H), 2.72 (s, 3H), 2.17 (s, 3H), 1.41, 1.34 (two s, 9H). MS: m/e = 420 (M^++1).

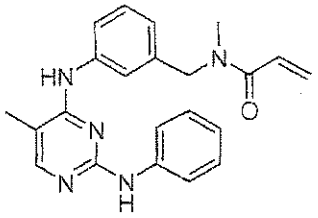
[001042] Step-3



6

[001043] To a stirred solution of **5** (0.05 mg, 0.11 mmol) in DCM (5 mL) was added 37% HCl (1.0 mL) and stirred at RT for 30 min. After the completion of the reaction (monitored by TLC), volatiles were removed under reduced pressure. The aqueous layer was cooled to 0 ^{0}C, basified up to pH ~ 8-9 with 10% NaOH solution and extracted with DCM (50 mL). The organic portion was separated, washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **6** (0.015 g, 48.36%) as light yellow solid. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ 7.95 - 7.85 (m, 2H), 7.68 -7.60 (m, 3H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.32 - 7.20 (m, 4H), 7.05 (d, *J* = 7.5 Hz, 1H), 7.00 - 6.95 (m, 1H), 6.40 (s, 1H), 3.84 (s, 2H), 2.48 (s, 3H), 2.06 (s, 3H). MS: m/e = 320 (M^{+}+1).

[001044] Step-4



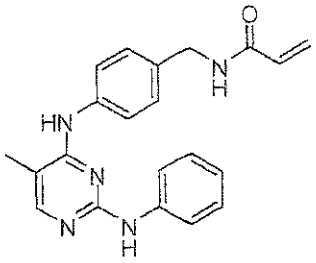
I-220

[001045] To a stirred solution of **6** (0.3 g, 0.94 mmol) in DCM (12 mL) was added TEA (0.10 g, 0.99 mmol) and **7** (0.08 g, 0.88 mmol) dropwise over a period of 5 min at -10 °C under inert atmosphere. The reaction mixture was then stirred at -10 °C for 5-10 min. After the completion of the reaction (monitored by TLC), the reaction mixture was quenched with cold water (5 mL) and extracted with DCM (2 x 50 mL). The DCM layer was washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography (60-120 mesh silica gel; 30% Ethyl acetate/Hexane) to afford **I-220** (0.15 g, 42.85%) as off white solid. ^{1}H-NMR (DMSO-d_6, 500 MHz, at 80°C): δ 8.48 (bs, 1H), 8.07 (s, 1H), 7.88 (s, 1H), 7.69 - 7.58 (m, 4H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.16 (t, *J*

= 8.0 Hz, 2H), 6.91 - 6.85 (m, 2H), 6.75 (dd, J = 2.5, 15.3 Hz, 1H), 6.13 (d, J = 15.0 Hz, 1H), 5.66 (d, J = 7.5 Hz, 1H), 4.60 (s, 2H), 2.95 (s, 3H), 2.12 (s, 3H). MS: m/e = 374 (M^++1).

EXAMPLE 178

[001046] Preparation of N-methyl-N-(4-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)benzyl)acrylamide **I-219**

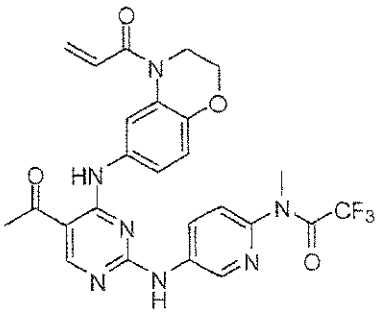


I-219

[001047] The title compound was prepared according to the schemes, steps and intermediates described in Example 177 using tert-butyl-4-aminobenzyl(methyl)-carbamate in place of **2** in step-1. ^{1}H NMR (DMSO-d_6, 500 MHz at 80°C): δ 8.55 (s, 1H), 8.03 (s, 1H), 7.86 (s, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.20 - 7.13 (m, 4H), 6.86 - 6.75 (m, 2H), 6.14 (dd, J = 2.5, 17.0 Hz, 1H), 5.67 (d, J = 15.0 Hz, 1H), 4.58 (s, 2H), 2.96 (s, 3H), 2.10 (s, 3H). MS: m/e = 374 (M^++1).

EXAMPLE 179

[001048] Preparation of N-(5-(5-acetyl-4-(4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)pyrimidin-2-ylamino)pyridin-2-yl)-2,2,2-trifluoro-N-methylacetamide **I-142**

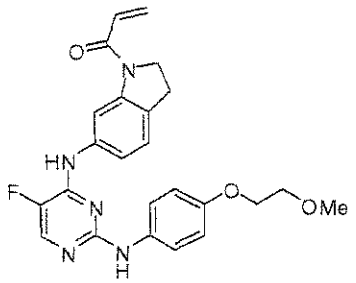


I-142

[001049] The title compound was prepared according to the schemes, steps and intermediates described in Example 42 using 5-amino-2(2,2,2-trifluoroacetamido)pyridine in place of 9 in step-5. LC-MS: m/z 542.2 (ES+), 540.2.2 (ES-).

EXAMPLE 180

[001050] Preparation of 1-(6-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)indolin-1-yl)prop-2-en-1-one **I-94**

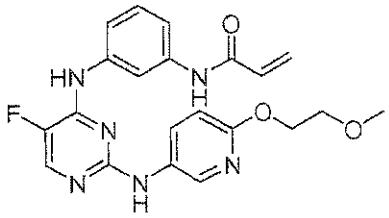


I-94

[001051] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 using N-Boc-6-aminoindoline in place of 2 in step-1. LC-MS: m/z 450.1 (ES+), 448.1 (ES-).

EXAMPLE 181

[001052] Preparation of N-(3-(5-fluoro-2-(6-(2-methoxyethoxy)pyridine-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-103**



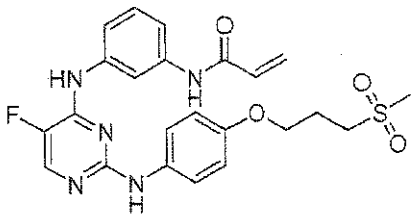
I-103

[001053] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 by using 3-amino-6-(2-methoxyethoxy)pyridine in place of 4 in Step-2. ^{1}H NMR ($CDCl_3$ + trace of DMSO-d_6) δ ppm: 3.44 (s, 3H), 3.75 (t, J = 4.4 Hz, 2H), 4.43 (t, J = 4.4 Hz, 2H), 5.81 (dd, J = 1.8 & 9.6 Hz, 1H), 6.45 (m, 1H), 6.80 (m, 3H), 7.17

(m, 1H), 7.29 (m, 1H), 7.43 (m, 1H), 7.49 (m, 1H), 7.60 (m, 1H), 7.80 (dd, J = 2.8 & 9.2 Hz, 1H), 7.94 (d, J = 3.1 Hz, 1H), 8.14 (s, 1H), 8.32 (d, J = 2.9 Hz, 1H); LCMS : *m/e* 425.1 (M+1).

EXAMPLE 182

[001054] Preparation of N-(3-(5-fluoro-2-(4-(3-methylsulfonylpropoxy)phenyl)aminopyrimidin-4-ylamino)phenyl)acrylamide **I-97**

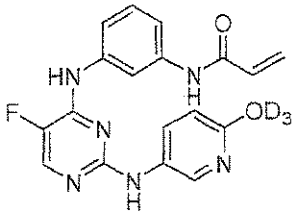


I-97

[001055] The title compound was prepared as a TFA salt according to the schemes, steps and intermediates described in Example 20 by using 4-(3-methylsulfonylpropoxy)aniline in place of 4 in Step-2. ^{1}H NMR ($CDCl_3$ + trace of DMSO-d_6) δ ppm: 1.95 (m, 2H), 2.67 (s, 3H), 2.98 (m, 5H), 3.74 (t, J = 6.0 Hz, 2H), 5.45 (dd, J = 4.1 & 7.3 Hz, 1H), 6.07 (m, 2H), 6.48 (d, J = 8.2 Hz, 1H), 6.77 (m, 4H), 7.09 (d, J = 7.4 Hz, 1H), 7.51 (d, J = 4.1 Hz, 1H), 7.70 (br, 1H); LCMS : *m/e* 486.1 (M+1).

EXAMPLE 183

[001056] Preparation of N-(3-(5-fluoro-2-(6-(trideutereomethoxy)pyridine-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-95**

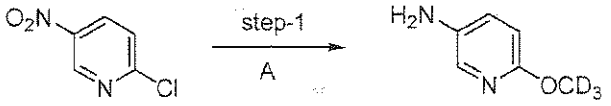


I-95

[001057] The title compound was prepared as a TFA salt according to the schemes, steps and intermediates described in Example 20 by using 6-(trideuteriomethoxy)pyridin-3-amine in place of 4 in Step-2. ^{1}H NMR ($CDCl_3$ + trace of DMSO-d_6) δ ppm: 5.78 (dd, J = 3.7 & 7.8 Hz,

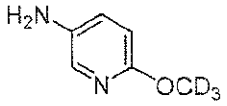
1H), 6.40 (m, 2H), 6.71 (d, J = 8.7 Hz, 1H), 7.3 (m, 3H), 7.75 (dd, J = 2.7 & 8.7 Hz, 1H), 7.82 (d, J = 4.6 Hz, 1H), 7.95 (s, 1H), 8.33 (d, J = 2.3 Hz, 1H); LCMS : *m/e* 384.1 (M+1).

[001058] The intermediate 6-(trideutratedmethoxy)pyridin-3-amine was prepared by the scheme shown below.



A) NaH, CD_3OD, rt; $BH_3{\cdot}NMe_3$, $Pd(OH)_2$

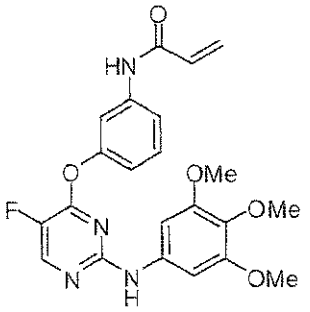
[001059] <u>Step 1</u>



[001060] To NaH (60%, 0.30 g) in 5 mL of CD_3OD at 0 °C was added 2-chloro-5-nitropyridine (1.0 g). The mixture was stirred at rt overnight. To this mixture were added $BH_3{\cdot}NMe_3$ (550 mg) and $Pd(OH)_2$ (100 mg). The resulting mixture was refluxed for 2 h. After cooling down, the mixture was concentrated and purified using silica gel chromatography to give the desired 6-(trideuteratedmethoxy)pyridin-3-amine (130 mg). ^{1}H NMR ($CDCl_3$) δ ppm: 3.30 (br, 2H), 6.60 (d, J = 8.7 Hz, 1H), 7.03 (dd, J = 3.2 & 8.7 Hz, 1H), 7.66 (d, J = 3.2 Hz, 1H).

EXAMPLE 184

[001061] Preparation of N-(3-(5-fluoro-2(3,4,5-trimethoxyphenylamino)pyrimidin-4-yloxy)phenyl)acrylamide **I-148**

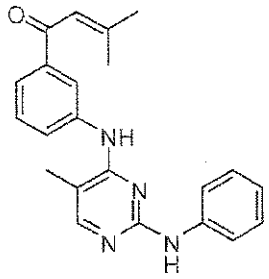


I-148

[001062] The title compound was prepared according to the schemes, steps and intermediates described in Example 98 by using 3,4,5-trimethoxyaniline in place of **4** in Step-2. MS: m/e 441 [M+1].

EXAMPLE 185

[001063] Preparation of 3-methyl-1-(3-(5-methyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl)but-2-en-1-one I-232

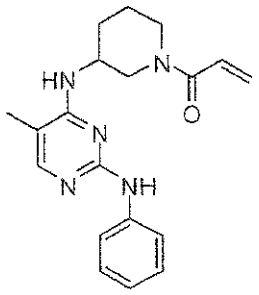


I-232

[001064] The title compound was prepared according to the schemes, steps and intermediates described in Example 112 using 2,4-dichloro-5-methylpyrimidine in place of 1 in step-1 and aniline in place of 4 in step-2. ^{1}H NMR ($CDCl_3$) δ ppm: 1.97 (s, 3H), 2.15 (s, 3H), 2.22 (s, 3H), 6.47 (s, 1H), 6.71 (s, 1H), 6.97 (t, J = 9.8 Hz, 1H), 7.17 (s, 1H), 7.24 (t, J = 10.36 Hz, 1H), 7.27 (s, 1H), 7.44 (t, J = 10.64 Hz, 1H), 7.53 (d, J = 10.48 Hz, 2H), 7.68 (d, J = 10.28 Hz, 1H), 7.94 (d, J = 10 Hz, 1H), 7.98 (s, 1H); LCMS : *m/e* 359 (M+1).

EXAMPLE 186

[001065] Preparation of 1-(3-(5-methyl-2-phenylamino)pyrimidin-4-ylamino(piperidin-1-yl)prop-2-en-one I-27



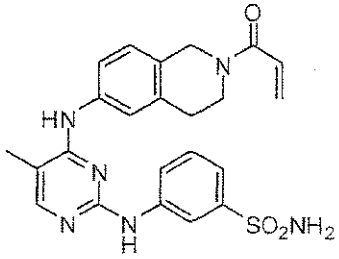
I-27

[001066] The title compound was prepared according to the schemes, steps and intermediates described in Example 1 using 1-tert-butoxycarbonyl-3-aminopiperidine in place of 1 in step-1. ^{1}H NMR (DMSO-d_6) δ ppm: 1.30-1.50 (m, 1H), 1.55-1.75 (m, 1H), 1.75-1.90 (m, 1H), 1.92 (s, 3H), 1.95-2.05 (m, 1H), 2.75-3.31 (m, 2H), 3.99-4.09 (m, 2H), 4.10-4.15 & 4.40-

4.47 (m, 1H), 5.49 & 5.70 (d, J = 10.8 Hz & d, J = 9.2 Hz respectively, together 1H), 6.02 & 6.13 (d, J = 17.6 Hz & d, J = 16.8 Hz respectively, together 1H), 6.25-6.40 (m, 1H), 6.63 & 6.80-6.90 (dd, J = 10.8, 16.8 Hz & m respectively, together 1H), 6.75-6.85 (m, 1H), 7.15 (t, J = 8 Hz, 2H), 7.69 (bs, 3H), 8.81 (s, 1H); LCMS: *m/e* 337.8 (M+1).

EXAMPLE 187

[001067] Preparation of 3-(4-(2-acryloyl-1,2,3,4-tetrahydroisoquinolin-6-ylamino)-5-methylpyrimidin-2-ylamino)benzenesulfonamide **I-40**

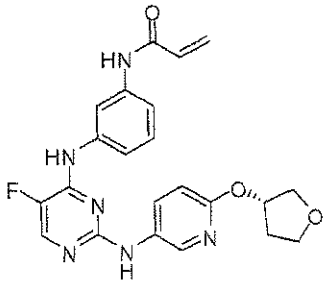


I-40

[001068] The title compound was prepared according to the schemes, steps and intermediates described in Example 1 using 6-amino-2-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline in place of **1** in step-1. ^{1}H NMR (DMSO-d_6) δ ppm: 2.10 (s, 3H), 2.80-2.83 (m, 2H), 3.75-3.90 (m, 2H), 4.66 (s, 1H), 4.76 (s, 1H), 5.71-5.74 (m, 1H), 6.16 (dd, J = 2.32 & 16.76 Hz, 1H), 6.87-6.91 (m, 1H), 7.13-7.18 (m, 1H), 7.25-7.31 (m, 4H), 7.53-7.57 (m, 2H), 7.90 (s, 1H), 8.05 (s, 2H), 8.28 (s, 1H), 9.31 (s, 1H); LCMS: *m/e* 464.8 (M+1).

EXAMPLE 188

[001069] Preparation of (S)-N-(3-(5-fluoro-2-(tetrahydrofuran-3-yloxy)pyridine-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-54**

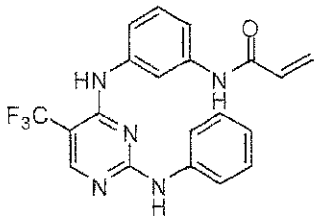


I-54

[001070] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 using (S)-3-amino-6-(tetrahydrofuran-3-yloxy)pyridine in place of 4 in step-2. MS: m/e = 437 [M+1].

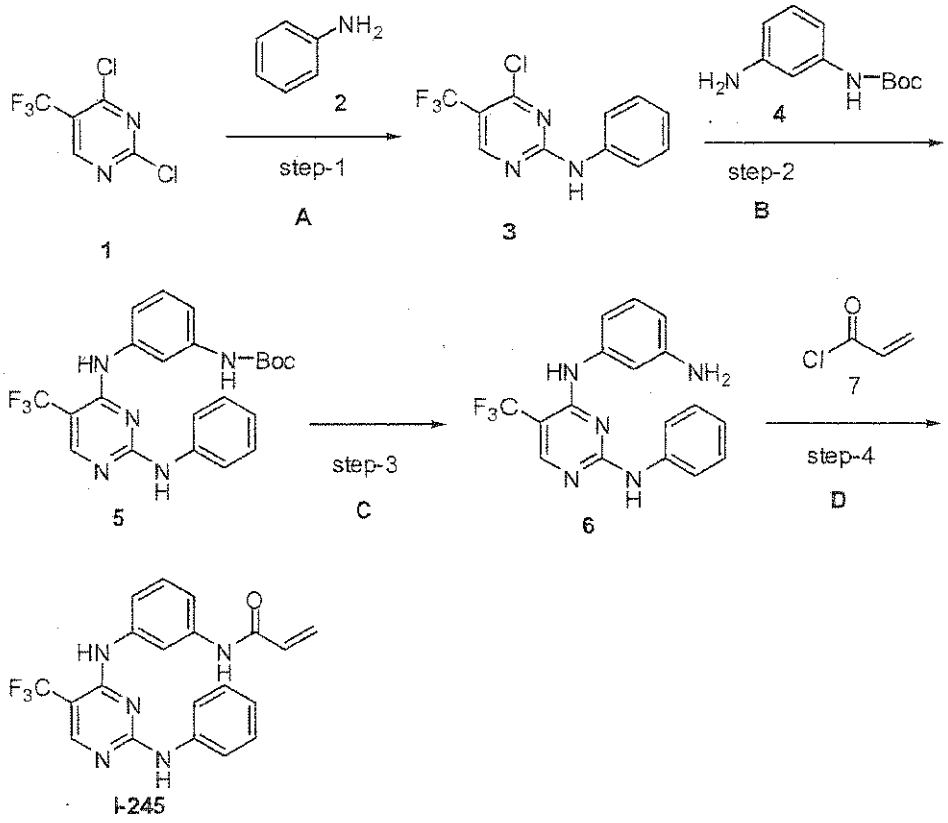
EXAMPLE 189

[001071] Preparation of N-(3-(5-trifluoromethyl-2-(phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-245



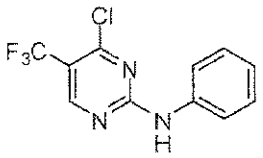
I-245

[001072] The title compound was prepared according to the schemes, steps, and intermediates described below.



A) 2, $ZnCl_2$, DCE, t-BuOH (1:1) , 0 °C, 30 min; B) 4, DMF, DIEPA, 70 °C, 16 hr; C) TFA, DCM, rt, 1 hr; D) 7, TEA, DCM.

[001073] Step-1

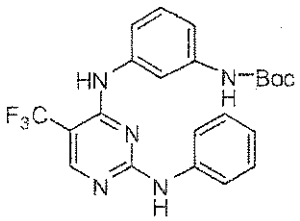


3

[001074] To a cold (0 °C) solution of 1 (2 g, 9.2 mmol) in 80 mL of a 1:1 mixture of tBuOH/DCE was added zinc chloride (11 mL of a 1 M solution in ether, 1.2 eq). After one hour, 2 (0.858g, 9.2 mmol) was added followed by dropwise addition of triethylamine (1.03 g; 1.1 eq) in 10 mL of DCE/t-BuOH. After stirring for 30 minutes, the solvents were removed under reduced pressure and the residue was dissolved in ethyl acetate (50 mL) and washed with brine (10 mL). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*.

The desired product **3** was obtained as a white solid following recrystalization from EtOAc/Hexane (1:9), (2g, 80%).

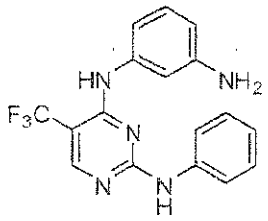
[001075] **Step-2**



5

[001076] To a solution of **3** (0.5 g, 1.82 mmol) and **4** (0.38 g, 1.83 mmol) in DMF (10 mL) was added DIPEA (0.283 g, 2.192 mmol) and the mixture was heated to 60 °C under an argon atmosphere for 16 h. The solvent was distilled off and the residue was dissolved in ethyl acetate (50 mL) and washed with brine (10 mL). The organic layer was dried over sodium sulphate, filtered and concentrated *in vacuo*. The crude mixture was purified by flash column chromatography (eluent: EtOAc/hexane 1:1) to afford **5** as a white solid (0.48 g, 60%).

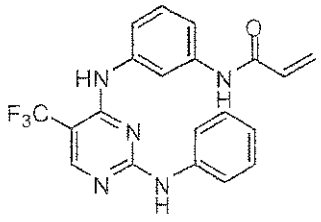
[001077] **Step-3**



6

[001078] To a solution of **6** (0.25 g, 0.63 mmol) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (2 mL) and the mixture was stirred at room temperature for 1 hour. Solvents were removed under reduced pressure and the residue was dissolved in CH_2Cl_2, washed with 10% aqueous $NaHCO_3$ solution, dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide the free amine as white solid.

[001079] **Step-4**

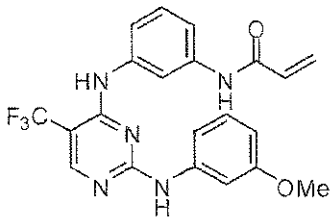


I-245

[001080] To a stirred solution of 6 (0.2 g) in DCM (20 mL) under argon atmosphere cooled to -40 °C was added triethylamine followed by dropwise addition of 7 (0.069 g, 0.686 mmol). The resulting mixture was stirred at -40 °C for 10 min. The reaction mixture was diluted with DCM (50 mL) and washed with brine (10 mL). The organic layer was dried over sodium sulfate, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel using (MeOH- EtOAc 5:95) as eluent to provide the target compound **I-245.** ^{1}H NMR (200 MHz, CD_3OD) δ 8.25 (s, 1H), 7.80 (s, 1H), 7.60–7.05 (m, 7H), 6.90 (m, 1H), 6.35 (m, 2H), 5.75 (dd, J = 8.0, 2.0 Hz, 1H).

EXAMPLE 190

[001081] Preparation of N-(3-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-242**

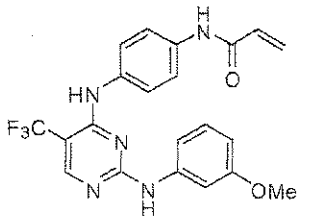


I-242

[001082] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1. ^{1}H NMR (200 MHz, CD_3OD) δ 8.31 (s, 1H), 7.84 (s, 1H), 7.59 (m, 1H), 7.37-7.09 (m, 5H) 6.53 (m, 1H), 6.41 (m, 2H), 5.79 (dd, J = 8.0, 2.0, Hz, 1H), 3.66 (s, 3H).

EXAMPLE 191

[001083] Preparation of N-(4-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-236**

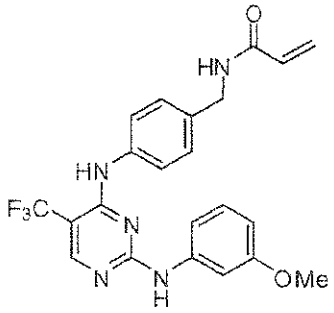


I-236

[001084] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and 4-amino-N-tert-butoxycarbonylaniline in place of 4 in step-2. ^{1}H NMR (200 MHz, CD_3OD) δ 8.27 (s, 1H), 7.70 (d, J = 6.0Hz) 1H), 7.46 (d, J = 6.0Hz, 1H), 7.09 (brs, 1H), 7.07 (m, 2H) 6.51 (m, 1H), 6.44 (m, 2H), 5.80 (dd, J = 8.0, 2.0 Hz, 1H), 3.56 (s, 3H).

EXAMPLE 192

[001085] Preparation of N-(4-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)methylacrylamide **I-235**

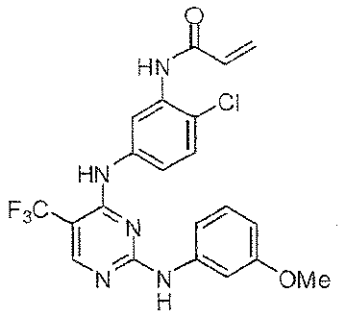


I-235

[001086] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and 4-aminophenylmethyl-N-tert-butoxycarbonylamine in place of 4 in step-2. ^{1}H NMR (200 MHz, CD_3OD) δ 8.30 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.10 (m, 3H), 6.60 (m, 1H) 6.34 (m, 2H), 5.75 (dd, J = 8.0, 2.0 Hz, 1H), 4.51(s, 2H), 3.68 (s, 3H).

EXAMPLE 193

[001087] Preparation of N-(4-chloro-3-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-227**

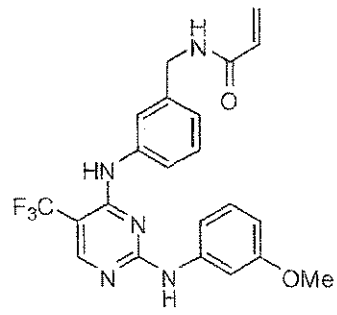


I-227

[001088] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and N-tert-butoxycarbony-3-amino-6-chloroaniline in place of **4** in step-2. ^{1}H NMR (200 MHz, CD_3OD) δ 8.33 (s, 1H), δ 8.08 (s, 1H), 7.45 (m, 2H), 7.21-7.07 (m, 3H), 6.60-6.36 (m, 3H), 5.84 (dd, J = 8.0, 2.0 Hz, 1H), 3.71 (s, 3H).

EXAMPLE 194

[001089] Preparation of N-(3-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)methylacrylamide **I-226**



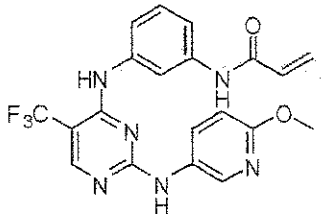
I-226

[001090] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and 3-aminophenylmethyl-N-tert-butoxycarbonylamine in place of 4 in step-2. ^{1}H NMR (200 MHz,

CD_3OD) δ 8.31 (s, 1H), 7.71-7.33 (m, 3H), 7.21-7.08 (m, 4H), 6.57 (m, 1H), 6.26 (d, J = 4Hz, 2H), 5.69 (dd, J = 8.0, 2.0 Hz, 1H), 4.47 (s, 2H), 3.67 (s, 3H).

EXAMPLE 195

[001091] Preparation of N-(4-(5-trifluoromethyl-2-(6-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-218**

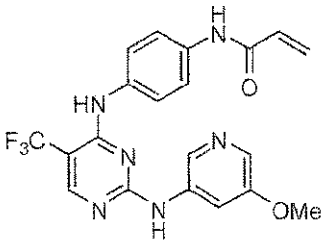


I-218

[001092] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-amino-6-methoxypyridine in place of **2** in step-1. ^{1}H NMR (200 MHz, CD_3OD) δ 8.21 (s, 1H), 7.90-7.78 (m, 3H), 7.48 (m, 2H), 7.30 (m, 2H), 6.40 (m, 2H), 5.75 (dd, J = 8.0, 2.0 Hz, 1H), 3.81 (s, 3H).

EXAMPLE 196

[001093] Preparation of N-(4-(5-trifluoromethyl-2-(5-methoxypyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-214**

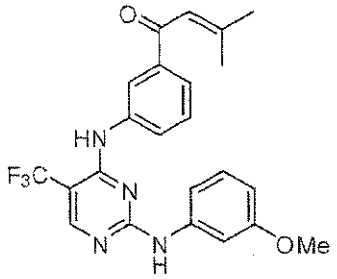


I-214

[001094] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-amino-5-methoxypyridine in place of **2** in step-1 and 4-amino-N-tert-butoxycarbonylaniline in place of **4** in step-2. MS: m/e = 431 [M+1].

EXAMPLE 197

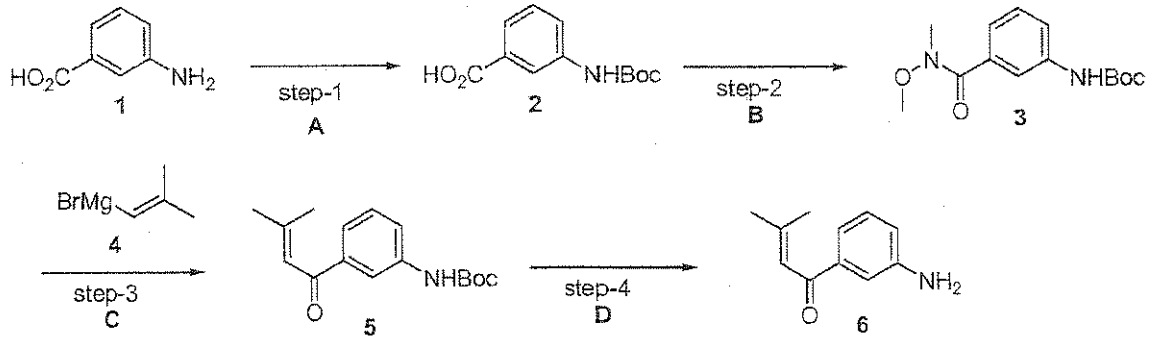
[001095] Preparation of 1-(3-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-3-methyl-but-2-en-1-one **I-225**



I-225

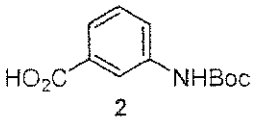
[001096] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and 1-(3-aminophenyl)-3-methylbut-2-en-1-one in place of **4** in step-2. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.33 (s, 1H), *δ* 8.38 (s, 1H), 7.99-7.77 (m, 4H), 7.50 (m, 2H), 7.20-7.01 (m, 4H), 6.68-6.60(m, 2H), 3.68 (s, 3H), 2.25 (s, 3H), 1.99 (s, 3H).

[001097] 1-(3-Aminophenyl)-3-methylbut-2-en-1-one was prepared according to the scheme, steps, and intermediates described below.



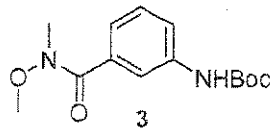
A) Boc_2O, NEt_3, DMAP, DCM; B) NHMe(OMe)-HCl, TBTU, DCM, 0 °C to rt; C) **4**, THF, 0 °C to rt; D) TFA, DCM.

[001098] **Step-1**



[001099] Di-*tert*-butyldicarbonate (6.54 g, 30 mmol, 1.5 eq.) was added to a solution of **1** (2.70 g, 20 mmol) in CH_2Cl_2 (100 mL) containing Et_3N (3.4 mL, 24 mmol, 1.2 eq.) and DMAP (122 mg, 1.0 mmol, 5 mol%). The mixture was stirred overnight under a $CaCl_2$ drying tube. The solvents were evaporated and the residue was partitioned between ether (50 mL) and water (50 mL). The aqueous phase was extracted with ether then acidified to pH 3 with 1N HCl and extracted with EtOAc (2 X 50 mL). The combined organic layers were washed with water and brine and dried over $NaSO_4$. Concentration afforded the crude product which was recrystallized from EtOAc/hexanes to give **2** (2.92 g, 62%).

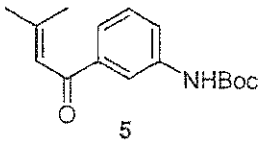
[001100] Step-2



3

[001101] To a mixture of 2 (1.5 g, 6.33 mmol), N-methoxy-N-methylamine hydrochloride (614 mg, 6.33 mmol), and TBTU (2.05 g, 6.33 mmol) in DCM (30 mL) at 0 °C was added NEt3 (2.7 mL, 19 mmol, 3 eq.). The mixture was stirred for 30 min at 0 °C then at room temperature for 2 h whereupon HPLC analysis indicated the reaction to be complete. The reaction mixture was poured into 150 mL of cold water and the product precipitated as a white solid which was collected and washed with cold water. The product was dried in a vacuum oven overnight to give **3** (1.34 g, 75%) as a white solid.

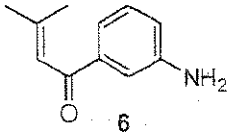
[001102] Step-3



5

[001103] To a solution of **3** (546 mg, 1.95 mmol) in THF (3 mL) at 0 °C under Ar was added dropwise **4** (0.5 M in THF, 9.75 mL, 4.9 mmol, 2.5 eq.). The reaction mixture was stirred at 0 oC for 30 min then the cooling bath was removed and the reaction was stirred at rt for 2 h. The reaction mixture was cooled to 0 °C and quenched with 5% citric acid solution. After dilution with water (10 mL) the aqueous phase was extracted with ether (2 X 15 mL) and the combined organic layers were washed with water and brine and dried over $NaSO_4$. Concentration afforded **5** (82%) as a yellow solid which was sufficiently pure to be used directly in the next step.

[001104] Step-4

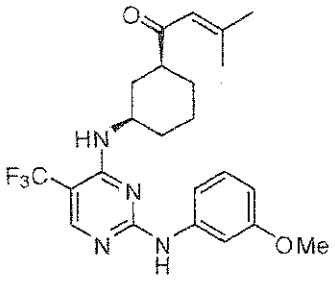


6

[001105] A sample of 400 mg of **5** was treated with 5 mL 1:3 CH_2Cl_2 : trifluoroacetic acid and the resulting solution stirred at room temperature for 15 minutes. The solvents were removed *in vacuo* and the residue redissolved in CH_2Cl_2 and re-evaporated three times. The residue was again taken up in CH_2Cl_2 and the solution washed with saturated sodium bicarbonate solution. The CH_2Cl_2 layer was dried over sodium sulphate, filtered and evaporated to afford **6** as a white solid that was used directly in the next reaction.

EXAMPLE 198

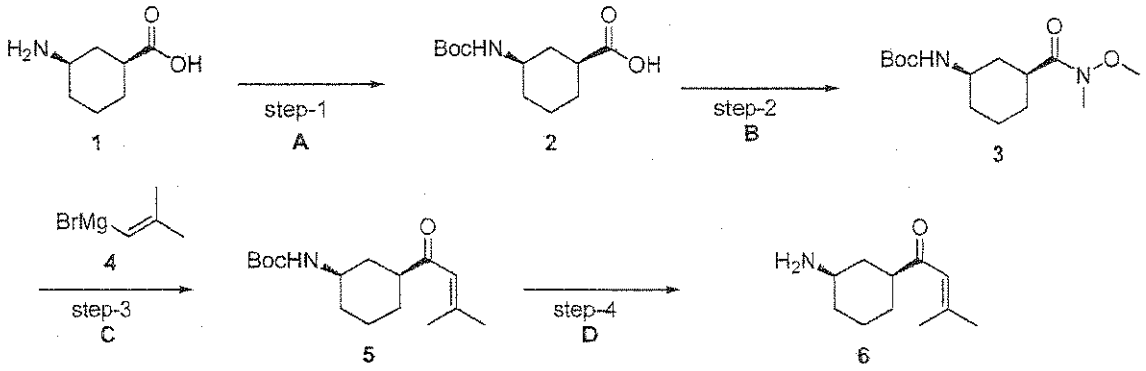
[001106] Preparation of 1-(3-(2-(3-Methoxy-phenylamino)-5-trifluoromethyl-pyrimidin-4-ylamino)-cyclohexyl)-3-methyl-but-2-en-1-one **I-213**



I-213

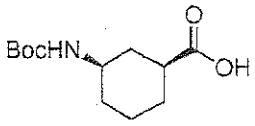
[001107] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and (d,l)-*cis*-1-(3-Amino-cyclohexyl)-3-methyl-but-2-en-1-one in place of **4** in step-2. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.33 (s, 1H), 7.19-7.0 (m, 3H), 6.54 (d, J = 2.7 Hz, 1H), 6.02 (s, 1H), 4.04 (m, 1H), 3.75 (s, 3H), 2.50 (m, 1H), 2.10 (m, 1H), 1.89-1.15 (m, 14H).

