ERK INHIBITORS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority to U.S. provisional application number 61/785,126, filed March 14, 2013, and U.S. provisional application number 61/762,408, filed February 8, 2013, the entirety of each of which is hereby incorporated by reference.

TECHNICAL FIELD OF THE INVENTION

[0002] The present invention relates to compounds useful as inhibitors of ERK kinases, for example one or both of ERK1 and ERK2 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

[0003] 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.

[0004] 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.).

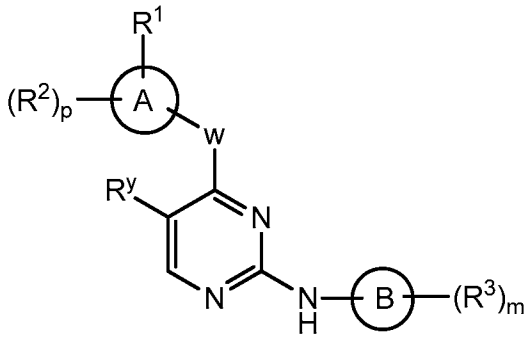
[0005] The processes involved in tumor growth, progression, and metastasis are mediated by signaling pathways that are activated in cancer cells. The ERK pathway plays a central role in regulating mammalian cell growth by relaying extracellular signals from ligand-bound cell surface tyrosine kinase receptors such as erbB family, PDGF, FGF, and VEGF receptor tyrosine kinase. Activation of the ERK pathway is via a cascade of phosphorylation events that begins with activation of Ras. Activation of Ras leads to the recruitment and activation of Raf, a serine-threonine kinase. Activated Raf then phosphorylates and activates MEK1/2, which then

phosphorylates and activates one or both of ERK1 and ERK2. When activated, one or both of ERK1 and ERK2 phosphorylates several downstream targets involved in a multitude of cellular events including cytoskeletal changes and transcriptional activation. The ERK/MAPK pathway is one of the most important for cell proliferation, and it is believed that the ERK/MAPK pathway is frequently activated in many tumors. Ras genes, which are upstream of one or both of ERK1 and ERK2, are mutated in several cancers including colorectal, melanoma, breast and pancreatic tumors. The high Ras activity is accompanied by elevated ERK activity in many human tumors. In addition, mutations of BRAF, a serine-threonine kinase of the Raf family, are associated with increased kinase activity. Mutations in BRAF have been identified in melanomas (60%), thyroid cancers (greater than 40%) and colorectal cancers.

[0006] Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events as described above. Accordingly, there remains a need to find protein kinase inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0007] It has now been found that compounds of this invention, and pharmaceutically acceptable compositions thereof, are effective as inhibitors of one or both of ERK1 and ERK2. Such compounds have general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, R^y, W, m, and p, with respect to the formula above, is as defined and described in embodiments herein. In certain embodiments, R^1 is a warhead group.

[0008] Compounds of the present invention, 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.

[0009] Compounds provided by this invention are 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.

BRIEF DESCRIPTION OF THE FIGURES

[0010] Figure 1 provides SEQ ID NO. 1, which is the amino acid sequence of ERK1.

[0011] Figure 2 provides SEQ ID NO. 3, which is the amino acid sequence of ERK2.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention:

[0012] In certain embodiments, the present invention provides irreversible inhibitors of one or both of ERK1 and ERK2 and conjugates thereof. In some embodiments, such compounds include those of the formulae described herein, or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

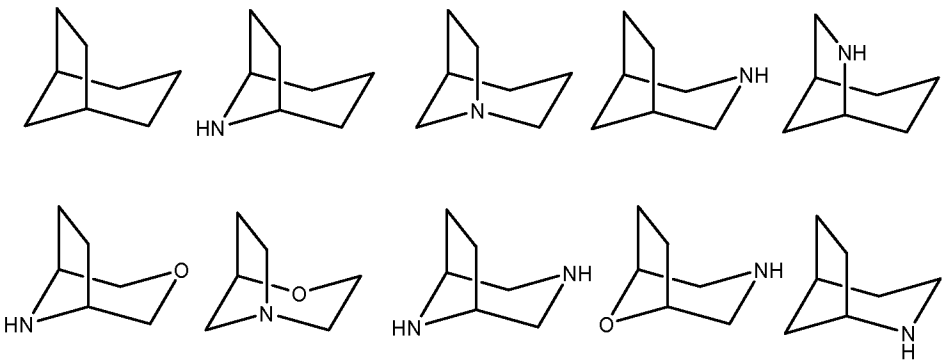
2. Compounds and Definitions:

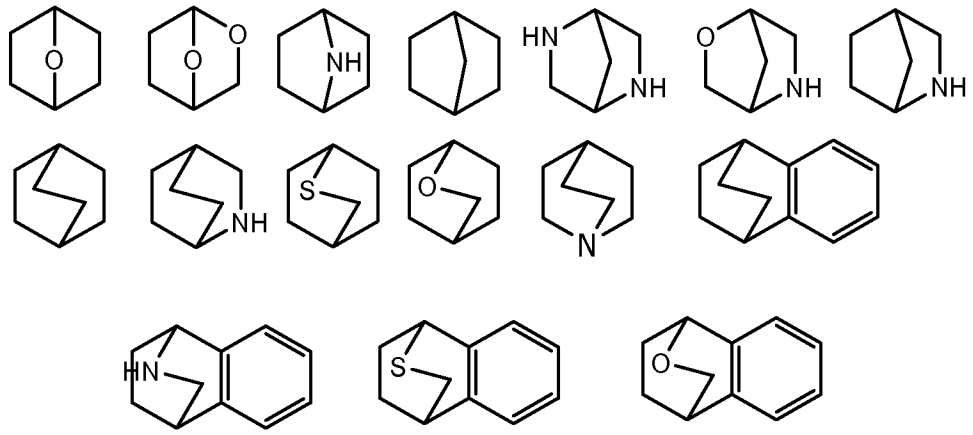
[0013] Compounds of this invention include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated. For purposes of this invention, the chemical elements are 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.

[0014] 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," "carbocyclic", "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, "carbocyclic" (or "cycloaliphatic" or "carbocycle" or "cycloalkyl") refers to a monocyclic C_3-C_8 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.

[0015] As used herein, the term "bridged bicyclic" refers to any bicyclic ring system, i.e. carbocyclic or heterocyclic, saturated or partially unsaturated, having at least one bridge. As defined by IUPAC, a "bridge" is an unbranched chain of atoms or an atom or a valence bond connecting two bridgeheads, where a "bridgehead" is any skeletal atom of the ring system which is bonded to three or more skeletal atoms (excluding hydrogen). In some embodiments, a bridged bicyclic group has 7-12 ring members and 0-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur. Such bridged bicyclic groups are well known in the art and include those groups set forth below where each group is attached to the rest of the molecule at any substitutable carbon or nitrogen atom. Unless otherwise specified, a bridged bicyclic group is optionally substituted with one or more substituents as set forth for aliphatic groups. Additionally or alternatively, any substitutable nitrogen of a bridged bicyclic group is optionally substituted. Exemplary bridged bicyclics include:





[0016] 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.

[0017] The term "lower haloalkyl" refers to a C_{1-4} straight or branched alkyl group that is substituted with one or more halogen atoms.

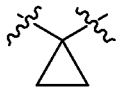
[0018] The term "heteroatom" means one or more of oxygen, sulfur, nitrogen, phosphorus, or silicon (including, any oxidized form of nitrogen, sulfur, phosphorus, or silicon; the quaternized form of any basic nitrogen or; a substitutable nitrogen of a heterocyclic ring, for example N (as in 3,4-dihydro-2*H*-pyrrolyl), NH (as in pyrrolidinyl) or NR^+ (as in N-substituted pyrrolidinyl)).

[0019] The term "unsaturated," as used herein, means that a moiety has one or more units of unsaturation.

[0020] 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.

[0021] 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.

[0022] 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.

[0023] As used herein, the term "cyclopropylenyl" refers to a bivalent cyclopropyl group of the following structure:  .

[0024] The term "halogen" means F, Cl, Br, or I.

[0025] The term "aryl" used alone or as part of a larger moiety as in "aralkyl," "aralkoxy," or "aryloxyalkyl," refers to monocyclic or bicyclic ring systems having a total of five to fourteen ring members, wherein at least one ring in the system is aromatic and wherein each ring in the system contains 3 to 7 ring members. The term "aryl" may be used interchangeably with the term "aryl ring." In certain embodiments of the present invention, "aryl" refers to an aromatic ring system and exemplary groups include 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.

[0026] 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. Exemplary heteroaryl groups include 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. Examplary groups 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

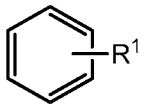
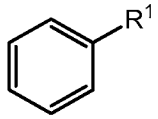
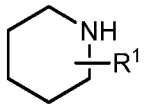
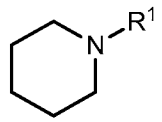
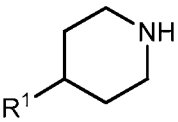
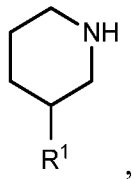
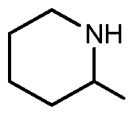
which terms include rings that are optionally substituted. The term "heteroaralkyl" refers to an alkyl group substituted by a heteroaryl, wherein the alkyl and heteroaryl portions independently are optionally substituted.

[0027] 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).

[0028] 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 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.

[0029] 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.

[0030] 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. "Substituted" applies to one or more hydrogens that are either explicit or implicit from the structure (e.g.,  refers to at least  ; and  refers to at least  ,   , or  . 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.

[0031] 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°; $-NO_2$; $-CN$; $-N_3$; $-(CH_2)_{0-4}N(R^\circ)_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)R^\circ$; $-N(R^\circ)C(S)R^\circ$; $-(CH_2)_{0-4}N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)C(S)NR^\circ_2$; $-(CH_2)_{0-4}N(R^\circ)C(O)OR^\circ$; $-N(R^\circ)N(R^\circ)C(O)R^\circ$; $-N(R^\circ)N(R^\circ)C(O)NR^\circ_2$; $-N(R^\circ)N(R^\circ)C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)R^\circ$; $-C(S)R^\circ$; $-(CH_2)_{0-4}C(O)OR^\circ$; $-(CH_2)_{0-4}C(O)SR^\circ$; $-(CH_2)_{0-4}C(O)OSiR^\circ_3$; $-(CH_2)_{0-4}OC(O)R^\circ$; $-OC(O)(CH_2)_{0-4}SR-$, $SC(S)SR^\circ$; $-(CH_2)_{0-4}SC(O)R^\circ$; $-(CH_2)_{0-4}C(O)NR^\circ_2$; $-C(S)NR^\circ_2$; $-C(S)SR^\circ$; $-SC(S)SR^\circ$, $-(CH_2)_{0-4}OC(O)NR^\circ_2$; $-C(O)N(OR^\circ)R^\circ$; $-C(O)C(O)R^\circ$; $-C(O)CH_2C(O)R^\circ$; $-C(NOR^\circ)R^\circ$; $-(CH_2)_{0-4}SSR^\circ$; $-(CH_2)_{0-4}S(O)_2R^\circ$; $-(CH_2)_{0-4}S(O)_2OR^\circ$; $-(CH_2)_{0-4}OS(O)_2R^\circ$; $-S(O)_2NR^\circ_2$; $-(CH_2)_{0-4}S(O)R^\circ$; $-N(R^\circ)S(O)_2NR^\circ_2$; $-N(R^\circ)S(O)_2R^\circ$; $-N(OR^\circ)R^\circ$; $-C(NH)NR^\circ_2$; $-P(O)_2R^\circ$; $-P(O)R^\circ_2$; $-OP(O)R^\circ_2$; $-OP(O)(OR^\circ)_2$; 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.

[0032] 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.

[0033] Suitable divalent substituents on a saturated carbon atom of an "optionally substituted" group include the following: =O ("oxo"), =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.

[0034] Suitable substituents on the aliphatic group of R^* include halogen, $-R^{\bullet}$, $-(haloR^{\bullet})$, -OH, $-OR^{\bullet}$, $-O(haloR^{\bullet})$, $-CN$, $-C(O)OH$, $-C(O)OR^{\bullet}$, $-NH_2$, $-NHR^{\bullet}$, $-NR^{\bullet}_2$, or

$-NO_2$, wherein each $R^\bullet$ is 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.

[0035] 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.

[0036] Suitable substituents on the aliphatic group of $R^\dagger$ are independently halogen, $-R^\bullet$, $-(haloR^\bullet)$, –OH, $-OR^\bullet$, $-O(haloR^\bullet)$, –CN, –C(O)OH, $-C(O)OR^\bullet$, $-NH_2$, $-NHR^\bullet$, $-NR^\bullet_2$, or $-NO_2$, wherein each $R^\bullet$ is 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.

[0037] As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge et al., describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66, 1–19, incorporated herein by reference. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid

or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2–hydroxy–ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2–naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3–phenylpropionate, phosphate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p–toluenesulfonate, undecanoate, valerate salts, and the like.

[0038] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, lower alkyl sulfonate and aryl sulfonate.

[0039] Unless otherwise stated, structures depicted herein are also meant to include all isomeric (e.g., enantiomeric, diastereomeric, and geometric (or conformational)) forms of the structure; for example, the R and S configurations for each asymmetric center, Z and E double bond isomers, and Z and E conformational isomers. Therefore, single stereochemical isomers as well as enantiomeric, diastereomeric, and geometric (or conformational) mixtures of the present compounds are within the scope of the invention. Unless otherwise stated, all tautomeric forms of the compounds of the invention are within the scope of the invention. Additionally, unless otherwise stated, structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures including the replacement of hydrogen by deuterium or tritium, or the replacement of a carbon by a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention. Such compounds are useful, for example, as analytical tools, as probes in biological assays, or as therapeutic agents in accordance with the present invention. In certain embodiments, a warhead moiety, R^1, of a provided compound comprises one or more deuterium atoms.

[0040] 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 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 with) a kinase, and therefore can become dissociated from the a kinase, an irreversible inhibitor will remain substantially bound to a 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. In certain embodiments, an irreversible inhibitor will remain substantially bound to a kinase once covalent bond formation has occurred and will remain bound for a time period that is longer than the life of the protein.

[0041] 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 a kinase, 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.

[0042] 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. In certain instances, a "pro-warhead group" is used in place of a warhead group. Such a pro-warhead group converts to a warhead group *in vivo* or *in vitro*.

[0043] As used herein, the term "inhibitor" is defined as a compound that binds to and /or inhibits a 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, less than about 10 nM, or less than about 1 nM.

[0044] The terms "measurable affinity" and "measurably inhibit," as used herein, means a measurable change in a kinase activity between a sample comprising a compound of the present invention, or composition thereof, and a kinase, and an equivalent sample comprising a kinase, in the absence of said compound, or composition thereof.

[0045] Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintains the integrity of the compound for a sufficient period of time to be useful for the purposes detailed herein (e.g., therapeutic or prophylactic administration to a subject).

[0046] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

3. Description of Exemplary Embodiments:

[0047] As described herein, the present invention provides irreversible inhibitors of one or both of ERK1 and ERK2 kinase. The compounds of the invention comprise a warhead group, designated as R^1, as described herein. 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 one or both of ERK1 and ERK2 kinase. One of ordinary skill in the art will appreciate that one or both of ERK1 and ERK2 kinase, and mutants thereof, have a cysteine residue in the binding domain. Without wishing to be bound by any particular theory, it is believed that proximity of a warhead group to the cysteine of interest facilitates covalent modification of that cysteine by the warhead group.

[0048] The cysteine residues of interest can also be described by an identifying portion of the Target's amino acid sequence which includes the cysteine of interest. Thus, in certain embodiments, Cys183 of ERK1 is characterized in that Cys183 is the cysteine embedded in the amino acid sequence of ERK1. Figure 1 provides SEQ ID NO. 1, which is the amino acid sequence of ERK1. Cys183 is more clearly provided in the abbreviated amino acid sequence below where Cysteine 183 is highlighted in bold with underlining:

SEQ ID NO. 2: NLLINTTCDL KI**C(183)**DFGLARI.