[001108] (D,L)-*cis*-1-(3-Amino-cyclohexyl)-3-methyl-but-2-en-1-one was prepared according to the scheme, steps, and intermediates described below.



A) Boc_2O, Na_2CO_3, acetone, H_2O; B) NHMe(OMe)-HCl, TBTU, DCM, 0 °C to rt; C) **4**, THF, 0 °C to rt; D) TFA, DCM.

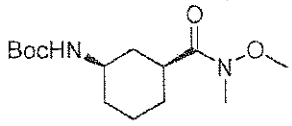
[001109] **Step-1**



2

[001110] To a stirred solution of (±)-**1** (4.05 g, 28.2 mmol) in water (150 mL) containing Na_2CO_3 (3.0 g, 28.2 mmol) and acetone (100 mL) was added BOC_2O (7.4 g, 33.8 mmol, 1.2 eq) and the mixture was stirred at 25°C overnight. The acetone was stripped and the aqueous layer was extracted with ether (2X). The aqueous layer was acidified to pH 3 and the precipitated product was collected and washed with water. The product was dried in a vacuum oven overnight to give **2** (5.90 g, 85%) as a white solid.

[001111] **Step-2**

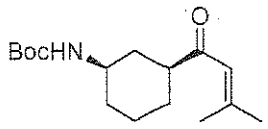


3

[001112] To a stirred solution of **2** (2.45 g, 10.1 mmol), TBTU (3.44 g, 10.6 mmol, 1.05 eq) and *N*-methyl-*N*-methoxyamine hydrochloride (1.03 g, 10.6 mmol, 1.05 eq) in CH_2Cl_2 (40 mL) at 0 °C was added triethylamine (4.25 mL, 30.3 mmol, 3 eq). The mixture was stirred at 0 °C for 20 min and the bath was removed and stirring was continued for 3 h at 25°C. After quenching with water, the CH_2Cl_2 was stripped and the residue was partitioned between ether and water. The aqueous phase was extracted with ether and the combined organic layers were washed with

water and brine and dried over $MgSO_4$. Evaporation of the solvents gave **3** (2.37 g, 82%) as a white solid.

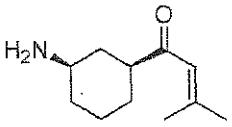
[001113] Step-3



5

[001114] To a solution of **3** (1.23 g, 4.32 mmol) in THF (20 mL) at 0 °C under argon was added dropwise **4** (27 mL, 0.5 M in THF, 10.8 mmol, 2.5 eq). After the addition was complete the mixture was stirred at 0 °C for 30 min, then at rt for 1 h. The reaction mixture was cooled to 0 °C then quenched with 5% citric acid solution (5 mL). After dilution with water the mixture was extracted with ether (2X) and the combined organic layers were washed with water and brine and dried over $NaSO_4$. Evaporation left an orange residue which was chromatographed on silica gel eluting with 20% EtOAc in hexanes to give **5** (600 mg, 56%) as a light yellow solid.

[001115] Step-4

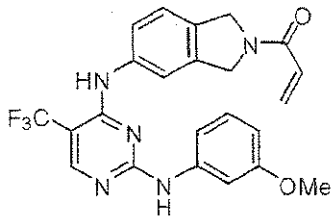


6

[001116] A sample of 500 mg of **5** was treated with 6 mL 1:3 CH_2Cl_2 : trifluoroacetic acid and the resulting solution stirred at room temperature for 15 minutes. The solvents were removed *in vacuo* and the residue redissolved in CH_2Cl_2 and re-evaporated three times. The residue was again taken up in CH_2Cl_2 and the solution washed with saturated sodium bicarbonate solution. The CH_2Cl_2 layer was dried over sodium sulphate, filtered and evaporated to afford **6** as a white solid that was used directly without purification.

EXAMPLE 199

[001117] Preparation of 1-(5-(5-trifluoromethyl-2-(3-methoxyphenylamino)pyrimidin-4-yl)amino-1,3-dihydroisoindol-2-yl)2-propen-1-one **I-132**

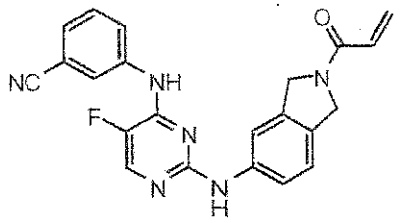


I-132

[001118] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-methoxyaniline in place of **2** in step-1 and 2-(N-tert-butoxycarbonyl)-5-aminoisoindoline in place of **4** in step-2. MS m/e =456 [M+1].

EXAMPLE 200

[001119] Preparation of 3-(2-(2-acryloylisoindolin-5-ylamino)-5-fluoropyrimidin-4-ylamino)benzonitrile **I-106**

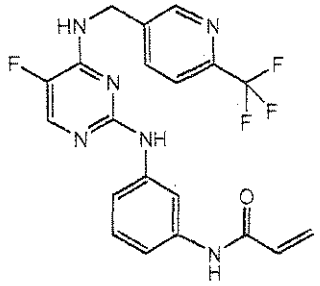


I-106

[001120] The title compound was prepared according to the schemes, steps and intermediates described in Example 2 using 5-fluoro-2,4-dichloropyrimidine in place of **1** and 3-aminobenzonitrile in place of **2** in step-1 and 2-(tert-butoxycarbonyl-5-aminoisoindoline in place of **4** in step-2. LC/MS (RT = 2.82/(M + H)) 401.1

EXAMPLE 201

[001121] Preparation of N-(3-(5-fluoro-4-((6-(trifluoromethyl)pyridin-3-yl)methylamino)pyrimidin-2-ylamino)phenyl)acrylamide **I-53**

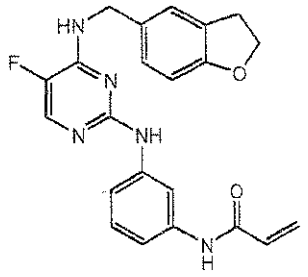


I-53

[001122] The title compound was prepared according to the schemes, steps and intermediates described in Example 2 using 5-fluoro-2,4-dichloropyrimidine in place of 1 and 3-aminomethyl-6-trifluoromethylpyridine in place of 2 in step-1. LC/MS (RT = 2.805/(M + H)) 433.0

EXAMPLE 202

[001123] Preparation of N-(3-(4-((2,3-dihydrobenzofuran-5-yl)methylamino)-5-fluoropyrimidin-2-ylamino)phenyl)acrylamide **I-6**

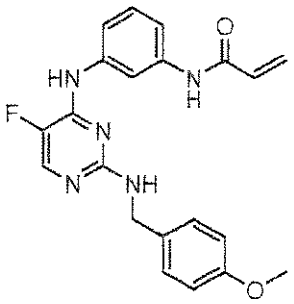


I-6

[001124] The title compound was prepared according to the schemes, steps and intermediates described in Example 2 using 5-fluoro-2,4-dichloropyrimidine in place of 1 and 3-aminomethyl-2,3-dihydrobenzofuran in place of 2 in step-1. LC/MS (RT = 2.815/(M + H)) 406.2

EXAMPLE 203

[001125] Preparation of N-(3-(5-fluoro-2-(4-methoxybenzylamino)pyrimidin-4-ylamino)phenyl)acrylamide I-241

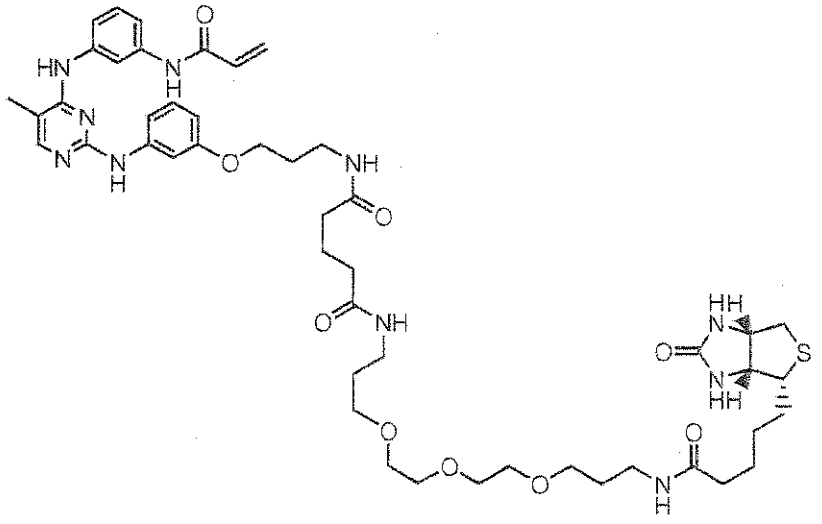


I-241

[001126] The title compound was prepared according to the schemes, steps and intermediates described in Example 20 using 4-methoxybenzylamine in place of 4 in step-2. LC/MS (RT = 2.801/(M + H)) 394.2

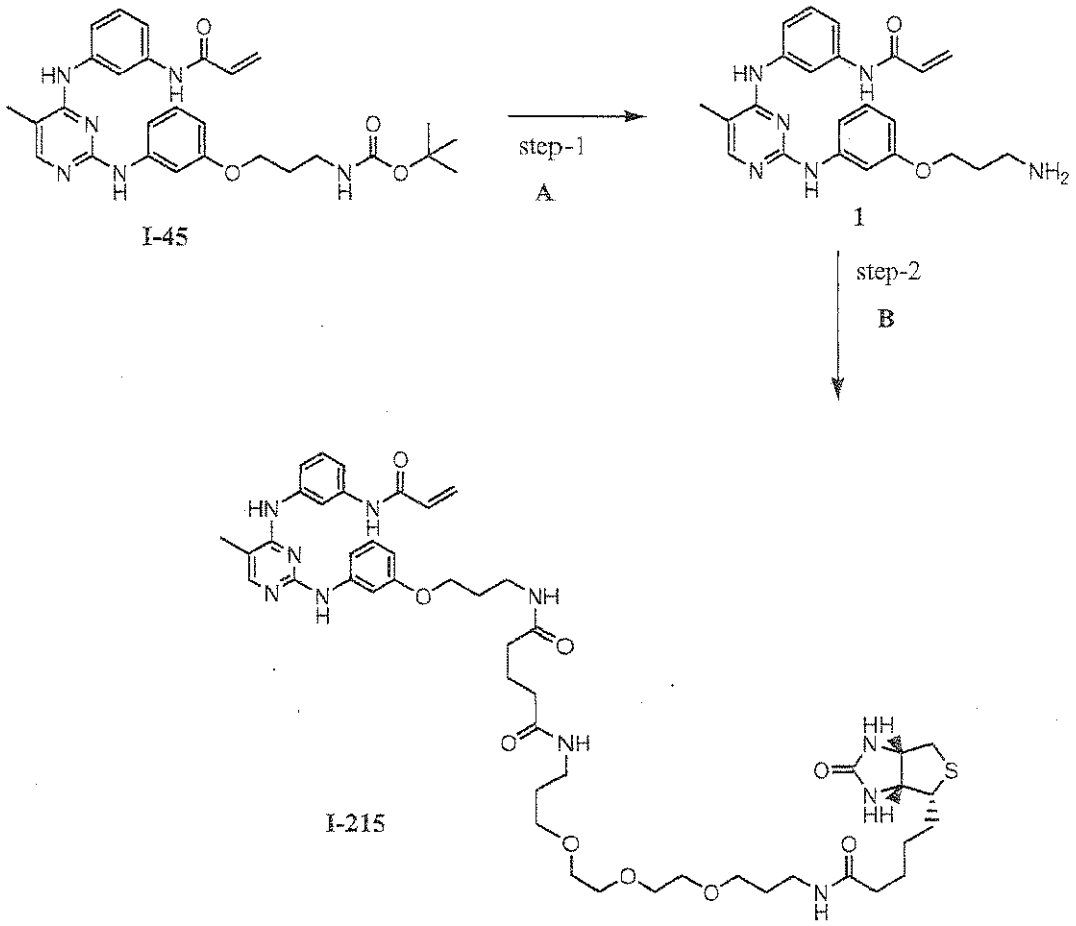
EXAMPLE 204

[001127] Preparation of N^1-(3-(3-(4-(3-acrylamidophenylamino)-5-methylpyrimidin-2-ylamino)phenoxy)propyl)-N^5-(15-oxo-19-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide I-215



I-215

[001128] The title compound was prepared according to the schemes steps and intermediates described below.



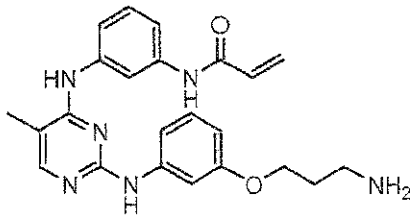
I-45

1

I-215

A) TFA, DCM; **B**) N-Biotinyl-NH-$(PEG)_2$-COOH-DIPEA, HOBt, EDC, NMM, DMF.

[001129] **Step-1**

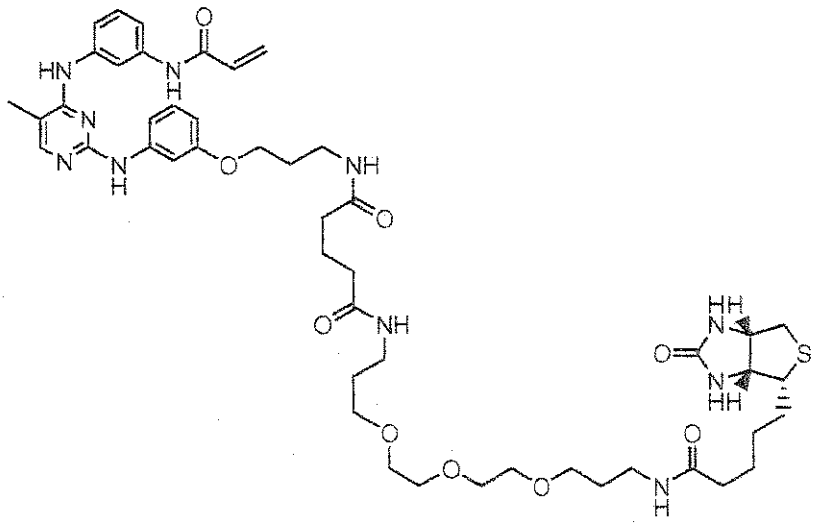


1

[001130] **I-45** (97 mg, 0.19 mmol; synthesis of **I-45** provided in Example 62) was dissolved in DCM (10 mL). Trifluoroacetic acid (200 µL) was added and allow to stir at rt for 24 hr. The

solvent was removed via rotary evaporation to give a tan-brown foam (130mg) which was used without purification in the next reaction. LC/MS (RT = 2.63/(MH+) 419.2)

[001131] Step-2

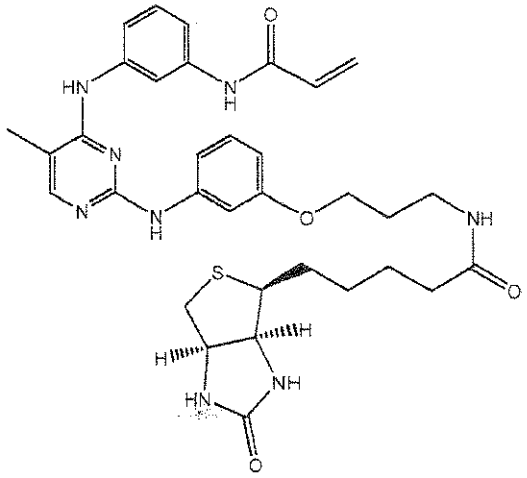


I-215

1 (80 mg, 0.15 mmoL) was dissolved in DMF (2 mL). To the mxiture was added N-Biotinyl-NH-$(PEG)_2$-COOH-DIPEA (114 mg, 0.16 mmol) and HOBt (25 mg, 0.16 mmoL (89%)), and the mixture was cooled in an ice-water bath. EDC (32 mg, 0.16mmoL) was added, followed by N-methylmorpholine (50 μL, 0.45 mmoL). The mixture was allowed to warm to room temperature and continue to stir for 30 min. Direct purification by flash chromatography using 10% gradient of MeOH in DCM gave 40 mg of **I-215** as a yellow film. LC/MS (RT = 2.654/(MH+) 961.3).

EXAMPLE 205

[001132] Preparation of N-(3-(3-(4-(3-acrylamidophenylamino)-5-methylpyrimidin-2-ylamino)phenoxy)propyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide **I-237**

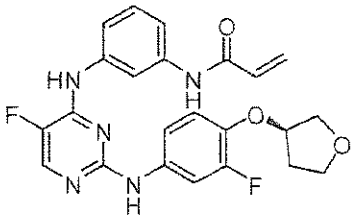


I-237

[001133] The title compound was prepared according to the schemes, steps and intermediates described in Example 204 using D-(+)-biotin in place of N-Biotinyl-NH-$(PEG)_2$-COOH-DIPEA in step-2. LC/MS (RT = 2.686/(M + H)) 645.2

EXAMPLE 206

[001134] Preparation of (R)-N-(3-(5-fluoro-2-(3-fluoro-4-(tetrahydrofuran-3-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-316**



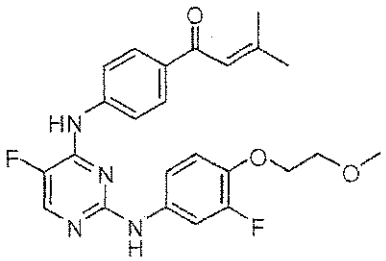
I-316

[001135] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-3-fluoro-4-(tetrahydrofuran-3-yloxyaniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.85-2.00 (m, 1H), 2.20 (m, 1H), 3.70-3.90 (m, 4H), 4.90 (s, 1H), 5.73 (dd, *J* = 1.56 & 10.04 Hz, 1H), 6.23 (dd, *J* = 1.76 & 17.00 Hz, 1H),

6.44 (dd, J = 10.08 & 16.88 Hz, 1H), 7.28 (t, J = 8.04 Hz, 1H), 7.40-7.47 (m, 2H), 7.67-7.71 (m, 2H), 7.68 (dd, J = 1.96 & 14.08 Hz, 1H), 7.92 (s, 1H), 8.1 (d, J = 3.64 Hz, 1H), 9.21 (s, 1H), 9.44 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 452.0 (M-1).

EXAMPLE 207

[001136] Preparation of 1-(4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one **I-325**

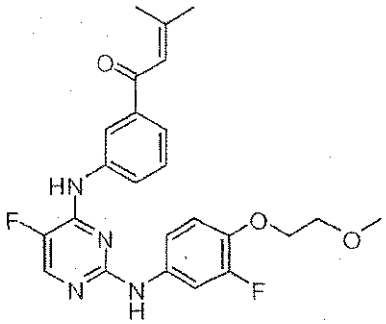


I-325

[001137] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using methyl 4-aminobenzoate in place of **2** in step 1 and 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.01 (s, 3H), 2.15 (d, J = 0.72 Hz, 3H), 3.31 (s, 3H), 3.66 (dd, J = 3.64 & 4.56 Hz, 2H), 4.11 (dd, J = 4.44 & 6.12 Hz, 2H), 6.93 (s, 1H), 7.08 (t, J = 9.44 Hz, 1H), 7.27 (d, J = 8.88 Hz, 1H), 7.74 (dd, J = 2.44 & 14.24 Hz, 1H), 7.93 (d, J = 8.96 Hz, 2H), 7.98 (d, J = 8.92 Hz, 2H), 8.20 (d, J = 3.64 Hz, 1H), 9.35 (s, 1H), 9.73 (s, 1H); LCMS : *m/e* 455 (M+1).

EXAMPLE 208

[001138] Preparation of 1-(3-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-2-en-1-one **I-323**

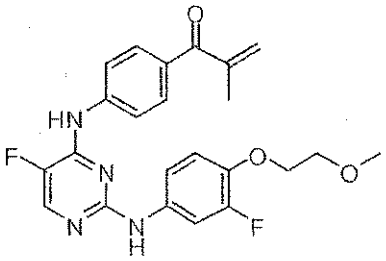


I-325

[001139] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using 2-(3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.95 (s, 3H), 2.14 (s, 3H), 3.31 (s, 3H), 3.63 (t, J = 4.64 Hz, 2H), 4.06 (t, J = 4.36 Hz, 2H), 6.85 (bs, 1H), 6.97 (t, J = 9.52 Hz, 1H), 7.26 (bd, J = 8.32 Hz, 1H), 7.48 (t, J = 7.92 Hz, 1H), 7.62-7.67 (m, 2H), 8.08 (bd, J = 7.04 Hz, 1H), 8.15-8.16 (m, 2H), 9.29 (s, 1H), 9.58 (s, 1H); LCMS : *m/e* 455 (M+1).

EXAMPLE 209

[001140] Preparation of 1-(4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-2-methylprop-2-en-1-one **I-324**



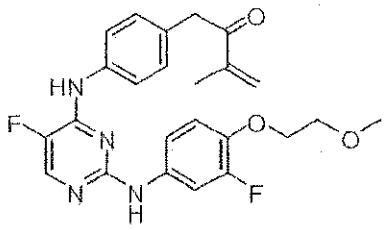
I-324

[001141] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using methyl 4-aminobenzoate in place of **2** in step 1, 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2 and isopropenylmagnesium bromide in place of **8** in step 5. ^{1}H NMR (DMSO-d_6) δ ppm: 2.0 (s, 3H), 3.32 (s, 3H), 3.66 (t, J

= 4.36 Hz, 2H), 4.11 (t, J = 4.44 Hz, 2H), 5.55 (s, 1H), 5.94 (s, 1H), 7.07 (t, J = 9.32 Hz, 1H), 7.26 (t, J = 9.4 Hz, 1H), 7.72-7.76 (m, 3H), 7.99 (d, J = 8.44 Hz, 2H), 8.21 (d, J = 3.56 Hz, 1H), 9.38 (s, 1H), 9.75 (s, 1H); LCMS : *m/e* 441.2 (M+1).

EXAMPLE 210

[001142] Preparation of 1-(4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-3-en-2-one **I-329**

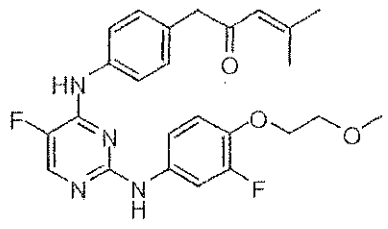


I-329

[001143] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using ethyl 4-aminophenylacetate in place of **2** in step 1, 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2 and isopropenylmagnesium bromide in place of **8** in step 5. ^{1}H NMR (DMSO-d_6) δ ppm: 1.79 (s, 3H), 3.30 (s, 3H), 3.62-3.65 (m, 2H), 4.06 (s, 2H), 4.08-4.10 (m, 2H), 5.95 (d, J = 1 Hz, 1H), 6.27 (s, 1H), 7.01 (t, J = 9.44 Hz, 1H), 7.15 (d, J = 8.52 Hz, 2H), 7.28 (d, J = 8.88 Hz, 1H), 7.64-7.70 (m, 3H), 8.08 (d, J = 3.72 Hz, 1H), 9.19 (s, 1H), 9.33 (s, 1H); LCMS : *m/e* 455.3 (M+1).

EXAMPLE 211

[001144] Preparation of 1-(4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-4-methylpent-3-en-2-one **I-331**



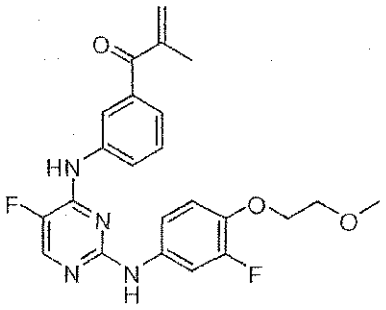
I-331

[001145] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using ethyl 4-aminophenylacetate in place of **2** in

step 1, 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.84 (d, J = 1 Hz, 3H), 2.05 (d, J = 0.92 Hz, 3H), 3.30 (s, 3H), 3.62-3.64 (m, 2H), 3.68 (s, 2H), 4.07-4.09 (m, 2H), 6.21 (t, J = 1.2 Hz, 1H), 7.01 (t, J = 8.68 Hz, 1H), 7.16 (d, J = 8.48 Hz, 2H), 7.26 (d, J = 8.96 Hz, 1H), 7.65-7.72 (m, 3H), 8.08 (d, J = 3.72 Hz, 1H), 9.20 (s, 1H), 9.34 (s, 1H); LCMS : *m/e* 469.3 (M+1).

EXAMPLE 212

[001146] Preparation of 1-(3-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-2-methylprop-2-en-1-one **I-322**

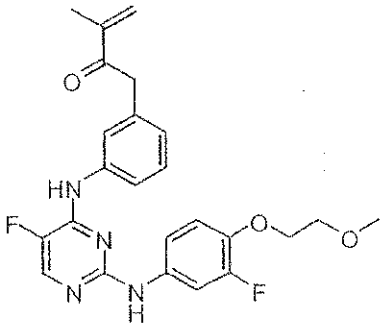


I-322

[001147] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using 1,3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2 and isopropenylmagnesium bromide in place of **8** in step 5. ^{1}H NMR (DMSO-d_6) δ ppm: 1.96 (s, 3H), 3.30 (s, 3H), 3.63 (t, J = 4.6 Hz, 2H), 4.07 (t, J = 4.36 Hz, 2H), 5.62 (s, 1H), 6.00 (s, 1H), 6.99 (t, J = 9.24 Hz, 1H), 7.26 (d, J = 8.92 Hz, 1H), 7.39 (d, J = 7.56 Hz, 1H), 7.46 (t, J = 7.72 Hz, 1H), 7.62 (bd, J = 14.4 Hz, 1H), 7.93 (s, 1H), 8.12-8.14 (m, 2H), 9.25 (s, 1H), 9.58 (s, 1H); LCMS : *m/e* 441.2 (M+1).

EXAMPLE 213

[001148] Preparation of 1-(3-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-3-methylbut-3-en-2-one **I-328**

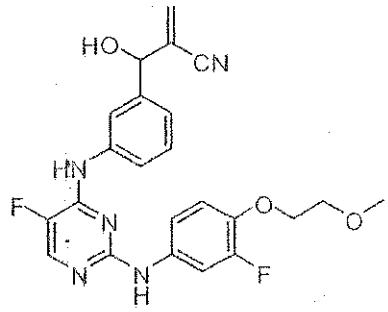


I-328

[001149] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using ethyl 3-aminophenylacetate in place of **2** in step 1, 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2 and isopropenylmagnesium bromide in place of **8** in step 5. ^{1}H NMR (DMSO-d_6) δ ppm: 1.8 (s, 3H), 3.31 (s, 3H), 3.64 (t, J = 4.56 Hz, 2H), 4.06 (s, 2H), 4.09 (t, J = 4.37 Hz, 2H), 5.95 (s, 1H), 6.23 (s, 1H), 6.92 (d, J = 7.52 Hz, 1H), 7.02 (t, J = 9.4 Hz, 1H), 7.27 (t, J = 7.8 Hz, 2H), 7.50 (s, 1H), 7.66-7.72 (m, 2H), 8.10 (d, J = 3.56 Hz, 1H), 9.21 (s, 1H), 9.36 (s, 1H); LCMS : *m/e* 455.1 (M+1).

EXAMPLE 214

[001150] Preparation of 2-((3-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-326**



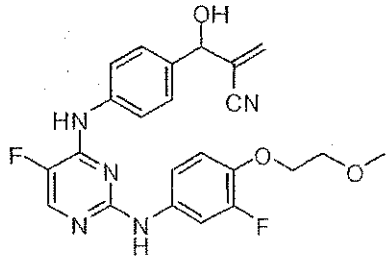
I-326

[001151] The title compound was prepared according to the schemes, steps and intermediates described in Example 107, by using 3-fluoro-4-(2-methoxyethoxy)aniline in place

of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.30 (s, 3H), 3.62-3.65 (m, 2H), 4.09 (t, *J* = 4.6 Hz, 2H), 5.29 (d, *J* = 3.84 Hz, 1H), 6.13 (s, 1H), 6.19 (s, 1H), 6.31 (d, *J* = 4.04 Hz, 1H), 7.03 (t, *J* = 9.24 Hz, 1H), 7.10 (d, *J* = 7.44 Hz, 1H), 7.28 (d, *J* = 8.72 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.62 (s, 1H), 7.66 (dd, *J* = 2.32 & 14.44 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 3.68 Hz, 1H), 9.14 (s, 1H), 9.45 (s, 1H); LCMS : *m/e* 454 (M+1).

EXAMPLE 215

[001152] Preparation of 2-((4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-327**

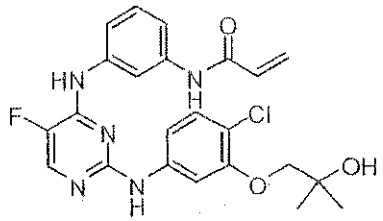


I-327

[001153] The title compound was prepared according to the schemes, steps and intermediates described in Example 107, by using methyl 4-aminobenzoate in place of **2** in step 1 and 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.30 (s, 3H), 3.64 (dd, *J* = 2.96 & 4.56 Hz, 2H), 4.08 (t, *J* = 4.48 Hz, 2H), 5.29 (d, *J* = 3.8 Hz, 1H), 6.11 (s, 1H), 6.21 (s, 1H), 6.24 (d, *J* = 4.12 Hz, 1H), 7.01 (t, *J* = 9.4 Hz, 1H), 7.29-7.34 (m, 3H), 7.68 (dd, *J* = 2.2 & 14.16 Hz, 1H), 7.77 (d, *J* = 8.52 Hz, 2H), 8.11 (d, *J* = 3.68 Hz, 1H), 9.23 (s, 1H), 9.42 (s, 1H); LCMS : *m/e* 454.0 (M+1).

EXAMPLE 216

[001154] Preparation of N-(3-(2-(4-chloro-3-(2-hydroxy-2-methylpropoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-249**

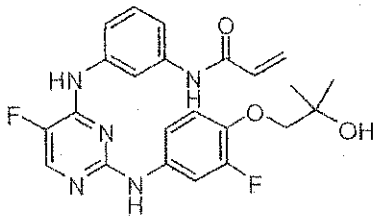


I-249

[001155] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-chloro-3-(2-hydroxy-2-methylpropoxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.20 (s, 6H), 3.61 (s, 2H), 4.61 (s, 1H), 5.75 (d, J = 11.4 Hz, 1H), 6.24 (d, J = 18.36 Hz, 1H), 6.44 (dd, J = 10.32 & 17.08 Hz, 1H), 7.13 (d, J = 8.64 Hz, 1H), 7.28 (t, J = 8 Hz, 1H), 7.37-7.44 (m, 3H), 7.55 (d, J = 7.08 Hz, 1H), 7.93 (s, 1H), 8.12 (d, J = 3.44 Hz, 1H), 9.23 (s, 1H), 9.47 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 472.0 (M+1).

EXAMPLE 217

[001156] Preparation of N-(3-(5-fluoro-2-(3-fluoro-4-(2-hydroxy-2-methylpropoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-315**



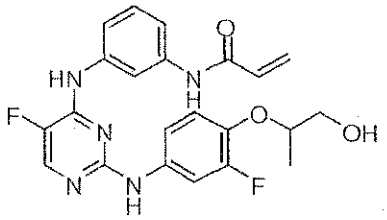
I-315

[001157] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-fluoro-4-(2-hydroxy-2-methylpropoxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.19 (s, 6H), 3.67 (s, 2H), 4.62 (s, 1H), 5.75 (d, J = 10.4 Hz, 1H), 6.25 (d, J = 17.2 Hz, 1H), 6.45 (dd, J = 10 & 16.8 Hz, 1H), 6.94 (t, J = 9.2 Hz, 1H), 7.29 (t, J = 8 Hz, 2H), 7.43 (d, J = 8.4 Hz, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.67 (d, J =

13.6 Hz, 1H), 7.94 (s, 1H), 8.11 (d, J = 3.6 Hz, 1H), 9.19 (s, 1H), 9.45 (s, 1H), 10.14 (s, 1H); LCMS : *m/e* 456 (M-1).

EXAMPLE 218

[001158] Preparation of N-(3-(5-fluoro-2-(3-fluoro-4-(1-hydroxypropan-2-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-333**

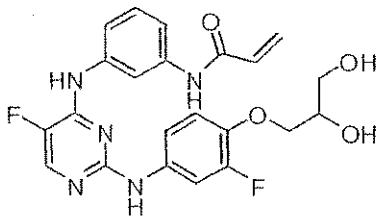


I-333

[001159] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-fluoro-4-(2-hydroxy-1-methylethoxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.16 (d, J = 6.12 Hz, 3H), 3.40-3.46 (m, 1H), 3.50-3.56 (m, 1H), 4.22 (sextet, J = 5.6 Hz, 1H), 4.84 (t, J = 5.68 Hz, 1H), 5.75 (dd, J = 1.96 & 10.08 Hz, 1H), 6.25 (dd, J = 1.92 & 16.92 Hz, 1H), 6.46 (dd, J = 10.08 & 16.92 Hz, 1H), 6.98 (t, J = 9.32 Hz, 1H), 7.26-7.31 (m, 2H), 7.43 (d, J = 8.76 Hz, 1H), 7.49 (d, J = 8 Hz, 1H), 7.68 (dd, J = 2.44 & 14.28 Hz, 1H), 7.95 (s, 1H), 8.11 (d, J = 3.68 Hz, 1H), 9.23 (s, 1H), 9.46 (s, 1H), 10.17 (s, 1H); LCMS : *m/e* 442.2 (M+1).

EXAMPLE 219

[001160] Preparation of N-(3-(2-(4-(2,3-dihydroxypropoxy)-3-fluorophenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-334**



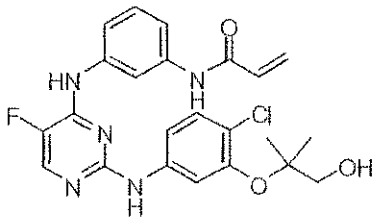
I-334

[001161] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-(2,3-dihydroxypropoxy)-3-fluoroaniline in

place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.42 (t, J = 5.6 Hz, 2H), 3.7-3.8 (m, 1H), 3.8-3.9 (m, 1H), 3.94 (dd, J = 4.36 & 9.92 Hz, 1H), 4.65 (t, J = 5.64 Hz, 1H), 4.93(d, J = 5.08 Hz, 1H), 5.7-5.8 (m, 1H), 6.24 (dd, J = 1.64 & 16.84 Hz, 1H), 6.44 (dd, J = 10 & 16.96 Hz, 1H), 6.94 (t, J = 9.32 Hz, 1H), 7.28 (t, J = 7.96 Hz, 2H), 7.40 (d, J = 8.28 Hz, 1H), 7.49 (d, J = 7.44 Hz, 1H), 7.66 (d, J = 14.24 Hz, 1H), 7.92 (s, 1H), 8.09 (d, J = 3.6 Hz, 1H), 9.17 (s, 1H), 9.45 (s, 1H), 10.15 (s, 1H); LCMS : *m/e* 456 (M-1).

EXAMPLE 220

[001162] Preparation of N-(3-(2-(4-chloro-3-(1-hydroxy-2-methylpropan-2-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-336**

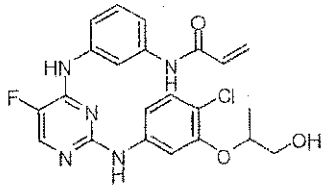


I-336

[001163] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-chloro-3-(1-hydroxy-2-methylpropan-2-yloxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.22 (s, 6H), 3.47 (d, J = 5.88 Hz, 2H), 4.88 (t, J = 5.84 Hz, 1H), 5.75 (dd, J = 3.24 & 10 Hz, 1H), 6.25 (dd, J = 2 & 16.92 Hz, 1H), 6.46 (dd, J = 10.12 & 17.08 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.31 (t, J = 8.2 Hz, 1H), 7.40-7.45 (m, 1H), 7.51-7.60 (m, 3H), 7.93 (s, 1H), 8.13 (d, J = 3.56 Hz, 1H), 9.24 (s, 1H), 9.47 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 472.2 (M+1).