[0049] Cys166 of ERK2 is characterized in that Cys166 is the cysteine embedded in the amino acid sequence of ERK2. Figure 2 provides SEQ ID NO. 3, which is the amino acid sequence of ERK2. Cys166 is more clearly provided in the abbreviated amino acid sequence below where Cysteine 166 is highlighted in bold with underlining:

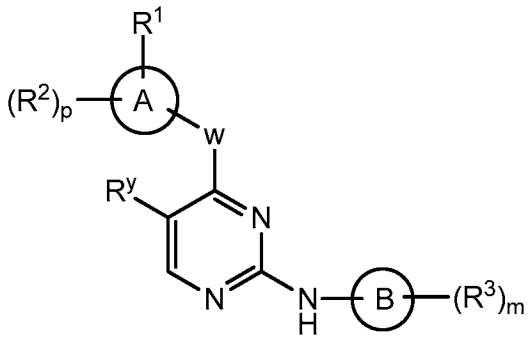
SEQ ID NO. 4: KPSNLLLNTT CDLKI**C(166)**DFGL.

[0050] In some embodiments, compounds of the present invention include a warhead group characterized in that provided compounds covalently modify one or more of Cys 183 of ERK1 or Cys166 of ERK2.

[0051] In certain embodiments, compounds of the present invention include a warhead group characterized in that provided compounds bind to a target of Cys183 of ERK1 or Cys166 of ERK2, thereby irreversibly inhibiting the kinase.

[0052] Thus, in some embodiments, the R^1 warhead group is characterized in that the -L-Y moiety, as defined and described below, is capable of covalently binding to a cysteine residue thereby irreversibly inhibiting the enzyme. In some embodiments, the cysteine residue is Cys183 of ERK1. In some embodiments, the cysteine residue is Cys166 of ERK2. In some embodiments, it is both Cys183 of ERK1 and Cys166 of ERK2. 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 *infra*.

[0053] According to one aspect, the present invention provides a compound of formula **I**,



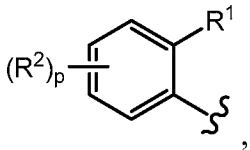
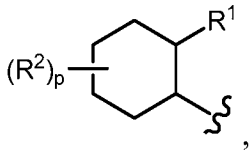
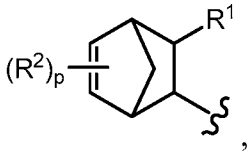
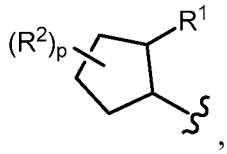
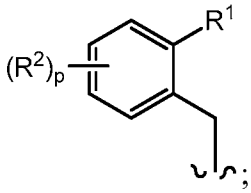
I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered

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

Ring A is selected from

 ,  ,  ,  , and  ;

R^1 is a warhead group, wherein when Ring A is a monocyclic ring, then R^1 is attached to an atom adjacent to where W is attached;

each R^2 is independently hydrogen, an optionally substituted C_{1-6} aliphatic, halogen, or –OR;

Ring B (a) is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic 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 7-12 membered bicyclic saturated, partially unsaturated or aryl ring, a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(b) is absent and $(R^3)_m$ is attached to –NH-;

each R^3 is independently selected from -R, -Cy, halogen, –OR, –SR, –CN, –NO_2, -SO_2NR, -SO_2R, -SOR, -C(O)R, -C(O)OR, -OC(O)R, -OC(O)N($R)_2$, -C(O)N($R)_2$, -C(O)N(R)-OR -C(O)C(O)R, -P(O)($R)_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N($R)_2$, -

$NRSO_2R$, or $-N(R)_2$; or two R^3 groups on the same carbon atom together form –C(O)-, -C(S)-, or -C(N-R)-;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, 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; or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7 membered heterocylic ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 4-7 membered heteroaryl ring having 0-4 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Cy is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^y is hydrogen, optionally substituted C_{1-6} aliphatic, halogen, haloalkyl, -CN, -C(O)R', $-C(O)N(R')_2$, $-C(=N-R'')R'$ or $-N(R')_2$;

each R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

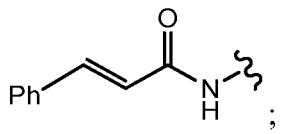
R" is hydrogen or –OR;

W is –O-, -NH-, -S-, $-CH_2-$, or -C(O)-; and

m and p are each independently 0-4;

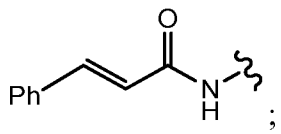
wherein:

(a) when R^y is Cl and Ring B is phenyl para-substituted with morpholine, then R^1 is not

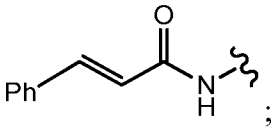


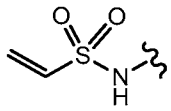
;

(b) when R^y is Cl and Ring B is phenyl di-substituted with methoxy, then R^1 is not

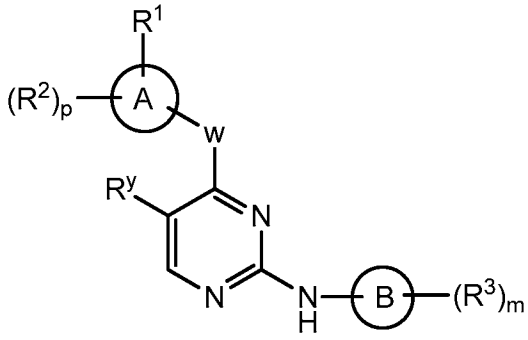


;

(c) when R^y is Cl and Ring B is a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, then R^1 is not  ; or

(d) when R^y is F and Ring B is phenyl tri-substituted with methoxy, then R^1 is not  .

[0054] According to one aspect, the present invention provides a compound of formula **I'**,

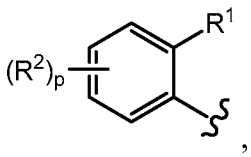
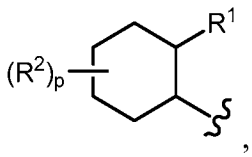
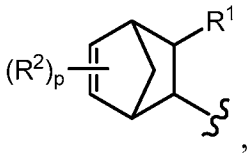
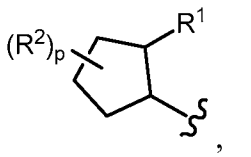
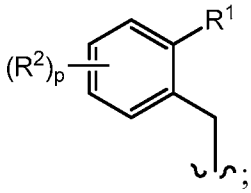


I'

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring which is optionally bridged, an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

Ring A is selected from

 ,  ,  ,  , and  ;

R^1 is a warhead group, wherein when Ring A is a monocyclic ring, then R^1 is attached to an atom adjacent to where W is attached;

each R^2 is independently hydrogen, an optionally substituted C_{1-6} aliphatic, -CN, halogen, -OR, or $-L^1-R^x$;

L^1 is a C_{1-6} saturated straight or branched hydrocarbon chain wherein one or two methylene units of L^1 is optionally and independently repaced by –Hy-, $-N(R^z)-$, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or $-SO_2-$, $-N(R^z)C(O)-$, $-C(O)N(R^z)-$, $-N(R^z)SO_2-$, or $-SO_2N(R^z)-$;

-Hy- is a bivalent saturated 6-membered heterocyclic ring having 1-2 nitrogens;

each R^z is independently hydrogen or C_{1-6} alkyl;

R^x is a 4-8 membered saturated, partially unsaturated, or heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^x is optionally substituted with 1-3 groups selected from C_{1-6} alkyl, $-C(O)R^z$, $-C(O)CH_2OR^z$, $-C(O)OR^z$, $-OC(O)C_{1-6}$ alkyl, $-C(O)N(R^z)_2$, $-OR^z$, $-SR^z$, $-SO_2R^z$, $-N(R^z)_2$, $-N(R^z)C(O)R^z$, $-N(R^z)S(O)_2C_{1-6}$ alkyl, or $-SO_2N(R^z)_2$;

Ring B (a) is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic 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 7-12 membered bicyclic saturated, partially unsaturated or aryl ring, a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(b) is absent and $(R^3)_m$ is attached to –NH-;

each R^3 is independently selected from -R, -Cy, halogen, –OR, –SR, –CN, –NO_2, -SO_2NR, -SO_2R, -SOR, -C(O)R, -C(O)OR, -OC(O)R, -OC(O)N$(R)_2$, -C(O)N$(R)_2$, -C(O)N(R)-OR -C(O)C(O)R, -P(O)$(R)_2$, -NRC(O)OR, -NRC(O)R, -NRC(O)N$(R)_2$, -$NRSO_2R$, or –N$(R)_2$; or two R^3 groups on the same carbon atom together form –C(O)-, -C(S)-, or -C(N-R)-;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, 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; or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7 membered heterocylic ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 4-7 membered heteroaryl ring having 0-4 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Cy is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^y is hydrogen, optionally substituted C_{1-6} aliphatic, halogen, haloalkyl, -CN, -OR, -C(O)R', -C(O)N$(R')_2$, -C(=N-R")R' or -N$(R')_2$;

each R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

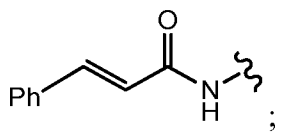
R" is hydrogen or –OR;

W is –O-, -NH-, -S-, -CH_2-, or -C(O)-; and

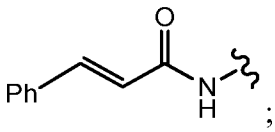
m and p are each independently 0-4;

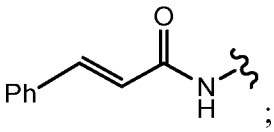
wherein:

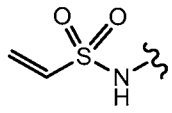
(a) when R^y is Cl and Ring B is phenyl para-substituted with morpholine, then R^1 is not



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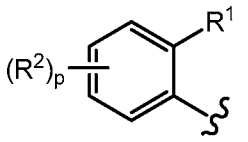
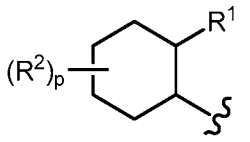
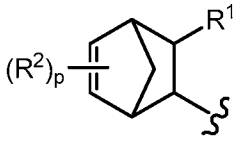
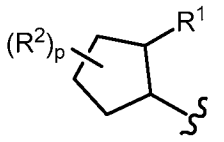
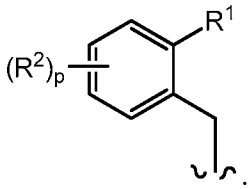
(b) when R^y is Cl and Ring B is phenyl di-substituted with methoxy, then R^1 is not  ;

(c) when R^y is Cl and Ring B is a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, then R^1 is not  ; or

(d) when R^y is F and Ring B is phenyl tri-substituted with methoxy, then R^1 is not  .

[0055] In certain embodiments, Ring A is an optionally substituted group selected from phenyl,a 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

Ring A is selected from

 ,  ,  ,  , and  .

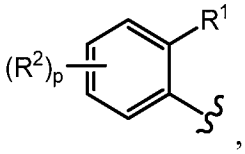
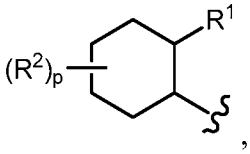
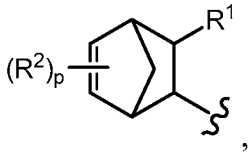
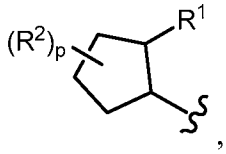
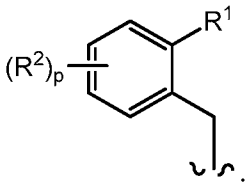
[0056] In certain embodiments, Ring A is phenyl.

[0057] In certain embodiments, Ring A is an optionally substituted 3-8 membered saturated or partially unsaturated carbocyclic ring, an optionally substituted 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-10 membered bicyclic saturated, partially unsaturated or aryl ring which is optionally bridged, an 8-10 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 7-10

membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0058] In some embodiments, Ring A is an optionally substituted group selected from phenyl, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-7 membered monocyclic heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

Ring A is selected from

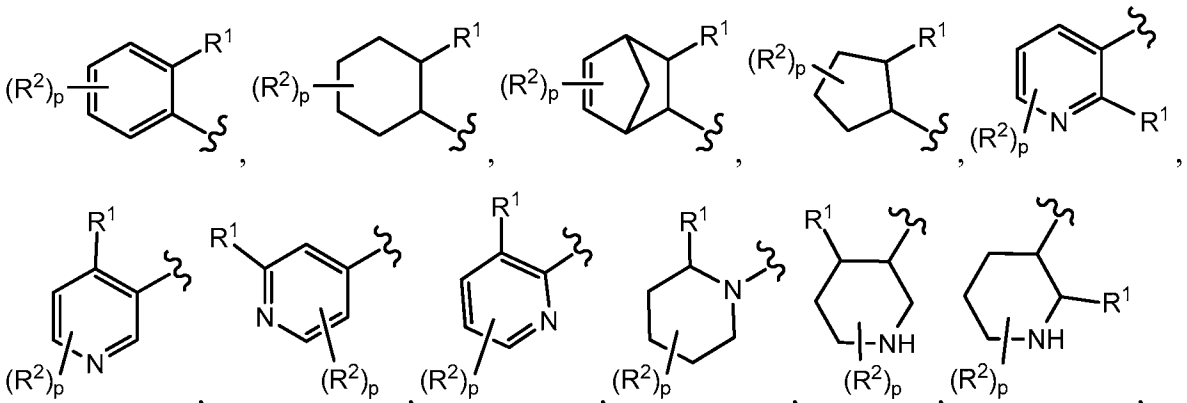
 ,  ,  ,  , and  .

[0059] As defined above, R^1 is a warhead group. In some embodiments, R^1 is attached to an atom adjacent to where W is attached.

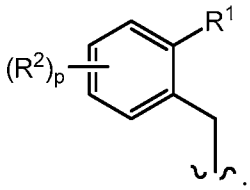
[0060] In various embodiments, Ring A is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctanyl, [4.3.0]bicyclononanyl, [4.4.0]bicyclodecanyl, [2.2.2]bicyclooctanyl, fluorenyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro [2,3-*b*] tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isoindolinyl, isoindolenyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl,

pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, or xanthenyl.

[0061] In certain embodiments, Ring A is

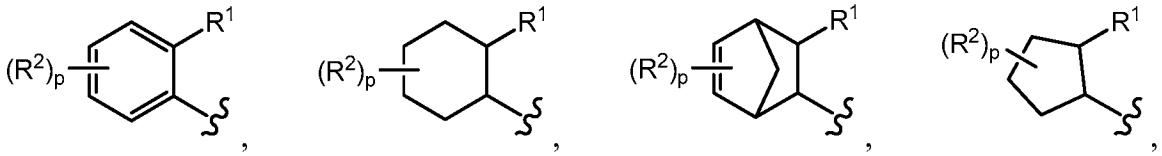


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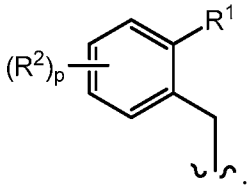


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[0062] In certain embodiments, Ring A is

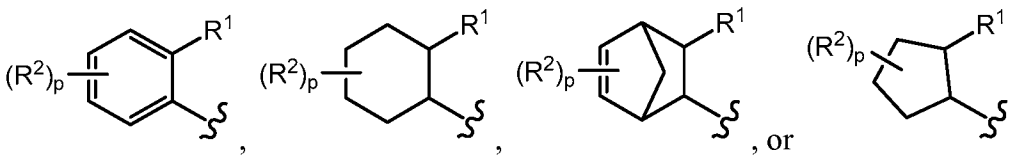


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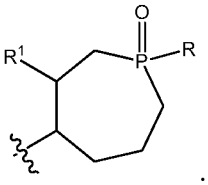


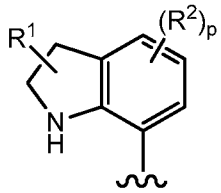
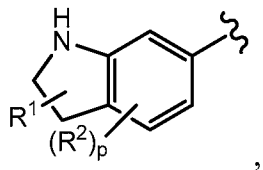
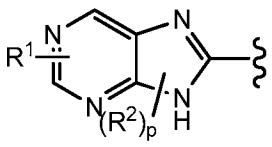
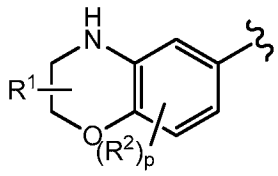
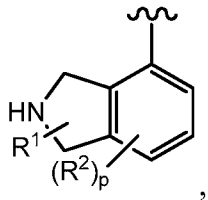
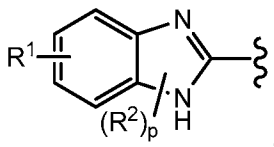
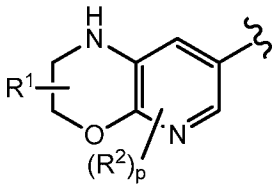
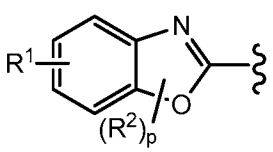
.

[0063] In certain embodiments, Ring A is



.

[0064] In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, sulfur, or –P(O)R-. In some embodiments, Ring A is a 4-7 membered saturated or partially unsaturated heterocylic ring having a –P(O)R- ring moiety. An exemplary Ring A group having a –P(O)R- ring moiety is  .

[0065] In some embodiments, Ring A is  ,  ,  ,  ,  ,  ,  ,  .

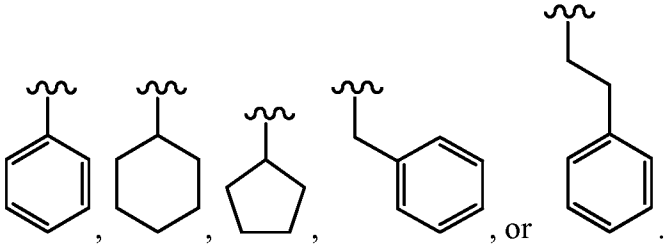
[0066] In certain embodiments, each R^2 is independently hydrogen.

[0067] In certain embodiments, each R^2 is independently an optionally substituted C_{1-6} aliphatic, halogen, or –OR.

[0068] In certain embodiments, each R^2 is independently an optionally substituted methyl, ethyl, propyl, i-propyl, butyl, s-butyl, t-butyl, straight or branched pentyl, or a straight or branched hexyl.

[0069] In certain embodiments, each R^2 is independently F, Cl, Br, or I.

[0070] In certain embodiments, each R^2 is independently –OMe, -OEt, -O-i-Pr, -O-t-Bu,



[0071] In certain embodiments, each R^2 is independently hydrogen, F, Cl, Me, CF_3, or OMe.

[0072] In certain embodiments, Ring B is phenyl.

[0073] As defined above for formula **I'**, in some embodiments, L^1 is a C_{1-6} saturated straight or branched hydrocarbon chain wherein one or two methylene units of L^1 is optionally and independently repaced by –Hy-, $-N(R^Z)-$, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or $-SO_2-$, $-N(R^Z)C(O)-$, $-C(O)N(R^Z)-$, $-N(R^Z)SO_2-$, or $-SO_2N(R^Z)-$; wherein -Hy- is a bivalent saturated 6-membered heterocyclic ring having 1-2 nitrogens; each R^Z is independently hydrogen or C_{1-6} alkyl; and R^X is a 4-8 membered saturated, partially unsaturated, or heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein R^X is optionally substituted with 1-3 groups selected from C_{1-6} alkyl, $-C(O)R^Z$, $-C(O)CH_2OR^Z$, $-C(O)OR^Z$, $-OC(O)C_{1-6}$ alkyl, $-C(O)N(R^Z)_2$, $-OR^Z$, $-SR^Z$, $-SO_2R^Z$, $-N(R^Z)_2$, $-N(R^Z)C(O)R^Z$, $-N(R^Z)S(O)_2C_{1-6}$ alkyl, or $-SO_2N(R^Z)_2$.

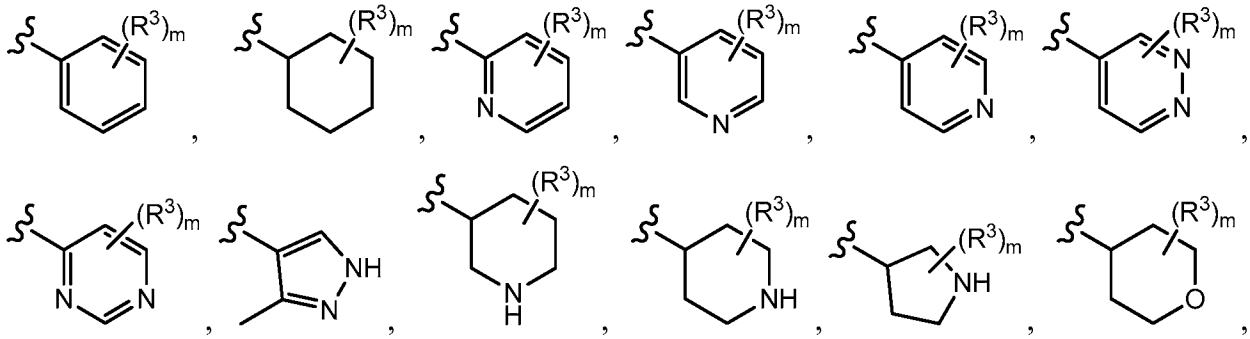
[0074] In some embodiments, R^2 is –CN. In some embodiments, R^2 is $-L^1-R^X$ wherein L^1 is $-CH_2$-piperazin-4-yl-, $-CH_2-$, -C(O)-, or $-O-CH_2C(O)-$.. In some embodiments, R^X is piperazin-4-yl or pyridazinyl. Exemplary R^2 groups are set forth in Table 3, below.

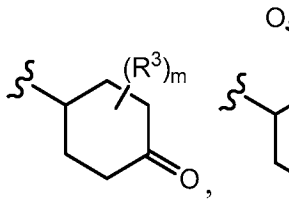
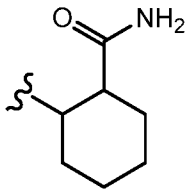
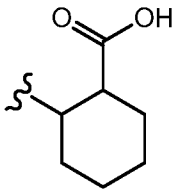
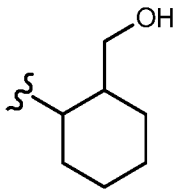
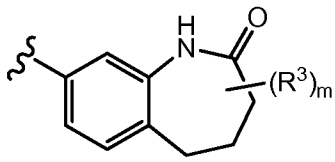
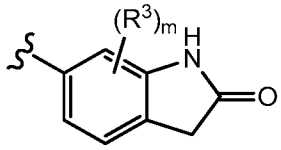
[0075] In certain embodiments, Ring B is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 7-12 membered bicyclic saturated, partially unsaturated or aryl ring, a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0076] In various embodiments, Ring B is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctanyl, [4.3.0]bicyclononanyl,

[4.4.0]bicyclodecanyl, [2.2.2]bicyclooctanyl, fluorenyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H,*6*H*-1,5,2-dithiazinyl, dihydrofuro [2,3-*b*] tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isoindolinyl, isoindolenyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, or xanthenyl.

[0077] In certain embodiments, Ring B is selected from:








, and

.

[0078] In certain embodiments, Ring B is absent and $(R^3)_m$ is attached to –NH.

[0079] As defined above, each R^3 is independently selected from -R, -Cy, halogen, –OR, –SR, –CN, $–NO_2$, $-SO_2NR$, $-SO_2R$, -SOR, -C(O)R, -C(O)OR, -OC(O)R, $-OC(O)N(R)_2$, $-C(O)N(R)_2$, -C(O)N(R)-OR -C(O)C(O)R, $-P(O)(R)_2$, -NRC(O)OR, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$; or two R^3 groups on the same carbon atom together form –C(O)-, -C(S)-, or -C(N-R)-.

[0080] In certain embodiments, each R^3 is independently hydrogen.

[0081] In certain embodiments, each R^3 is independently –R. In other embodiments, one R^3 is –Cy.

[0082] In certain embodiments, each R^3 is independently an optionally substituted C_{1-6} aliphatic.

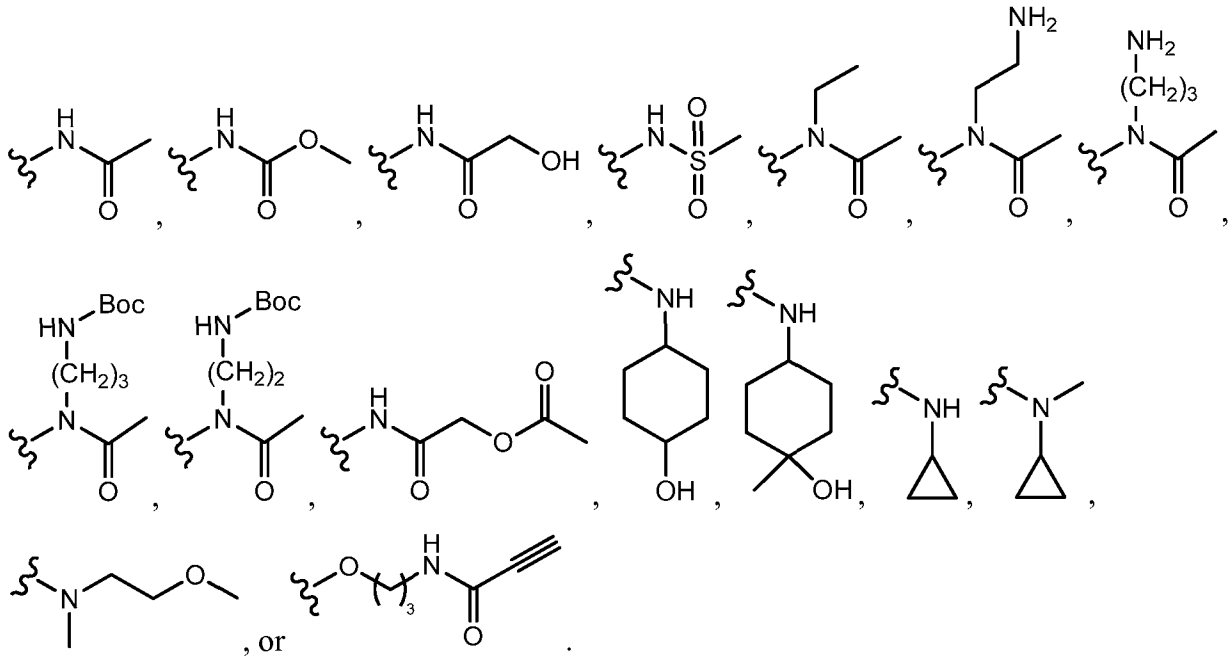
[0083] In certain embodiments, each R^3 is independently an optionally substituted 3-8 membered saturated or partially unsaturated carbocyclic ring, a 4-7 membered heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur.

[0084] In certain embodiments, each R^3 is independently halogen, –OR, –SR, –CN, $–NO_2$, $-SO_2R$, -SOR, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$.

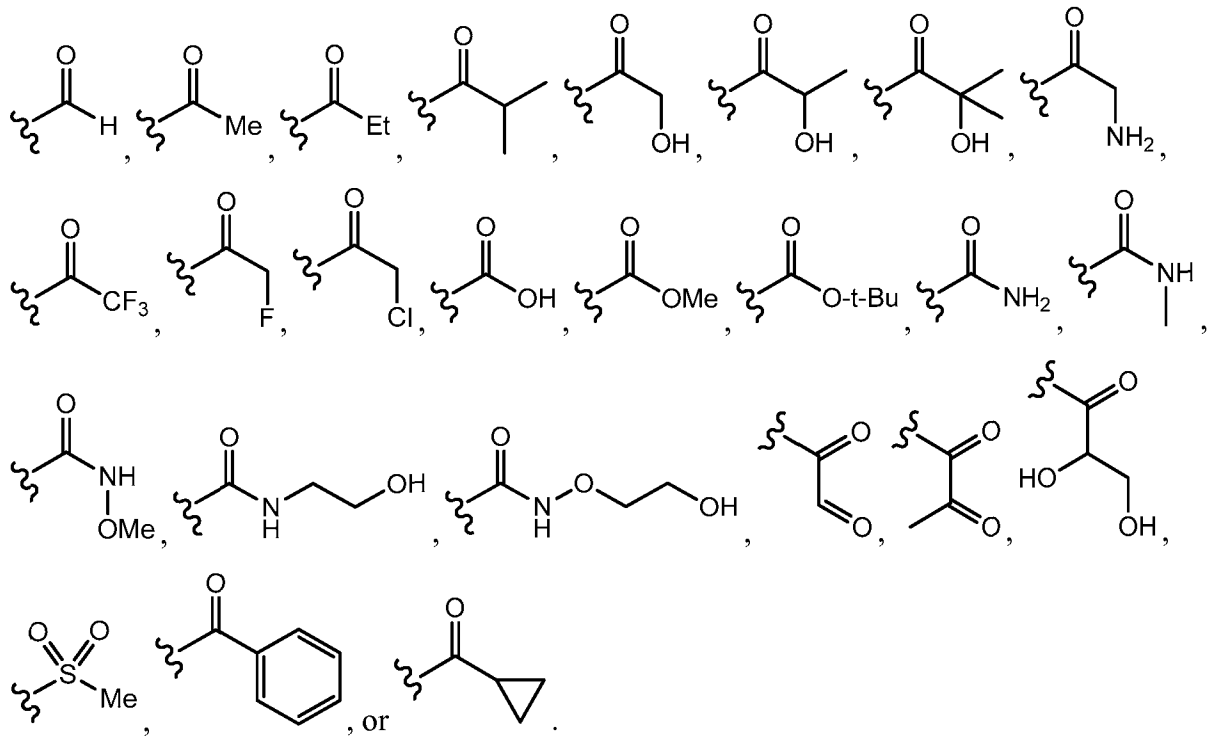
[0085] In certain embodiments, each R^3 is independently halogen, –OR, –CN, $-SO_2R$, -C(O)R, $-CO_2R$, $-C(O)N(R)_2$, -NRC(O)R, $-NRC(O)N(R)_2$, $-NRSO_2R$, or $–N(R)_2$.

[0086] In certain embodiments, each R^3 is independently -Me, -Et, -t-Bu, $-CH_2OH$, , $-CF_3$, $-(CH_2)_3NHBoc$, $-(CH_2)_3NH_2$, -CN, –F, -Cl, -Br, –OH, -OMe, -OEt, $-OCH_2CH_2OMe$, $-NHCH_2CH_2OMe$, $-OCH_2F$, $-OCHF_2$, $-OCF_3$, $-OCH_2CCH$, -NH(Me), or $-P(O)(Me)_2$.