EXAMPLE 221

[001164] Preparation of N-(3-(2-(4-chloro-3-(1-hydroxypropan-2-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-337**

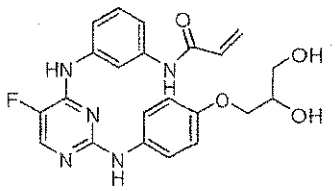


I-337

[001165] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-chloro-3-(1-hydroxypropan-2-yloxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.18 (d, *J* = 6.12 Hz, 3H), 3.40-3.47 (m, 1H), 3.50-3.56 (m, 1H), 4.20-4.30 (m, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 5.75 (dd, *J* = 1.88 & 10.08 Hz, 1H), 6.25 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.92 Hz, 1H), 7.12 (d, *J* = 8.76 Hz, 1H), 7.29 (t, *J* = 8.08 Hz, 1H), 7.40-7.44 (m, 3H), 7.52 (d, *J* = 8.44 Hz, 1H), 7.91 (s, 1H), 8.12 (d, *J* = 3.64 Hz, 1H), 9.21 (s, 1H), 9.45 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 458.0 (M+1).

EXAMPLE 222

[001166] Preparation of N-(3-(2-(4-(2,3-dihydroxypropoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-335**

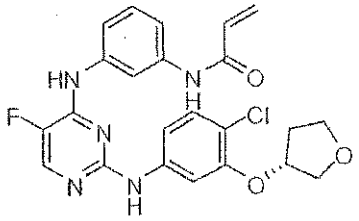


I-335

[001167] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-(1-hydroxypropan-2-yloxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.43 (dd, *J* = 0.64 & 6.84 Hz, 2H), 3.70-3.80 (m, 2H), 3.85-3.95 (m, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 4.88 (d, *J* = 4.76 Hz, 1H), 5.75 (dd, *J* = 1.76 & 10.08 Hz, 1H), 6.25 (dd, *J* = 1.72 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.88 Hz, 1H), 6.74 (d, *J* = 9 Hz, 2H), 7.27 (t, *J* = 8.08 Hz, 1H), 7.39 (d, *J* = 8.04 Hz, 1H), 7.38-7.53 (m, 3H), 7.93 (s, 1H), 8.05 (d, *J* = 3.68 Hz, 1H), 8.93 (s, 1H), 9.35 (s, 1H), 10.11 (s, 1H); LCMS : *m/e* 440.3 (M+1).

EXAMPLE 223

[001168] Preparation of (R)-N-(3-(2-(4-chloro-3-(tetrahydrofuran-3-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-341**

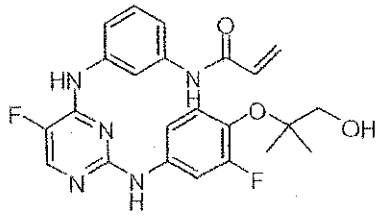


I-341

[001169] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)- 4-chloro-3-(tetrahydrofuran-3-yloxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.85-1.95 (m, 1H), 2.0-2.15 (m, 1H), 3.60-3.70 (m, 1H), 3.73-3.83 (m, 3H), 4.68 (s, 1H), 5.74 (dt, *J* = 1.92 & 10.0 Hz, 1H), 6.23 (dd, *J* = 1.88 & 16.92 Hz, 1H), 6.43 (dd, *J* = 10.12 & 16.96 Hz, 1H), 7.14 (d, *J* = 8.72 Hz, 1H), 7.29 (t, *J* = 8.08 Hz, 1H), 7.33 (dd, *J* = 4.16 & 8.76 Hz, 1H), 7.41-7.47 (m, 3H), 7.90 (s, 1H), 8.13 (d, *J* = 3.56 Hz, 1H), 9.28 (s, 1H), 9.47 (s, 1H), 10.13 (s, 1H); LCMS : *m/e* 469.8 (M+1).

EXAMPLE 224

[001170] Preparation of N-(3-(5-fluoro-2-(3-fluoro-4-(1-hydroxy-2-methylpropan-2-yloxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-332**



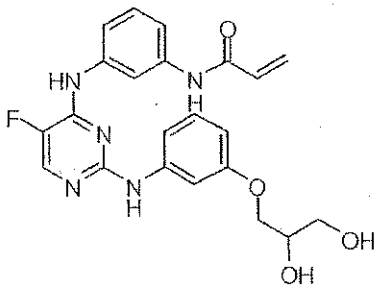
I-332

[001171] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-fluoro-4-(1-hydroxy-2-methylpropan-2-yloxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.13 (s, 6H), 3.36 (d, *J* = 5.84 Hz, 2H), 4.86 (t, *J* = 5.84 Hz, 1H), 5.73 (dd, *J* = 1.96 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.96 & 16.96 Hz, 1H), 6.44 (dd, *J* = 10.08 & 16.92 Hz, 1H), 6.95 (t, *J* = 9.16 Hz, 1H), 7.23 (dd, *J* =

1.64 & 8.96 Hz, 1H), 7.28 (t, J = 8.12 Hz, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.48 (d, J = 7.92 Hz, 1H), 7.70 (dd, J = 2.48 & 13.84 Hz, 1H), 7.92 (s, 1H), 8.11 (d, J = 3.68 Hz, 1H), 9.25 (s, 1H), 9.45 (s, 1H), 10.10 (s, 1H); LCMS: *m/e* 456.2 (M+1).

EXAMPLE 225

[001172] Preparation of N-(3-(2-(3-(2,3-dihydroxypropoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-339**

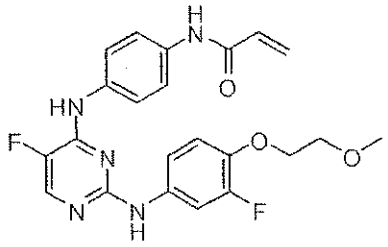


I-339

[001173] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-(2,3-dihydroxypropoxy)aniline in place of **4** in step 2. ^{1}H NMR (MeOD) δ ppm: 3.59-3.69 (m, 2H), 3.88-3.98 (m, 3H), 5.78 (dd, J = 2.16 & 9.6 Hz, 1H), 6.36 (dd, J = 2.24 & 17.04 Hz, 1H), 6.44 (dd, J = 9.56 & 16.96 Hz, 1H), 6.54-6.57 (m, 1H), 7.08-7.12 (m, 2H), 7.32 (t, J = 7.92 Hz, 2H), 7.44 (dd, J = 7.88 & 13.4 Hz, 2H), 7.94 (d, J = 3.8 Hz, 1H), 8.09 (s, 1H); LCMS : *m/e* 440.1 (M+1).

EXAMPLE 226

[001174] Preparation of N-(4-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-351**

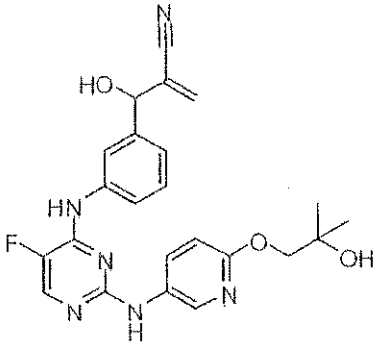


I-351

[001175] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using tert-butoxycarbonylamino-4-aminoaniline in place of 2 in step 1 and 3-fluoro-4-(2-methoxyethoxy)aniline in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.30 (s, 3H), 3.63 (t, J = 4.6 Hz, 2H), 4.08 (t, J = 4.48 Hz, 2H), 5.74 (dd, J = 2 & 10.08 Hz, 1H), 6.25 (dd, J = 1.96 & 16.92 Hz, 1H), 6.44 (dd, J = 10.04 & 16.96 Hz, 1H), 7.02 (t, J = 9.48 Hz, 1H), 7.23 (bd, J = 7.44 Hz, 1H), 7.64 (d, J = 9 Hz, 2H), 7.70-7.74 (m, 3H), 8.07 (d, J = 3.72 Hz, 1H), 9.19 (s, 1H), 9.34 (s, 1H), 10.13 (s, 1H); LCMS : *m/e* 442.0 (M+1).

EXAMPLE 227

[001176] Preparation of 2-((3-(5-fluoro-2-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)(hydroxy)methyl)acrylonitrile **I-312**

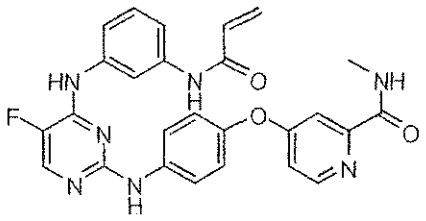


I-312

[001177] The title compound was prepared according to the schemes, steps and intermediates described in Example 107, by using 3-amino-6-(2-hydroxy-2-methylpropoxy)pyridine in place of 4 in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.18 (s, 6H), 3.98 (s, 2H), 4.61 (s, 1H), 5.31 (d, J = 3.88 Hz, 1H), 6.13 (s, 1H), 6.19 (s, 1H), 6.32 (d, J = 4 Hz, 1H), 6.75 (d, J = 8.88 Hz, 1H), 7.10 (d, J = 7.72 Hz, 1H), 7.33 (t, J = 7.84 Hz, 1H), 7.68 (s, 1H), 7.84 (d, J = 7.52 Hz, 1H), 7.96 (dd, J = 2.72 & 8.88 Hz, 1H), 8.08 (d, J = 3.64 Hz, 1H), 8.33 (d, J = 1.76 Hz, 1H), 9.06 (s, 1H), 9.44 (s, 1H); LCMS : *m/e* 451 (M+1).

EXAMPLE 228

[001178] Preparation of 4-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)phenoxy)-N-methylpicolinamide **I-342**

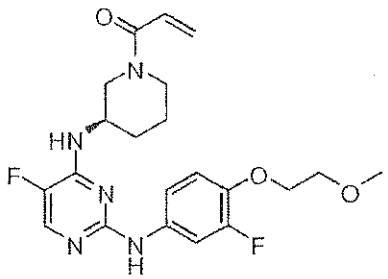


I-342

[001179] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-(4-aminophenoxy)-N-methylpicolinamide in place of **4** in step 2. LC/MS (M + H) 500.2

EXAMPLE 229

[001180] Preparation of (R)-1-(3-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-344**

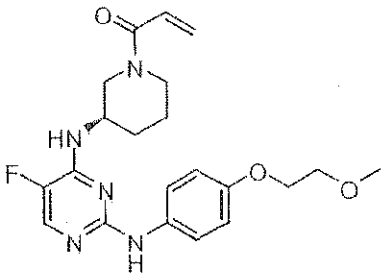


I-344

[001181] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-1-tert-butoxycarbonyl-3-aminopiperidine in place of **2** in step 1 and 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. LC/MS (M + H) 434.1.

EXAMPLE 230

[001182] Preparation of (R)-1-(3-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-345**

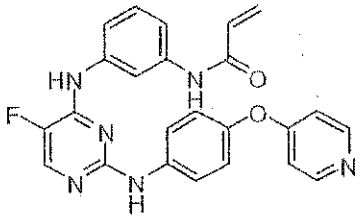


I-345

[001183] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-1-tert-butoxycarbonyl-3-aminopiperidine in place of 2 in step 1 and 4-(2-methoxyethoxy)aniline in place of 4 in step 2. LC/MS (M + H) 416.2

EXAMPLE 231

[001184] Preparation of 4-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)phenoxy) pyridine **I-346**

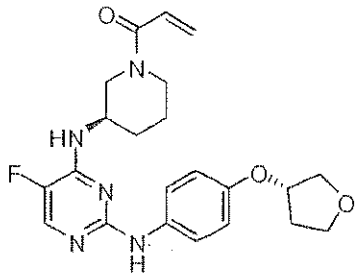


I-346

[001185] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-(4-aminophenoxy)pyridine in place of 4 in step 2. LC/MS (RT = 2.802/(M + H)) 500.2

EXAMPLE 232

[001186] Preparation of 1-((R)-3-(5-fluoro-2-(4-((S)-tetrahydrofuran-3-yloxy)phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-347**

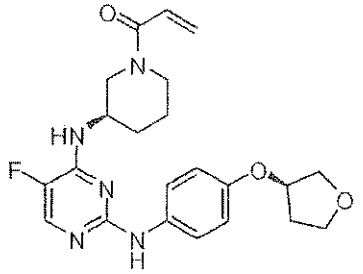


I-347

[001187] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-1-tert-butoxycarbonyl-3-aminopiperidine in place of **2** in step 1 and 4-(S)-(tetrahydrofuran-3-yloxy)aniline in place of **4** in step 2. LC/MS (M + H) 428.3.

EXAMPLE 233

[001188] Preparation of 1-((R)-3-(5-fluoro-2-(4-((R)-tetrahydrofuran-3-yloxy)phenylamino)pyrimidin-4-ylamino)piperidin-1-yl)prop-2-en-1-one **I-348**

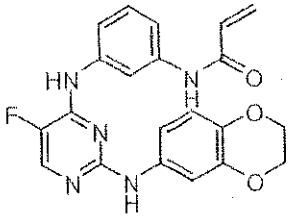


I-348

[001189] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (R)-1-tert-butoxycarbonyl-3-aminopiperidine in place of **2** in step 1 and 4-(R)-(tetrahydrofuran-3-yloxy)aniline in place of **4** in step 2. LC/MS (M + H) 428.3.

EXAMPLE 234

[001190] Preparation of N-(3-(2-(2,3-dihydrobenzo[*b*]1,4]dioxin-6-ylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-349**

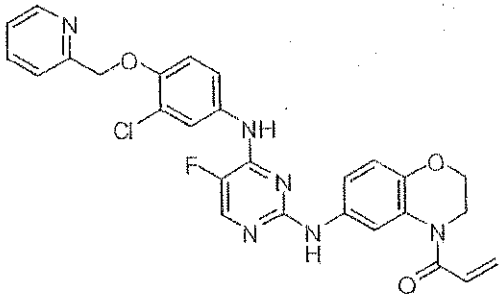


I-349

[001191] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 6-amino-2,3-dihydrobenzo[*b*]1,4]dioxane in place of **4** in step 2. LC/MS (M + H) 408.

EXAMPLE 235

[001192] Preparation of 1-(6-(4-(3-chloro-4-(pyridine-2-ylmethoxy)phenylamino)-5-fluoropyrimidin-2-ylamino)-2*H*-benzo[*b*][1,4]oxazin-4(3*H*)-yl)prop-2-en-1-one **I-343**

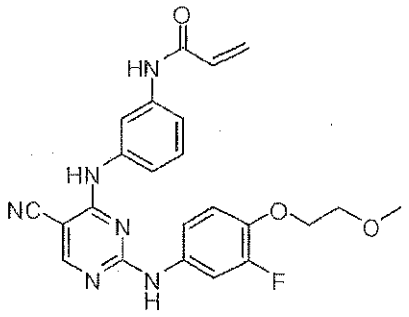


I-343

[001193] The title compound was prepared according to the schemes, steps and intermediates described in Example 35, using 3-chloro-4-(pyridine-2-ylmethoxy)aniline in place of **2** in step 1. LC/MS (M + H) 533.1.

EXAMPLE 236

[001194] Preparation of N-(3-(5-cyano-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-350**

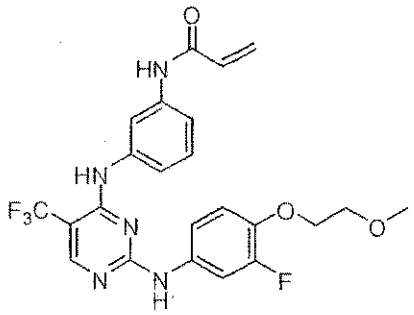


I-350

[001195] The title compound was prepared according to the schemes, steps and intermediates described in Example 94, by using 3-fluoro-4-(2-methoxyethoxy)aniline for **4** in step 2. LC/MS (M + H) 449.1

EXAMPLE 237

[001196] Preparation of N-(3-(5-trifluoromethyl-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-352**

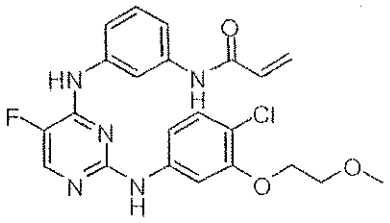


I-352

[001197] The title compound was prepared according to the schemes, steps and intermediates described in Example 189 using 3-fluoro-4-(2-methoxyethoxy)aniline for **2** in step 1. LC/MS (M + H) 492.1

EXAMPLE 238

[001198] Preparation of N-(3-(2-(4-chloro-3-(2-methoxyethoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-321**

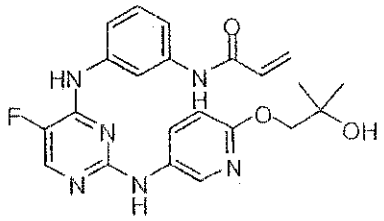


I-321

[001199] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 4-chloro-3-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 3.30 (s, 3H), 3.60 (t, *J* = 4.56 Hz, 2H), 3.88 (t, *J* = 3.48 Hz, 2H), 5.74 (dd, *J* = 4.36 & 10.0 Hz, 1H), 6.24 (dd, *J* = 1.8 & 16.88 Hz, 1H), 6.44 (dd, *J* = 4.36 & 10.0 Hz, 1H), 7.13 (d, *J* = 8.72 Hz, 1H), 7.28 (t, *J* = 8.04 Hz, 1H), 7.33 (dd, *J* = 2.16 & 8.8 Hz, 1H), 7.41 (d, *J* = 7.96 Hz, 1H), 7.47-7.49 (m, 2H), 7.84 (s, 1H), 8.13 (d, *J* = 3.6 Hz, 1H), 9.27 (s, 1H), 9.47 (s, 1H), 10.12 (s, 1H); LCMS : m/e 458.0 (M+1).

EXAMPLE 239

[001200] Preparation of N-(3-(5-fluoro-2-(6-(2-hydroxy-2-methylpropoxy)pyridin-3-ylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-313**



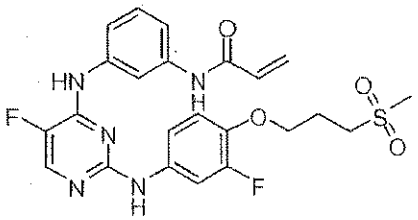
I-313

[001201] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-amino-6-(2-hydroxy-2-methylpropoxy)pyridine in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.16 (s, 6H), 3.93 (s, 2H), 4.57 (s, 1H), 5.74 (dd, *J* = 1.68 & 10.04 Hz, 1H), 6.24 (dd, *J* = 1.84 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.04 & 16.88 Hz, 1H), 6.65 (d, *J* = 8.88 Hz, 1H), 7.26 (t, *J* = 8.04 Hz, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.91 (s, 1H), 7.99 (dd, *J* = 2.72 & 8.92 Hz, 1H), 8.07

(d, J = 3.68 Hz, 1H), 8.27 (d, J = 2.52 Hz, 1H), 9.06 (s, 1H), 9.41 (s, 1H), 10.1 (s, 1H); LCMS : *m/e* 439.0 (M+1).

EXAMPLE 240

[001202] Preparation of N-(3-(5-fluoro-2-(3-fluoro-4-(3-(methylsulfonyl)propoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-318**

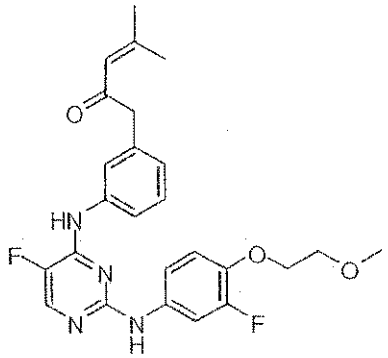


I-318

[001203] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using 3-fluoro-4-(3-(methylsulfonyl)propoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 2.05-2.15 (m, 2H), 3.01 (s, 3H), 3.24 (t, J = 7.56 Hz, 2H), 4.05 (t, J = 6.12 Hz, 2H), 5.74 (dd, J = 1.84 & 9.72 Hz, 1H), 6.24 (dd, J = 1.72 & 16.96 Hz, 1H), 6.44 (dd, J = 10 & 16.84 Hz, 1H), 6.96 (t, J = 9.36 Hz, 1H), 7.28 (t, J = 8.04 Hz, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 8.32 Hz, 1H), 7.69 (dd, J = 2.2 & 14.4 Hz, 1H), 7.91 (s, 1H), 8.10 (d, J = 3.64 Hz, 1H), 9.20 (s, 1H), 9.44 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 504.2 (M+1).

EXAMPLE 241

[001204] Preparation of 1-(3-(5-fluoro-2-(3-fluoro-4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino)phenyl)-4-methylpent-3-en-2-one **I-330**

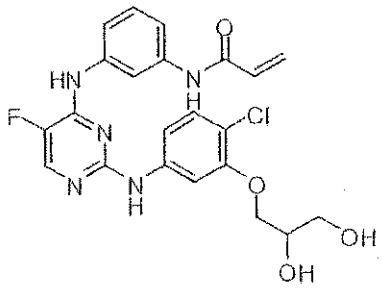


I-330

[001205] The title compound was prepared according to the schemes, steps and intermediates described in Example 112, by using ethyl 4-aminomethylbenzoate in place of **2** in step 1 and 3-fluoro-4-(2-methoxyethoxy)aniline in place of **4** in step 2. ^{1}H NMR (DMSO-d_6) δ ppm: 1.83 (s, 3H), 2.05 (s, 3H), 3.31 (s, 3H), 3.64 (t, J = 4.56 Hz, 2H), 3.69 (s, 2H), 4.08 (t, J = 4.4 Hz, 2H), 6.18 (s, 1H), 6.92 (d, J = 7.44 Hz, 1H), 7.01 (t, J = 9.36 Hz, 1H), 7.27 (t, J = 7.84 Hz, 2H), 7.51 (s, 1H), 7.64-7.71 (m, 2H), 8.09 (d, J = 3.64 Hz, 1H), 9.19 (s, 1H), 9.34 (s, 1H); LCMS : *m/e* 469.1 (M+1).

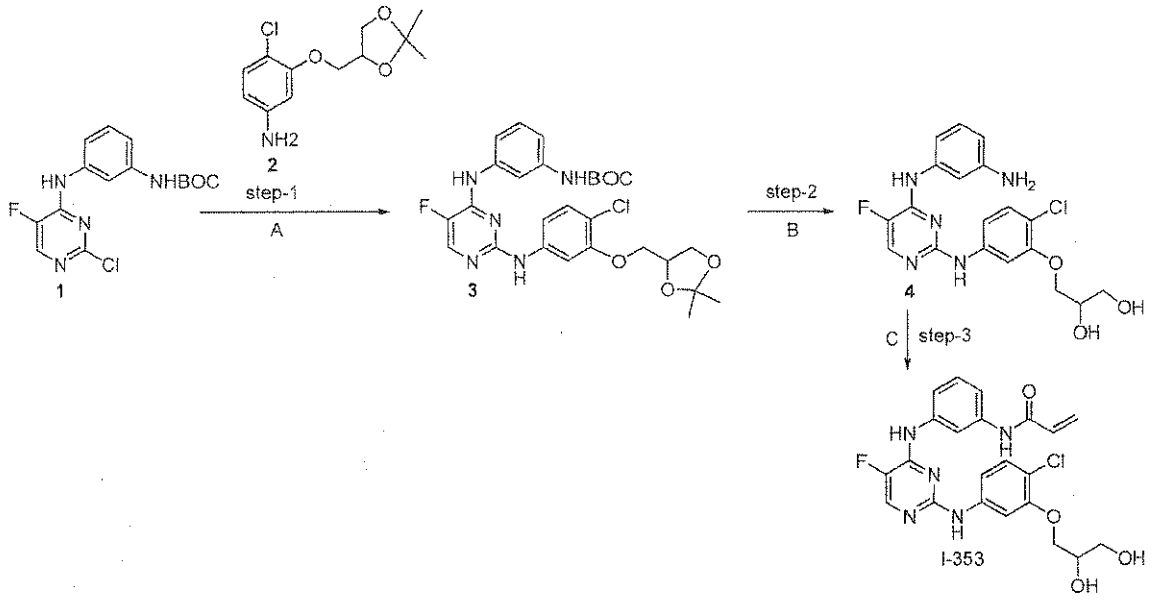
EXAMPLE 242

[001206] Preparation of N-(3-(2-(4-chloro-3-(2,3-dihydroxypropoxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-353**



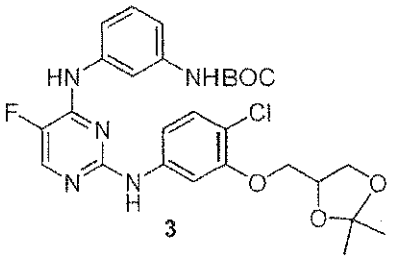
I-353

[001207] The title compound was prepared according to the schemes, steps and intermediates described below.



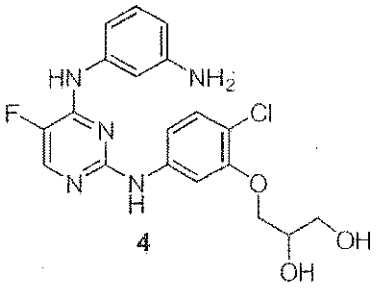
A) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 °C 16 h; **B**) TFA, CH_2Cl_2, rt, 2 h; **C**) acryloyl chloride, K_2CO_3, NMP, rt, 45 min.

[001208] **Step-1**



[001209] A solution of **2** (200 mg, 0.77 mmol), **1** (262 mg, 0.77 mmol), $Pd(OAc)_2$ (17.3 mg, 0.07 mmol), BINAP (24 mg, 0.038 mmol) and Cs_2CO_3 (630 mg, 1.9 mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated for 16 h at 100 °C under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (15 mL) and filtered through Celite®. The filtrate was washed with water (5 mL) and brine (3 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give **3** (0.3 g, 69 %) as a yellow solid.

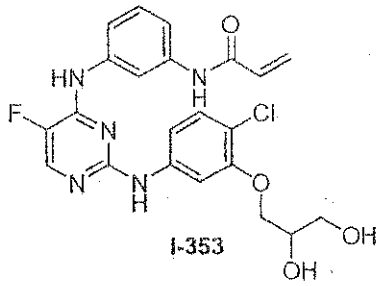
[001210] Step-2



4

[001211] To a stirred solution of **3** (300 mg, 0.5 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C was added CF_3COOH (3 mL), and the reaction mixture was kept at this temperature for 30 min. The reaction was allowed to come to rt and stirred at this temperature for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was quenched with water (5 mL), basified with $NaCO_3$ solution, and extracted with ethyl acetate (2x10 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to get **4** (200 mg, 88 %) as a yellow solid.

[001212] Step-3

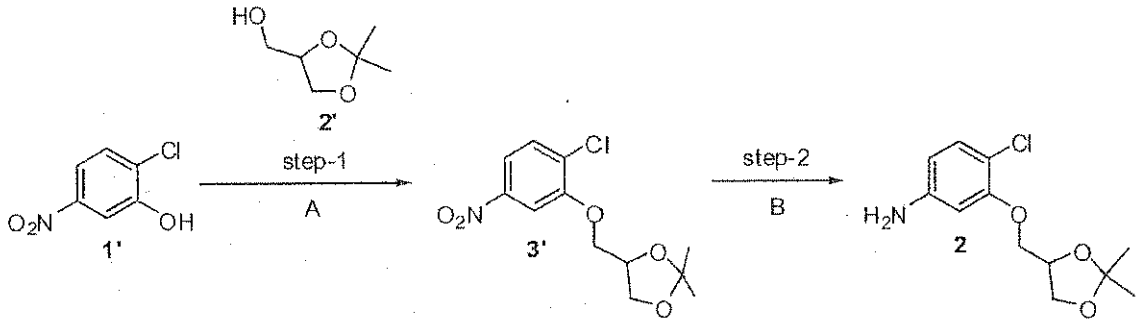


I-353

[001213] To a stirred solution of **4** (240 mg, 0.5 mmol), in NMP (1.5 mL) at 0 °C was added potassium carbonate (780 mg, 5.7 mmol) and acryloyl chloride (57 mg, 0.5 mmol), and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was further stirred at rt for 30 min and quenched by dropwise addition to a cold, stirring solution of 10% $NaHCO_3$ and stirred at 0 °C for 30 min. A solid precipitated out and was isolated by filtration through a Buchner funnel. The solid was washed with cold water, dissolved in EtOAc (20 mL) and was basified by using triethylamine and washed with water (2 mL), brine (1 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative HPLC to give the title compound (45 mg, 15.5 %) as a white solid. ^{1}H NMR (DMSO-d6) δ ppm: 3.43-3.50 (m,

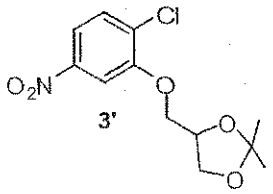
2H), 3.78-3.85 (m, 2H), 3.89-3.92 (m, 1H), 4.65 (t, J = 5.6 Hz, 1H), 4.93 (d, J = 4.8 Hz, 1H), 5.76 (dd, J = 1.92 & 10.04 Hz, 1H), 6.26 (dd, J = 1.92 & 16.92 Hz, 1H), 6.46 (dd, J = 10.08 & 16.92 Hz, 1H), 7.14 (d, J = 8.72 Hz, 1H), 7.30 (t, J = 8.08 Hz, 1H), 7.39-7.43 (m, 2H), 7.46 (dd, J = 2.2 & 8.72 Hz, 1H), 7.56 (d, J = 8.04 Hz, 1H), 7.94 (s, 1H), 8.14 (d, J = 3.6 Hz, 1H), 9.24 (s, 1H), 9.48 (s, 1H), 10.13 (s, 1H); LCMS : *m/e* 473.8 (M+).

[001214] **Synthesis of intermediate 2**



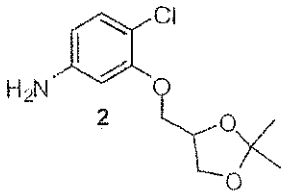
A) DIAD, PPh_3, Et_3N, dry THF, rt, 1 h; **B**) H_2, Ra Ni, methanol, 2 h.

[001215] **Step-1**



[001216] To a stirred solution of **2'** (0.640 g, 3.7 mmol) in THF (20 mL) were added **1'** (0.5 g, 3.7 mmol), PPh_3 (1.09 g, 4.1 mmol) and Et_3N (0.73 g, 5.6 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 °C and DIAD (0.84 g, 4.1 mmol) was added. The reaction mixture was allowed to come to rt and stir for 1 h. The reaction was quenched with water, extracted with ethyl acetate (3x10 mL), and the combined extracts were washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 9/1) to give **3'** (0.6 g, 60 %) as a white solid.

[001217] Step-2

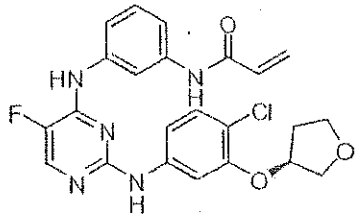


2

[001218] To a solution of 3' (0.3 g, 1.04 mmol) in methanol was added Raney Ni (60 mg, 20% w/w) under N_2, and the reaction mixture was kept under H_2 atmosphere (bladder pressure) for 16 h. The reaction mixture was filtered through a bed of Celite®, and the filtrate was concentrated under reduced pressure. The residue was diluted with 1.5 N HCl (2 mL) and washed with ethyl acetate (5 mL) to remove organic impurities. The aqueous layer was basified with $NaHCO_3$ solution (5 mL), extracted with ethyl acetate, washed with water (2 mL) and brine (2 mL), and dried over anhydrous Na_2SO_4. Filtration followed by concentration under reduced pressure gave 2 (0.2 g, 76.9 %) as a brown liquid.

EXAMPLE 243

[001219] Preparation of (S)-N-(3-(2-(4-chloro-3-(tetrahydrofuran-3-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide I-354

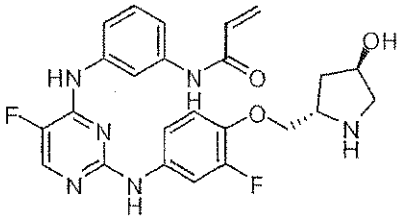


I-354

[001220] The title compound was prepared according to the schemes, steps and intermediates described in Example 20, by using (S)- 4-chloro-3-(tetrahydrofuran-3-yloxy)aniline in place of 4 in step 2. LCMS : *m/e* 469.8 (M+1).

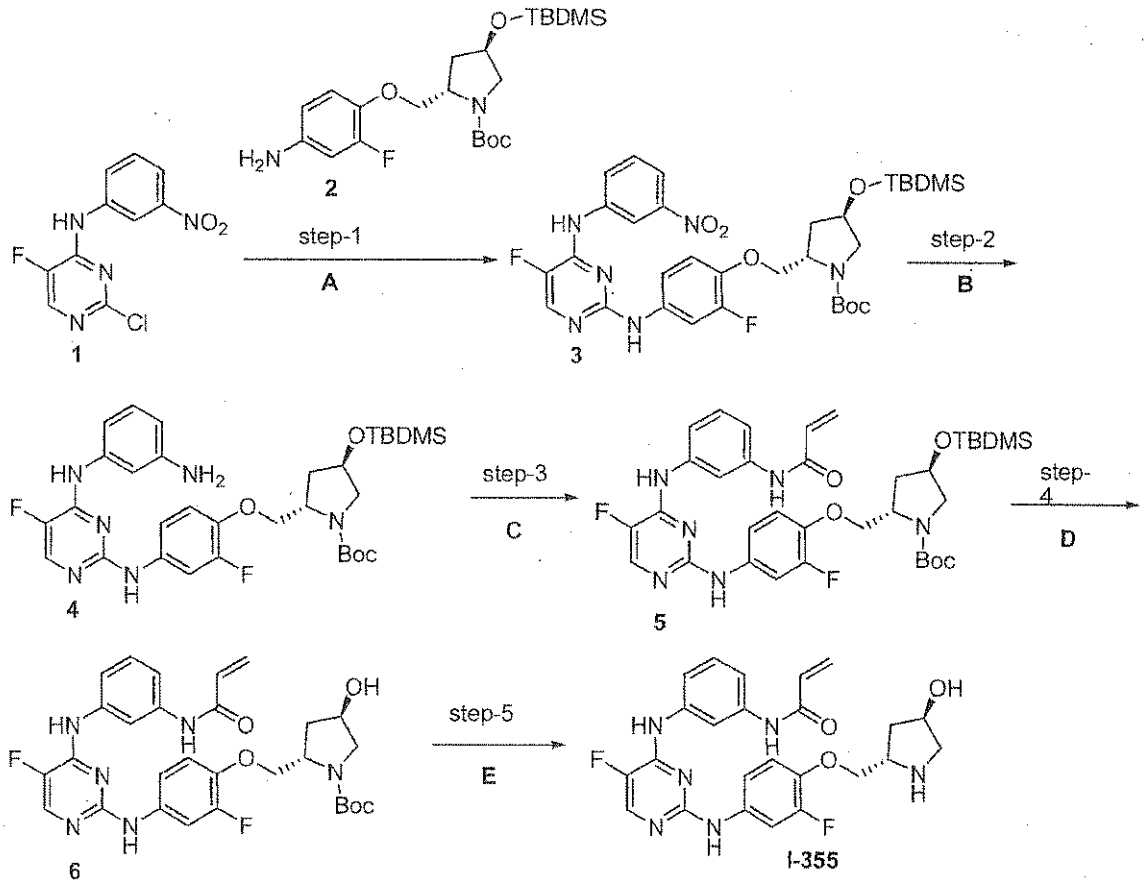
EXAMPLE 244

[001221] Preparation of (N-(3-(5-fluoro-2-(3-fluoro-4-(((2S,4R)-4-hydroxypyrrolidin-2-yl)methoxy)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-355**



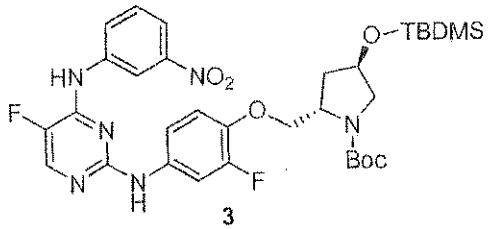
I-355

[001222] The title compound was prepared according to the schemes, steps and intermediates described below.



A) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 ^{0}C, 6 h; **B)** TFA, CH_2Cl_2, rt, 1 h; **C)** $(Boc)_2O$, 30 min then acryloyl chloride, K_2CO_3, NMP, 0 ^{0}C, 90 min; **D)** HF (49% aq. Solution), CH_3CN, rt, 2 h; **E)** TFA, DCM, rt, 2 h.

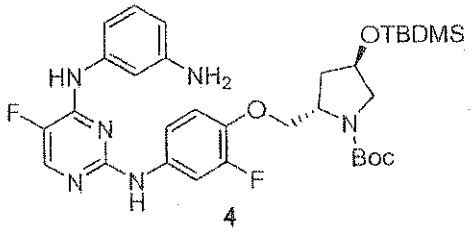
[001223] Step-1



3

[001224] A solution of 2 (0.50 g, 1.13 mmol), 1 (0.30g, 1.13 mmol), $Pd(OAc)_2$ (0.0025 g, 0.1 mmol), BINAP (0.0035 g, 0.05 mmol) and Cs_2CO_3 (0.92 g, 2.8 mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated at 110 ^{0}C for 16 h under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further washed with hexane to give 3 (0.3 g, 42.8%) as a yellow solid.

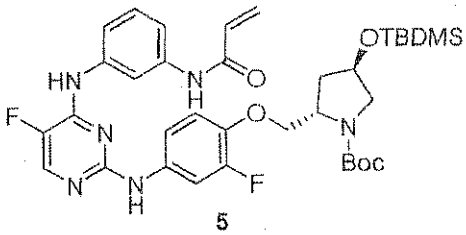
[001225] Step-2



4

[001226] To a solution of 3 (0.3 g, 0.44 mmol) in methanol (5 mL)) was added Pd/C (0.030 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (balloon) at rt for 16 h. The reaction mixture was filtered through a pad of Celite® and was concentrated under reduced pressure to give 4 (0.19 g, 67.6%) as a yellow solid.

[001227] Step-3

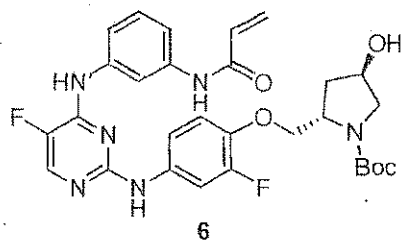


5

[001228] To a stirred solution of 4 (0.1 g, 0.15 mmol) in NMP (1.0 mL) at rt was added Boc anhydride (0.046 g, 0.212 mmol) and the reaction mixture was stirred at rt for 60 min. It

was then cooled to 0 ^{0}C and to it was added K_2CO_3 (0.107 g, 0.77 mmol), acryloyl chloride (0.016 g, 0.18 mmol) and the reaction mixture was stirred at 0 ^{0}C for 90 min. The reaction mixture was added drop wise, to a cold, stirring solution of 10% $NaHCO_3$. After the addition was over, the solution was stirred for another 30 min at 0 ^{0}C, and the solid was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and was dissolved in methanol: dichloromethane (50:50, 10 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (5 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x10 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further purified by column chromatography (SiO_2, methanol/chloroform: 4/96) to give **5** (0.075 g, 71.4%) as yellow solid.

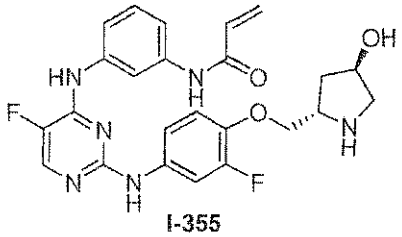
[001229] **Step-4**



6

[001230] To a solution of **5** (15 mg, 0.02 mmol) in acetonitrile was added HF (49% aq. Solution, 0.0048 mL, 0.024 mmol) at 0 ^{0}C. The reaction mixture stirred at rt for 2 h, was extracted with ethyl acetate (2 mL), was washed with water (1 mL), and was dried over Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure. The residue showed 60% purity by LCMS and was used in the next step without further purification.

[001231] **Step-5**

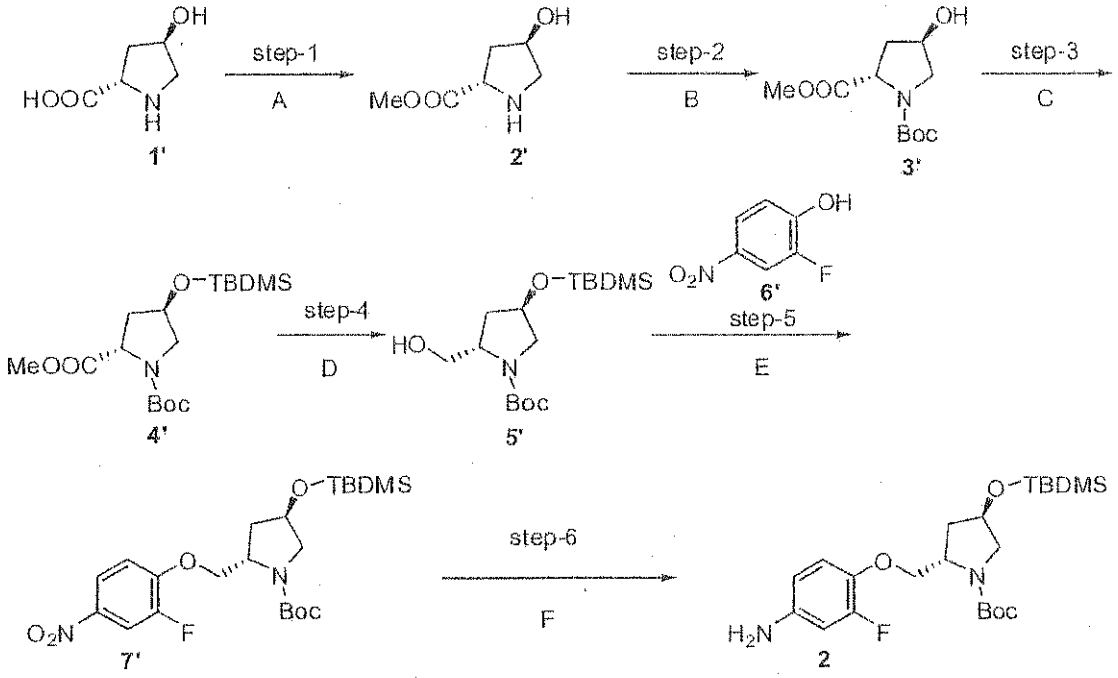


I-355

[001232] To a stirred solution of **6** (0.008 g, 0.013 mmol) in CH_2Cl_2 (0.024 mL) was added TFA (0.016 mL) at 0 ^{0}C. The reaction mixture was allowed to come to rt and was stirred for additional 2 h. It was then concentrated and was stirred with cold 10% $NaHCO_3$ (1.0 mL). It was

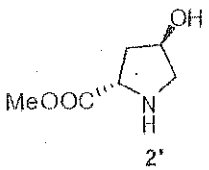
extracted with EtOAc (2x2 mL) and the combined EtOAc extract was washed with brine (1 mL), was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude residue was further purified by column chromatography (SiO_2, methanol/chloroform: 2/98) and was then purified by preparative TLC to give the title compound (2 mg, 81% purity by HPLC, and 79% purity by LCMS) as a white solid. LCMS : *m/e* 483 (M+).

[001233] Compound 2 was prepared according to the schemes, steps and intermediates described below.



A) MeOH, $SOCl_2$, reflux, 5 h; **B)** $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 5 h; **C)** TBDMS-Cl, imidazole, DMF, rt, 16 h; **D)** LAH solution (1M in THF), -20 ^{0}C, 20 min; **E)** DIAD, PPh_3, Et_3N, THF, 16 h; **F)** H_2, Pd/C, methanol, rt, 16 h.

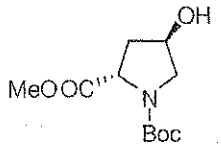
[001234] **Step-1**



[001235] To a stirred solution of 1' (2 g, 15.26 mmol) was added a solution prepared by adding thionyl choride (2 mL) to methanol (20 mL). The reaction mixture was heated at reflux

for 5 h. After completion of the reaction, methanol was removed under reduced pressure to give **2'** as colorless salt (3.0 g) it was used as such in the next reaction.

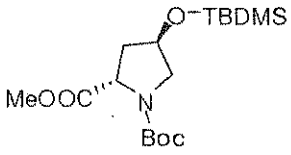
[001236] **Step-2**



3'

[001237] To a stirred solution of **2'** (3.0 g, 12.24 mmol) in DCM (30 mL) was added Et_3N (1.85 g, 18.31 mmol) and Boc anhydride (2.92 g, 13.46 mmol). Stirring was continued at rt for 5 h after which the reaction was quenched with water. The organic layer was separated, dried and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, 60-120, 100% ethyl acetate) to give **3'** (3.2 g, 64%) as a white solid.

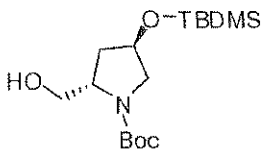
[001238] **Step-3**



4'

[001239] To a stirred solution of **3'** (3 g, 12.24 mmol) in DMF (30 mL) was added imidazole (1.2 g, 18.36 mmol) followed by TBDMS chloride (1.84 g, 12.24 g). Stirring was continued for 16 h. The reaction mixture was diluted with ethyl acetate (50 mL) and the ethyl acetate layer was separated. It was washed with water (5 mL), brine solution (5 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was purified by column chromatography (SiO_2, 60-120, petroleum ether/ ethyl acetate : 6/4) to give **4'** (3.2 g, 80%) as a colorless liquid.

[001240] **Step-4**

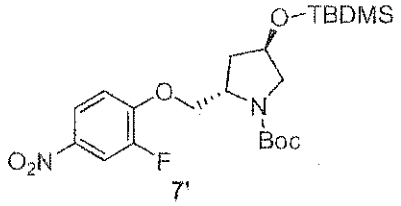


5'

[001241] To a stirred solution of **4'** (0.5 g, 1.39 mmol) in THF (5 mL) was added LAH (1.39 mL, 1M solution, 1.39 mmol) at -20 ^{0}C. The reaction was continued at the same

temperature for 15 min after which it was quenched with Na_2SO_4 solution. The reaction mass was filtered through celite® and filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced under reduced pressure to give 5' (0.3 g, 65%) as a colorless liquid.

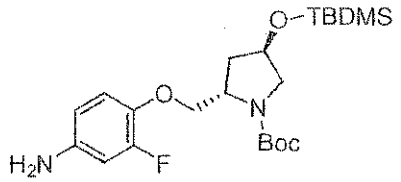
[001242] **Step-5**



7'

[001243] To a stirred solution of 5' (0.1 g, 0.3 mmol) in THF (6 mL) were added 6' (0.047 g, 0.3 mmol), PPh_3 (0.16 g, 0.64 mmol) and Et_3N (0.048 g, 0.48 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 ^{0}C and to it was added DIAD (0.094 g, 0.48 mmol). The reaction mixture was allowed to come to rt and stirred at it for 1 h. It was quenched with water, was extracted with ethyl acetate (2x5 mL) and the combined ethyl acetate extract was washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 9/1) to give 7' (0.120 g, 85%) as a yellow solid

[001244] **Step-6**

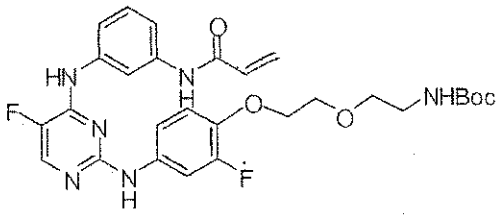


2

[001245] To a solution of 7' (0.1 g, 0.21 mmol) in methanol (5 mL)) was added Pd/C (0.010 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (bladder) at rt for 16 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to give 2 (0.085 g, 91%) as a brownish viscous oil. It was used in the next step without further purification.

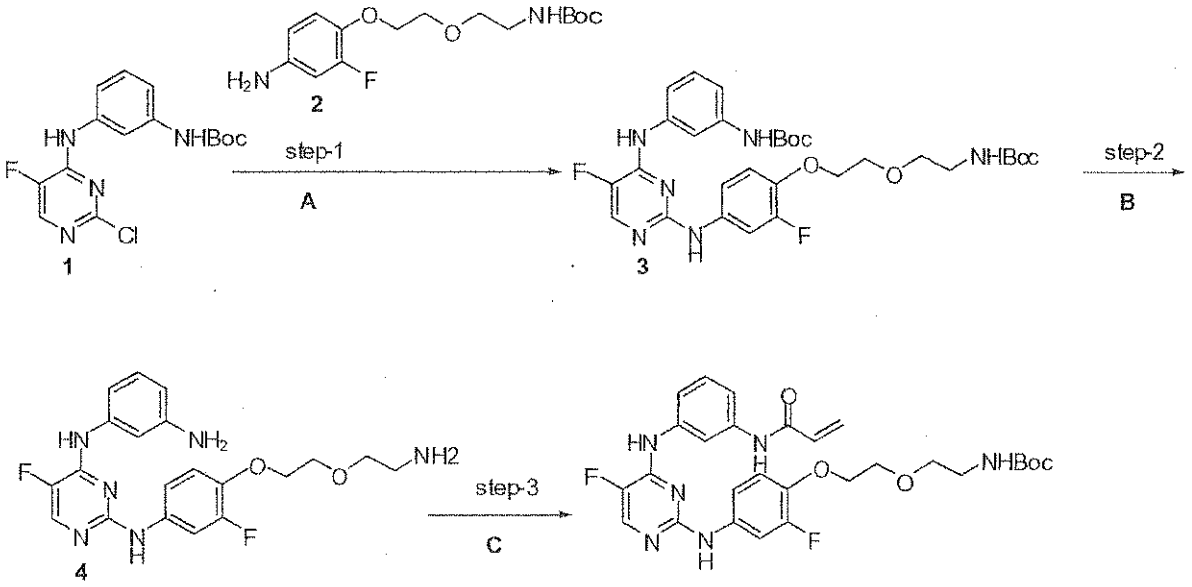
EXAMPLE 245

[001246] Preparation of tert-butyl 2-(2-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)-2-fluorophenoxy)ethoxy)ethylcarbamate **I-356**



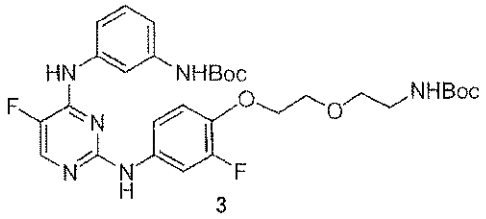
I-356

[001247] The title compound was prepared according to the schemes, steps and intermediates described below.



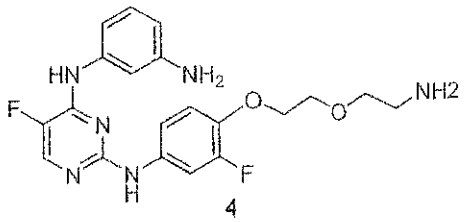
A) $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 ^{0}C, 6 h; **B)** TFA, CH_2Cl_2, RT 1 h; **C)** $(Boc)_2O$, 30 min then acryloyl chloride, K_2CO_3, NMP, 0 ^{0}C, 90 min.

[001248] <u>Step-1</u>



[001249] A solution of 2 (0.050 g, 0.159 mmol), 1 (0.053 g, 0.159 mmol), $Pd(OAc)_2$ (0.0035 g, 0.01590 mmol), BINAP (0.0049 g, 0.0079 mmol) and Cs_2CO_3 (0.129 g, 0.3975mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated at 110 ^{0}C for 16 h under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further washed with hexane to give 3 (0.049 g, 50%) as a brown solid.

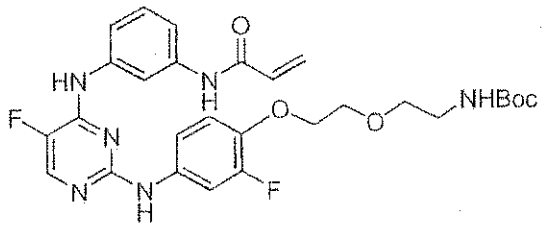
[001250] Step-2



4

[001251] To a stirred solution of 3 (0.047 g, 0.0762 mmol) in dry CH_2Cl_2 (3 mL) at 0 ^{0}C was added CF_3COOH (1.0 mL) and the reaction mixture was stirred at 0 ^{0}C for 30 min. The reaction was allowed to come to rt and stirred at it for 1 h. It was concentrated under reduced pressure and the residue was quenched with $NaHCO_3$ solution (3 mL). The contents were extracted with ethyl acetate (3x10 mL) and the combined EtOAc extract was washed with water (10 mL) followed by 10% citric acid solution (3x10 mL). The combined citric acid extract was basified with 10% NaOH solution and extracted with EtOAc (3x25 mL). The EtOAc extract was washed with water (20 mL), brine (10 mL) and dried over Na_2SO_4. to get 4 (0.028 g, 88%) as a light yellow solid.

[001252] Step-3

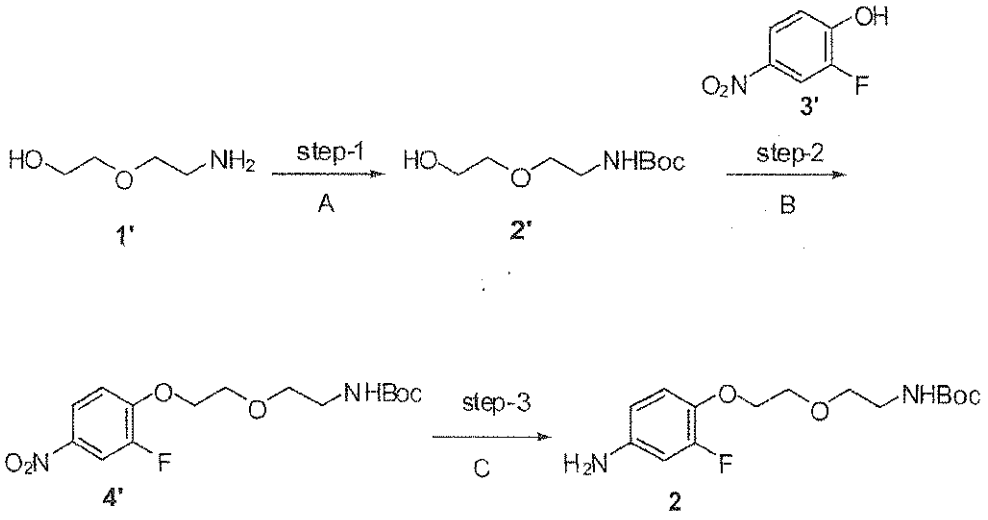


I-356

[001253] To a stirred solution of 4 (0.028 g, 0.06731 mmol) in NMP (1.0 mL) at rt was added $(Boc)_2O$ (0.016 g, 0.07404 mmol) and the reaction mixture was stirred at rt for 30 min. It was cooled to 0 ^{0}C and to it was added K_2CO_3 (0.051 g, 0.372 mmol) and acryloyl chloride

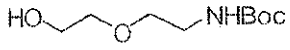
(0.0067 g, 0.07404 mmol) and the reaction mixture was stirred at 0 ^{0}C for 30 min. The reaction mixture was added dropwise, to a cold, stirring solution of 10% $NaHCO_3$. After the addition was over, the solution was stirred for another 30 min at 0 ^{0}C, and the solid was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and was dissolved in methanol: dichloromethane (50:50, 5 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (3 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x5 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (0.016 g, 42 %) as a grey solid. ^{1}H NMR (DMSO-d6) δ ppm: 1.37 (s, 9H), 3.09 (d, J = 5.5 Hz, 2H), 3.43 (d, J = 5.84 Hz, 2H), 3.69 (s, 2H), 4.05 (s, 2H), 5.75 (d, J = 11.12 Hz, 1H), 6.25 (d, J = 16.76 Hz, 1H), 6.46 (dd, J = 10.12 & 16.84 Hz, 1H), 6.81 (s, 1H), 6.96 (t, J = 9.12 Hz, 1H), 7.24-7.31 (m, 2H), 7.43 (d, J = 7.96 Hz, 1H), 7.49 (d, J = 7.56 Hz, 1H), 7.68 (d, J = 14 Hz, 1H), 7.94 (s, 1H), 8.11 (d, J = 3.24 Hz, 1H), 9.21 (s, 1H), 9.46 (s, 1H), 10.15 (s, 1H); LCMS : m/e 571.1 (M+1).

[001254] The intermediate **2** was prepared according to the schemes, steps and intermediates described below.



A) $(Boc)_2O$, aq. NaOH, rt, 16 h; **B)** DIAD, PPh_3, Et_3N, dry THF, rt, 1 h; **C)** H_2, Pd/C, ethanol, rt, 16 h.

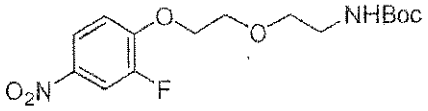
[001255] **Step-1**



2'

[001256] To a solution of NaOH (0.76 g, 0.019 mmol) in water (9.6 mL) at rt was added 1' (2.0 g, 19.022 mmol) and the reaction was stirred for 30 min. A solution of Boc-anhydride (4.561 g, 20.92 mmol) in THF (12.0 mL) was added dropwise over 5 min to it. The reaction mixture was stirred at rt for 16 h. It was concentrated under reduced pressure, diluted with water (20 mL) and extracted with EtOAc (4x50 mL). The combined EtOAc extract was washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 to give 2' (3.2 g, 82%) as a viscous oil.

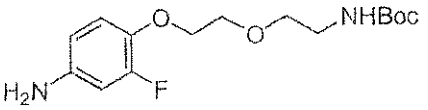
[001257] **Step-2**



4'

[001258] To a stirred solution of 2' (0.38 g, 1.851 mmol) in THF (6 mL) were added 3' (0.29 g, 1.851 mmol), PPh_3 (0.534 g, 2.0361 mmol) and Et_3N (0.280 g, 2.776 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 ^{0}C and to it was added DIAD (0.411 g, 2.0361 mmol). The reaction mixture was allowed to come to rt and stirred at it for 1 h. It was quenched with water, extracted with ethyl acetate (3x5 mL) and the combined ethyl acetate extract was washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 9/1) to give 4' (0.360 g, crude) as a yellow solid

[001259] **Step-3**

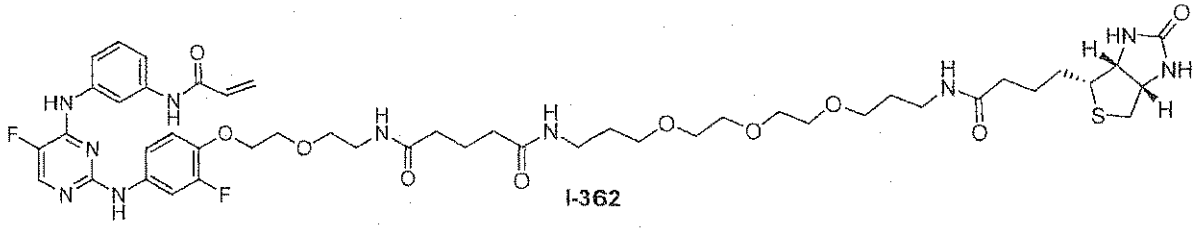


2

[001260] To a solution of 4' (0.360 g, 1.0456 mmol) in ethanol (10 mL)) was added Pd/C (0.072 g, 20% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (1.5 Kg hydrogen pressure) at rt for 16 h. The reaction mixture was filtered through a pad of celite® and concentrated under reduced pressure to give 2 (0.28 g, 85%) as a brownish viscous oil. It was used in the next step without further purification.

EXAMPLE 246

[001261] Preparation of N^1-(2-(2-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)-2-fluorophenoxy)ethoxy)ethyl)-N^5-(15-oxo-18-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azaoctadecyl)glutaramide **I-362**

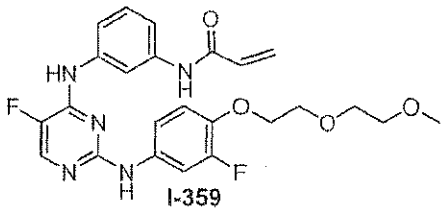


I-362

[001262] The title compound was prepared according to the schemes, steps and intermediates described in Example 204, by using tert-butyl 2-(2-(4-(4-(3-acrylamidophenylamino)-5-fluoropyrimidin-2-ylamino)-2-fluorophenoxy)ethoxy)ethylcarbamate (**I-356**, described in Example 245) in place of **I-45** in step 1. ^{1}H NMR (DMSO-d_6) δ ppm: 10.1 (s, 1H), 9.87 (s, 1H), 9.52 (s, 1H), 8.09 (d, J = 4.1 Hz, 1H), 7.86 (s, 1H), 7.78 (t, J = 5.5 Hz, 1H), 7.66 (m, 3H), 7.48 (dd, J = 2.3 & 13.8 Hz, 1H), 7.33 (m, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.11 (d, J = 9.2 Hz, 1H), 6.90 (t, J = 9.2 Hz, 1H), 6.34 (m, 2H), 6.14 (dd, J = 2.3 & 17.0 Hz, 1H), 5.66 (dd, J = 2.3 & 17.0 Hz, 1H), 4.20 (dd, J = 5.0 & 7.3 Hz, 1H), 3.99 (m, 3H), 3.61 (m, 2H), 3.12 (q, J = 6.0 Hz, 2H), 2.97 (m, 9H), 2.72 (m, 2H), 2.46 (m, 2H), 1.95 (m, 9H), 1.1-1.6 (m, 18H); LCMS : *m/e* 1013. (M+1).

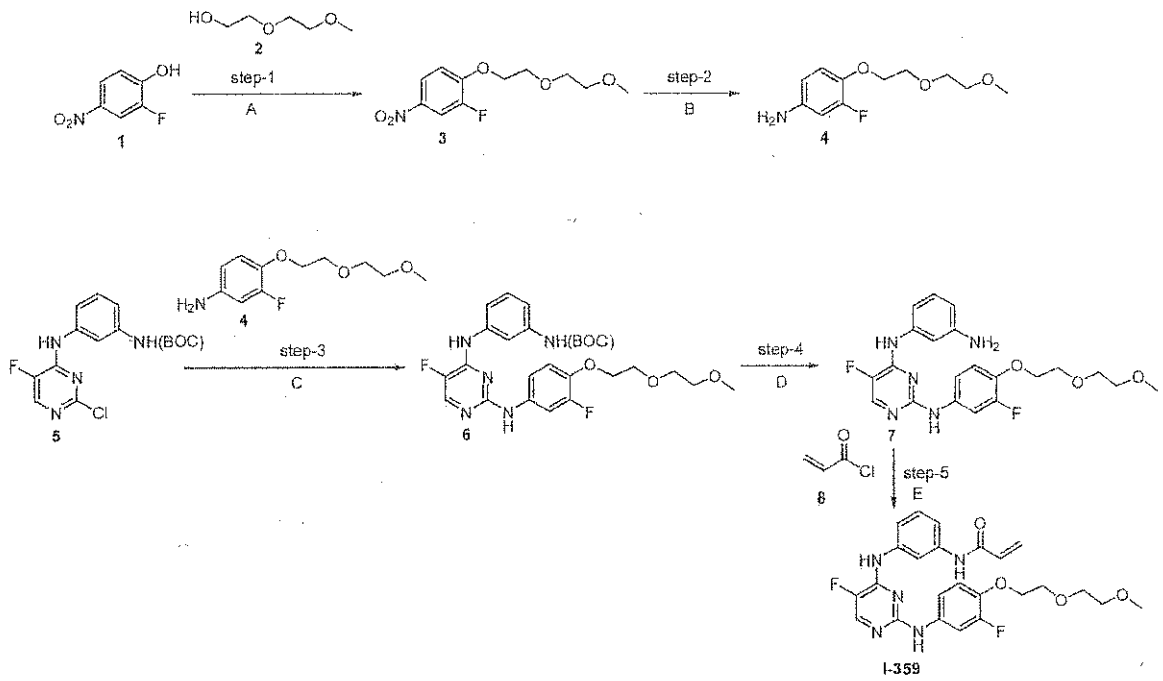
EXAMPLE 247

[001263] Preparation of N-(3-(5-fluoro-2-(3-fluoro-4-(2-(2-methoxyethoxy)ethoxy)-phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide **I-359**



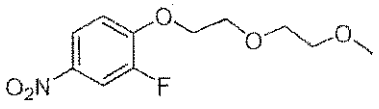
I-359

[001264] The title compound was prepared according to the schemes, steps and intermediates described below.



A) DIAD, PPh_3, Et_3N, dry THF, rt, 1 h; **B)** H_2, Pd/C, methanol, rt, 16 h; **C)** $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 °C, 6 h; **D)** TFA, CH_2Cl_2, rt, 1 h; **E)** $(BOC)_2O$, 30 min, then K_2CO_3, NMP, 0 °C, 15 min.

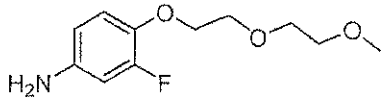
[001265] **Step-1**



3

[001266] To a stirred solution of **1** (0.5 g, 3.18 mmol) in THF (10 mL) were added **2** (0.38 g, 3.18 mmol), PPh_3 (0.91 g, 3.498 mmol) and Et_3N (0.48 g, 4.776 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 ^{0}C and to it was added DIAD (0.707 g, 3.5 mmol). The reaction mixture was allowed to come to rt and stirred at it for 1 h. It was quenched with water, extracted with ethyl acetate (3x5 mL) and the combined EtOAc extract was washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 7/3) to give **3** (0.61 g, 65%) as a white solid.

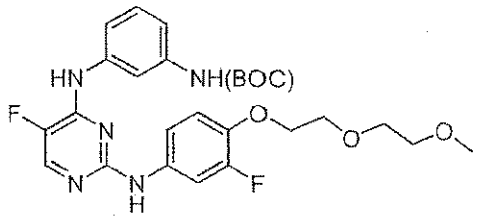
[001267] Step-2



4

[001268] To a solution of **3** (0.6 g, 2.31 mmol) in ethanol (20 mL)) was added Pd/C (0.060 g, 10% w/w) and the reaction mixture was allowed to stir under H_2 atmosphere (bladder pressure) at rt for 16 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure to give **4** (0.375 g, 70.7%) as a brownish viscous oil.

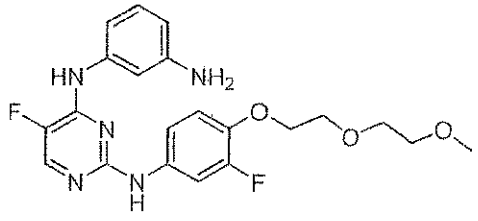
[001269] Step-3



6

[001270] A solution of **4** (0.275 g, 1.19 mmol), **5** (0.403 g, 1.19 mmol), prepared according to Step-1 of Example 20, $Pd(OAc)_2$ (0.0026 g, 0.11 mmol), BINAP (0.0037 g, 0.059 mmol) and Cs_2CO_3 (0.969 g, 2.95 mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated at 110 °C for 16 h under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate 5/5) to give **6** (0.350 g, 55%) as a yellow solid.

[001271] Step-4

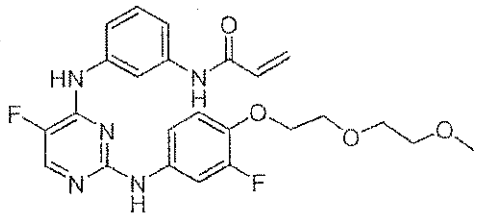


7

[001272] To a stirred solution of **6** (0.3 g, 0.56 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C was added CF_3COOH (1.0 mL) and the reaction mixture was stirred at 0 °C for 30 min. The reaction was allowed to come to rt and stirred at it for 1 h. It was concentrated under reduced pressure and

the residue was quenched with $NaHCO_3$ solution (3 mL) and extracted with EtOAc (3x25 mL). The combined EtOAc extract was washed with water (20 mL), brine (10 mL) and dried over Na_2SO_4 to give 7 (0.15 g, 62.5%) as a light brown viscous liquid.

[001273] **Step-5**

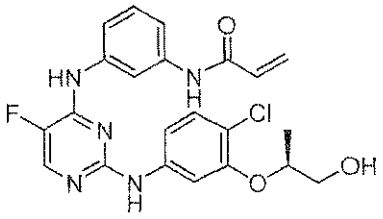


I-359

[001274] To a cooled solution of 7 (0.1 g, 0.23 mmol) in NMP (1.0 mL) at about 0 °C was added K_2CO_3 (0.15 g, 1.1 mmol), acryloyl chloride (0.0022 g, 0.25 mmol) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was added dropwise to a cold, stirring solution of 10% $NaHCO_3$. After the addition was over, the solution was stirred for another 30 min at 0 °C, and the solid was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and was dissolved in methanol: dichloromethane (50:50, 25 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (3 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x5 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (0.055 g, 50%) as yellow solid. ^1H NMR (DMSO-d6) δ ppm: 3.24 (s, 3H), 3.44 (t, *J* = 4.88 Hz, 2H), 3.57 (t, *J* = 4.04 Hz, 2H), 3.69 (t, *J* = 4.24 Hz, 2H), 4.04 (t, *J* = 4.04 Hz, 2H), 5.73 (d, *J* = 10.12 Hz, 1H), 6.23 (d, *J* = 16.8 Hz, 1H), 6.45 (dd, *J* = 10.12 & 16.92 Hz, 1H), 6.95 (t, *J* = 9.4 Hz, 1H), 7.28-7.30 (m, 2H), 7.42 (d, *J* = 8.04 Hz, 1H), 7.48 (d, *J* = 7.48 Hz, 1H), 7.67 (d, *J* = 14.36 Hz, 1H), 7.93 (s, 1H), 8.10 (d, *J* = 3.44 Hz, 1H), 9.20 (s, 1H), 9.44 (s, 1H), 10.14 (s, 1H); LCMS : *m/e* 486.1 (M+1).

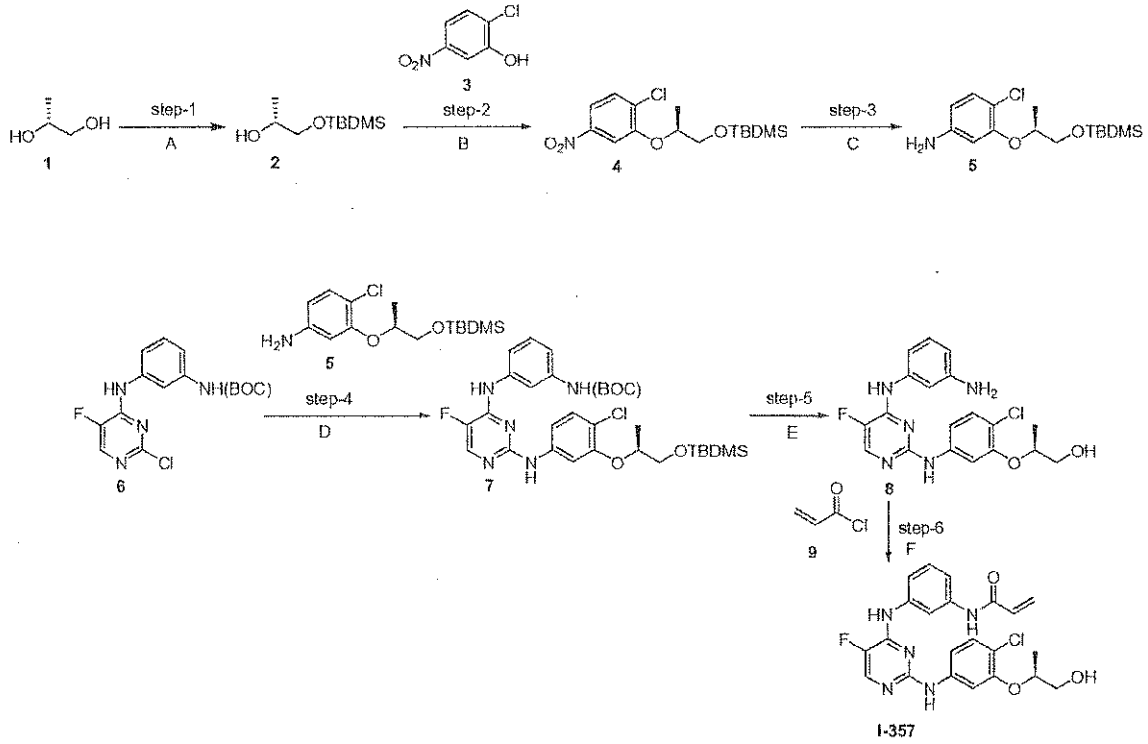
EXAMPLE 248

[001275] Preparation of (S)-N-(3-(2-(4-chloro-3-(1-hydroxypropan-2-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-357**



I-357

[001276] The title compound was prepared according to the schemes, steps and intermediates described below.