[0087] In certain embodiments, each R^3 is independently



[0088] In certain embodiments, each R^3 is independently

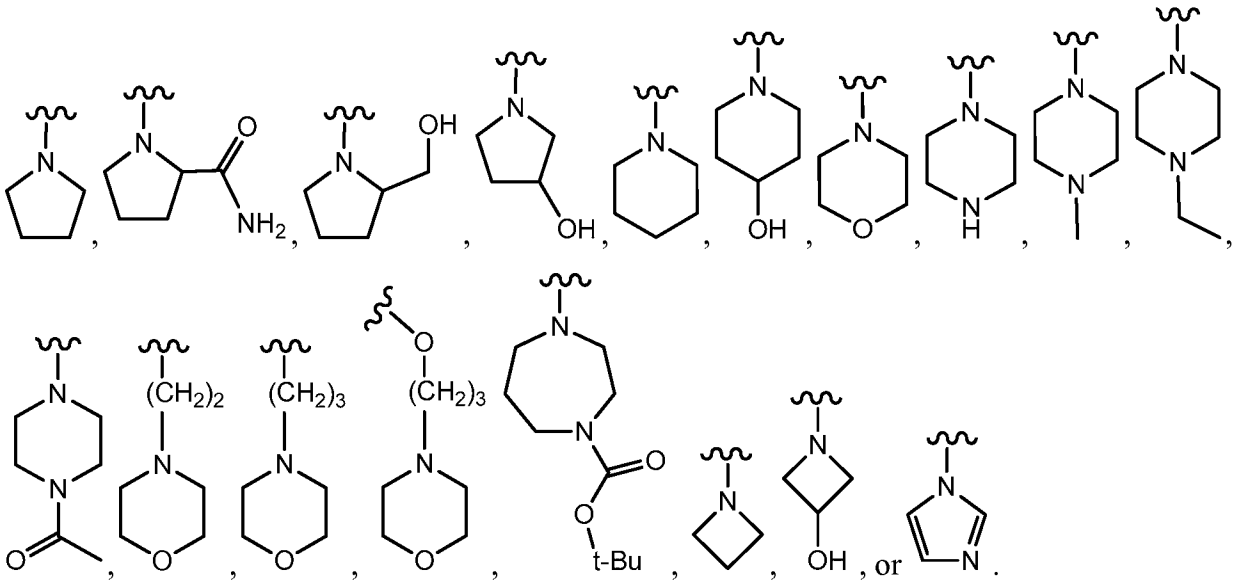


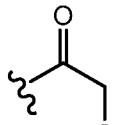
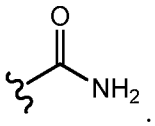
[0089] In certain embodiments, each R^3 is independently an optionally substituted ring selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctanyl, [4.3.0]bicyclononanyl, [4.4.0]bicyclodecanyl, [2.2.2]bicyclooctanyl, fluorenyl, phenyl, naphthyl, indanyl, tetrahydronaphthyl, acridinyl,

azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro [2,3-*b*] tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isoindolinyl, isoindolenyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl;- 1,2,5oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, or xanthenyl.

[0090] In certain embodiments, each R^3 is independently an optionally substituted ring selected from piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, or azetidinyl In some embodiments, R^3 is optionally substituted morpholinyl or thiomorpholinyl. In certain embodiments, the ring is substituted with Me, Et, OH, $C(O)NH_2$, or C(O)Me. In certain embodiments, the ring is substituted with C(O)Me.

[0091] In certain embodiments, each R^3 is independently



In certain embodiments, each R^3 is independently -Me, -OMe, $-NHCH_2CH_2OMe$,  , or  .

[0092] In some embodiments, each R^3 is independently selected from those depicted in Table 3, below.

[0093] In certain embodiments, R^y is hydrogen, optionally substituted C_{1-6} aliphatic, halogen, -Cl, $-CF_3$, -CN, -C(O)R', $-C(O)N(R')_2$, $-C(=N-R'')R'$ or $-N(R')_2$; wherein each R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic; and R" is hydrogen or –OR. In certain embodiments, each R' is independently hydrogen, Me, or Et.

[0094] In certain embodiments, R^y is hydrogen.

[0095] In certain embodiments, R^y is –Me, -Cl, -F, $-CF_3$, -CN, -C(O)Me, $-C(O)NH_2$, -C(O)NH(Me), -C(O)NH(Et), -C(=N-OH)Me, -C(=N-OMe)Me, or $-NH_2$.

[0096] In some embodiments, R^y is haloaliphatic. In certain embodiments, R^y is $–CF_3$.

[0097] In certain embodiments, R^y is halogen. In certain embodiments, R^y is –Cl.

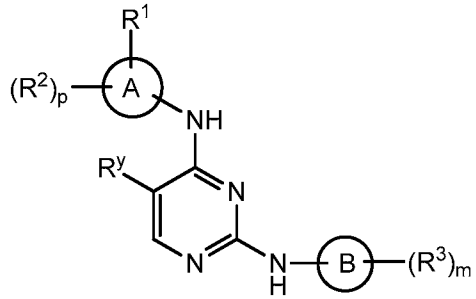
[0098] In some embodiments, R^y is selected from those depicted in Table 3, below.

[0099] In certain embodiments, W is NH. In certain embodiments, W is O.

[00100] In certain embodiments, R' is independently hydrogen, Me, or Et.

[00101] In various embodiments, the invention provides a compound of formula **I**, wherein each of Ring A, Ring B, R^1, R^2, R^3, R^y, W, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

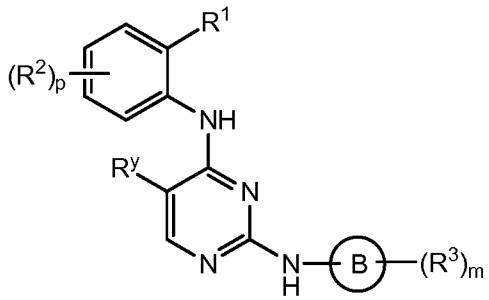
[00102] In various embodiments, the invention provides a compound of formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

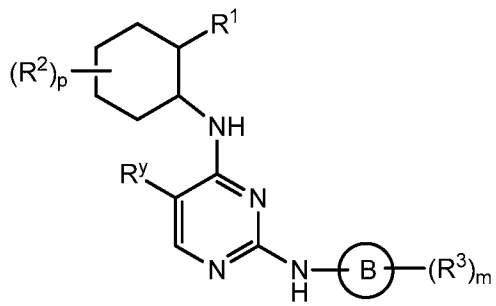
[00103] In various embodiments, the invention provides a compound of formula **I-b**:



I-b

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

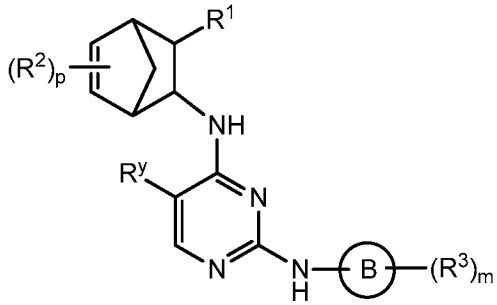
[00104] In various embodiments, the invention provides a compound of formula **I-c**:



I-c

or a pharmaceutically acceptable salt thereof, wherein each of R^y,Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

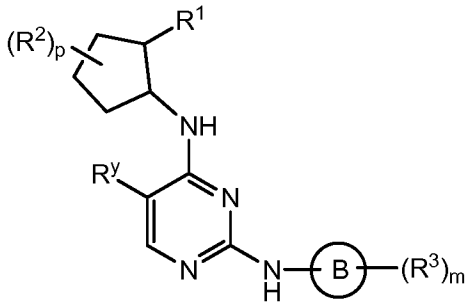
[00105] In various embodiments, the invention provides a compound of formula **I-d**:



I-d

or a pharmaceutically acceptable salt thereof, wherein each of R^y,Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

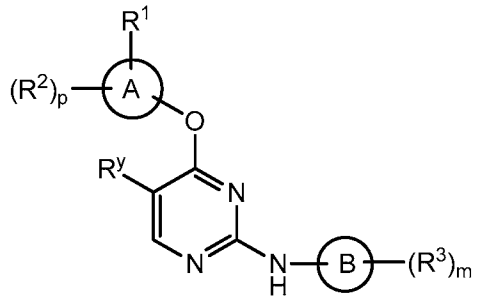
[00106] In various embodiments, the invention provides a compound of formula **I-e**:



I-e

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

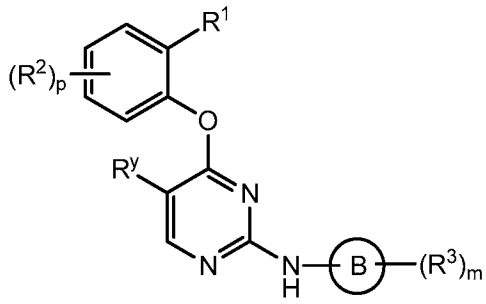
[00107] In various embodiments, the invention provides a compound of formula **I-f**:



I-f

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

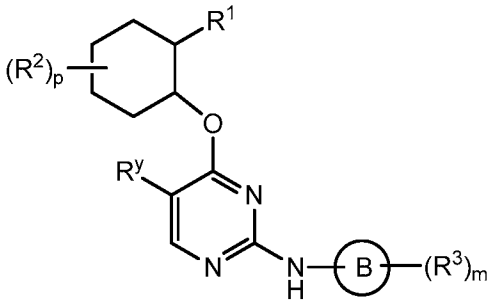
[00108] In various embodiments, the invention provides a compound of formula **I-g**:



I-g

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

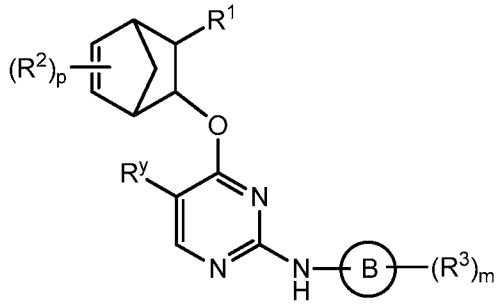
[00109] In various embodiments, the invention provides a compound of formula **I-h**:



I-h

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

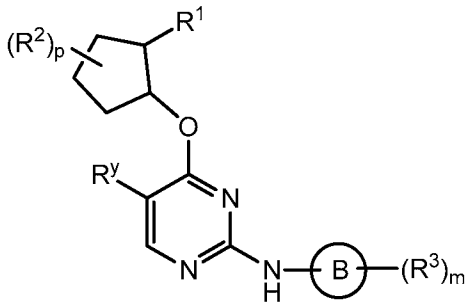
[00110] In various embodiments, the invention provides a compound of formula **I-j**:



I-j

or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00111] In various embodiments, the invention provides a compound of formula **I-k**:



I-k

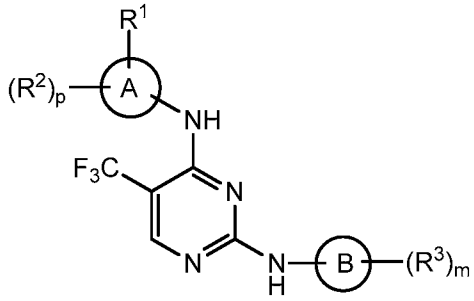
or a pharmaceutically acceptable salt thereof, wherein each of R^y, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00112] In various embodiments, the invention provides a compound selected from formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, and **I-k**, wherein R^y is haloaliphatic. In various embodiments, the invention provides a compound selected from formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, and **I-k**, wherein R^y is $-CF_3$. In various embodiments, the invention provides a compound of formula **I'**, wherein R^y is haloaliphatic. In various embodiments, the invention provides a compound of formula **I'**, wherein R^y is $-CF_3$.

[00113] In various embodiments, the invention provides a compound selected from formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, and **I-k**, wherein R^y is halogen. In various embodiments, the invention provides a compound selected from formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, and

I-k, wherein R^y is –Cl. In various embodiments, the invention provides a compound of formula **I'**, wherein R^y is halogen. In various embodiments, the invention provides a compound of formula **I'**, wherein R^y is –Cl.

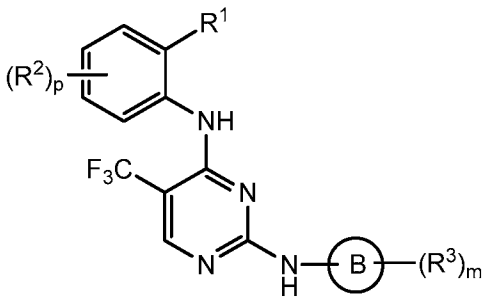
[00114] In various embodiments, the invention provides a compound of formula **II**:



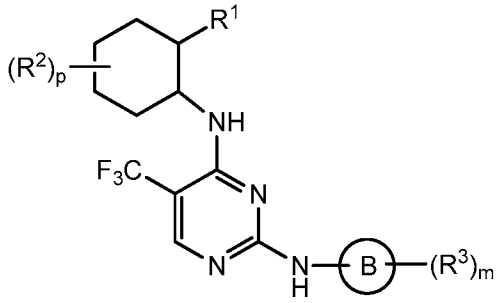
II

or a pharmaceutically acceptable salt thereof, wherein each of Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

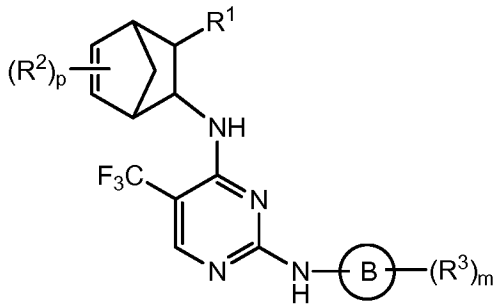
[00115] In various embodiments, the invention provides a compound of any of formula **II-a**, **II-b**, **II-c**, or **II-d:**



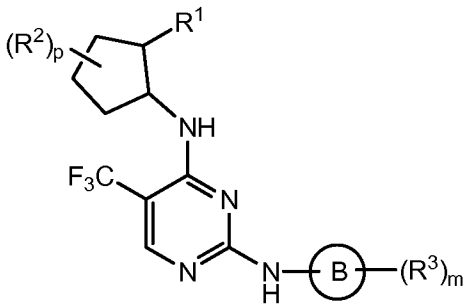
II-a



II-b



II-c

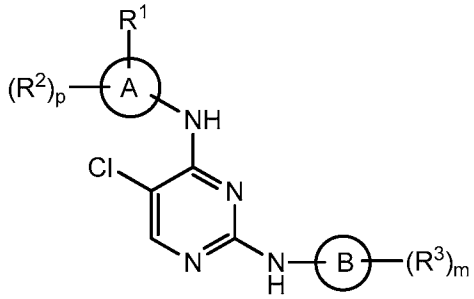


II-d

or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00116] According to another embodiment, the present invention provides a compound of formula **III**:

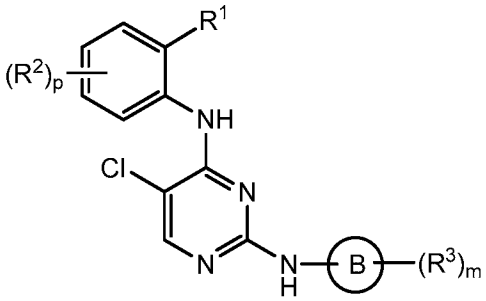


III

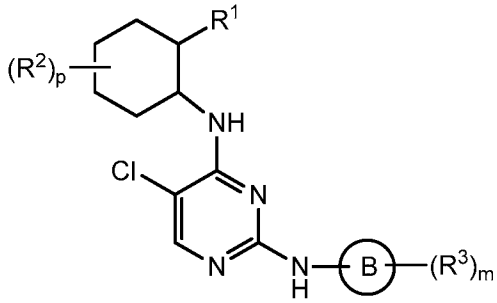
or a pharmaceutically acceptable salt thereof,

wherein, each of Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

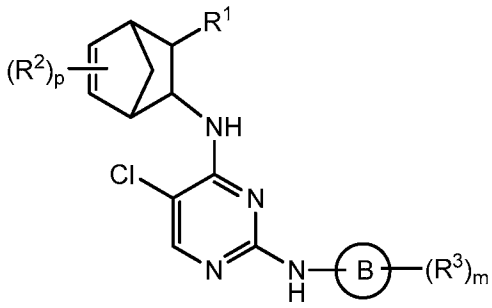
[00117] According to another embodiment, the present invention provides a compound of any of formula **III-a**, **III-b**, **III-c**, or **III-d**:



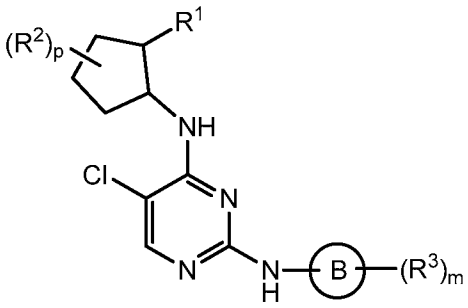
III-a



III-b



III-c

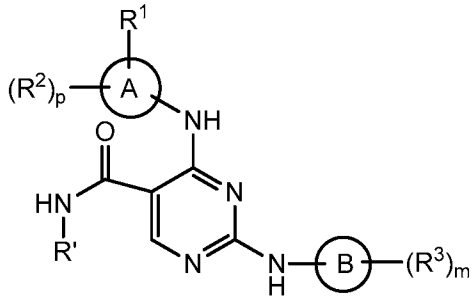


III-d

or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00118] According to another embodiment, the present invention provides a compound of formula **IV**:

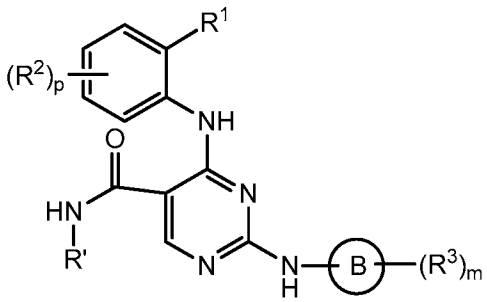


IV

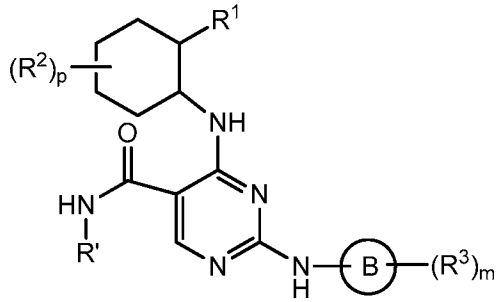
or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, R', m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

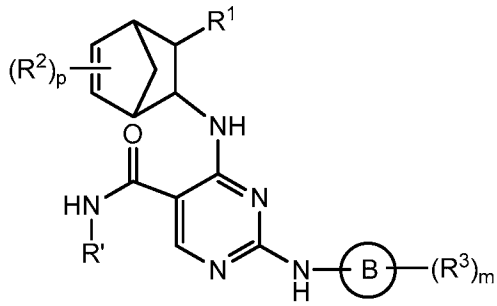
[00119] According to another embodiment, the present invention provides a compound of any of formula **IV-a**, **IV-b**, **IV-c**, or **IV-d**:



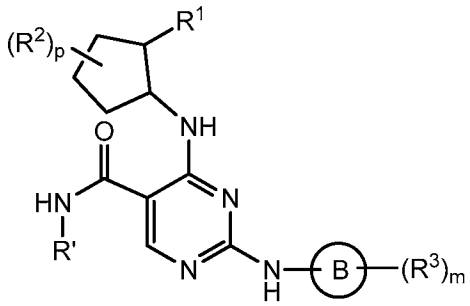
IV-a



IV-b



IV-c

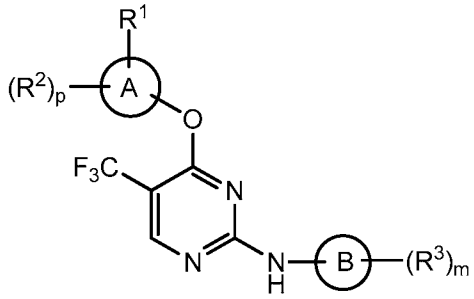


IV-d

or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, R', m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00120] According to another embodiment, the present invention provides a compound of formula **V**:

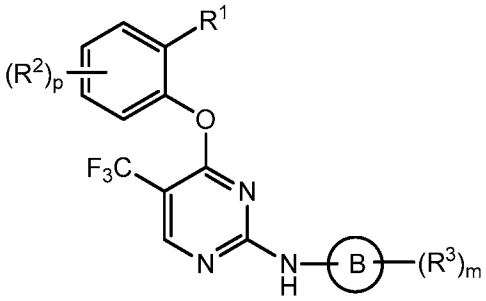


V

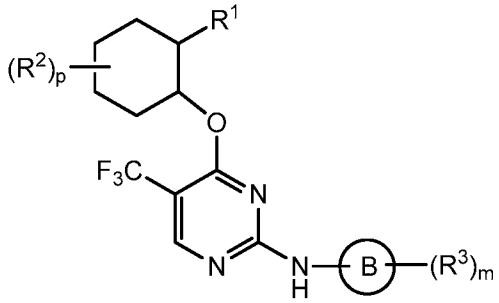
or a pharmaceutically acceptable salt thereof,

wherein each of Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

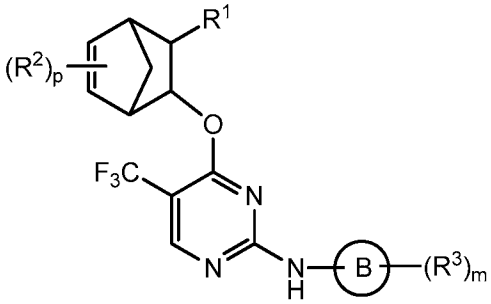
[00121] According to another embodiment, the present invention provides a compound of any of formula **V-a**, **V-b**, **V-c**, or **V-d**:



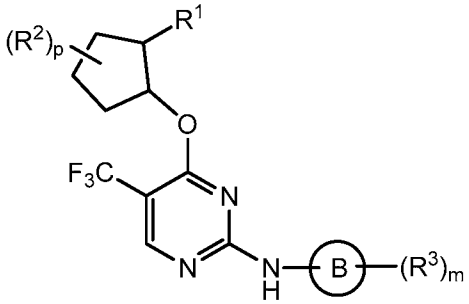
V-a



V-b



V-c

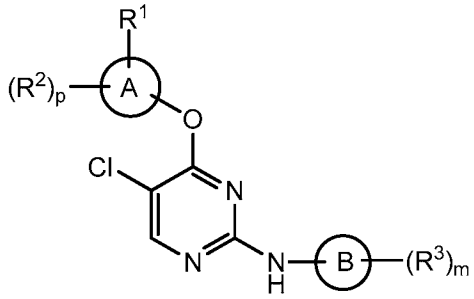


V-d

or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00122] According to another embodiment, the present invention provides a compound of formula **VI**:

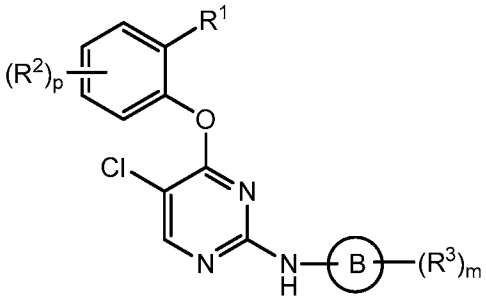


VI

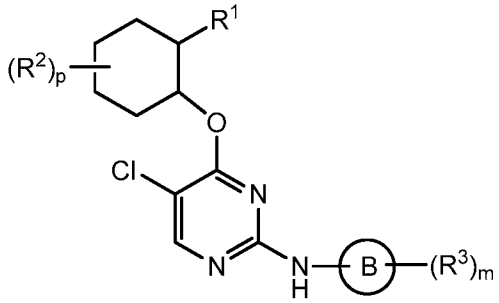
or a pharmaceutically acceptable salt thereof,

wherein each of Ring A, Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

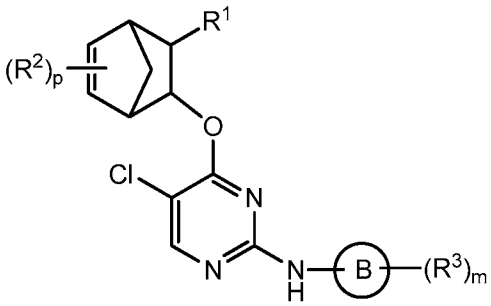
[00123] According to another embodiment, the present invention provides a compound of any of formula **VI-a**, **VI-b**, **VI-c**, or **VI-d**:



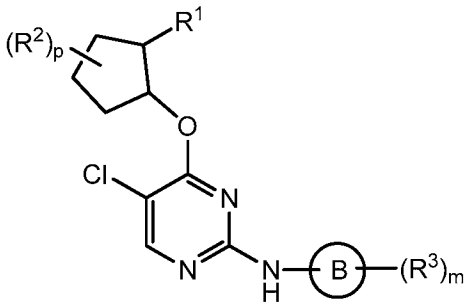
VI-a



VI-b



VI-c

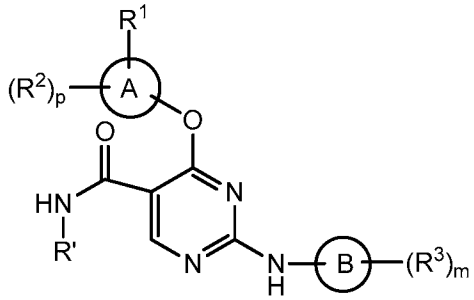


VI-d

or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00124] According to another embodiment, the present invention provides a compound of formula **VII**:

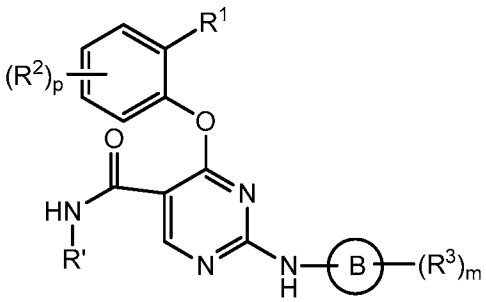


VII

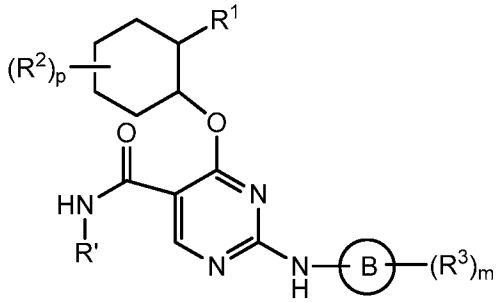
or a pharmaceutically acceptable salt thereof,

wherein each of Ring A, Ring B, R^1, R^2, R^3, R', m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

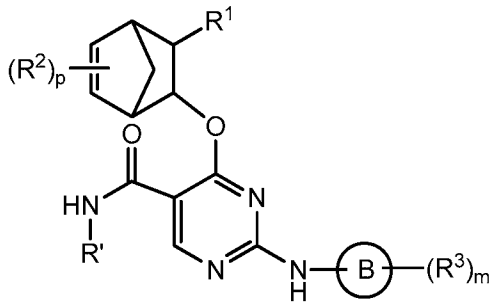
[00125] According to another embodiment, the present invention provides a compound of any of formula **VII-a**, **VII-b**, **VII-c**, or **VII-d**:



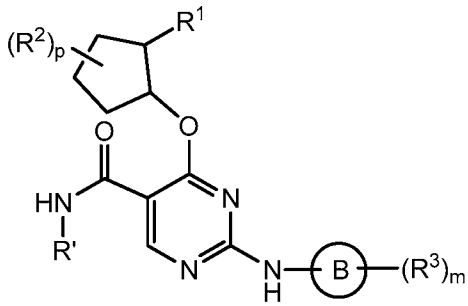
VII-a



VII-b



VII-c



VII-d

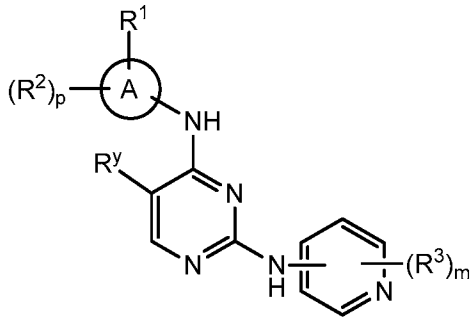
or a pharmaceutically acceptable salt thereof,

wherein each of Ring B, R^1, R^2, R^3, R', m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00126] In certain embodiments, the present invention provides a compound of any of formula **I**, **II, III**, **IV**, **V**, **VI**, or **VII** wherein Ring B is phenyl. In other embodiments, the present invention provides a compound of any of formula **I**, **II, III**, **IV**, **V**, **VI**, or **VII** wherein Ring B is pyridyl. In other embodiments, the present invention provides a compound of any of formula **I**, **II, III**, **IV**, **V**, **VI**, or **VII** wherein Ring B is piperdinyl. In other embodiments, the present invention provides a compound of any of formula **I**, **II, III**, **IV**, **V**, **VI**, or **VII** wherein Ring B is cyclohexyl.

[00127] In certain embodiments, the present invention provides a compound of formula **I'** wherein Ring B is phenyl. In other embodiments, the present invention provides a compound of formula **I'** wherein Ring B is pyridyl. In other embodiments, the present invention provides a compound of formula **I'** wherein Ring B is piperdinyl. In other embodiments, the present invention provides a compound of formula **I'** wherein Ring B is cyclohexyl.

[00128] In some embodiments, the present invention provides a compound of formula **VIII**:



VIII

or a pharmaceutically acceptable salt thereof,

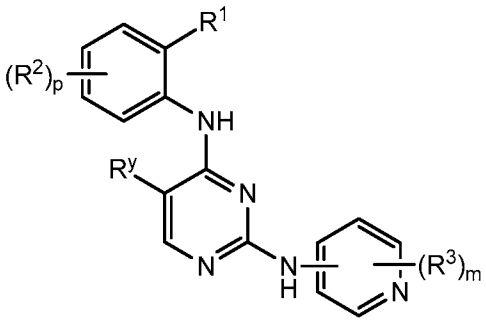
wherein each of Ring A, R^1, R^2, R^3, R^y, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00129] In some embodiments, the present invention provides a compound of formula **VIII** wherein R^y is haloaliphatic. In certain embodiments, the present invention provides a compound of formula **VIII** wherein R^y is $-CF_3$.

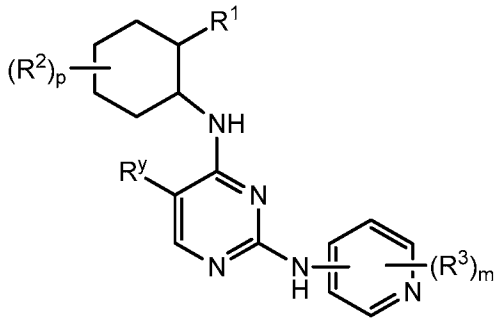
[00130] In some embodiments, the present invention provides a compound of formula **VIII** wherein R^y is halogen. In certain embodiments, the present invention provides a compound of formula **VIII** wherein R^y is –Cl.

[00131] In certain embodiments, the present invention provides a compound of formula **VIII** wherein at least one R^3 is –OMe.

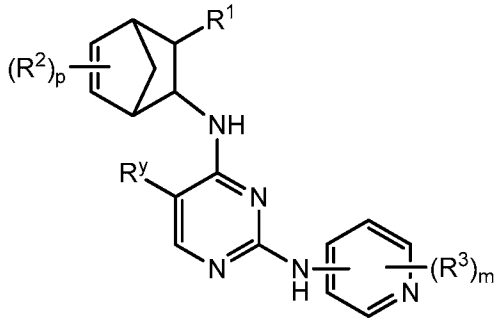
[00132] In some embodiments, the present invention provides a compound of any of formula **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d**:



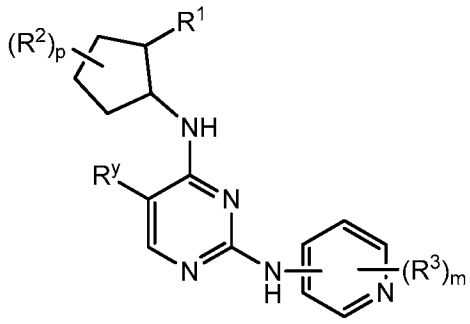
VIII-a



VIII-b



VIII-c



VIII-d

or a pharmaceutically acceptable salt thereof,

wherein each of R^1, R^2, R^3, R^y, m and p is as defined above and described in embodiments, classes and subclasses above and herein, singly or in combination.

[00133] In some embodiments, the present invention provides a compound of any of formula **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d** wherein R^y is haloaliphatic. In certain embodiments, the present invention provides a compound of formula **VIII** wherein R^y is $-CF_3$.

[00134] In some embodiments, the present invention provides a compound of any of formula **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d** wherein R^y is halogen. In certain embodiments, the present invention provides a compound of formula **VIII** wherein R^y is –Cl.

[00135] In certain embodiments, the present invention provides a compound of any of formula **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d** wherein at least one R^3 is –OMe.

[00136] As defined generally above, the R^1 group of any of formula **I, I', II, III**, **IV**, **V**, **VI**, **VII**, or **VIII** is a warhead group. In certain embodiments, 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, 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.

[00137] In certain embodiments, L is a covalent bond.

[00138] 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-.

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-.

[00139] In certain embodiments, L is a bivalent C_{1-8} hydrocarbon chain wherein at least one methylene unit of L is replaced by -C(O)-. In certain embodiments, L is a bivalent C_{1-8} hydrocarbon chain wherein at least two methylene units of L are replaced by -C(O)-. In some embodiments, L is –C(O)CH_2CH_2C(O)-, -C(O)CH_2NHC(O)-, -C(O)CH_2NHC(O)CH_2CH_2C(O)-, or –C(O)$CH_2CH_2CH_2$NHC(O)CH_2CH_2C(O)-.

[00140] In certain embodiments, L is a bivalent C_{1-8} hydrocarbon chain wherein at least one methylene unit of L is replaced by -$S(O)_2$-. In certain embodiments, L is a bivalent C_{1-8} hydrocarbon chain wherein at least one methylene unit of L is replaced by -$S(O)_2$- and at least one methylene unit of L is replaced by -C(O)-. In certain embodiments, L is a bivalent C_{1-8} hydrocarbon chain wherein at least one methylene unit of L is replaced by -$S(O)_2$- and at least

two methylene units of L are replaced by -C(O)-. In some embodiments, L is –$S(O)_2CH_2CH_2NHC(O)CH_2CH_2C(O)$- or –$S(O)_2CH_2CH_2NHC(O)$-.

[00141] 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)-.

[00142] 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)-.

[00143] 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)-.

[00144] 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 -$NHC(O)C(=CH_2)CH_2$-.

[00145] 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 –$CH(CH_3)OC(O)CH=CH$-.

[00146] 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)-.

[00147] 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 –CH2OC(O)CH=CHCH2–, -CH2-OC(O)CH=CH–, or -CH(CH=CH2)OC(O)CH=CH–.

[00148] In certain embodiments, L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH2N(CH3)-, -NRC(O)CH=CHCH2O-, -CH2NRC(O)CH=CH-, -NRSO2CH=CH-, -NRSO2CH=CHCH2-, -NRC(O)(C=N_2)C(O)-, -NRC(O)CH=CHCH_2N(CH_3)-, -NRC(O)CH=CHCH_2O-, -NRC(O)C(=CH_2)CH_2-, -CH_2NRC(O)-, -CH_2CH_2NRC(O)-, or -CH_2NRC(O)cyclopropylene-, wherein each R is independently hydrogen or optionally substituted C_{1-6} aliphatic.

[00149] In certain embodiments, L is -NHC(O)CH=CH-, -NHC(O)CH=CHCH_2N(CH_3)-, -NHC(O)CH=CHCH_2O-, -CH_2NHC(O)CH=CH-, -NHSO$_2$CH=CH-, -NHSO$_2$CH=CHCH_2-, -NHC(O)(C=N_2)C(O)-, -NHC(O)C(=CH_2)CH_2-, -CH_2NHC(O)-, -CH_2CH_2NHC(O)-, or -CH_2NHC(O)cyclopropylene-.

[00150] 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-.

[00151] Exemplary L groups include -C≡C-, -C≡CCH_2N(isopropyl)-, -NHC(O)C≡CCH_2CH_2-, -CH_2-C≡C-CH_2-, -C≡CCH_2O-, -CH_2C(O)C≡C-, -C(O)C≡C-, or -CH_2OC(=O)C≡C-.

[00152] In some embodiments, L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein 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)-.

[00153] 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_2N(R)-. Exemplary L groups include -NHC(O)-cyclopropylene-SO_2- and -NHC(O)-cyclopropylene-.

[00154] 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.

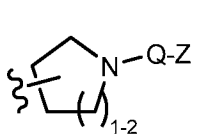
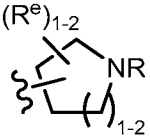
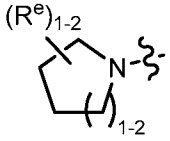
[00155] In certain embodiments, Y is hydrogen.

[00156] 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. In certain embodiments, Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

[00157] 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.

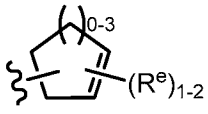
[00158] In certain embodiments, Y is a saturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein Y is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein.

[00159] 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.

[00160] 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  ,  , or  , wherein each R, Q, Z, and R^e is as defined above and described herein. In certain embodiments, Y is piperazine.

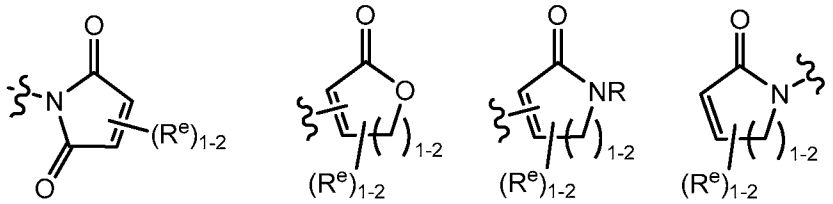
[00161] In some embodiments, Y is a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, wherein each ring is substituted 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. In certain embodiments, Y is cyclopropyl substituted with halogen, CN or NO_2.

[00162] 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.

[00163] 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.

[00164] 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

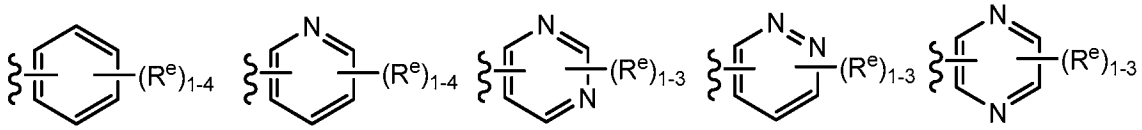
ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein. In certain embodiments, Y is selected from:



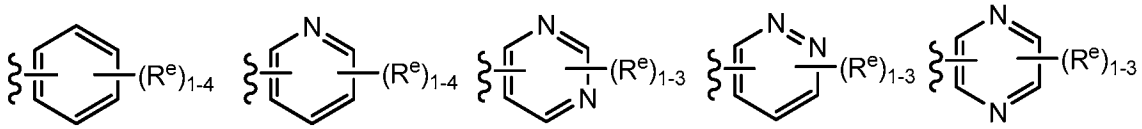
wherein each R and R^e is as defined above and described herein.

[00165] 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. 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 –Q-Z wherein 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 some embodiments, -Q-Z is -NHC(O)CH=CH_2 or -C(O)CH=CH_2. In certain embodiments, each R^e is independently selected from from -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, or -C(O)CH_2CN.

[00166] In some embodiments, Y is selected from:



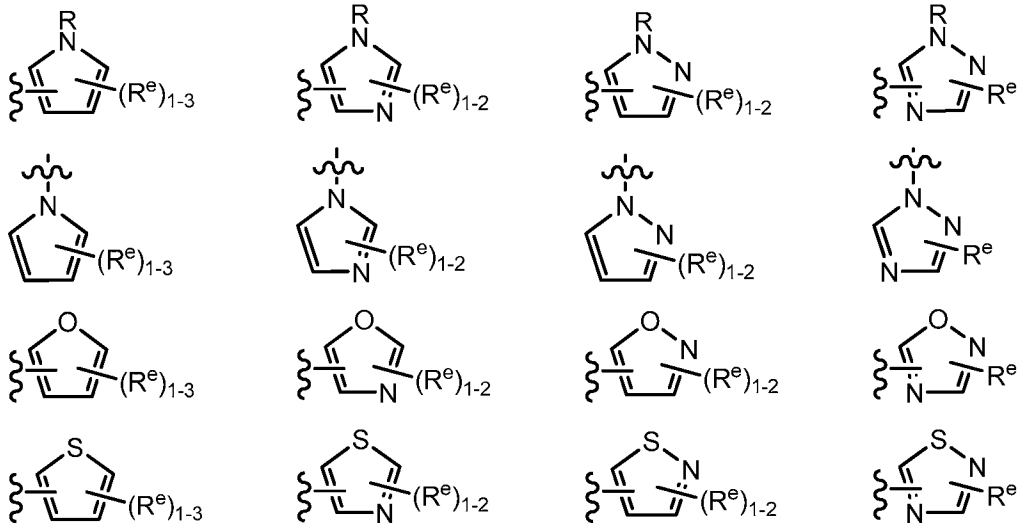
wherein each R^e is as defined above and described herein. In some embodiments, Y is selected from:



wherein each R^e is –Q-Z wherein 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 some embodiments, -Q-Z is -NHC(O)CH=CH_2 or -C(O)CH=CH_2. In certain embodiments, each

R^e is independently selected from from $-NHC(O)CH=CH_2$, $-C(O)CH=CH_2$, $-CH_2CH=CH_2$, $-C\equiv CH$, $-C(O)OCH_2Cl$, $-C(O)OCH_2F$, $-C(O)OCH_2CN$, $-C(O)CH_2Cl$, $-C(O)CH_2F$, or $-C(O)CH_2CN$.

[00167] 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.

[00168] 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.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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, acyloxy, 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).

[00174] 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:

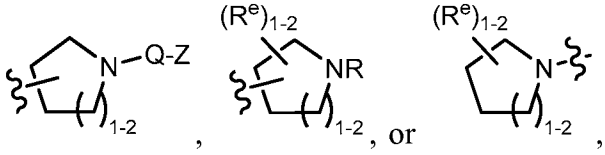
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

(*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

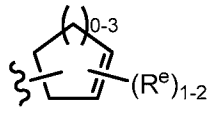
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

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

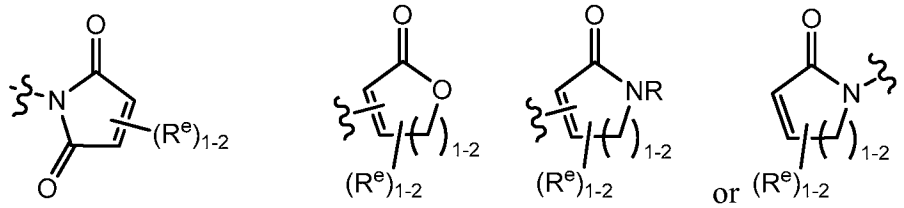
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*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

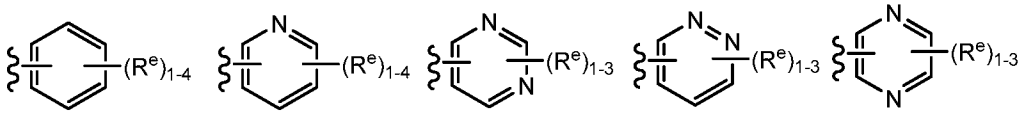
(*x*)  , wherein each R^e is as defined above and described herein; or

(*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*) 

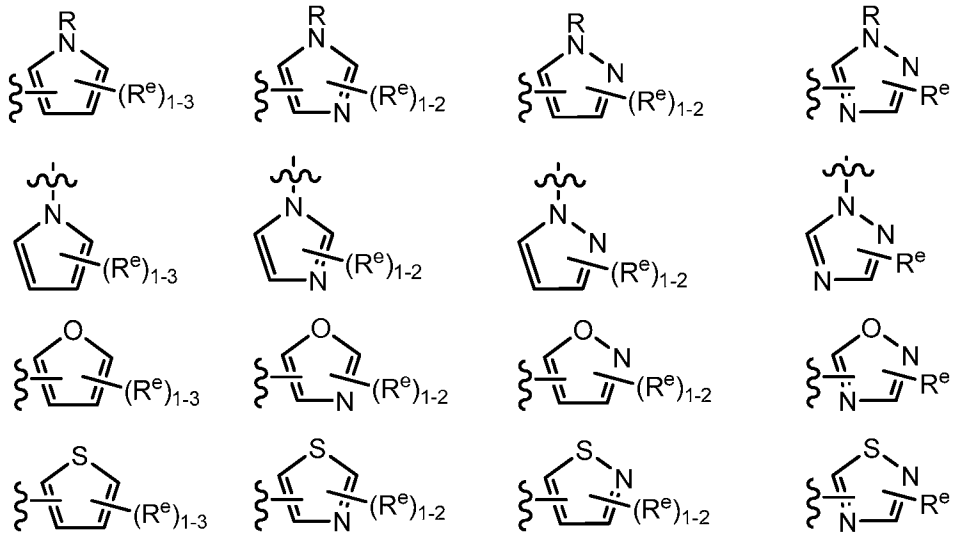
wherein each R and R^e is as defined above and described herein; or

(*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:

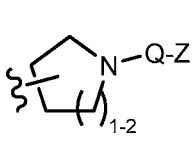
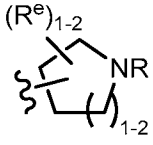
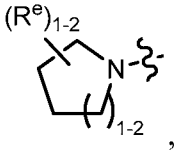
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*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

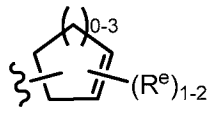
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

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

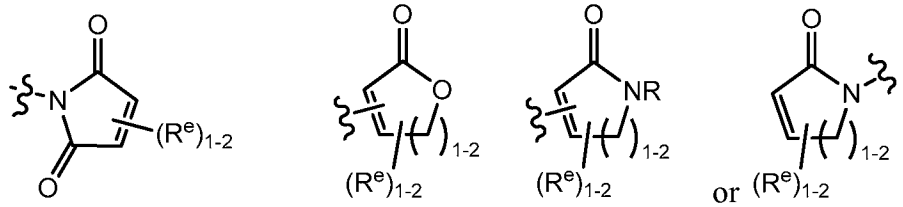
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*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

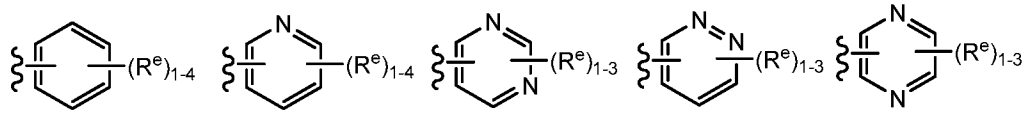
(*x*)  , wherein each R^e is as defined above and described herein; or

(*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*) 