A) TBDMSCl, imidazole, CH_2Cl_2, 0 °C, 2 h; **B)** DIAD, PPh_3, Et_3N, dry THF, rt, 1 h; **C)** H_2, Raney Ni, MeOH, 2 h; **D)** $Pd(OAc)_2$, BINAP, Cs_2CO_3, toluene, 110 °C, 6 h; **E)** TFA, CH_2Cl_2, rt, 1 h; **F)** $(BOC)_2O$, 30 min, then K_2CO_3, NMP, 0 °C, 15 min.

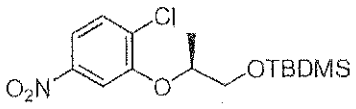
[001277] Step-1



2

[001278] To stirred solution of **1** (1 g, 13.1 mmol) in DCM was added at 0 °C, imidazole (0.875 g, 13.1 mmol) and tert-butyldimethylsilyl chloride (1.98 g, 13.1 mmol). The same temperature was maintained for 2 h, and then the reaction mixture was filtered and concentrated. The residue was purified by column chromatography (neutral alumina, pet ether/ethyl acetate 7/3) to give **2** (1.4 g, 56%) as a colorless liquid.

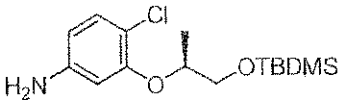
[001279] Step-2



4

[001280] To a stirred solution of **2** (1.5 g, 7.89 mmol) in THF (15 mL) were added **3** (1.36 g, 7.89 mmol), PPh_3 (2.27 g, 8.6 mmol) and Et_3N (1.19 g, 11.1 mmol) under N_2 atmosphere. The reaction mixture was cooled to 0 °C and to it was added DIAD (1.75 g, 8.6 mmol). The reaction mixture was allowed to come to rt and stirred at it for 1 h. It was quenched with water, extracted with ethyl acetate (3x5 mL) and the combined EtOAc extract was washed with water and brine solution (5 mL each). The residue obtained after concentration under reduced pressure was purified by column chromatography (SiO_2, 60-120, pet ether/ethyl acetate, 7/3) to give **4** (2.1 g, 76.9%) as a yellow oil.

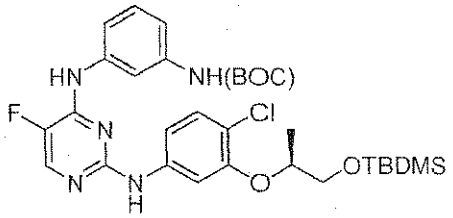
[001281] Step-3



5

[001282] To a solution of **4** (2 g, 5.7 mmol) in methanol (20 mL)) was added Raney Ni (3 g). The reaction mixture was allowed to stir under H_2 atmosphere (bladder pressure) at room temperature for 2 h. The reaction mixture was filtered through a pad of Celite® and concentrated under reduced pressure and the residue was purified by column chromatography (neutral alumina, pet ether/ ethyl acetate, 8/2) to give **5** (1.4 g, 77%) as a brownish viscous oil.

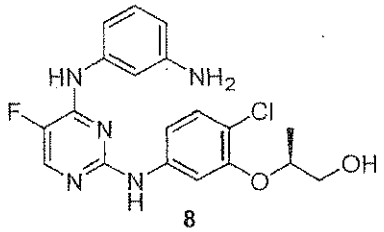
[001283] Step-4



7

[001284] A solution of 6 (0.2 g, 0.63 mmol), prepared according to Step-1 of Example 20, **1** (0.213. g, 0.63 mmol), $Pd(OAc)_2$ (0.014 g, 0.063 mmol), BINAP (0.0019 g, 0.031 mmol) and Cs_2CO_3 (0.511 g, 1.5 mmol) in degassed toluene (toluene was purged with N_2 for 30 min) was heated at 110 ^{0}C for 16 h under N_2 atmosphere. The reaction mixture was cooled, diluted with EtOAc (20 mL), washed with water (10 mL), brine (10 mL) and dried over Na_2SO_4. Filtration followed by concentration under reduced pressure offered a residue which was further purified using column chromatography (SiO_2, 60-120, pet ether/ethyl acetate 7/3) to give 7 (0.15 g, 38.4%) as a yellow solid.

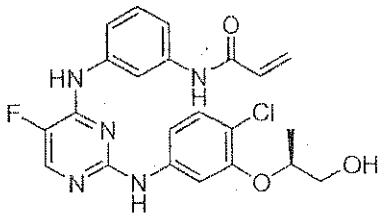
[001285] Step-5



8

[001286] To a stirred solution of 7 (0.15 g, 0.24 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added CF_3COOH (1.5 mL) and the reaction mixture was stirred at 0 °C for 30 min. The reaction was allowed to come to rt and stirred at it for 1 h. It was concentrated under reduced pressure and the residue was quenched with $NaHCO_3$ solution (3 mL) and extracted with EtOAc (3x25 mL). The combined EtOAc extract was washed with water (20 mL), brine (10 mL) and dried over Na_2SO_4 and concentrated under reduced pressure to give **8** (0.085 g, 86.7%) as a white solid.

[001287] Step-6

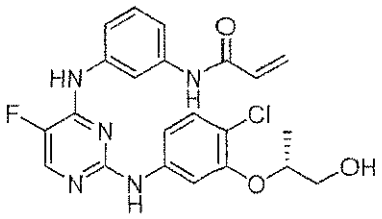


I-357

[001288] A stirred solution of **8** (0.085 g, 0.21 mmol) in NMP (2.0 mL) was cooled to 0 °C and to it was added K_2CO_3 (0.29 g, 2.1 mmol) and acryloyl chloride (1 M solution in THF, 0.21 mL, 0.21 mmol) and the reaction mixture was stirred at 0 °C for 30 min. The reaction mixture was added dropwise to a cold, stirring solution of 10% $NaHCO_3$. After the addition was over, the solution was stirred for another 30 min at 0 °C, and the solid was isolated by filtration through a Buchner funnel. The solid was washed with cold water, hexane and was dissolved in methanol: dichloromethane (50:50, 25 mL) and concentrated under reduced pressure. The residue obtained was suspended in cold water (3 mL), Et_3N was added to it and it was extracted with ethyl acetate (2x5 mL). The combined ethyl acetate extract was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the title compound (65 mg, 67%) as yellow solid. ^{1}H NMR (DMSO-d6) δ ppm: 1.18 (d, *J* = 6.12 Hz, 3H), 3.40-3.47 (m, 1H), 3.50-3.56 (m, 1H), 4.20-4.30 (m, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 5.75 (dd, *J* = 1.88 & 10.08 Hz, 1H), 6.25 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.92 Hz, 1H), 7.12 (d, *J* = 8.76 Hz, 1H), 7.29 (t, *J* = 8.08 Hz, 1H), 7.40-7.44 (m, 3H), 7.52 (d, *J* = 8.44 Hz, 1H), 7.91 (s, 1H), 8.12 (d, *J* = 3.64 Hz, 1H), 9.21 (s, 1H), 9.45 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 458.0 (M+1).

EXAMPLE 249

[001289] Preparation of (R)-N-(3-(2-(4-chloro-3-(1-hydroxypropan-2-yloxy)phenylamino)-5-fluoropyrimidin-4-ylamino)phenyl)acrylamide **I-358**

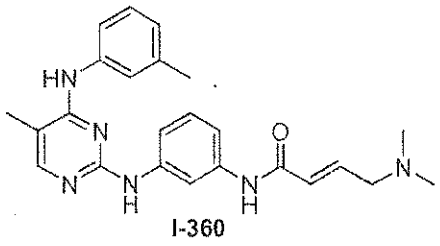


I-358

[001290] The title compound was prepared according to the schemes, steps and intermediates described in Example 248 by using (R)-propane-1,2-diol in place of **1** in Step-1. ^{1}H NMR (DMSO-d6) δ ppm: 1.18 (d, *J* = 6.12 Hz, 3H), 3.40-3.47 (m, 1H), 3.50-3.56 (m, 1H), 4.20-4.30 (m, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 5.75 (dd, *J* = 1.88 & 10.08 Hz, 1H), 6.25 (dd, *J* = 1.92 & 16.92 Hz, 1H), 6.45 (dd, *J* = 10.08 & 16.92 Hz, 1H), 7.12 (d, *J* = 8.76 Hz, 1H), 7.29 (t, *J* = 8.08 Hz, 1H), 7.40-7.44 (m, 3H), 7.52 (d, *J* = 8.44 Hz, 1H), 7.91 (s, 1H), 8.12 (d, *J* = 3.64 Hz, 1H), 9.21 (s, 1H), 9.45 (s, 1H), 10.12 (s, 1H); LCMS : *m/e* 458.0 (M+1).

EXAMPLE 250

[001291] Preparation of (E)-4-(dimethylamino)-N-(3-(5-methyl-4-(m-tolylamino)pyrimidin-2-ylamino)phenyl)but-2-enamide **I-360**



I-360

[001292] The title compound was prepared according to the schemes, steps and intermediates described in Example 3 by using (E)-4-(dimethylamino)but-2-enoyl chloride place of acryloyl chloride in Step-3. ^{1}H NMR (DMSO-d6) δ ppm: 7.91 (s, 1H), 7.85 (s, 1H), 7.52 (d, *J* = 6.4 Hz, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.34 (s, 1H), 7.31-7.26 (m, 1H), 7.21 (dd, *J* = 8.2, 8.0 Hz, 1H), 7.01-6.92 (m, 4H); 6.27 (s, 1H), 6.06 (d, *J* = 15.1 Hz, 1H), 3.14 (d, *J* = 5.5 Hz, 2H), 2.37 (s, 3H), 2.31 (s, 6H), 2.13 (s, 3H); LCMS *m/z* 417 (M+1).

Biological Examples

[001293] Described below are assays used to measure the biological activity of provided compounds as inhibitors of BTK, TEC, ITK, BMX, ErbB1 (EGFR), ErbB2, ErbB4, and JAK3.

EXAMPLE 251

Omnia Assay Protocol for Potency Assessment Against BTK

[001294] Below describes the protocol using EGFR-WT and EGFR-T790M/L858R and the protocol BTK-optimized reagent conditions then follow.

[001295] The mechanics of the assay platform are best described by the vendor (Invitrogen, Carlsbad, CA) on their website at the following URL: www.invitrogen.com/content.cfm?pageid=11338 or www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/Drug-Discovery/Target-and-Lead-Identification-and-Validation/KinaseBiology/KB-Misc/Biochemical-Assays/Omnia-Kinase-Assays.html.

[001296] Briefly, 10X stocks of EGFR-WT (PV3872) from Invitrogen and EGFR-T790M/L858R (40350) from BPS Bioscience, San Diego, CA, 1.13X ATP (AS001A) and appropriate Tyr-Sox conjugated peptide substrates (KCZ1001) were prepared in 1X kinase reaction buffer consisting of 20 mM Tris, pH 7.5, 5 mM $MgCl_2$, 1 mM EGTA, 5 mM β-glycerophosphate, 5% glycerol (10X stock, KB002A) and 0.2 mM DTT (DS001A). 5 μL of each enzyme were pre-incubated in a Corning (#3574) 384-well, white, non-binding surface microtiter plate (Corning, NY) for 30 min. at 27°C with a 0.5 μL volume of 50% DMSO and serially diluted compounds prepared in 50% DMSO. Kinase reactions were started with the addition of 45 μL of the ATP/Tyr-Sox peptide substrate mix and monitored every 30-90 seconds for 60 minutes at $\lambda_{ex}360/\lambda_{em}485$ in a Synergy^4 plate reader from BioTek (Winooski, VT). At the conclusion of each assay, progress curves from each well were examined for linear reaction kinetics and fit statistics (R^2, 95% confidence interval, absolute sum of squares). Initial velocity (0 minutes to ~30 minutes) from each reaction was determined from the slope of a plot of relative fluorescence units *vs* time (minutes) and then plotted against inhibitor concentration to estimate IC_{50} from log[Inhibitor] vs Response, Variable Slope model in GraphPad Prism from GraphPad Software (San Diego, CA).

[001297] The modified BTK-optimized reagent conditions for the above protocol are:

[BTK] = 5 nM, [ATP] = 40 mM, [Y5-Sox] = 10 mM (ATP KMapp ~ 36 mM).

EXAMPLE 252

[001298] Table 6 shows the activity of selected compounds of this invention in the BTK inhibition assay. The compound numbers correspond to the compound numbers in Table 5. Compounds having an activity designated as "A" provided an IC_{50} ≤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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an IC_{50} ≥10,000 nM.

Table 6. BTK Inhibition Data

Compound #	BTK Inhibition
I-1	A
I-2	A
I-3	A
I-4	A
I-5	A
I-7	A
I^R-7	C
I-8	A
I-9	A
I-10	C
I-11	A
I-23	B
I-27	A
I-28	A
I-33	A
I-34	B
I-35	A
I-38	A
I-39	A
I-40	A
I-45	A
I-54	A
I-55	A
I-56	C
I-60	C
I-69	A
I-70	A
I-71	A

Compound #	BTK Inhibition
I-72	A
I-73	A
I-74	A
I-75	A
I-76	A
I-77	A
I-78	A
I-79	A
I-80	A
I-81	A
I-82	A
I-83	A
I-84	A
I-85	B
I-86	A
I-87	A
I-88	A
I-89	A
I-90	A
I-91	A
I-92	A
I-93	A
I-94	A
I-95	A
I-96	A
I-97	A
I-98	C
I-99	A
I-100	C
I-101	B
I-102	B
I-103	A
I-104	A
I-105	A
I-106	B
I-107	A
I-108	A
I-109	A
I-110	A
I-111	A
I-112	A
I-113	A
I-114	A
I-115	B

Compound #	BTK Inhibition
I-116	A
I-117	A
I-118	A
I-119	B
I-120	A
I-121	A
I-122	A
I-123	B
I-124	A
I-125	A
I-126	A
I-127	B
I-128	A
I-129	A
I-130	A
I-131	A
I-132	A
I-133	A
I-134	A
I-135	A
I-136	A
I-137	C
I-138	A
I-139	A
I-140	A
I-141	A
I-142	A
I-143	A
I-144	A
I-145	A
I-146	A
I-147	A
I-148	D
I-149	A
I-150	A
I-151	A
I-152	A
I-153	A
I-154	A
I-155	A
I-156	A
I-157	A
I-158	A
I-159	A

Compound #	BTK Inhibition
I-160	A
I-161	A
I-162	A
I-163	B
I-164	A
I-165	A
I-166	A
I-167	A
I-168	A
I-169	A
I-170	A
I-171	A
I-172	A
I-173	A
I-174	A
I-175	C
I-176	A
I-177	A
I-178	A
I-179	C
I-180	A
I-181	A
I-182	A
I-183	A
I-184	A
I-185	A
I-186	A
I-187	B
I-188	A
I-189	A
I-190	A
I-191	A
I-192	A
I-193	C
I-194	A
I-195	A
I-196	B
I-197	C
I-198	A
I-199	A
I-200	A
I-201	A
I-202	A
I-203	B

Compound #	BTK Inhibition
I-204	A
I-205	B
I-206	E
I-207	A
I-208	A
I-209	A
I-210	A
I-211	D
I-212	D
I-213	E
I-214	B
I-215	A
I-216	C
I-217	A
I-218	A
I-219	A
I-220	A
I-221	B
I-222	B
I-223	E
I-224	B
I-225	C
I-226	B
I-227	A
I-228	A
I-229	B
I-230	A
I-231	C
I-232	B
I-233	A
I-234	D
I-235	B
I-236	B
I-237	A
I-238	D
I-241	D
I-242	A
I-243	A
I-244	A
I-245	A
I-246	B
I-247	A
I-248	A
I-249	A

Compound #	BTK Inhibition
I-312	A
I-313	A
I-315	A
I-316	A
I-318	A
I-321	A
I-322	A
I-323	C
I-324	A
I-325	C
I-326	A
I-327	A
I-328	A
I-329	A
I-330	B
I-331	B
I-332	A
I-333	A
I-334	A
I-335	A
I-336	A
I-337	A
I-339	A
I-341	A
I-342	A
I-343	B
I-344	A
I-345	A
I-346	A
I-347	A
I-348	A
I-349	A
I-350	A
I-351	A
I-352	A
I-353	A
I-354	A
I-355	A
I-356	A
I-357	A
I-358	A
I-359	A
I-360	A
I-362	A

EXAMPLE 253

BTK Ramos Cellular Assay

[001299] Compounds **I-2**, **I-4**, and **I-7** were assayed in Ramos human Burkitt lymphoma cells. Ramos cells were grown in suspension in T225 flasks, spun down, resuspended in 50 ml serum-free media and incubated for 1 hour. Compound was added to Ramos cells in serum free media to a final concentration of 1, 0.1, 0.01, or 0.001 μM. Ramos cells were incubated with compound for 1 hour, washed again and resuspended in 100ul serum-free media. Cells were then stimulated with 1μg of goat F(ab')2 Anti-Human IgM and incubated on ice for 10 minutes to activate B cell receptor signaling pathways. After 10 minutes, the cells were washed once with PBS and then lysed on ice with Invitrogen Cell Extraction buffer. 16 μg total protein from lysates were loaded on gel and blots were probed for phosphorylation of the BTK substrate PLCγ2. Dose response inhibition of BTK signaling in Ramos cells is depicted in **Figures 1, 2, 3, 4** and **5**.

[001300] Table 7 shows the activity of selected compounds of this invention in the BTK Ramos cellular inhibition assay. The compound numbers correspond to the compound numbers in Table 5. Compounds having an activity designated as "A" provided an IC_{50} ≤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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an IC_{50} ≥10,000 nM.

Table 7. BTK Ramos Cellular Inhibition Data

Compound #	BTK Inhibition
I-3	B
I-4	B
I-7	A
I-8	C
I-27	B
I-33	A
I-35	A
I-38	B
I-39	B
I-40	B
I-45	A
I-77	A
I-78	A

Compound #	BTK Inhibition
I-79	A
I-80	A
I-86	A
I-87	A
I-95	A
I-96	A
I-97	A
I-103	A
I-105	A
I-107	B
I-108	B
I-110	B
I-114	B
I-116	A
I-118	A
I-121	B
I-122	A
I-124	A
I-125	B
I-126	B
I-128	B
I-129	A
I-131	A
I-133	B
I-134	B
I-135	B
I-138	A
I-139	B
I-140	B
I-142	B
I-143	A
I-147	B
I-149	B
I-150	B
I-151	A
I-152	B
I-153	A
I-154	A
I-156	A
I-157	A
I-158	B
I-159	C
I-160	B
I-162	A

Compound #	BTK Inhibition
I-163	B
I-164	A
I-165	B
I-166	B
I-167	B
I-168	B
I-169	A
I-170	B
I-172	A
I-173	A
I-174	A
I-176	C
I-177	C
I-178	B
I-180	C
I-182	A
I-185	C
I-186	A
I-188	A
I-189	B
I-190	B
I-192	B
I-194	A
I-195	B
I-198	A
I-201	C
I-202	C
I-204	A
I-207	C
I-208	B
I-209	B
I-210	A
I-217	A
I-219	B
I-220	B
I-227	A
I-228	A
I-230	A
I-233	A
I-242	A
I-243	A
I-244	B
I-245	A
I-247	A

Compound #	BTK Inhibition
I-248	A
I-249	A
I-313	A
I-315	A
I-316	A
I-318	A
I-321	A

EXAMPLE 254

Washout Experiment with Ramos cells

[001301] Ramos cells were serum starved for one hour in RPMI media +1% glutamine at 37°C. After starvation, Ramos cells were treated with 100nM compound diluted in serum free RPMI media for 1 hour. After compound treatment, the media was removed and cells were washed with compound-free media. Subsequently, Ramos cells were washed every 2 hours and resuspended in fresh compound-free media. Cells were collected at specified timepoints, treated with 1ug anti-human IgM (Southern Biotech cat # 2022-01) for 10 minutes on ice to induce BCR signaling and then washed in PBS. Ramos cells were then lysed in Cell Extraction Buffer (Invitrogen FNN0011) supplemented with Roche complete protease inhibitor tablets (Roche 11697498001) and phosphatase inhibitors (Roche 04 906 837 001) and 18ug total protein lysate was loaded in each lane. Inhibition of BTK kinase activity was assayed by measuring its substrate (PLCγ2) phosphorylation by western blot with phospho-specific antibodies from Cell Signaling Technologies cat# 3871. The results of this experiment with compounds **I-2**, **I-4** and **I-7** are depicted in Figures 1, 2 and 3.

[001302] Table 8 provides data for selected compounds in the Ramos washout assay.

Table 8. BTK Washout Data

Compound #	BTK Inhibition Type
I-2	irreversible
I-4	irreversible
I-7	irreversible
I-28	irreversible
I-35	irreversible
I-38	reversible
I-228	irreversible
I-230	irreversible
I-242	irreversible

Compound #	BTK Inhibition Type
I-243	irreversible
I-247	irreversible
I-248	irreversible

EXAMPLE 255

Mass Spectrometry for BTK

[001303] Intact BTK was incubated for 1 hr at a 10X fold excess of I-7 to protein. Aliquots (2 µl) of the samples were diluted with 10 µl of 0.1% TFA prior to micro C4 ZipTipping directly onto the MALDI target using Sinapinic acid as the desorption matrix (10 mg/ml in 0.1% TFA:Acetonitrile 20:80). See Figure 15. Top panel shows the mass spec trace of the intact BTK protein (m/z 81,032 Da). The bottom panel shows mass spec trace when BTK was incubated with **I-7** (mw=345.4). The centroid mass (m/z= 81,403 Da) shows a positive shift of about 371.1 Da indicating complete modification of BTK by **I-7**. Other compounds that completely modify BTK include **I-96**, **I-71**, **I-149**, **I-161**, **I-163**, **I-182**, **I-195**, **I-207**, **I-219**, and **I-244**.

EXAMPLE 256

Human primary B cell proliferation assay

[001304] Human naïve B cells were purified from 100 mL whole blood using a MACS purification kit designed to isolate CD19+, IgD+ cells by negative selection. Purified naïve B cells were resuspended in RPMI complete and stimulated with 5µg/ml α-IgM for 72 hours. ^{3}H-Thymidine was included in the culture media for the final 16h, cells were harvested and ^{3}H incorporation measured. Inhibition of B cell proliferation correlates with inhibition of BTK substrate phosphorylation after α-IgM stimulation. Importantly, a molecule with the same scaffold as **I-7** but biochemically inactive against BTK, I^{R}-7, is not active in the naïve B cell proliferation assay.

Table 9.

Compound #	EC_{50} (nM)
I-7	1-10
I^{R}-7	>1000
I-190	10-100
I-182	1-10
I-96	1-10

EXAMPLE 257

B cell lymphoma proliferation assay

[001305] Provided compounds inhibit proliferation of various B cell lymphoma cell lines, as shown in Table 10. The compound numbers correspond to the compound numbers in Table 5. Compounds having an activity designated as "A" provided an EC_{50} <0.1 μM; compounds having an activity designated as "B" provided an EC_{50} 0.1-1 μM; compounds having an activity designated as "C" provided an EC_{50} of 1-10 μM; and compounds having an activity designated as "D" provided an EC_{50} of >10 μM.

Table 10.

Compound #	EC50 (μM)		
	DOHH2	WSU-DLCL2	DHL4
I-2	B	-	-
I-3	B	-	-
I-4	B	B	B
I-7	C	C	C
I-27	C	D	-
I-28	C	C	-
I-35	C	C	-
I-38	C	C	-
I-39	C	C	-
I-40	B	C	-
I-77	B	-	-
I-78	B	-	-
I-79	C	-	-
I-80	B	-	-
I-81	B	-	-
I-86	D	-	-
I-87	C	-	-
I-88	C	-	-
I-89	C	-	-
I-90	B	-	-
I-91	C	C	-
I-96	B	C	
I-103	-	C	-
I-105	B	C	-
I-116	D	D	-
I-121	C	-	-
I-122	C	-	-
I-124	C	-	-
I-126	A	-	-
I-128	C	-	-

Compound #	EC50 (μM)		
	DOHH2	WSU-DLCL2	DHL4
I-129	C	-	-
I-132	C	-	C
I-133	B	-	A
I-134	B	-	A
I-135	D	-	D
I-138	C	-	C
I-141	C	-	-
I-142	C	-	-
I-143	C	C	C
I-147	C	-	-
I-149	C	-	-
I-150	C	C	C
I-151	C	-	C
I-152	C	-	-
I-153	C	C	C
I-154	C	C	C
I-155	C	C	C
I-156	B	C	C
I-157	C	C	C
I-158	C	C	C
I-159	C	-	-
I-160	C	C	C
I-161	C	-	C
I-162	C	C	C
I-163	C	C	C
I-164	C	C	C
I-165	C	C	C
I-166	C	C	C
I-167	C	-	-
I-168	C	-	-
I-169	C	-	-
I-170	C	-	-
I-171	C	-	-
I-172	C	-	-
I-173	C	-	-
I-174	C	-	-
I-178	C	D	D
I-182	C	C	C
I-184	C	-	-
I-186	C	-	C
I-188	C	-	-
I-189	D	D	C
I-190	D	-	-

Compound #	EC50 (μM)		
	DOHH2	WSU-DLCL2	DHL4
I-192	C	D	-
I-194	C	C	C
I-195	C	D	D
I-204	C	C	-
I-207	B	C	-
I-208	C	C	-
I-209	D	C	-
I-210	C	C	-
I-217	D	D	-
I-227	C	C	-
I-228	D	D	-
I-230	C	C	-
I-242	C	C	-
I-243	C	C	-
I-244	B	C	C
I-245	C	D	-
I-247	B	C	-
I-248	C	C	-
I-298	-	C	-

EXAMPLE 258

In vivo Thymus-Independent (TI-2) B cell Activation

[001306] C57/B6 mice were dosed daily with 100 mg/kg of the appropriate compound on day 0 through 5. Mice were immunized once with 25 μg TNP-Ficoll on day 1, serum was collected on day 6 and analyzed for circulating α-TNP IgM (1:1600 serum dilution) and IgG3 (1:200 serum dilution) antibody production by ELISA. Results represent the average of 10 mice per treatment group and are given in Table 11 as % inhibition of TI-2 independent B cell activation.

Table 11.

Compound #	% Inhibition	
	IgM (1:1600)	IgG3 (1:100)
I-7	48	57
I-182	25	40
I-96	43	37.2

EXAMPLE 259

Collagen Antibody Induced Arthritis Model

[001307] On day 0 baseline footpad measurements were made and animals were distributed to the experimental groups in such a way as to generate groups with no significant differences between the groups. Each animal was then inoculated intravenously with 2 mg Arthritomab monoclonal antibody cocktail. Treatment with test agents began at this time. On day 6, each animal was injected intraperitoneally with 50 μg LPS in 200 μl of sterile PBS. Footpad measurements and clinical scoring were conducted on days 6, 7, 8, 9, 10, 11, 12, 14, 18, and 21. Table 12 shows the results.

Table 12.

Compound #	Dose	% inhibition foot pad swelling
I-7	30 mg/kg	83

EXAMPLE 260

PG-PS Arthritis Model

[001308] On day 0, female Lewis rats received an intraperitoneal (IP) bolus of peptidoglycan-polysaccharide (PG-PS) in an amount of 15μg/g rat body weight. Baseline control rats received an IP bolus of PBS. The vehicle and treatment groups were dosed via oral gavage just prior to PG-PS administration. Treatment with vehicle and compound continued each day through day 22. Maximal lateral ankle width measurements of both rear limbs were collected with a caliper throughout the study. On day 23, study was terminated and the final change in ankle swelling was calculated and compared to vehicle controls. Table 13 shows the results for two compounds (n = number of experiments).

Table 13.

Compound #	n	% inhibition ankle swelling
I-7	1	77.5
I-96	2	82.8

EXAMPLE 261

Mass Spectrometry for TEC Kinase (Compound I-2)

[001309] TEC kinase (45 pmols; Invitrogen) was incubated with (**I-2**) (450 pmols) for 3 hrs at 10X excess prior to tryptic digestion. Iodoacetamide was used as the alkylating agent after compound incubation. A control sample (45 pmols) was also prepared which did not have the addition of (**I-2**). For tryptic digests a 5ul aliquot (7.5 pmols) was diluted with 15 ul of 0.1% TFA prior to micro C18 Zip Tipping directly onto the MALDI target using alpha cyano-4-hydroxy cinnamic acid as the matrix (5mg/ml in 0.1% TFA:Acetonitrile 50:50).

[001310] As depicted in Figure 6, the expected peptide (GCLLNFLR) to be modified was immediately evident after reaction with **I-2** (MI mass of 359.17 Da) at MH+ of 1294.72. The peptide was also quite evident in the control sample as modified by Iodacetamide at MH+ of 992.56. Interestingly the iodoacetamide modified peptide was not evident in the digest reacted with compound **I-2** indicating that the reaction was complete. There was no evidence of other modified peptides.

[001311] Evidence of compound **I-2** was observed at MH+ of 360.17 in the low mass range of the spectra. The fragmentation spectra of the 360.17 peak did show diagnostic fragments that were apparent in the PSD spectra of the modified peptide at 1294.72 (See Figure 6).

[001312] To further verify the presence of the modified peptides, both the iodoacetamide labeled (992.56) and **I-2** labeled (1294.72) were subjected to PSD (MS/MS) analsysis. After a database search of the NCBI nr Homo sapien database using Mascot MS/MS Ion Search program the top match was the expected peptide in both cases.

Instrumental:

[001313] For tryptic digests the instrument was set in Reflectron mode with a pulsed extraction setting of 2200. Calibration was done using the Laser Biolabs Pep Mix standard (1046.54, 1296.69, 1672.92, 2093.09, 2465.20). For CID/PSD analysis the peptide was selected using cursors to set ion gate timing and fragmentation occurred at a laser power about 20% higher and He was used as the collision gas for CID. Calibration for fragments was done using the P14R fragmentation calibration for the Curved field Reflectron.

EXAMPLE 262

Mass Spectrometry for TEC Kinase (Compound I-4)

[001314] TEC kinase (45 pmols; Invitrogen) was incubated with (**I-4**) (450 pmols) for 3hrs at 10X excess prior to tryptic digestion. Iodoacetamide was used as the alkylating agent after compound incubation. A control sample (45 pmols) was also prepared which did not have the addition of (**I-4**). For tryptic digests a 5ul aliquot (7.5 pmols) was diluted with 15 ul of 0.1% TFA prior to micro C18 Zip Tipping directly onto the MALDI target using alpha cyano-4-hydroxy cinnamic acid as the matrix (5mg/ml in 0.1%TFA:Acetonitrile 50:50).

[001315] As depicted in Figure 7, the expected peptide (GCLLNFLR) to be modified was immediately evident at MH+ of 1355.72. This is the mass to be expected when compound **I-4**, with an adduct mass of 420.21, is added to the peptide mass of 935.51. The peptide was also quite evident in the control sample as modified by Iodacetamide at MH^+ of 992.56. Interestingly the iodoacetamide modified peptide was not evident in the digest reacted with compound **I-4** indicating that the reaction was complete. There was no evidence of other modified peptides.

[001316] Evidence of compound **I-4** was observed at MH+ of 421.35 in the low mass range of the spectra. The fragmentation spectra of the 421.35 peak did reveal two prominent peaks that were apparent in the PSD spectra of the modified peptide at 1355.72 (See Figure 7).

[001317] To further verify the presence of the modified peptide with compound **I-4**, the peptide at MH+ of 1355.72 was subjected to PSD (MS/MS) analsysis. Because of the low intensity of fragments, a database correlation was not possible. However, diagnostic fragments from the **I-4** molecule itself provided confidnece in the identification. Diagnostic fragments at MH+ of 376.38 and 421.83 are from **I-4**.

Instrumental: .

[001318] For tryptic digests the instrument was set in Reflectron mode with a pulsed extraction setting of 1800. Calibration was done using the Laser Biolabs Pep Mix standard (1046.54, 1296.69, 1672.92, 2093.09, 2465.20). For CID/PSD analysis the peptide was selected using cursors to set ion gate timing and fragmentation occurred at a laser power about 20% higher and He was used as the collision gas for CID. Calibration for fragments was done using the P14R fragmentation calibration for the Curved field Reflectron.

EXAMPLE 263

Mass Spectrometry for TEC Kinase (Compound I-7)

[001319] TEC kinase (45 pmols; Invitrogen) was incubated with (**I-7**) (450 pmols) for 3hrs at 10X excess prior to tryptic digestion. Iodoacetamide was used as the alkylating agent after compound incubation. A control sample (45 pmols) was also prepared which did not have the addition of (**I-7**). For tryptic digests a 5ul aliquot (7.5 pmols) was diluted with 15 ul of 0.1% TFA prior to micro C18 Zip Tipping directly onto the MALDI target using alpha cyano-4-hydroxy cinnamic acid as the matrix (5mg/ml in 0.1%TFA:Acetonitrile 50:50).

[001320] As depicted in Figure 8, the expected peptide (GCLLNFLR) to be modified was immediately evident at MH+ of 1280.73. This is the mass to be expected when compound **I-7**, with an adduct mass of 345.16, is added to the peptide mass of 935.51. The peptide was also quite evident in the control sample as modified by Iodacetamide at MH+ of 992.56. Interestingly the iodoacetamide modified peptide was not evident in the digest reacted with compound **I-7** indicating that the reaction was complete. There was no evidence of any other modified peptide at MH+ of 1985.93 (TIDELVECEETFGR).

[001321] Evidence of compound **I-7** was observed at MH+ of 346.32 in the low mass range of the spectra. The fragmentation spectra of the 346.32 peak did show many diagnostic fragments that were apparent in the PSD spectra of the two modified peptides (See Figure 8).

[001322] To further verify the presence of the modified peptides with compound **I-7**, the peptides at MH+ of 1280.73 and 1985.93 were subjected to PSD (MS/MS) analsysis. A correlational analysis with the homosapien database identified the correct peptide modified by **I-7**.

Instrumental:

[001323] For tryptic digests the instrument was set in Reflectron mode with a pulsed extraction setting of 2200. Calibration was done using the Laser Biolabs Pep Mix standard (1046.54, 1296.69, 1672.92, 2093.09, 2465.20). For CID/PSD analysis the peptide was selected using cursors to set ion gate timing and fragmentation occurred at a laser power about 20% higher and He was used as the collision gas for CID. Calibration for fragments was done using the P14R fragmentation calibration for the Curved field Reflectron.

EXAMPLE 264

Omnia Assay Protocol for Potency Assessment Against Active Forms of ITK Kinase

[001324] This example describes continuous-read kinase assays to measure inherent potency of compound against active forms of ITK enzymes as described in Example 251 above except that the modified ITK-optimized reagent conditions are:

[ITK] = 10 nM, [ATP] = 25 μM, [Y6-Sox] = 10 μM (ATP K_{Mapp} = 33 μM).