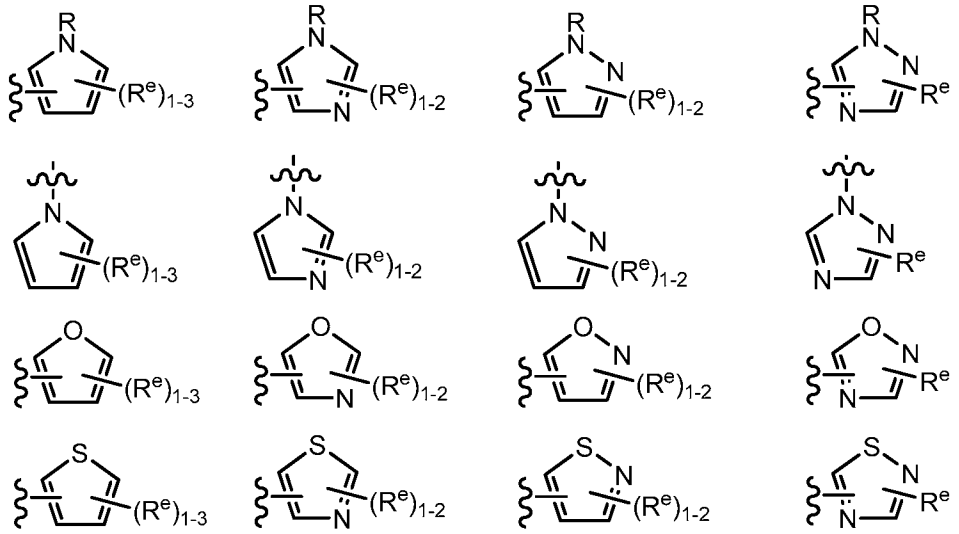
wherein each R and R^e is as defined above and described herein; or

(*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;

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

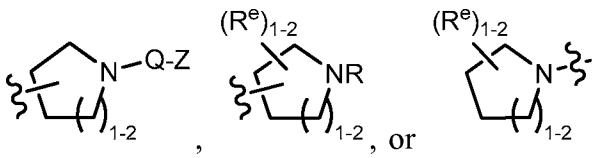
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

(*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

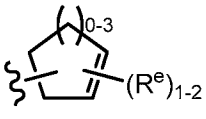
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

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

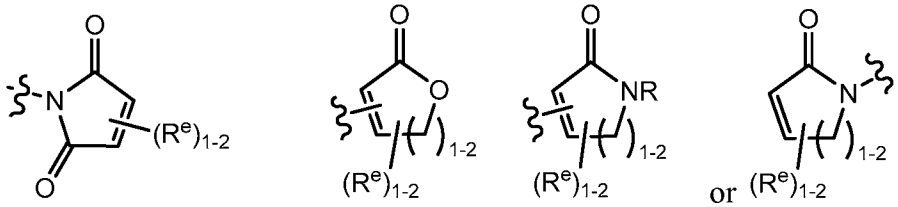
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*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

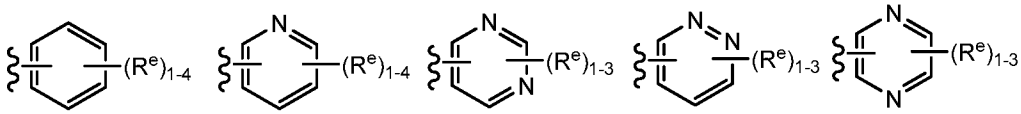
(*x*)  , wherein each R^e is as defined above and described herein; or

(*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*) 

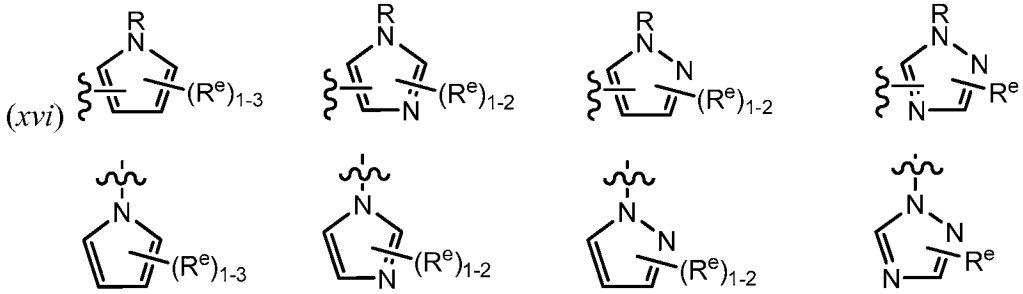
wherein each R and R^e is as defined above and described herein; or

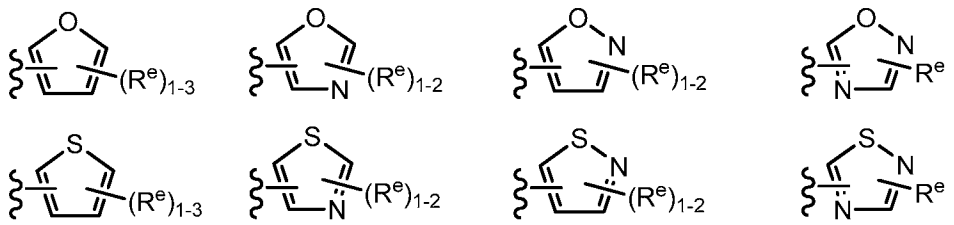
(*xiii*) a 6-membered aromatic ring having 0-2 nitrogens wherein said ring is substituted with 1-4 R^e groups, wherein each R^e group is as defined above and described herein; or

(*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:

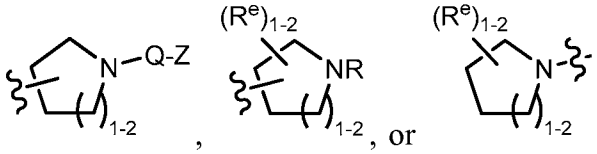
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

(*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

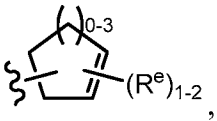
(*v*) a saturated 5-6 membered heterocyclic ring having 1-2 heteroatom selected from oxygen or nitrogen wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

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

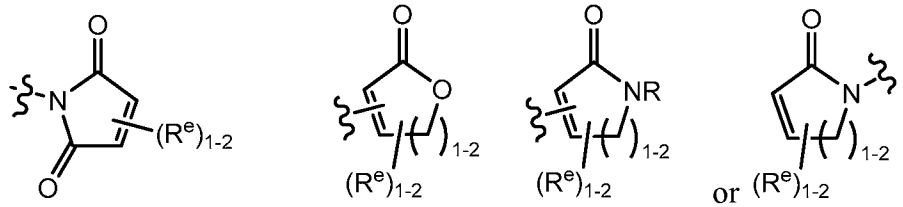
(*vii*) a saturated 3-6 membered carbocyclic ring, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*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

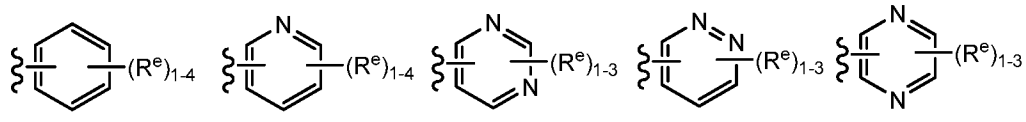
(*x*)  , wherein each R^e is as defined above and described herein; or

(*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*) 

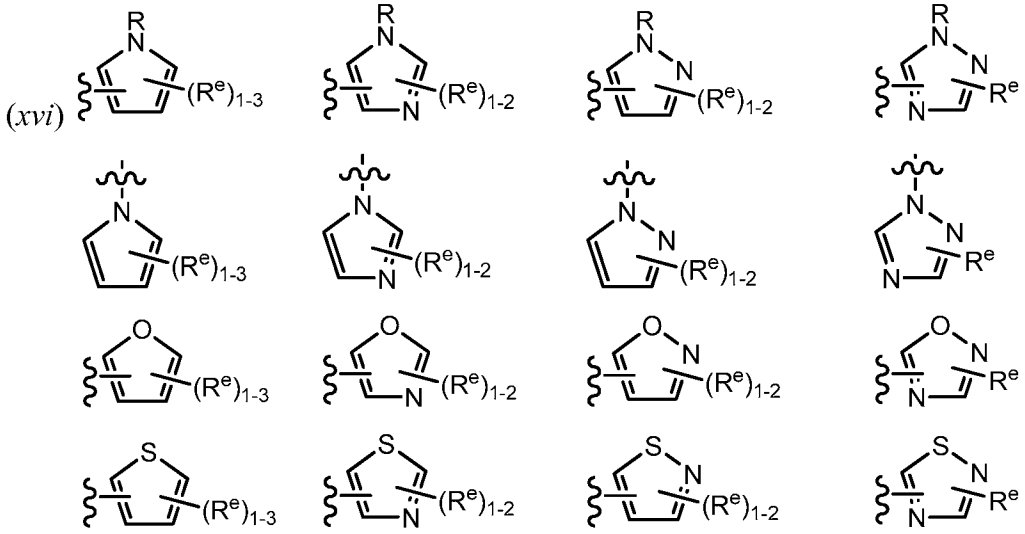
wherein each R and R^e is as defined above and described herein; or

(*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:

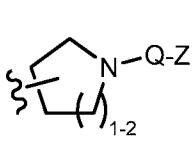
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN; or

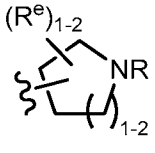
(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

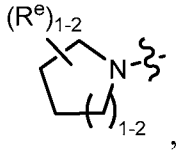
(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*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*) 

, 

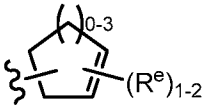
, or 

, 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

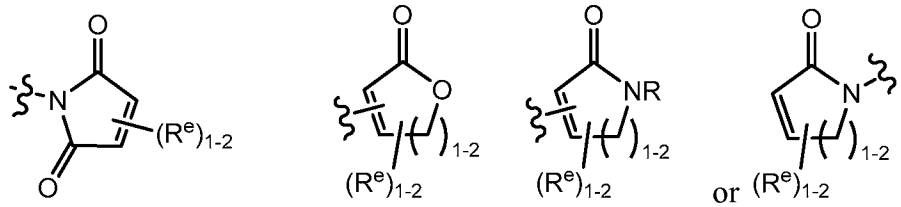
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein each R^e is as defined above and described herein; or

(*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*) 

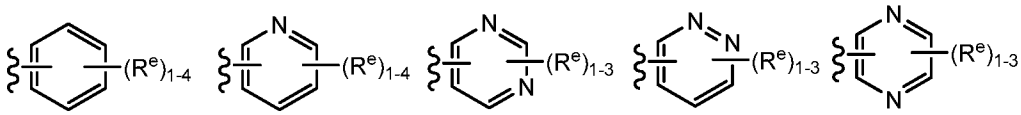
, wherein each R^e is as defined above and described herein; or

(*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*)  or

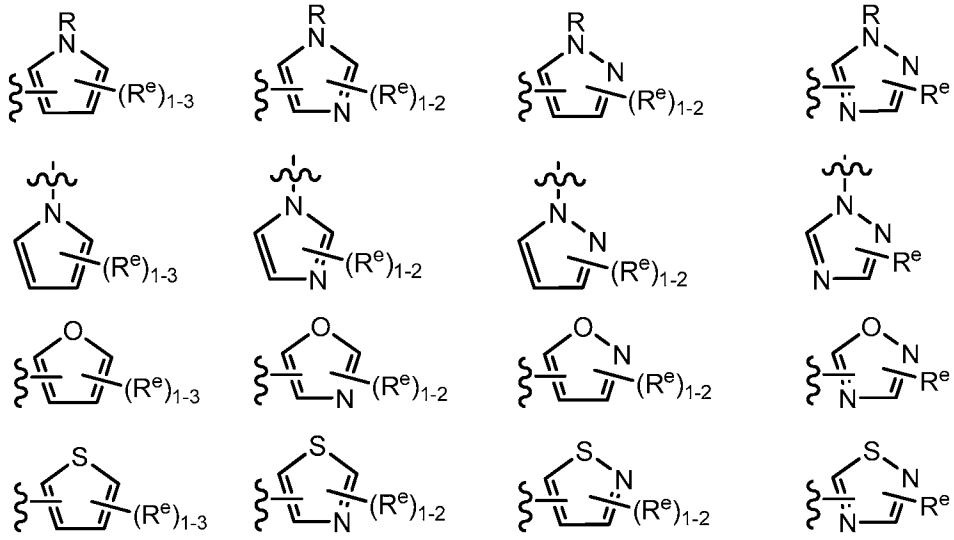
wherein each R and R^e is as defined above and described herein; or

(*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*) 

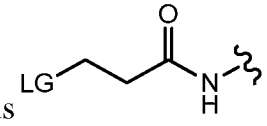
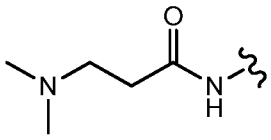
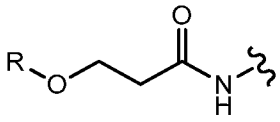
wherein each R and R^e is as defined above and described herein; or

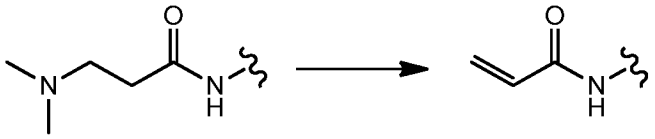
(*xvii*) an 8-10 membered bicyclic, saturated, partially unsaturated, or aryl ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups, wherein R^e is as defined above and described herein.

(q) L is a bivalent C_{2-8} straight or branched, hydrocarbon chain wherein two or three methylene units of L are optionally and independently replaced by -NRC(O)-, -C(O)NR-, -N(R)SO_2-, -

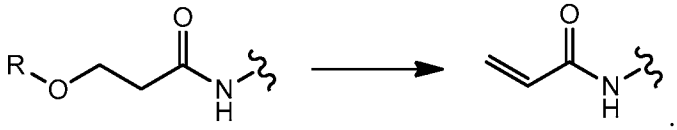
$SO_2N(R)$-, –S-, -S(O)-, $-SO_2$-, -OC(O)-, –C(O)O-, cyclopropylene, –O-, -N(R)-, or -C(O)- ; and Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

(r) L-Y is "pro-warhead" that is converted *in vitro* or *in vivo* to an irreversible warhead.

[00175] In certain embodiments, L-Y is  , wherein LG is a leaving group as understood by one of ordinary skill in the art. In certain embodiments, L-Y is  or  wherein R is as defined and described above and herein. In certain embodiments, the "pro-warhead" is converted to a warhead group (e.g., an acrylamide group) according to the following:

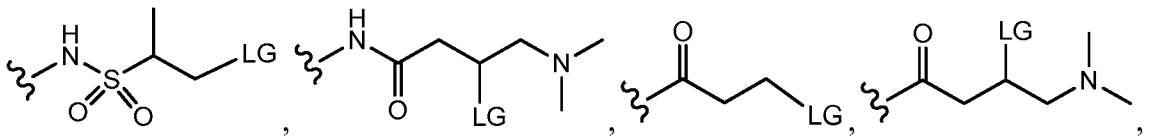


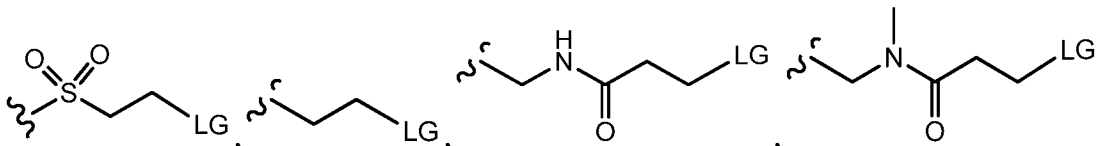
or



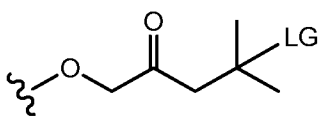
.