EXAMPLE 265

[001325] Table 14 shows the activity of selected compounds of this invention in the ITK inhibition assay. The compound numbers correspond to the compound numbers in Table 5. 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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an $IC_{50} \geq 10{,}000$ nM.

Table 14. ITK Inhibition Data

Compound #	ITK Inhibition
I-1	C
I-2	B
I-4	B
I-7	A
I-27	B
I-28	B
I-33	A
I-35	B
I-38	B
I-39	C
I-40	A
I-45	B
I-54	B
I-55	B
I-56	C
I-69	B
I-70	A
I-72	A
I-73	A
I-75	A

Compound #	ITK Inhibition
I-76	A
I-77	B
I-78	A
I-79	B
I-80	A
I-88	B
I-89	B
I-90	A
I-91	B
I-94	B
I-95	B
I-96	B
I-97	B
I-103	B
I-105	B
I-107	C
I-108	B
I-110	B
I-114	D
I-116	A
I-118	B
I-121	A
I-122	A
I-124	A
I-125	B
I-126	B
I-128	A
I-129	A
I-131	A
I-133	C
I-134	B
I-135	B
I-138	B
I-139	A
I-140	B
I-142	A
I-143	B
I-146	B
I-147	A
I-149	D
I-150	A
I-151	B
I-152	A
I-153	A

Compound #	ITK Inhibition
I-154	A
I-155	A
I-156	A
I-157	A
I-158	B
I-159	C
I-160	A
I-162	A
I-163	D
I-164	B
I-165	A
I-166	A
I-167	A
I-168	A
I-169	A
I-170	A
I-172	B
I-173	A
I-174	A
I-176	B
I-177	B
I-178	B
I-180	C
I-182	B
I-183	C
I-185	A
I-186	A
I-188	A
I-189	A
I-190	B
I-192	A
I-194	A
I-195	B
I-198	C
I-199	B
I-200	E
I-201	C
I-202	C
I-204	B
I-207	A
I-208	B
I-209	A
I-210	B
I-215	B

Compound #	ITK Inhibition
I-217	B
I-218	A
I-219	B
I-220	C
I-227	A
I-228	B
I-230	A
I-233	A
I-237	A
I-242	A
I-243	B
I-244	C
I-245	A
I-247	B
I-248	A
I-249	C
I-313	B
I-315	B
I-316	B
I-318	B
I-321	C
I-322	A
I-324	A
I-329	A
I-333	B
I-336	C
I-337	B
I-342	B
I-353	B
I-354	C
I-355	B
I-356	B
I-357	B
I-359	A
I-362	B

EXAMPLE 266

Omnia Assay Protocol for Potency Assessment Against Active Forms of BMX Kinase

[001326] This example describes continuous-read kinase assays to measure inherent potency of compound against active forms of BMX enzymes as described in Example 251 above except that the modified BMX-optimized reagent conditions are:

[BMX] = 2.5 nM, [ATP] = 100 μM, [Y5-Sox] = 7.5 μM (ATP K_{Mapp} = 107 μM).

EXAMPLE 267

[001327] Table 15 shows the activity of selected compounds of this invention in the BMX inhibition assay. The compound numbers correspond to the compound numbers in Table 5. Compounds having an activity designated as "A" provided an IC_{50} ≤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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an IC_{50} ≥10,000 nM.

Table 15. BMX Inhibition Data

Compound #	BMX Inhibition
I-4	A
I-7	A
I-27	A
I-28	A
I-33	A
I-35	A
I-38	A
I-39	A
I-40	A
I-45	A
I-126	A
I-128	A
I-129	A
I-131	A
I-133	A
I-134	A
I-135	A
I-244	A
I-245	A
I-247	A
I-248	A

EXAMPLE 268

Cloning, Expression and Purification of EGFR-WT and EGFR C797S Mutant Using Baculovirus and Insect Cells

(i) Subcloning of EGFR-WT and mutant kinase domains

[001328] Amino acids 696 to 1022 of the EGFR-WT kinase domain (NM_005228, NP_005219.2) was subcloned into the NcoI and HindIII sites of the pFastHTa vector (Invitrogen, Carlsbad, CA). To make the EGFR-mutant protein, the cysteine at position 797 was changed to a serine using the Stratagene QuikChange kit (Stratagene, Cedar Creek, TX), according to manufacturer's instructions.

(ii) Expression

[001329] P1 baculovirus stocks were generated in SF9 cells via Blue Sky Biotech's suspension transfection protocol (Worcester, MA). Expression analysis was conducted in 125 ml culture of SF21 insect cells ((grown in SF900I SFM (Invitrogen cat # 10902-088), supplemented with 10mg/L gentamicin (Invitrogen, Carlsbad, CA, cat# 15710-064)) using a viral load of 0.1ml of virus per 100 ml of cell suspension. Expression was optimized using Blue Sky Biotech's Infection Kinetics Monitoring system (Worcester, MA).

(iii) Purification

[001330] Infected insect cells were pelleted. Cell pellets were resuspended in Blue Sky Biotech's lysis buffer (Worcester, MA, 1X WX; solubilization buffer, containing a protease inhibitor cocktail of leupeptin, pepstatin, PMSF, aprotinin and EDTA) at a ratio of 10 ml per gram of wet cell paste.Cells were lysed by sonication and the lysate was clarified by centrifugation at 9,000 RPM for 30 minutes in a GSA rotor. 500 µl bed volume of NiNTA resin (Qiagen, Valencia, CA) was added to the supernatants and batch bound for two hours with constant agitation. The material was transferred by gravity into an empty 2ml column. The column was washed with 2 ml of wash buffer (Blue Sky Biotech, Worcester, MA, 1X WX, 25mM imidazole).The protein was eluted with 1X WX + imidazole at varying concentrations: Elution 1: 75 mM imidazole (2 fractions, 1 column volume); Elution 2 : 150 mM imidazole (2 fractions, 1 column volume); Elution 3 : 300 mM imidazole (2 fractions, 1 column volume). All the elution fractions were analyzed by SDS page followed by Coomassie staining and Western Blotting using anti-penta-his antibody (Qiagen, Valencia, CA). The carboxy-terminal six-histidine "tag" was removed from some of the purified protein using AcTEV Protease kit (

Invitrogen, Carlsbad, CA, Cat# 12575-015), following manufacturer's instructions. All the samples (pre- and post- Tev cut) were analyzed by SDS page followed by Coomassie staining and Western Blotting, as described above.

EXAMPLE 269

Mass Spectrometry for EGFR

[001331] EGFR wild type and EGFR (mutant C797S) is incubated with 10-fold excess of test compound for 1 hr and 3 hrs. 1 µl aliquots of the samples (total volume 5-8 ul) are diluted with 10 ul of 0.1% TFA prior to micro C4 ZipTipping directly onto the MALDI target using Sinapinic acid as the desorption matrix (10 mg/ml in 0.1%TFA:Acetonitrile 50:50). Intact mass measurement reveals that the wild type has a nominal mass of about 37557 and the mutant slightly lower at 37500. Reactivity is only observed for the wild type EGFR with a new peak appearing at a mass consistent with a single site covalent modification with test compound which has a mass of 410 Da.

EXAMPLE 270

Omnia Assay Protocol for Potency Assessment Against EGFR (WT) and EGFR (T790M/L858R) Active Enzymes

[001332] The Omnia Assay Protocol for potency assessment against EGFR is performed as described in Example 251 above except that the EGFR-WT- and EGFR T790M/L858R-modified optimized reagent conditions are:

[001333] [EGFR-WT] = 5 nM, [ATP] = 15 mM, [Y12-Sox] = 5 mM (ATP KMapp ~ 12 mM); and [EGFR-T790M/L858R] = 3 nM, [ATP] = 50 mM, [Y12-Sox] = 5 mM (ATP KMapp ~ 45 mM).

EXAMPLE 271

[001334] Tables 16 and 17 show the activity of selected compounds of this invention in the EGFR inhibition assay. Table 16 shows wild-type EGFR data; Table 17 shows data for two EGFR mutants. The compound numbers correspond to the compound numbers in Table 5. Compounds having an activity designated as "A" provided an IC_{50} ≤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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an $IC_{50} \geq 10{,}000$ nM.

Table 16. EGFR Wild Type Inhibition Data

Compound #	EGFR
I-1	A
I-2	B
I-3	A
I-4	A
I-5	A
I-7	A
I-8	A
I-9	B
I-10	B
I-11	A
I-23	C
I-27	B
I-28	B
I-33	A
I-34	C
I-35	B
I-38	B
I-39	D
I-45	C
I-56	B
I^R-7	D
I-54	B
I-55	C
I-60	D
I-69	B
I-70	B
I-71	B
I-72	A
I-74	C
I-75	A
I-76	A
I-77	B
I-78	A
I-79	C
I-80	B
I-81	A
I-82	A
I-83	B

Compound #	EGFR
I-84	A
I-85	D
I-86	D
I-87	B
I-88	B
I-89	B
I-90	A
I-91	B
I-92	B
I-93	B
I-94	C
I-95	C
I-96	B
I-97	B
I-98	C
I-99	A
I-100	D
I-101	B
I-102	C
I-103	B
I-104	A
I-105	B
I-106	D
I-107	C
I-108	C
I-109	A
I-110	B
I-111	C
I-112	B
I-113	C
I-114	D
I-115	D
I-116	A
I-117	D
I-118	B
I-119	C
I-120	A
I-121	B
I-122	B
I-123	B
I-124	B
I-125	C
I-126	B
I-127	C

Compound #	EGFR
I-128	B
I-129	B
I-130	B
I-131	A
I-132	B
I-133	C
I-134	B
I-135	B
I-136	C
I-137	E
I-138	B
I-139	B
I-140	B
I-141	B
I-142	B
I-143	B
I-144	A
I-145	A
I-146	D
I-147	A
I-148	D
I-149	D
I-150	A
I-151	B
I-152	B
I-153	B
I-154	B
I-155	A
I-156	A
I-157	A
I-158	B
I-159	A
I-160	A
I-161	B
I-162	A
I-163	D
I-164	B
I-165	C
I-166	C
I-167	A
I-168	B
I-169	A
I-170	B
I-171	B

Compound #	EGFR
I-172	C
I-173	A
I-174	A
I-175	D
I-176	A
I-177	A
I-178	A
I-179	E
I-180	C
I-181	A
I-182	A
I-183	D
I-184	A
I-185	B
I-186	A
I-187	C
I-188	A
I-189	B
I-190	C
I-191	D
I-192	B
I-193	D
I-194	B
I-195	B
I-196	D
I-197	C
I-198	A
I-199	B
I-200	A
I-201	B
I-202	C
I-203	C
I-204	B
I-205	B
I-206	D
I-207	C
I-208	B
I-209	B
I-210	B
I-211	D
I-212	D
I-213	C
I-214	C
I-215	B

Compound #	EGFR
I-216	D
I-217	B
I-218	A
I-219	B
I-220	C
I-221	B
I-222	C
I-223	D
I-224	C
I-225	D
I-226	D
I-227	C
I-228	B
I-229	D
I-230	B
I-231	E
I-232	D
I-233	A
I-234	E
I-235	E
I-236	D
I-237	B
I-238	E
I-241	D
I-242	B
I-243	B
I-244	C
I-245	A
I-246	D
I-247	B
I-248	A
I-249	C
I-312	B
I-313	B
I-315	B
I-316	B
I-318	B
I-321	C
I-322	B
I-323	E
I-324	B
I-325	D
I-326	C
I-327	B

Compound #	EGFR
I-328	A
I-329	B
I-330	E
I-331	D
I-332	B
I-333	B
I-334	A
I-335	A
I-336	C
I-337	B
I-339	A
I-341	C
I-342	C
I-343	C
I-344	C
I-345	C
I-346	C
I-347	B
I-348	B
I-349	B
I-350	A
I-351	C
I-352	A
I-353	B
I-354	C
I-355	B
I-356	C
I-357	C
I-358	C
I-359	B
I-360	A
I-362	B

Table 17. EGFR mutant (T790M/L858R and T790M) Inhibition Data

Compound #	EGFR (T790M/L858R)	EGFR (T790M)
I-1	A	-
I-2	A	A
I-3	A	A
I-4	A	A
I-5	A	-
I-7	A	-
I-8	A	-
I-9	B	-

Compound #	EGFR (T790M/L858R)	EGFR (T790M)
I-10	B	-
I-11	A	-
I-23	B	-
I-35	A	-
I-38	A	-
I-39	C	-
I-56	A	B
I^R-7	D	-
I-96	A	A

EXAMPLE 272

Cellular Assays for EGFR Activity

[001335] Compounds were assayed in A431 human epidermoid carcinoma cells using a method substantially similar to that described in Fry, et al., *Proc. Natl. Acad. Sci. USA* Vol 95, pp 12022-12027, 1998. Specifically, A431 human epidermoid carcinoma cells were grown in 6-well plates to 90% confluence and then incubated in serum-free media for 18 hr. Duplicate sets of cells were treated with 1 μM designated compound for 2, 5, 10, 30, or 60 min. Cells were washed free of the compound with warmed serum-free medium, incubated for 2 hr, washed again, incubated another 2 hr, washed again, and then incubated another 2 hr washed again and incubated for additional 2 hr and then stimulated with 100 ng/ml EGF for 5 min. Extracts were made as described Fry, et al.

[001336] Compounds were assayed in A431 human epidermoid carcinoma cells using a method substantially similar to that described in Fry, et al. Specifically, A431 human epidermoid carcinoma cells were grown in 6-well plates to 90% confluence and then incubated in serum-free media for 18 hr. Cells were then treated with 10, 1, 0.1, 0.01, or 0.001μM test compound for 1 hr. Cells were then stimulated with 100 ng/ml EGF for 5 min, and extracts were made as described in Fry, et al. 20ug total protein from lysates were loaded on gel and blots were probed for either EGFR phosphorylation or p42/p44 Erk phosphorylation.

EXAMPLE 273

Washout Experiment for EGFR Activity

[001337] A431 human epidermoid carcinoma cells were grown in 6-well plates to '90% confluence and then incubated in serum-free media for 18 hr. Duplicate sets of cells were treated

with 1 μM designated compound for 1 hr. One set of cells was then stimulated with 100 ng/ml EGF for 5 min, and extracts were made as described. The other set of cells was washed free of compound **I-7** with warmed compound-free medium, incubated for 2 hr, washed again, incubated another 2 hr, washed again, and then incubated another 2 hr washed again and incubated for additional 2 hr and then stimulated with EGF. The results of this experiment with compound **I-7** are depicted in Figure 10.

EXAMPLE 274

Washout Experiment in HCC827 cells containing EGFR deletion mutantHCC827

[001338] Cells (ATCC, Manassas,VA) were plated in Growth Media (RPMI 1640) supplemented with 10% FBS,10uM HEPES, 2mM l-glutamine, 1mM NaPyruvate and pen/strep (Invitrogen, Carlsbad, CA) at a density of 2.5 x 10^5 cells per well in 6 well tissue culture plates. Twenty four hours later the cells were washed 2 x with PBS then serum starved overnight in Basal Media (Growth Media without FBS).

[001339] The following morning the media was removed and 2 ml fresh Basal Media containing 1uM compound in 0.1% DMSO was added to duplicate wells. At 1 hour, one well of cells was treated with 100 ng/ml of EGF for 5 minutes, rinsed with PBS, then lysed by scraping into 75 ul of Cell Extraction Buffer (Invitrogen, Carlsbad, CA) plus PhosSTOP Phosphatase Inhibitor and Complete Protease Inhibitor (Roche, Indianapolis, IN) for the 0h time point. The compound was removed from the second set of wells and they were washed 2X with Basal Media. The cells were washed with Basal Media every 2 hours until 8 hours when they were treated with EGF and lysed as at the 0 h time point.

[001340] Lysate protein concentrations were determined by BCA Assay (Pierce, Rockford, IL) and 10 ug of each lysate was separated by 4-12% gradient SDS-PAGE (Invitrogen), transferred to Immobilon-FL membrane (Millipore) and probed with rabbit anti-Phospho-EGFR (Tyr1068) (Zymed-now Invitrogen) and mouse anti-EGFR (Cell Signaling Technologies, Danvers, MA) antibodies. Phospho-protein signals were quantitated using Odyssey Infrared Imagning (Li-Cor Biosciences, Lincoln, Nebraska). The results of this experiment are depicted in Figure 9 where it shows compound **I-2** compared to results of compound **I-4** and compound **I-7** in the same "washout" experiment.

EXAMPLE 275

Mass Spectrometry for ERBB4

[001341] Erbb4 kinase domain (Upstate) was incubated with compound for 60 minutes at 10-fold excess of compound **I-4** and **I-11** to protein. 1 µl aliquots of the samples (total volume of 4.24ul) were diluted with 10 µl of 0.1% TFA prior to micro C4 ZipTipping directly onto the MALDI target using Sinapinic acid as the desorption matrix (10 mg/ml in 0.1%TFA:Acetonitrile 50:50). For intact protein mass measurement the instrument was set in Linear mode using a pulsed extraction setting of 16,952 for the myoglobin standard used to calibrate the instrument (Shimadzu Axima TOF^2).

[001342] Intact ErbB4 protein occurs at MH+ of 35850 with corresponding sinapinic (matrix) adducts occurring about 200 Da higher. A stochiometric incorporation of the test compound (**I-4** and **I-11**) (Mw of 410 Da) produced a new mass peak which is approximately 410 Da higher (MH+ of 36260). This is consistent with covalent modification of ErbB4 with compounds **I-4** and **I-11**.

EXAMPLE 276

ErbB1, ErbB2 and/or ErbB4 Kinase Inhibition

[001343] Compounds of the present invention were assayed as inhibitors of one or more of ErbB1, ErbB2, and/or ErbB4 in a manner substantially similar to the method described by Invitrogen Corp (Invitrogen Corporation, 1600 Faraday Avenue, Carlsbad, California, CA; http://www.invitrogen.com/downloads/Z-LYTE_Brochure_1205.pdf) using the Z'-LYTE™ biochemical assay procedure or similar biochemical assay. The Z'-LYTE™ biochemical assay employs a fluorescence-based, coupled-enzyme format and is based on the differential sensitivity of phosphorylated and non-phosphorylated peptides to proteolytic cleavage. Using this assay, Compound **I-56** was found to inhibit ERBB1 with an IC_{50} of 2,233 nM. Using this assay, Compound **I-56** was found to inhibit ERBB4 (HER4) with an IC_{50} of 2,165 nM.

EXAMPLE 277

Mass Spectrometry for Janus-3 Kinase (JAK3)

[001344] JAK3 kinase (33 pmols; Invitrogen) was incubated with (I-7) (327 pmols) for 3hrs at 10X excess prior to tryptic digestion. Iodoacetamide was used as the alkylating agent after compound incubation. For tryptic digests a 5ul aliquot (5.5 pmols) was diluted with 15 ul

of 0.1% TFA prior to micro C18 Zip Tipping directly onto the MALDI target using alpha cyano-4-hydroxy cinnamic acid as the matrix (5mg/ml in 0.1%TFA:Acetonitrile 50:50).

[001345] As depicted in Figure 11, the expected peptide (LVMEYLPSGCLR) to be modified was immediately evident as the largest peak at MH+ of 1725.88. This is the mass to be expected when compound **I-7**, with an adduct mass of 345.16, is added to the peptide mass of 1380.70. Interestingly the iodoacetamide modified peptide was not evident at MH+ of 1437.73 in the digest reacted with compound **I-7** indicating that the reaction was not entirely complete. There was also evidence for a number of other modified peptides, however, their signals were low.

[001346] Evidence of compound **I-7** was observed at MH+ of 346.12 in the low mass range of the spectra. The fragmentation spectra of the 346.12 peak did not show diagnostic fragments that were apparent in the PSD spectra of the modified peptides (See Figure 11).

[001347] To further verify the presence of the modified peptides with compound **I-7**, the peptides at MH+ of 1725.88 and 1118.55 were subjected to PSD (MS/MS) analsysis. A correlational analysis with the homosapien database identified the correct peptides as being modified by I-7. Compound **I-11** was also tested using the same procedure and showed measurable modification.

Instrumental:

[001348] For tryptic digests the instrument was set in Reflectron mode with a pulsed extraction setting of 2200. Calibration was done using the Laser Biolabs Pep Mix standard (1046.54, 1296.69, 1672.92, 2093.09, 2465.20). For CID/PSD analysis the peptide was selected using cursors to set ion gate timing and fragmentation occurred at a laser power about 20% higher and He was used as the collision gas for CID. Calibration for fragments was done using the P14R fragmentation calibration for the Curved field Reflectron.

EXAMPLE 278

Omnia Assay Protocol for Potency Assessment Against the Active Form of JAK3:

[001349] The Omnia Assay Protocol for potency assessment against JAK3 was performed in a substantially similar manner as that described in Example 251 above except that the modified JAK3-optimized reagent conditions were:

[JAK3] = 5 nM, [ATP] = 5 μM, [Y12-Sox] = 5 μM (ATP KMapp ~5 μM).

EXAMPLE 279

[001350] Table 18 shows the activity of selected compounds of this invention in the JAK3 inhibition assay. The compound numbers correspond to the compound numbers in Table 5. 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} of 100-1000 nM; compounds having an activity designated as "D" provided an IC_{50} of 1000-10,000 nM; and compounds having an activity designated as "E" provided an $IC_{50} \geq 10{,}000$ nM.

Table 18. JAK3 Inhibition Data

Compound #	JAK3 Inhibition
I-1	A
I-2	A
I-3	A
I-4	A
I-5	A
I-7	A
I-8	A
I-9	A
I-10	B
I-11	A
I-23	A
I-27	B
I-28	A
I-33	A
I-34	B
I-35	A
I-38	B
I-39	A
I-40	A
I-45	A
I-56	B
I^R-7	D
I-96	A
I-182	A
I-238	D
I-241	C
I-242	A
I-243	A
I-244	A
I-245	A

Compound #	JAK3 Inhibition
I-246	C
I-247	A
I-248	A
I-323	E
I-360	A

EXAMPLE 280

JAK3 Cellular Assay Protocol in CTLL2 Cells

[001351] Compounds **I-2**, **I-4** and **I-7** were tested in the following protocol.

CTLL2: murine lymphoma cell line ATCC: TIB-214. $5x10^6$ cells/sample were IL-2 starved in RPMI-1640 media for 2 hours. Designated samples were then treated with compound for 90 minutes. Samples, except DMSO control were then stimulated with 100nM IL-2 for 10 minutes. Samples were lysed and subjected to Western Analysis. The results are displayed in Figure 12, Figure 13 and Figure 14.

EXAMPLE 281

BTK occupancy in Ramos cells with I-7 and I-215 using streptavidin beads

[001352] Ramos cells were incubated with 0.1, 0.05, 0.01, or 0.001 μM **I-7** in serum free media for 1 hour at 37 °C. The cells were pelleted by centrifugation and lysed in Cell Extraction buffer (Invitrogen) for 10 minutes on ice, centrifuged (10 minutes at 14,000 rpm) and the supernatant was collected. Cell lysates were incubated with 1 μM **I-215** for 1 hour at room temperature, then incubated with streptavidin-coupled agarose beads (ThermoFisher) overnight at 4 °C. The beads were washed three times with lysis buffer and the bound proteins were boiled off the beads at 95 °C for 5 minutes in 4X LDS Sample Buffer. The amount of BTK associated with the probe **I-215** was assessed by BTK western blot. All values were normalized to the DMSO-treated sample which is set to 100%. **Figure 16** shows the western blot; **Figure 17** shows quantitation of Figure 16 demonstrating unoccupied BTK protein is available to the probe **I-215** when the cells have been exposed to low concentrations (10 nM, 1 nM) of **I-7** but at higher concentrations of **I-7** the BTK protein is fully occupied and cannot interact with **I-215**.

EXAMPLE 282

Washout Experiment with I-7 and probe compound I-215

[001353] Ramos cells were incubated with 0.1 μM **I-7** or a reversible BTK inhibitor control compound in serum free media for 1 hour at 37 °C. The cells were then washed in compound-free media and lysed 0, 4, 6, or 8 hours after compound removal. Cell lysates were incubated with 1 μM **I-215** for 1 hour at room temperature, then overnight at 4 °C with streptavidin-coupled agarose beads. Protein was boiled off the beads and BTK association was assessed by western blot. Figure 18 shows the Western blot; Figure 19 shows the quantitation of Figure 18 and demonstrates all the BTK protein remains occupied by **I-7** for over 8 hours. This suggests that the timeframe for re-synthesis of detectable BTK protein in Ramos cells is greater than 8 hours. In contrast, with the reversible inhibitor control, 45% of BTK protein is unbound and available to the probe at 0 hours and by 4 hours 100% of BTK protein is unbound and available to bind the probe. All samples were normalized to the DMSO-treated cells harvested at 0 hours.

EXAMPLE 283

Measuring BTK occupancy from *in vitro* samples by ELISA

[001354] In order to determine the amount of free BTK in cell or tissue lysates, an ELISA protocol was employed that utilizes a biotinylated probe compound that binds only to free, unoccupied BTK. The conjugated biotin is captured on a streptavidin-coated ELISA plate and detected with a mouse anti-BTK antibody (Becton Dickinson, Franklin Lakes, NJ, USA) and a secondary goat anti-mouse HRP antibody (Zymed, South San Francisco, CA, USA).

[001355] All samples were prepared with equal concentrations of Biorad lysis buffer (Hercules, CA, USA), 0.5% bovine serum albumin in PBS with 0.05% Tween-20 to give a final concentration of 1 μM **I-215**. Samples were incubated in a mixing plate for 1 hr at room temperature while shaking to allow probe compound **I-215** to bind to free BTK. After incubation with **I-215**, samples were added to a washed, streptavidin-coated ELISA plate (Pierce, Rockford, IL, USA) and incubated for 1 hr at room temperature while shaking. The plate was then washed with PBS containing 0.05% Tween-20 using an automatic plate washer. Anti-BTK antibody was prepared at 1 : 1000 dilution in 0.5% BSA in PBS (0.05% Tween-20) and added to the ELISA plate. The plate was incubated for 1 hr at room temperature while shaking. The plate was washed as described above and the secondary HRP antibody was prepared at 1 : 5000 dilution in 0.5%

BSA in PBS (0.05% Tween-20). The plate was incubated and washed as described above. TMB was added to the plate, and OD_{650} was monitored until reaching 1 OD unit. The reaction was then stopped with addition of H_2SO_4. The plate was analyzed using Gen 5 software, and a 4 Parameter Logistic curve was employed to quantitate samples. Recombinant BTK (Invitrogen, Carlsbad, CA, USA) was used for the standard curve.

[001356] Table 19 shows results with Ramos cells reported as concentration at which >50% or >90% of BTK is occupied. A concentration designated as "A" is greater than 1 nM; a concentration designated as "B" is greater than 10 nM; and a concentration designated as "C" is greater than 50 nM.

Table 19.

Compound #	>50% occupancy	>90% occupancy
I-7	A	B
I-182	A	C
I-96	A	B

EXAMPLE 284

Human primary B cell covalent probe occupancy *in vitro*

[001357] Human primary B cells were isolated as described in Example 256, then resuspended in RPMI media (10% serum). The compound to be analyzed was added at a 1:1000 dilution to media. Cells were incubated with compound in a tissue culture incubator for 1 h at 37 °C. After incubation, the cells were pelleted, washed with 1X PBS, and lysed on ice for 45 min with occasional agitation. Samples were spun in a chilled microcentrifuge for 30 min at 14,000 rpm and the supernatant was isolated. The supernatant was analyzed as described in Example 283 using **I-215**. **I-96** and **I-182** occupied at least 50% of BTK at concentrations greater than 10 nM.

EXAMPLE 285

Dog primary B cell covalent probe occupancy *in vitro*

[001358] Canine whole blood (30 mL) was diluted to 50 mL total with 1X PBS and layered on top of Histopaque-1077 (Sigma Aldrich). The whole blood-Histopaque was spun at 400 x g for 30 min in a Beckman centrifuge with no brake. Peripheral blood mononuclear cells (PBMCs) were collected and pelleted at 400 x g for 15 min. Red blood cells (RBCs) were lysed

with 2.5 mL RBC lysis buffer (Boston Bioproducts) and the remaining PBMCs were washed 3 times in 1X PBS at 250 x g. PBMCs were treated with compound at a 1:1000 dilution for one hour at 37 °C, washed with PBS and lysed on ice for 45 minutes. The lysate was centrifuged for 30 minutes at 14,000 x g and the supernatant collected. The supernatant was analyzed as described in Example 283 using **I-215**. **I-96** occupied at least 50% of BTK at concentrations greater than 10 nM.

EXAMPLE 286

Measuring BTK occupancy from *in vivo* samples by ELISA

[001359] Rats were dosed orally with 30 mg/kg of compound and spleens were harvested either 2 or 24 hours after compound treatment. Rat spleens were disrupted between two microscope slides coated with frosted glass to recover single cell suspensions. Red blood cells were lysed by incubating with RBC lysis buffer (Boston BioProducts) for 2 minutes at room temperature, the cells were then resuspended in RPMI complete media and pelleted by centrifugation. Rat B cells were isolated by positive selection with B220+ antibody-magnetic bead conjugates, purified by MACS column and lysed in Bio-Rad lysis buffer at a concentration of 10 million cells/100 µl. Lysates were analyzed employing the biotinylated probe compound **I-215** in an ELISA protocol as described in detail in Example 278. Table 20 shows the results.

Table 20.

Treatment	% BTK Occupancy 2 h	% BTK Occupancy 24 h
Vehicle	0	0
I-96	87	60
I-4	87	68
I-7	98	78
I-190	18	13
I-182	99	79

EXAMPLE 286

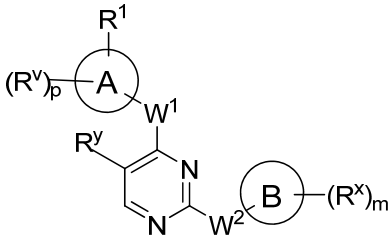
Proteomics analysis

[001360] Proteins that are covalently bound to **I-215** in a cell lysate are identified using mass spectrometry. Cell lysate is incubated with 1 µM **I-215** for 1 hour at room temperature, followed by the addition of streptavidin-coupled agarose beads. Mass spectrometry is used to identify proteins other than BTK. These are potential "off-target" interactions.

[001361] While a number of embodiments of this invention are described herein, it is apparent that the basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

Claims

1. A compound of formula **I-b**:



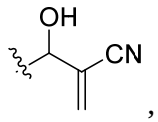
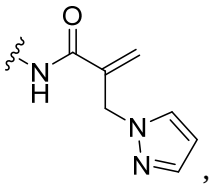
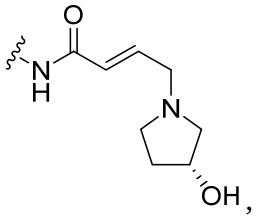
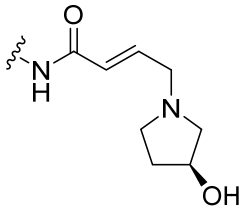
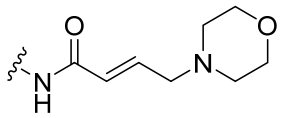
I-b

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is phenyl;

Ring B is phenyl;

R^1 is a warhead group –L-Y, wherein R^1 is in a meta- or para-position of the phenyl ring relative to W^1;

-L-Y is , , ,  or ; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one or two methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)-; and Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one alkylidenyl double bond and at least one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-, and one or two additional methylene units of L are optionally and independently replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-; or

L is -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O- or -NRSO_2CH=CHCH_2-; and

Y is hydrogen, C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a 3-10 membered monocyclic or bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and wherein said ring is substituted with 1-4 R^e groups; or

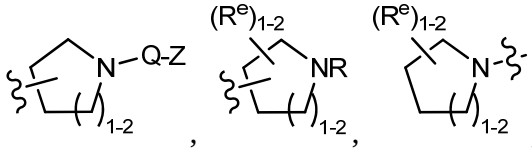
L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein one methylene unit of L is replaced by cyclopropylene and one or two additional methylene units of L are independently replaced by –C(O)-, -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-; and Y is C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN; or

L is a covalent bond and Y is:

(*ii*) C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

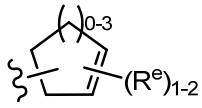
(*vi*) 

; or

(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

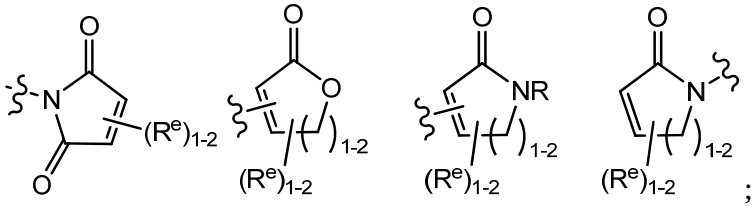
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*) 

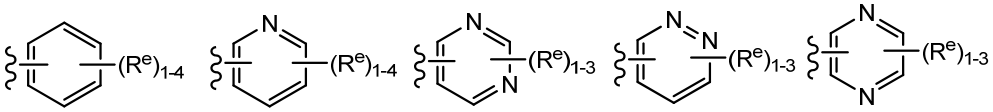
; or

(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

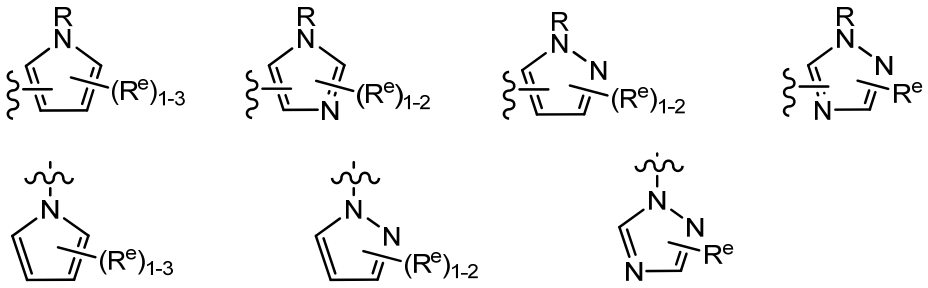
(*xii*) 

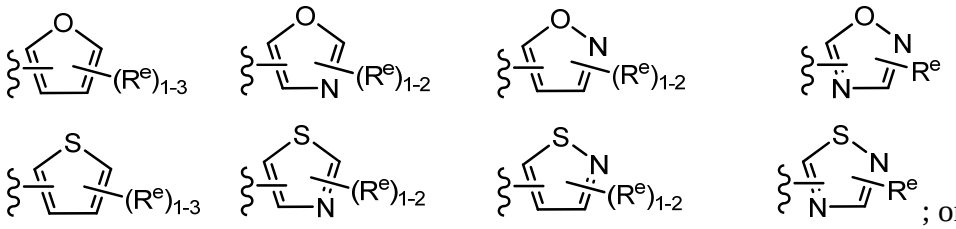
; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*) 

; or

(*xvi*) 


; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is –C(O)- and Y is:

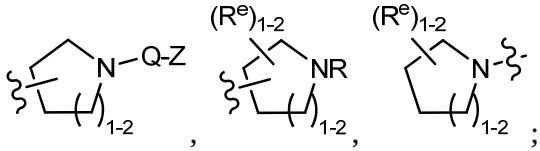
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

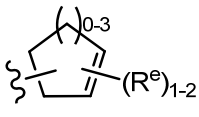
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

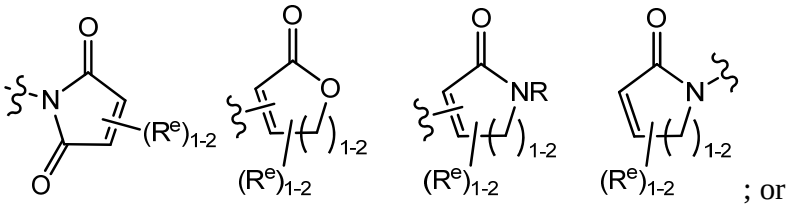
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

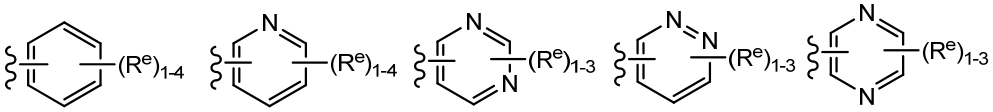
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

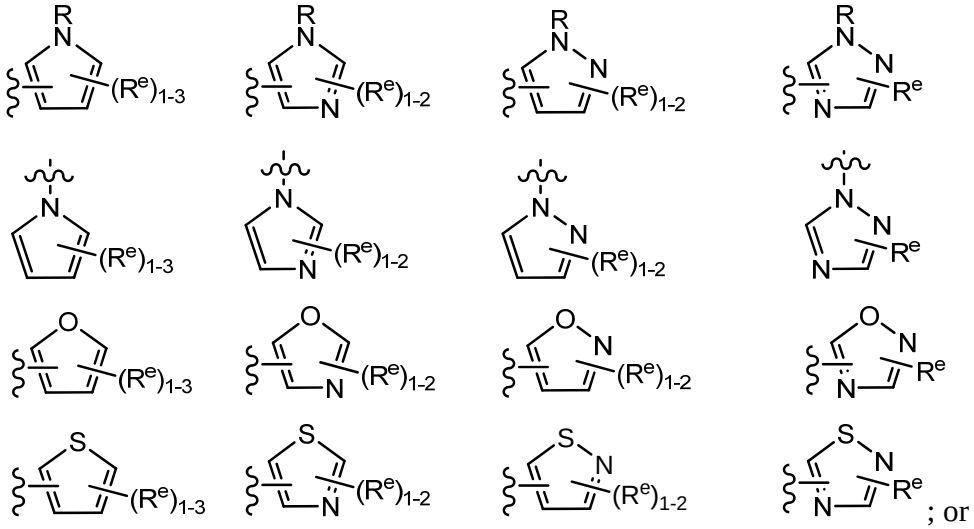
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*)  ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is –N(R)C(O)- and Y is:

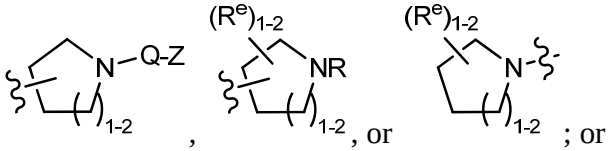
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

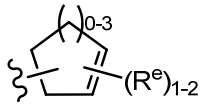
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

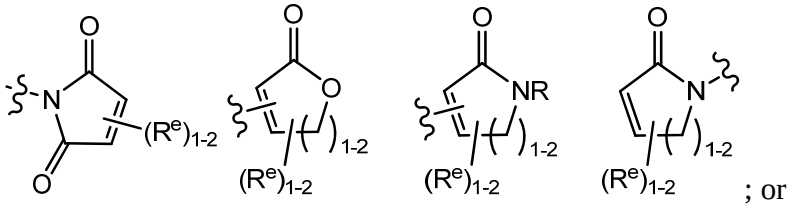
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

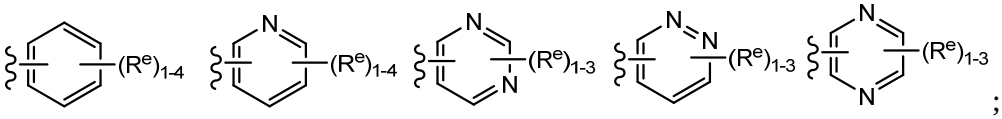
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*)  ; or

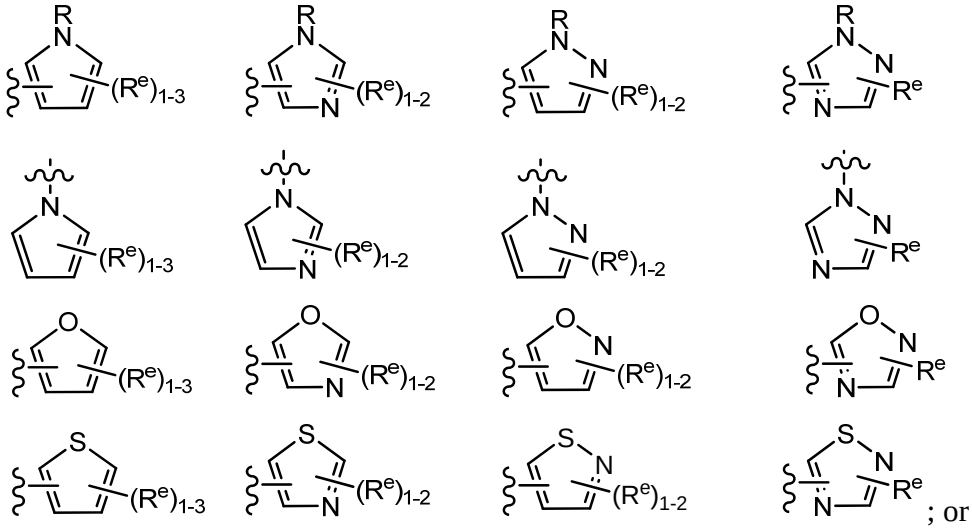
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*) 

; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

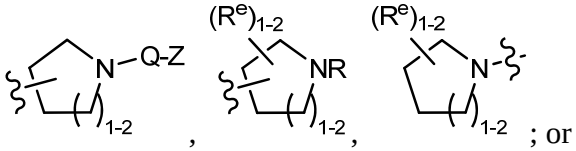
L is a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and Y is:

(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-2 R^e groups; or

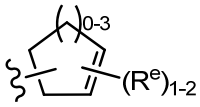
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*)  ; or

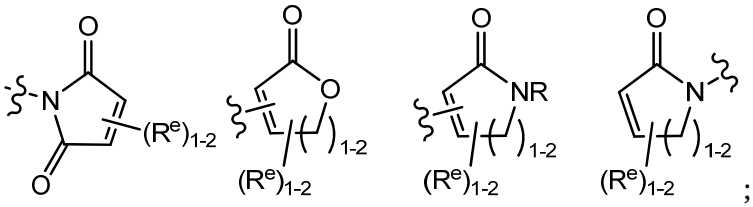
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

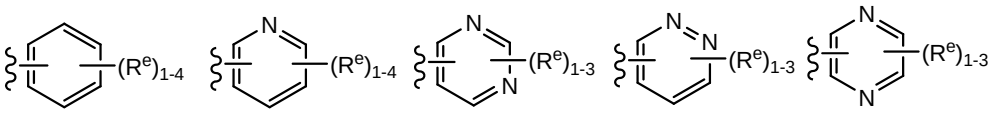
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*x*) ; or

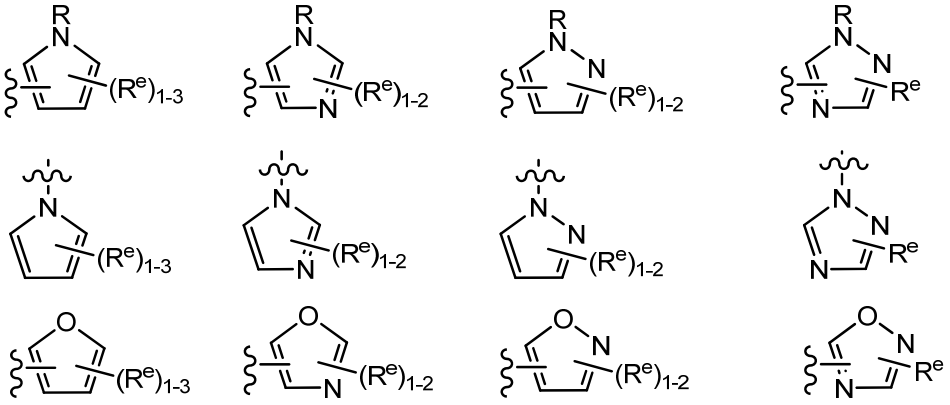
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*) ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*) ; or

(*xv*) a 5-membered heteroaryl ring having 1-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-3 R^e groups; or

(*xvi*) 


; or

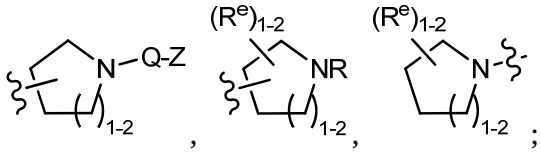
(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

L is $–CH_2$-, -NH-, -C(O)-, $-CH_2NH$-, $-NHCH_2$-, –NHC(O)-, $-NHC(O)CH_2OC(O)$-, $-CH_2NHC(O)$-, $-NHSO_2$-, $-NHSO_2CH_2$-, or $-SO_2NH$-; and Y is:

(*ii*) C_{2-6} alkenyl substituted with oxo, halogen, NO_2, or CN; or

(*iv*) a saturated 3-4 membered heterocyclic ring having 1 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-2 R^e groups; or

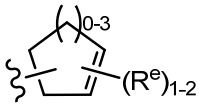
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of oxygen and nitrogen wherein said ring is substituted with 1-4 R^e groups; or

(*vi*) 
; or

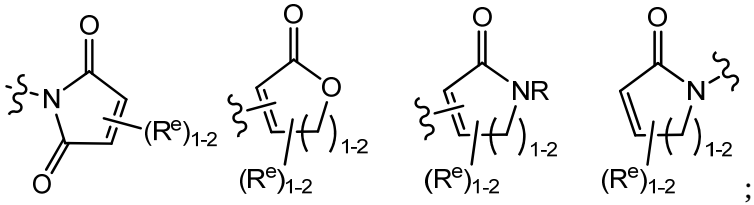
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

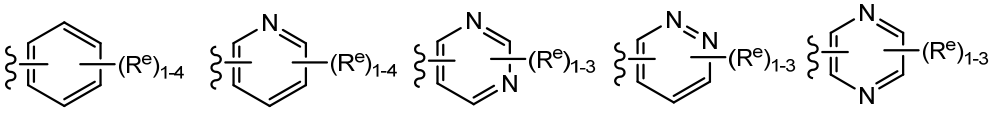
(*ix*) a partially unsaturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups; or

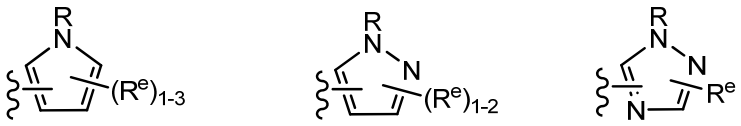
(*x*) 
; or

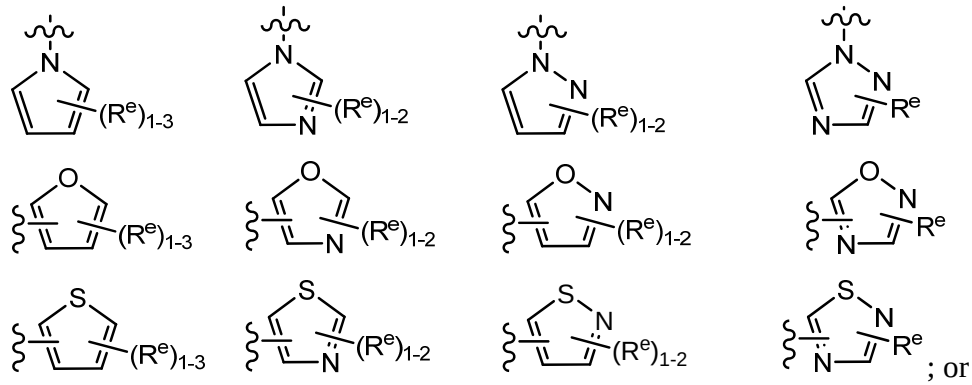
(*xi*) a partially unsaturated 4-6 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups; or

(*xii*)  ; or

(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups; or

(*xiv*)  ; or

(*xvi*) 

 ; or

(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, wherein said ring is substituted with 1-4 R^e groups;

each R^e is independently–Q-Z, oxo, NO_2, halogen, CN, C_{1-6} saturated aliphatic substituted with oxo, halogen, NO_2, or CN, C_{2-6} unsaturated aliphatic optionally substituted with oxo, halogen, NO_2, or CN, or a suitable leaving group selected from the group consisting of alkoxy, sulfonyloxy, optionally substituted alkylsulfonyloxy, optionally substituted alkenylsulfonyloxy, optionally substituted arylsulfonyloxy, acyl, and diazonium, wherein:

Q is a bivalent C_{2-6} unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-,

-S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-; and

each Z is hydrogen or C_{1-6} aliphatic substituted with oxo, halogen, NO_2, or CN;

R^y is halogen;

each R group is independently hydrogen or an optionally substituted group selected from the group consisting of $C_{1–6}$ aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur, and a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur;

W^1 is –NR^2-;

W^2 is –NR^2-;

R^2 is hydrogen, optionally substituted C_{1-6} aliphatic, or –C(O)R;

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

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

each instance of R^x is independently–R, -OR, -O$(CH_2)_q$OR, or halogen, wherein q is 1, 2, 3 or 4; and

each instance of R^v is independently R, halogen, –OR, -O$(CH_2)_q$OR, –CN, –NO_2, -SO_2R, -SO_2N$(R)_2$, -SOR, -C(O)R, -CO_2R, –C(O)N$(R)_2$, -NRC(O)R, -NRC(O)N$(R)_2$, -NRSO_2R, or -N$(R)_2$, wherein q is 1, 2, 3 or 4.

2. The compound according to claim 1, wherein –L-Y is -NHC(O)CH=CH_2.

3. The compound according to claim 2, wherein each R^2 is hydrogen.

4. The compound according to claim 3, wherein m is 1.

5. The compound according to claim 4, wherein R^x is C_{1-6} alkyl, –OC_{1-6} alkyl,–O$(CH_2)_q$OC_{1-6} alkyl, or halogen.

6. The compound according to claim 5, wherein R^x is methyl, methoxy, methoxyethoxy, or fluoro.

7. The compound according to claim 6, wherein R^x is methoxyethoxy.

8. The compound according to claim 7, wherein R^y is fluoro.

9. The compound according to claim 1, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, -NRC(O)-, -C(O)NR-, -SO_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or –C(O)O-.

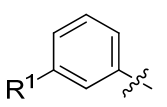
10. The compound according to claim 9, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -OC(O)-.

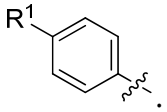
11. The compound according to claim 1, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O-, -CH_2NRC(O)CH=CH-, -NRSO_2CH=CHCH_2-, or -NRC(O)C(=CH_2)CH_2-; wherein the R group of L is H or optionally substituted C_{1-6} aliphatic; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

12. The compound according to claim 11, wherein L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH_2N(CH_3)-, -NHC(O)CH=CHCH_2O-, -CH_2NHC(O)CH=CH-, -NHSO_2CH=CHCH_2-, or -NHC(O)C(=CH_2)CH_2-.

13. The compound according to claim 1, wherein L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein L has at least one double bond and one methylene unit of L is replaced by -C(O)-, and one additional methylene unit of L is optionally replaced by cyclopropylene, –O-, -N(R)-, or -C(O)-.

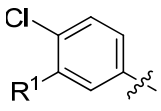
14. The compound according to claim 1, wherein Ring A is:

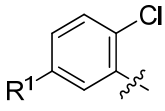


or


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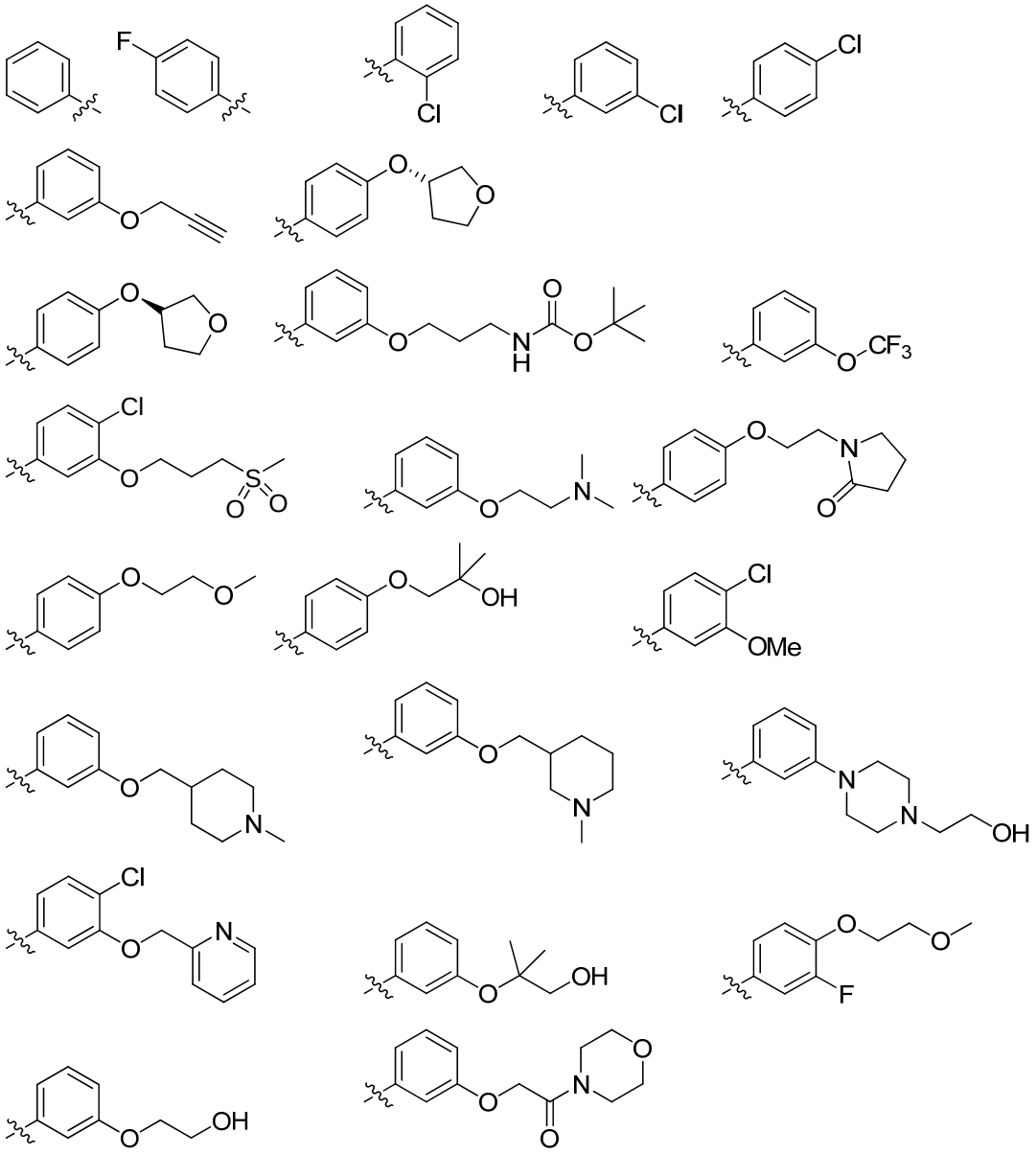
15. The compound according to claim 1, wherein Ring A is:

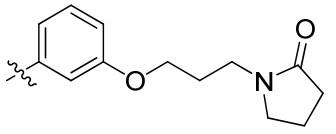
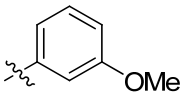
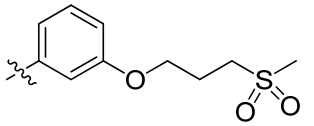
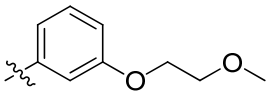
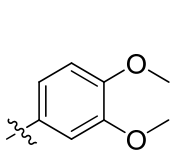
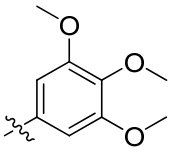
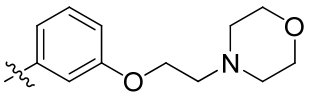
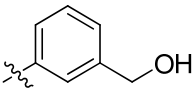
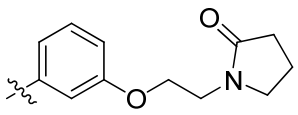
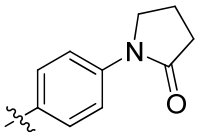
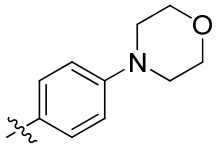
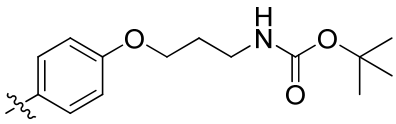
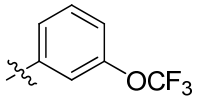
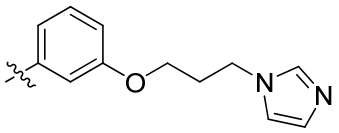
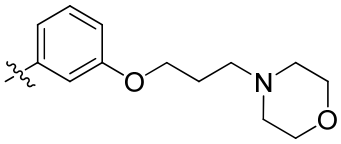
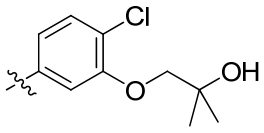
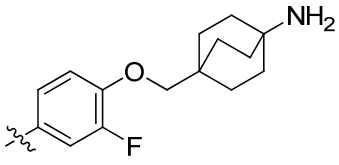
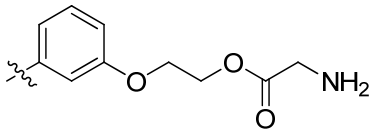
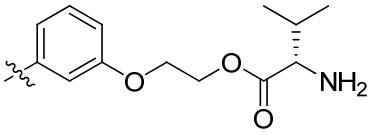
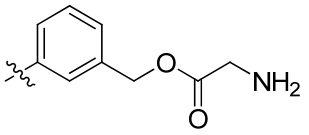
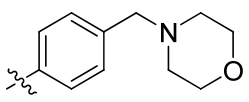
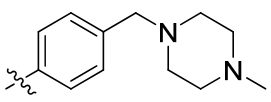
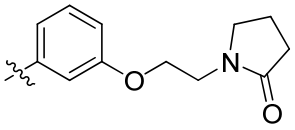
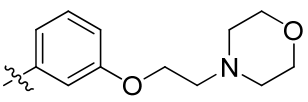
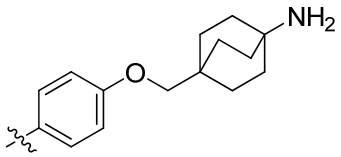
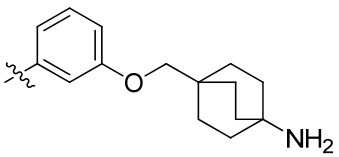
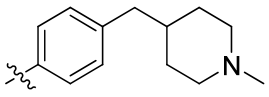
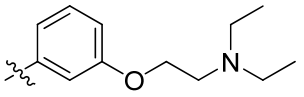


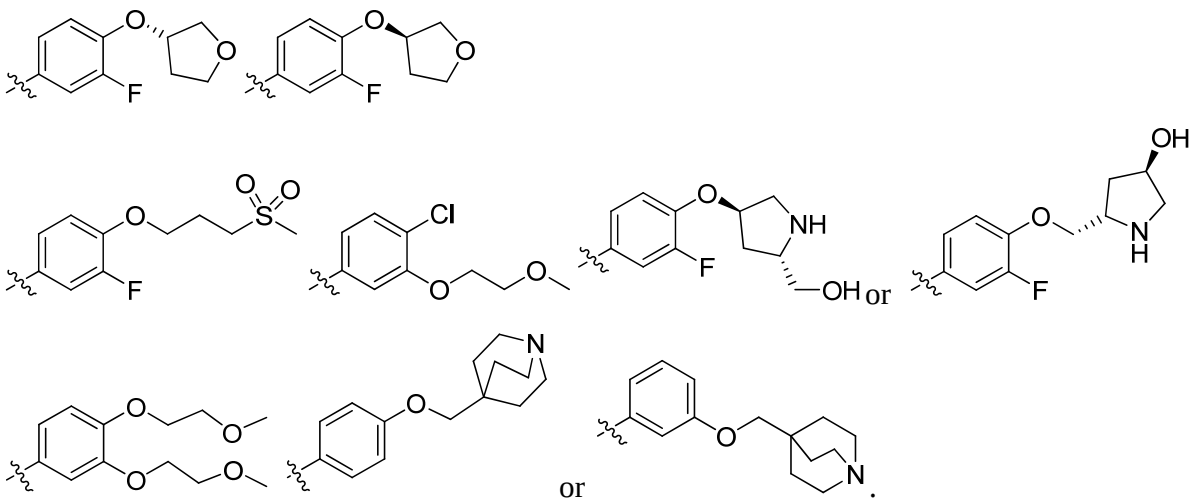
or


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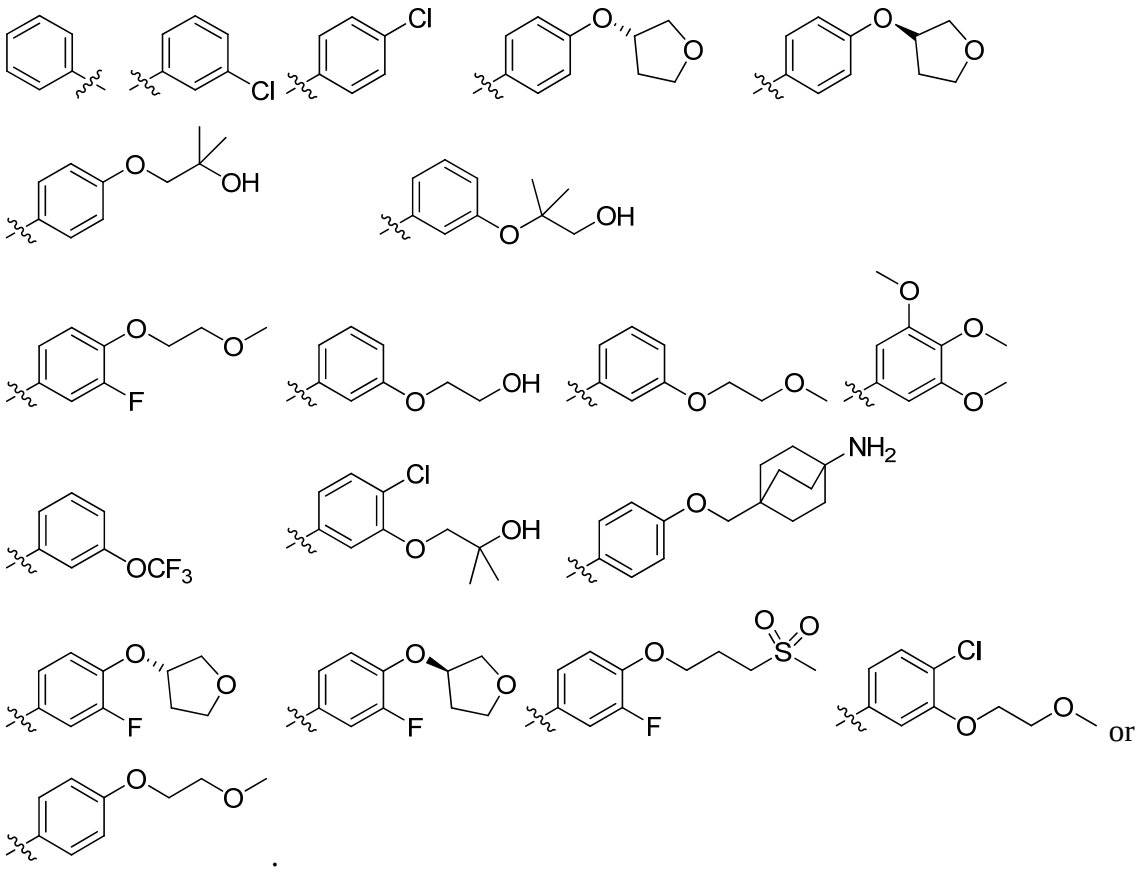
16. The compound according to claim 1, wherein Ring B is:





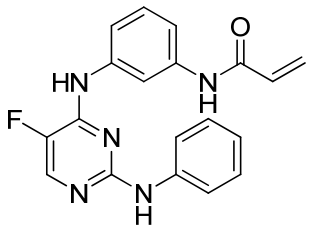
17. The compound according to claim 16, wherein Ring B is:



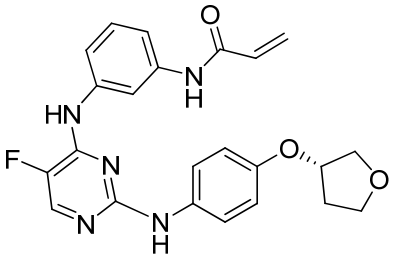
18. The compound according to claim 1, wherein R is independently hydrogen, C_{1-6} aliphatic, phenyl, a 4-7 membered heterocyclic ring having 1-2 heteroatoms independently

selected from the group consisting of nitrogen, oxygen, and sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from the group consisting of nitrogen, oxygen, and sulfur.

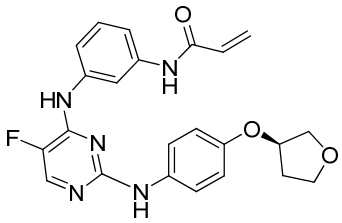
19. The compound according to claim 1, wherein said compound is:



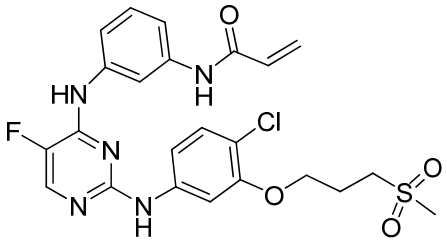
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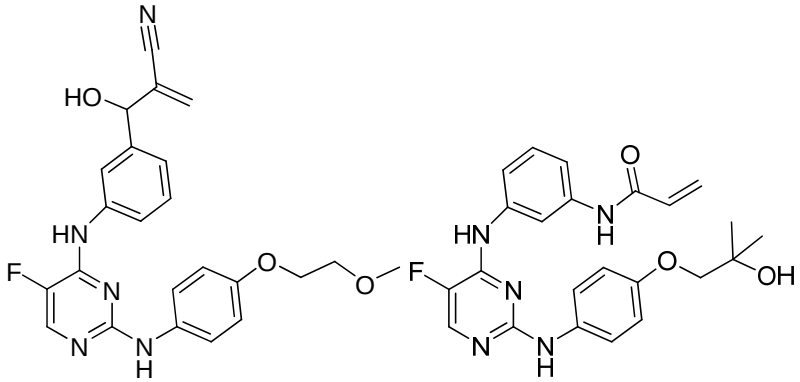
I-43



I-46

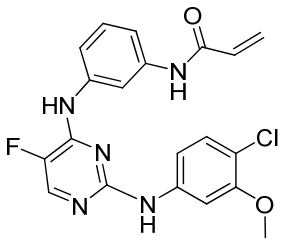


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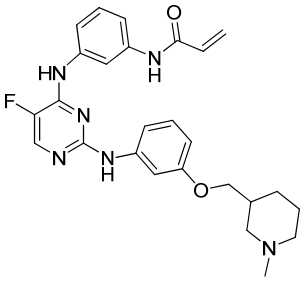


I-71

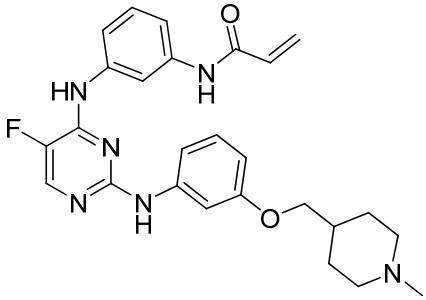
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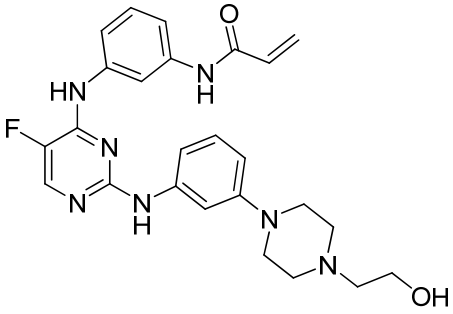
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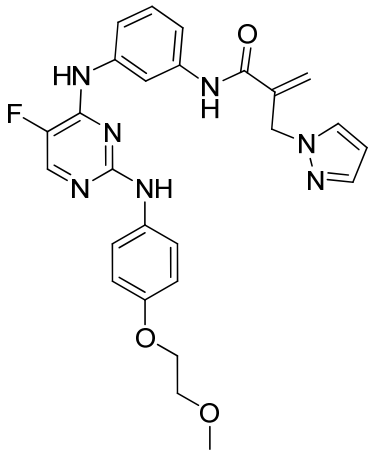
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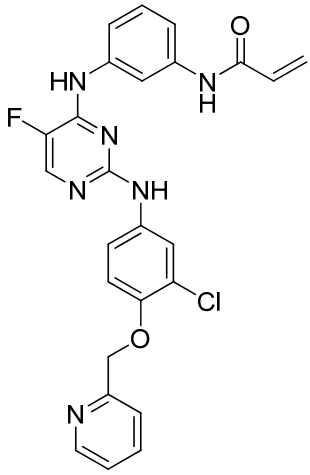
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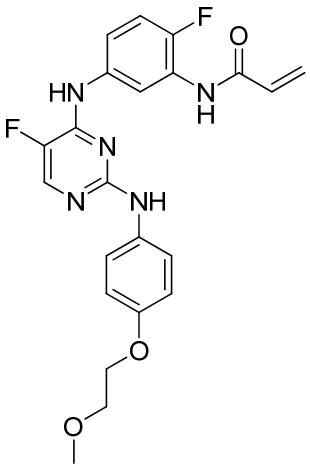
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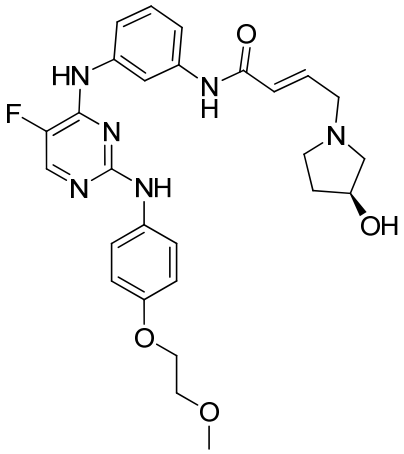
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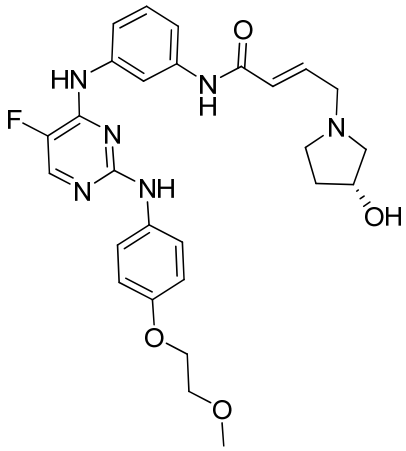
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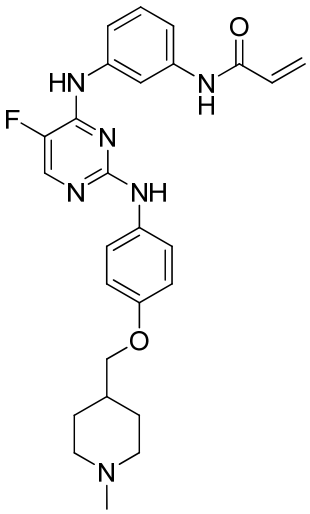
I-87



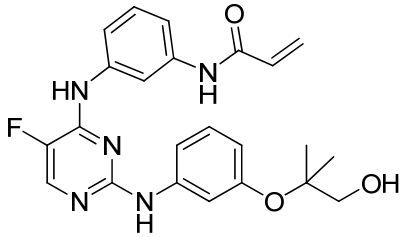
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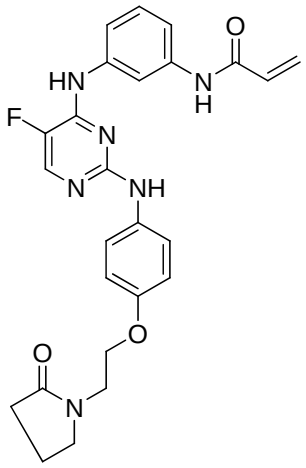
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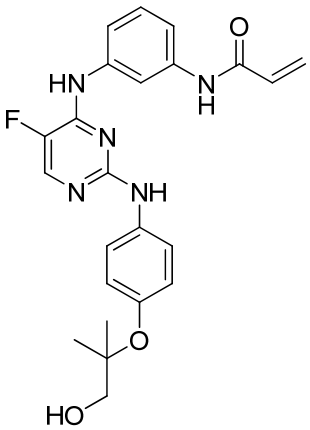
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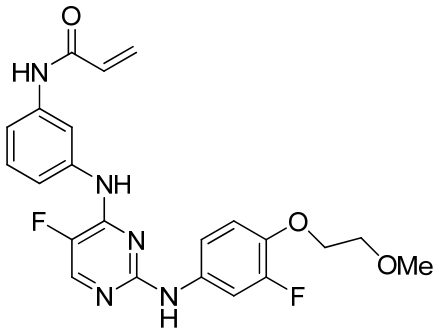
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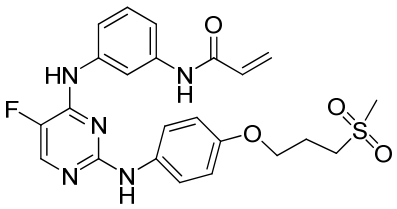
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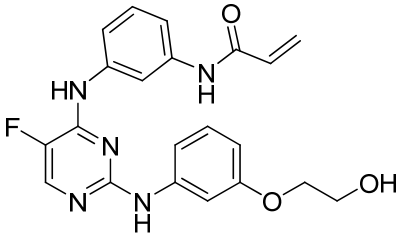
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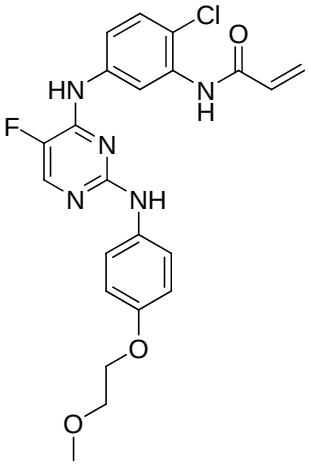
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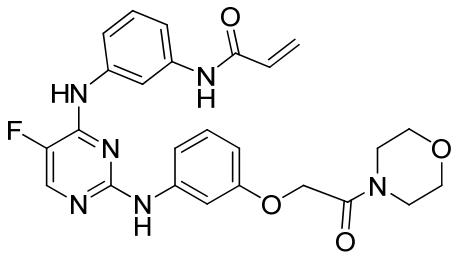
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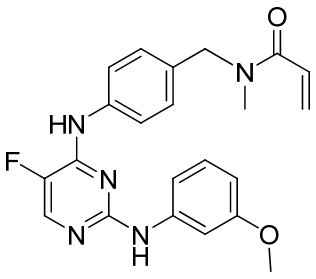
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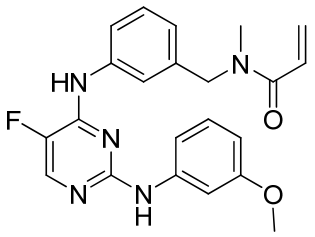
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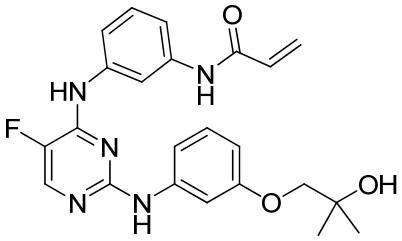
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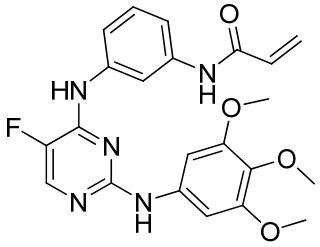
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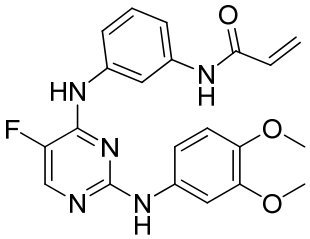
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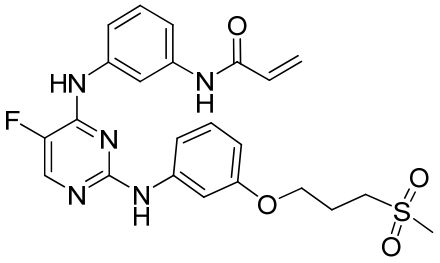
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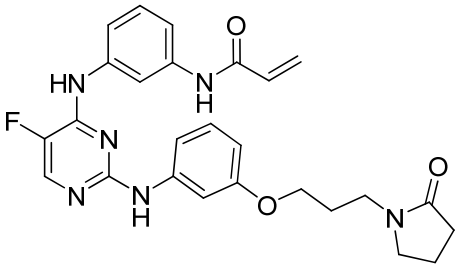
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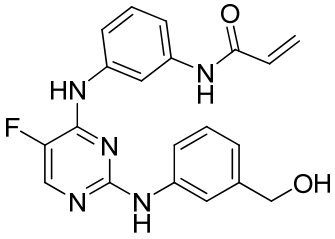
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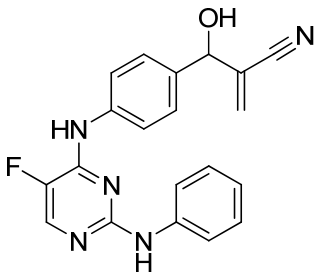
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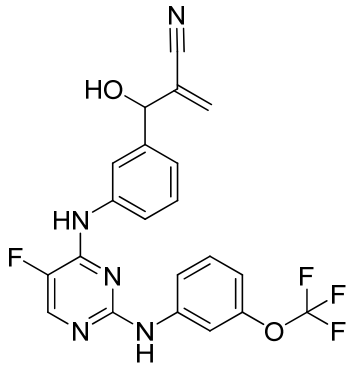
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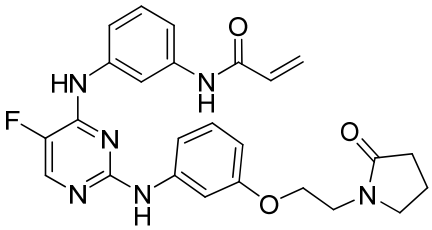
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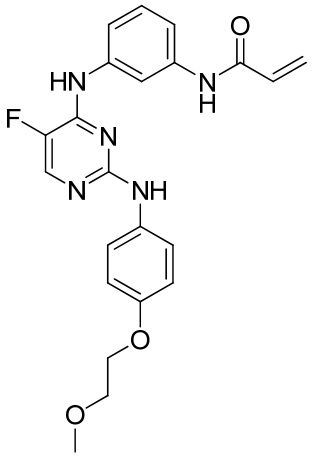
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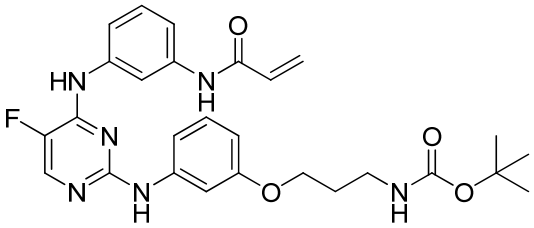
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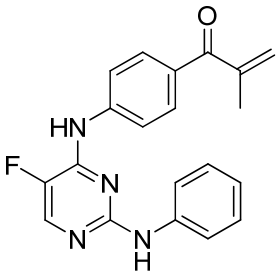
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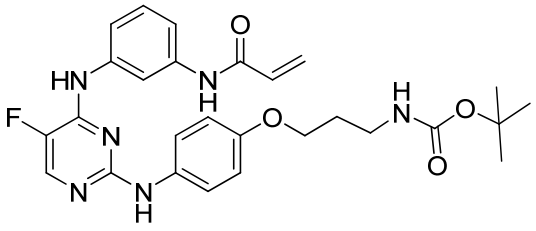
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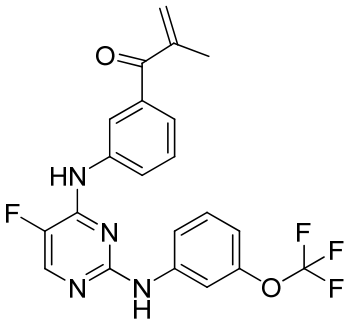
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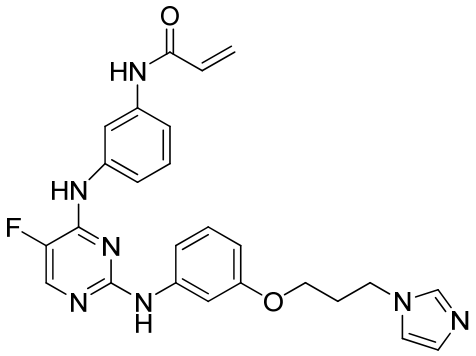
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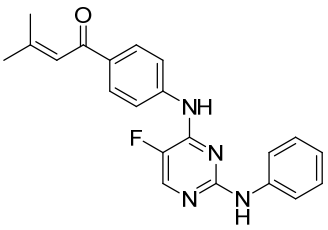
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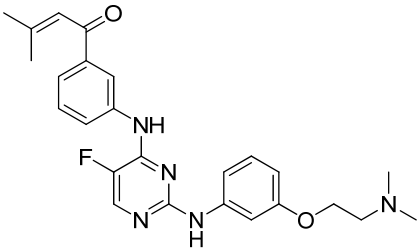
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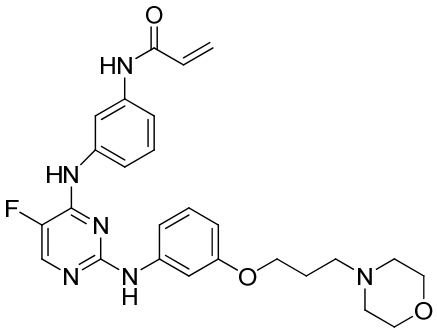
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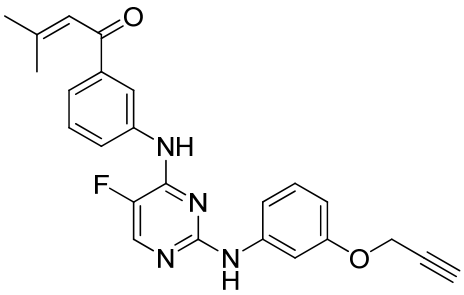
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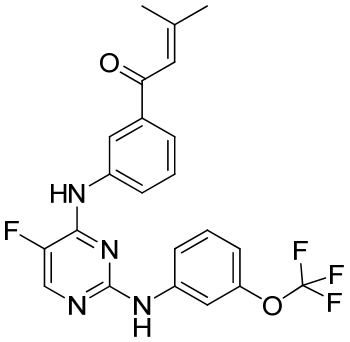
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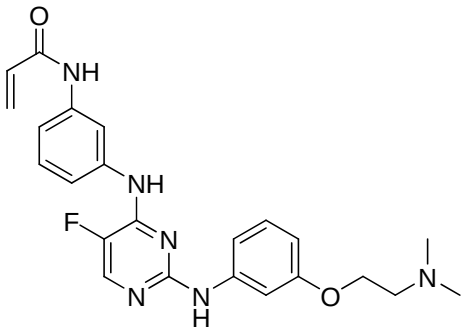
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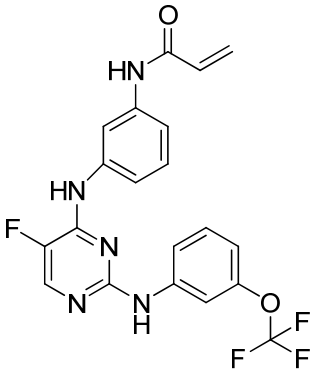
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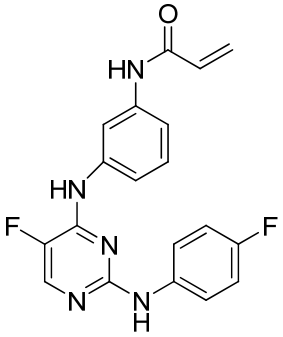
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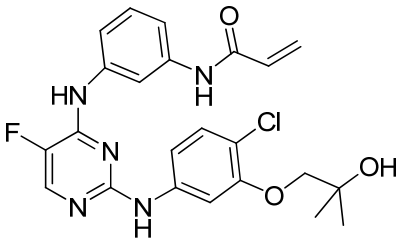
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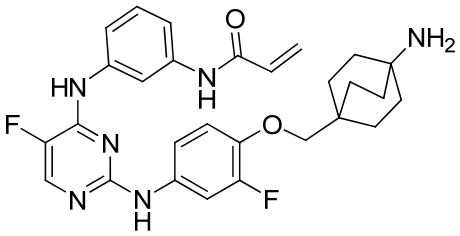
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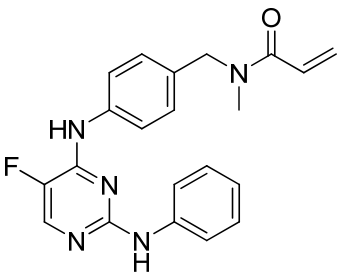
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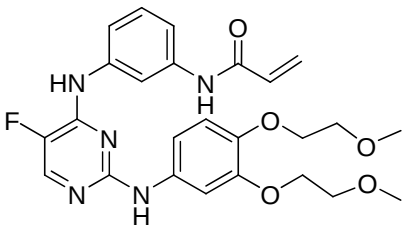
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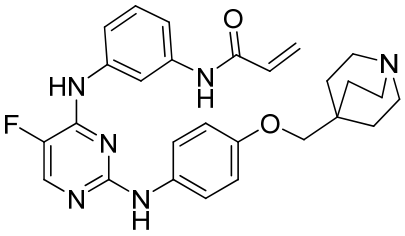
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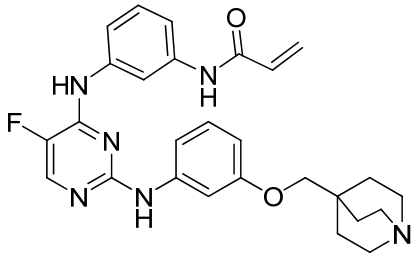
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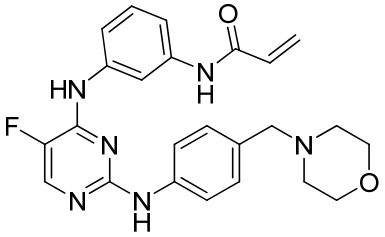
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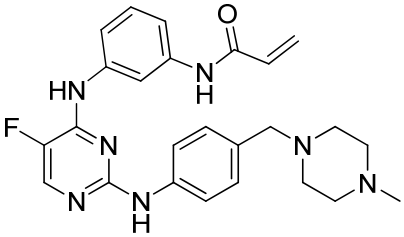
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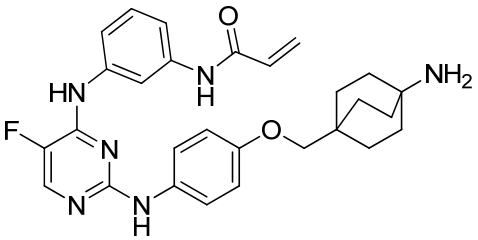
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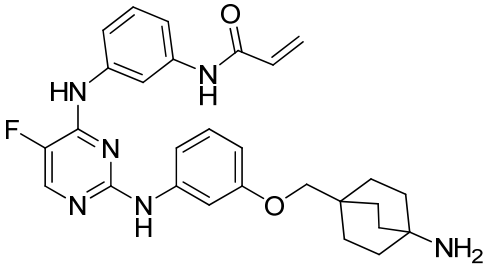
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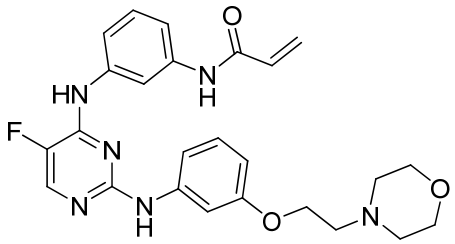
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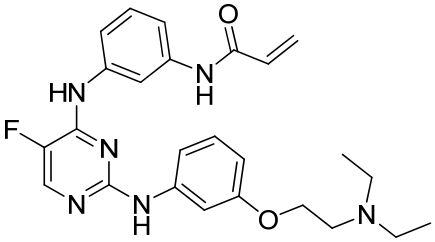
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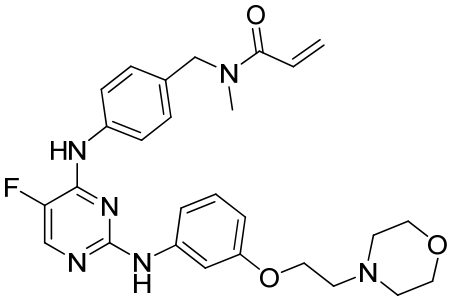
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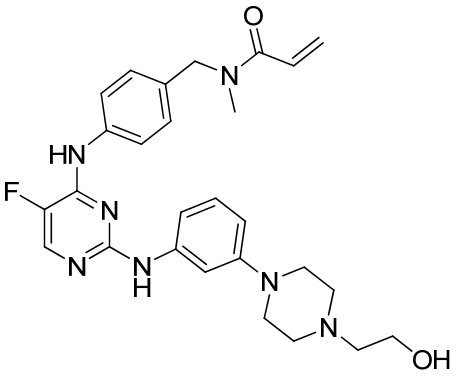
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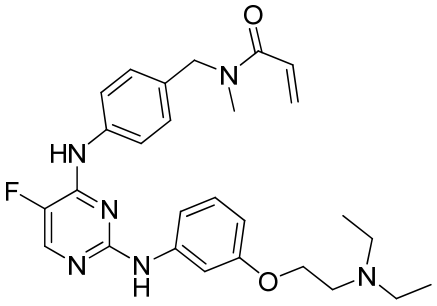
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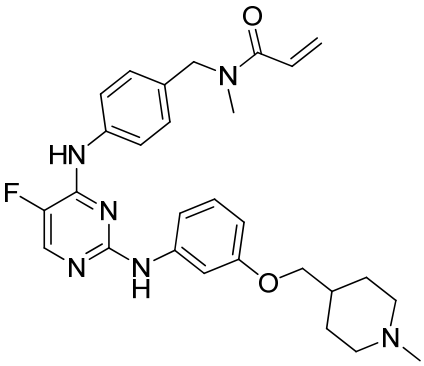
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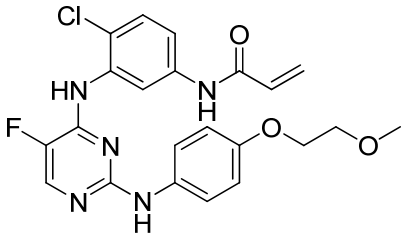
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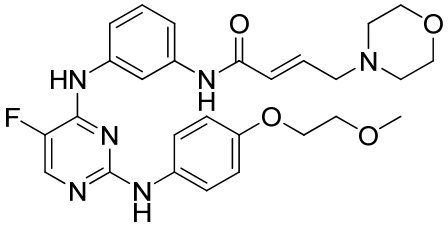
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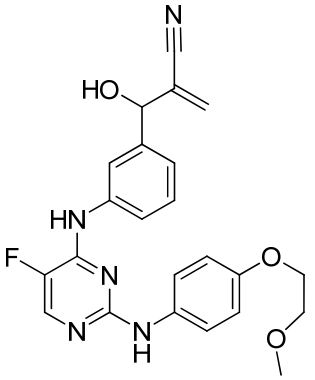
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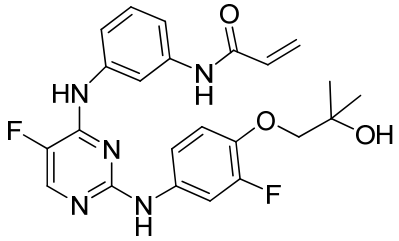
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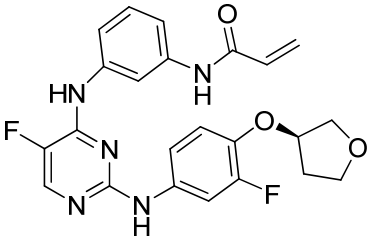
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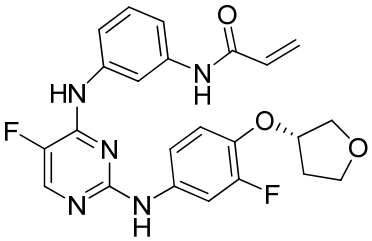
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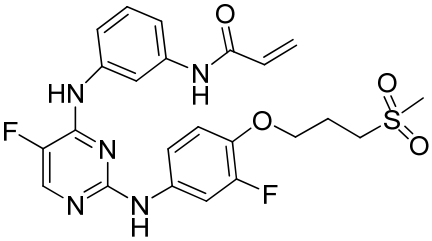
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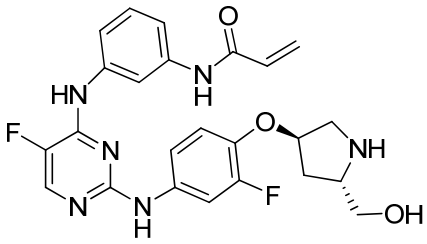
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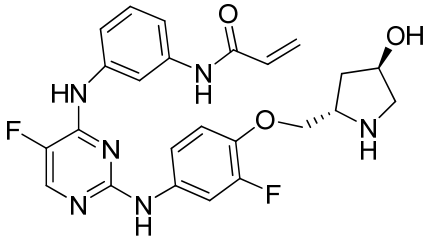
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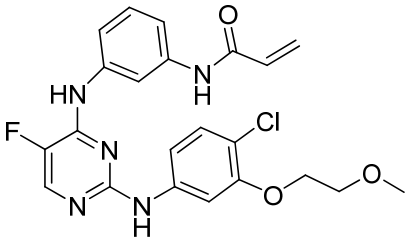
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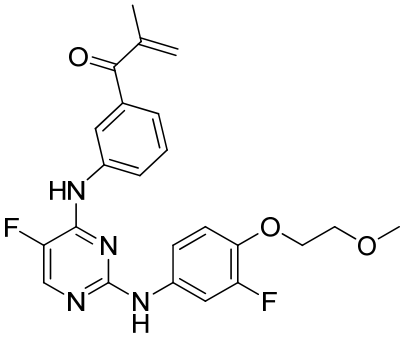
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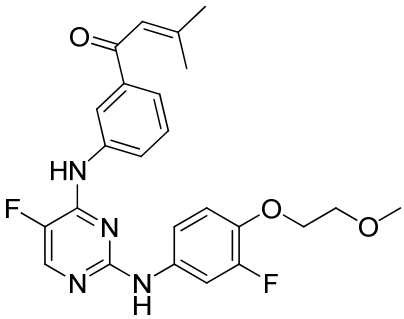
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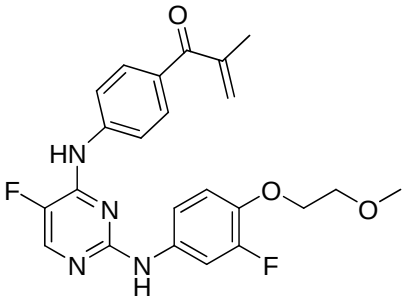
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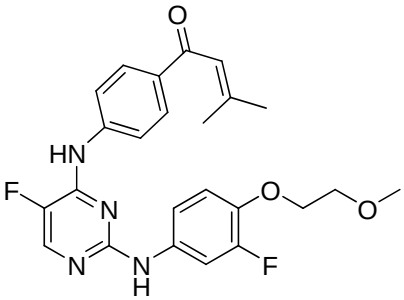
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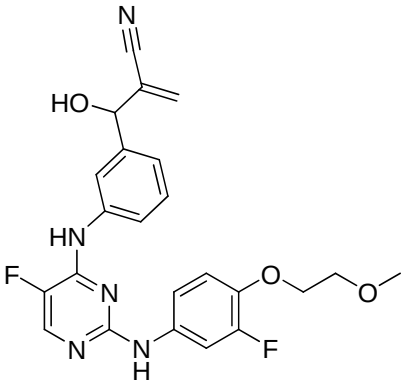
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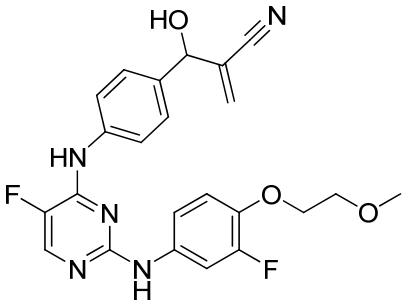
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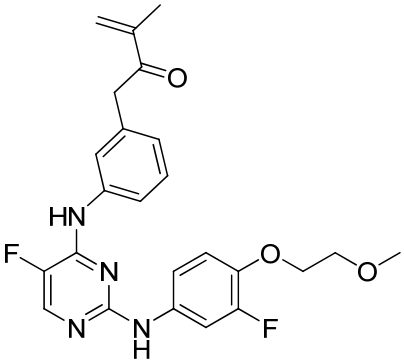
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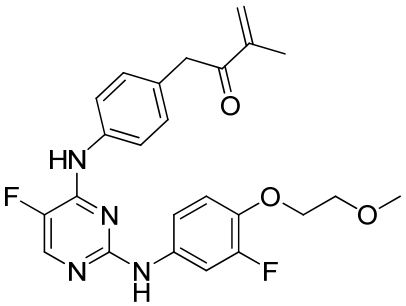
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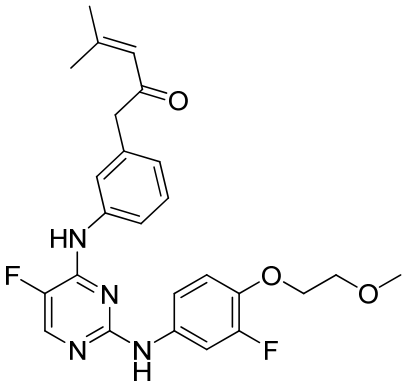
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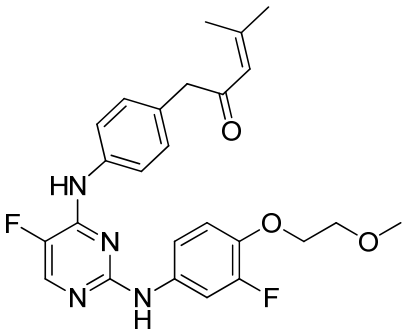
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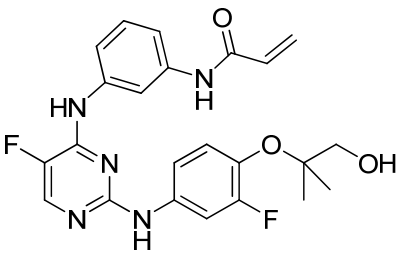
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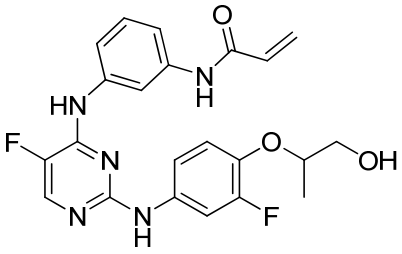
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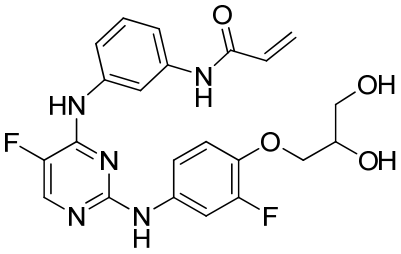
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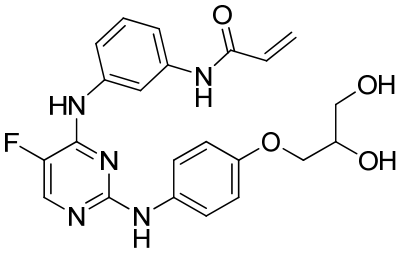
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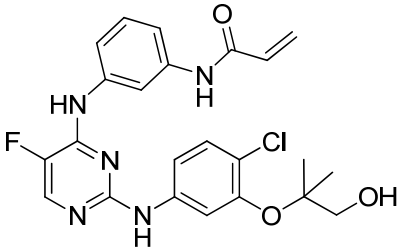
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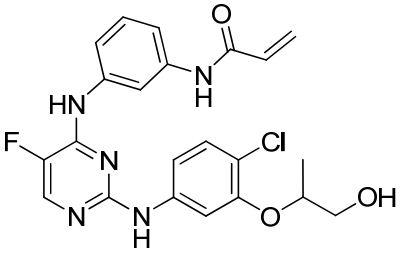
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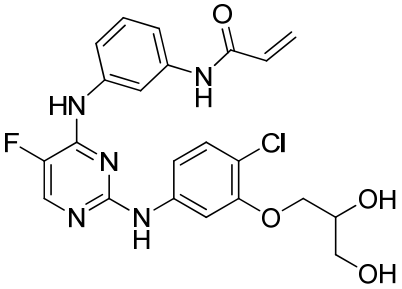
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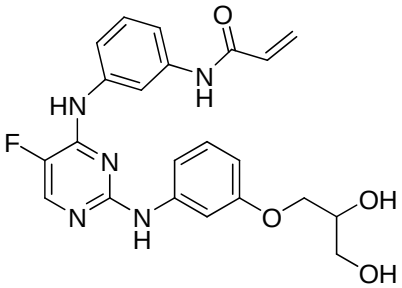
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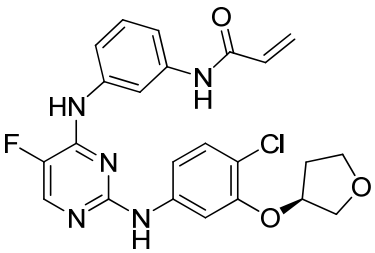
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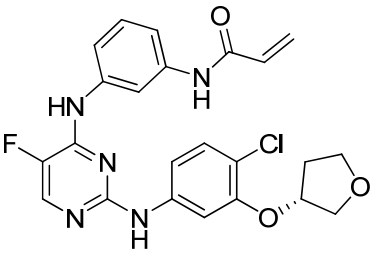
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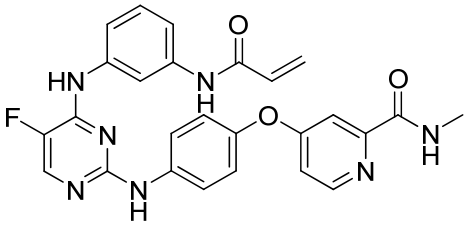
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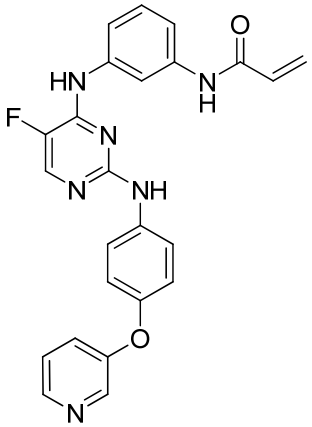
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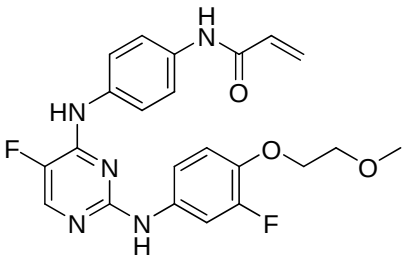
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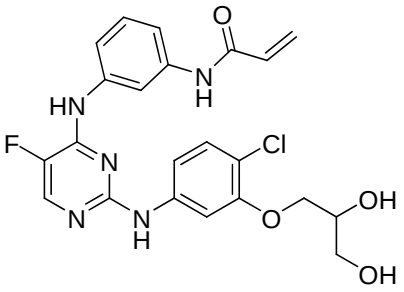
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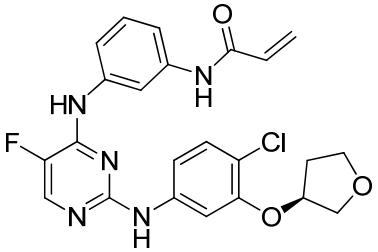
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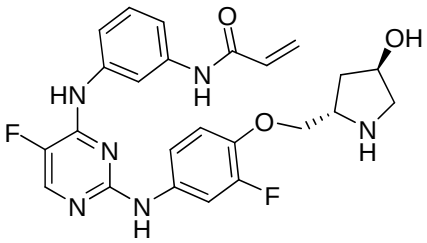
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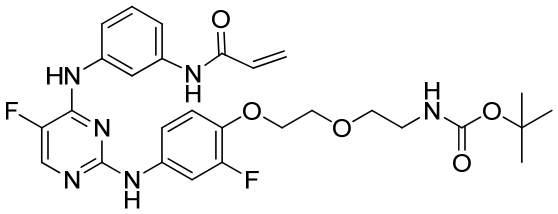
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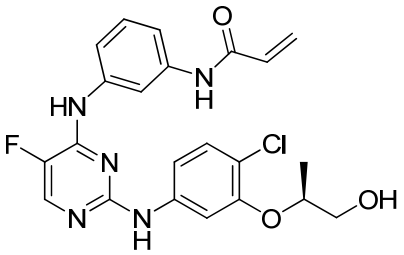
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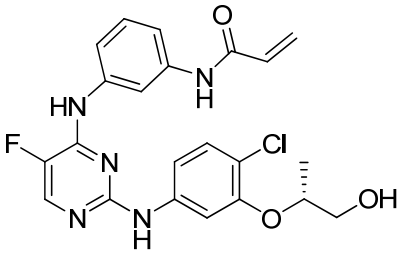
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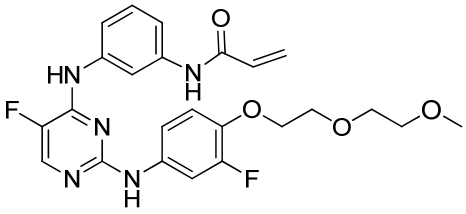
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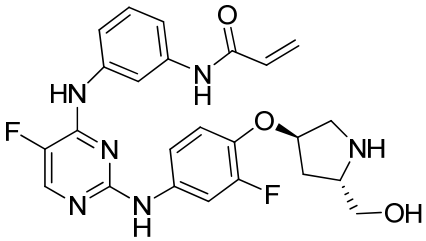


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or

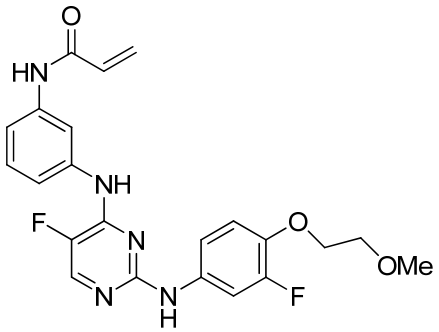
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I-361,

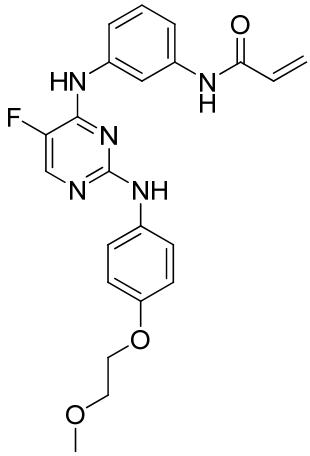
or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 19, wherein said compound is:



I-96

or

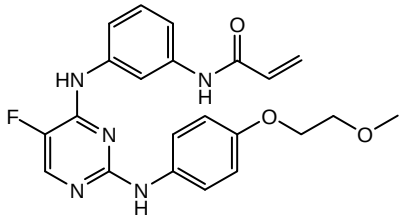


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or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

22. A compound of the following structure:



or a pharmaceutically acceptable salt thereof.

23. A pharmaceutical composition comprising the compound according to claim 22, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

24. The pharmaceutical composition according to claim 23, wherein said composition is formulated for parenteral administration.

25. The pharmaceutical composition according to claim 23, wherein said compound is formulated for oral administration.