Such "pro-warheads" are applicable to any α,β unsaturated system, e.g.,





or



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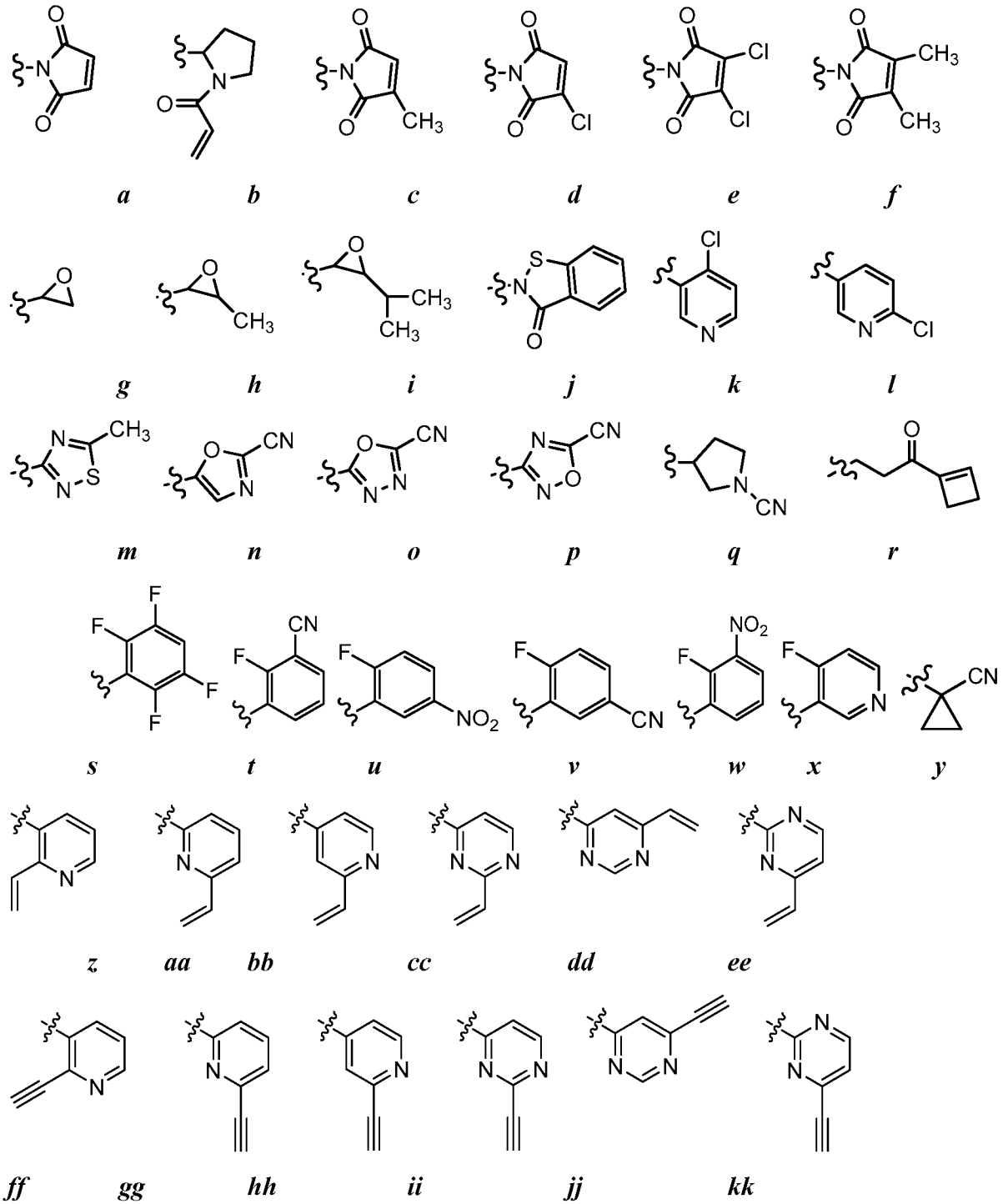
[00176] In certain embodiments, R^1 is –L-Y, wherein:

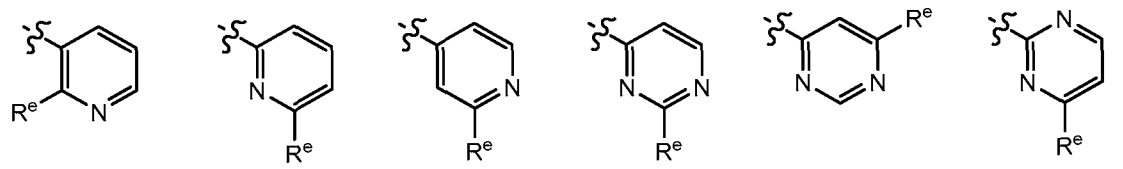
L is a covalent bond or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one, two, or three methylene units of L are optionally and independently replaced by -N(R)C(O)-, $-N(R)SO_2$-, -O-, -C(O)-, or $-SO_2$-; and

Y is hydrogen, or C_{1-6} aliphatic optionally substituted with oxo, halogen, $N(R)_2$, NO_2, or CN.

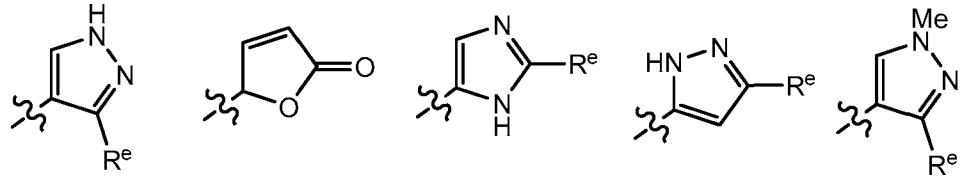
[00177] In certain embodiments, the Y group of R^1 group, -L-Y, is selected from those set forth in Table 1, below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

Table 1. Exemplary Y groups:

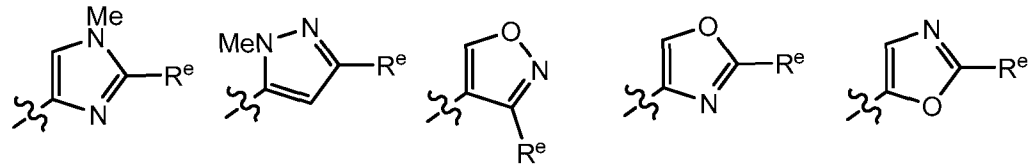




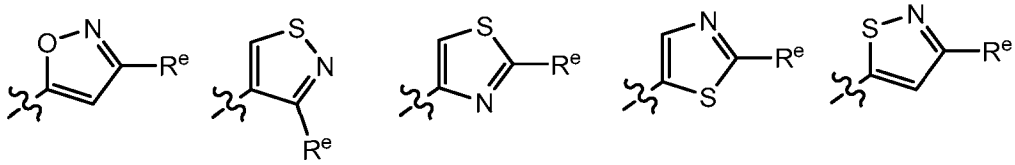
ll *mm* *nn* *oo* *pp* *qq*



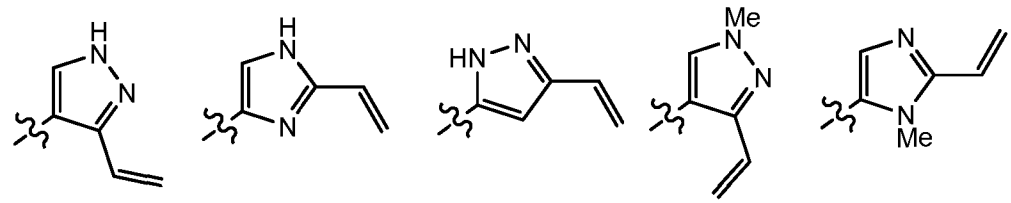
rr *ss* *tt* *uu* *vv*



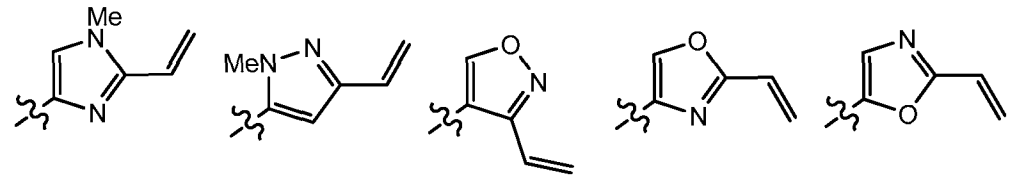
ww *xx* *yy* *zz* *aaa*



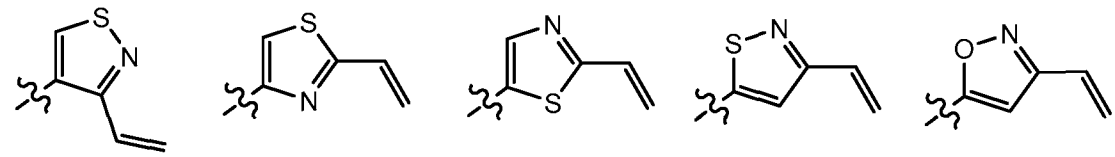
bbb *ccc* *ddd* *eee* *fff*



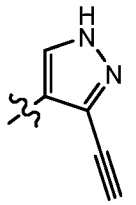
ggg *hhh* *iii* *jjj* *kkk*



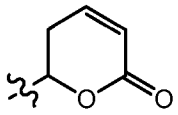
lll *mmm* *nnn* *ooo* *ppp*



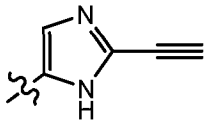
qqq *rrr* *sss* *ttt* *uuu*



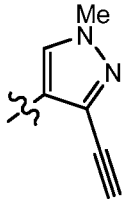
vvv



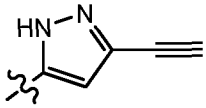
qqq



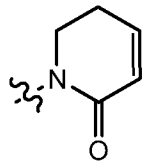
www



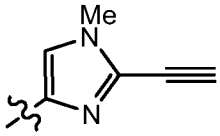
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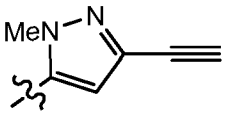
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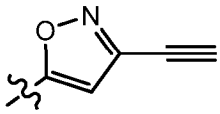
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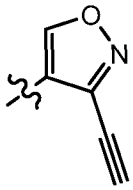
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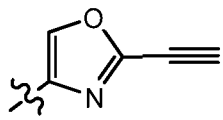
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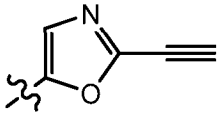
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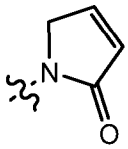
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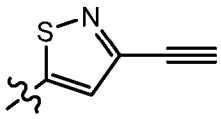
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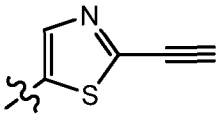
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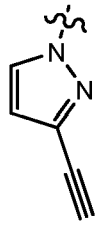
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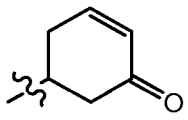
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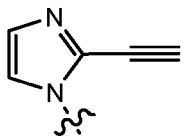
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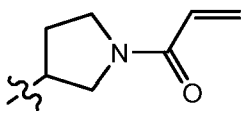
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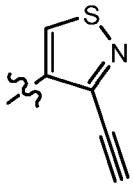
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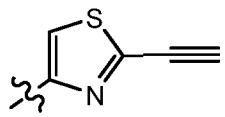
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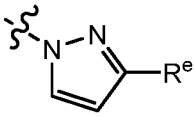
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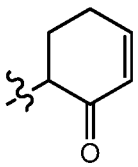
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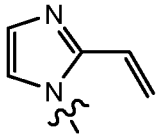
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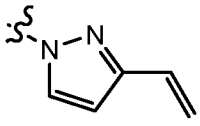
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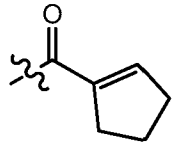
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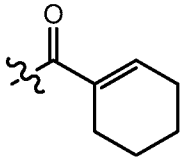
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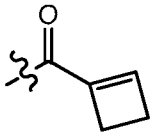
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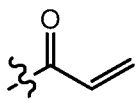
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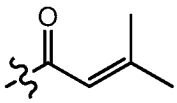
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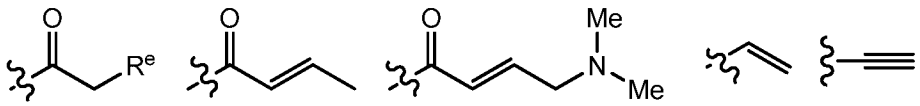
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wherein each R^e is independently a suitable leaving group, NO_2, CN, or oxo.

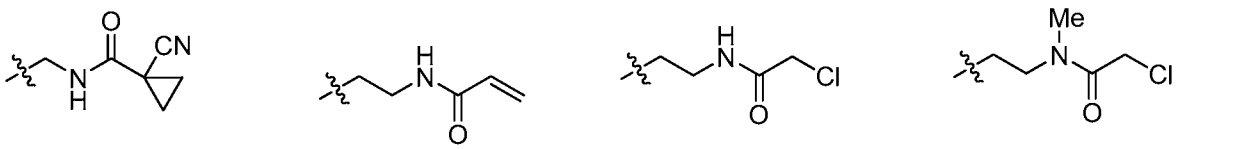
[00178] In certain embodiments, R^1 is -C≡CH, -C≡CCH$_2$NH(isopropyl), -NHC(O)C≡CCH$_2$CH$_3$, -CH$_2$-C≡C-CH$_3$, -C≡CCH$_2$OH, -CH$_2$C(O)C≡CH, -C(O)C≡CH, or -CH$_2$OC(=O)C≡CH. In some embodiments, R^1 is selected from -NHC(O)CH=CH$_2$, -NHC(O)CH=CHCH$_2$N(CH$_3$)$_2$, or -CH$_2$NHC(O)CH=CH$_2$.

[00179] In some embodiments, R^1 is 6-12 atoms long. In certain embodiments, R^1 is 6-9 atoms long. In certain embodiments, R^1 is 10-12 atoms long. In certain embodiments, R^1 is at least 8 atoms long.

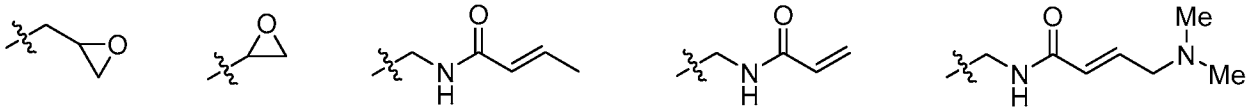
[00180] In certain embodiments, R^1 is –C(O)CH$_2$CH$_2$C(O)CH=C(CH$_3$)$_2$, –C(O)CH$_2$CH$_2$C(O)CH=CH(cyclopropyl), –C(O)CH$_2$CH$_2$C(O)CH=CHCH$_3$, –C(O)CH$_2$CH$_2$C(O)CH=CHCH$_2$CH$_3$, or –C(O)CH$_2$CH$_2$C(O)C(=CH$_2$)CH$_3$. In certain embodiments, R^1 is –C(O)CH$_2$NHC(O)CH=CH$_2$, –C(O)CH$_2$NHC(O)CH$_2$CH$_2$C(O)CH=CHCH$_3$, or –C(O)CH$_2$NHC(O)CH$_2$CH$_2$C(O)C(=CH$_2$)CH$_3$. In certain embodiments, R^1 is –S(O)$_2$CH$_2$CH$_2$NHC(O)CH$_2$CH$_2$C(O)CH=C(CH$_3$)$_2$, –S(O)$_2$CH$_2$CH$_2$NHC(O)CH$_2$CH$_2$C(O)CH=CHCH$_3$, or –S(O)$_2$CH$_2$CH$_2$NHC(O)CH$_2$CH$_2$C(O)CH=CH$_2$. In certain embodiments, R^1 is –C(O)(CH$_2$)$_3$NHC(O)CH$_2$CH$_2$C(O)CH=CHCH$_3$ or –C(O)(CH$_2$)$_3$NHC(O)CH$_2$CH$_2$C(O)CH=CH$_2$.

[00181] In certain embodiments, R^1 is selected from those set forth in Table 2, below, wherein each wavy line indicates the point of attachment to the rest of the molecule.

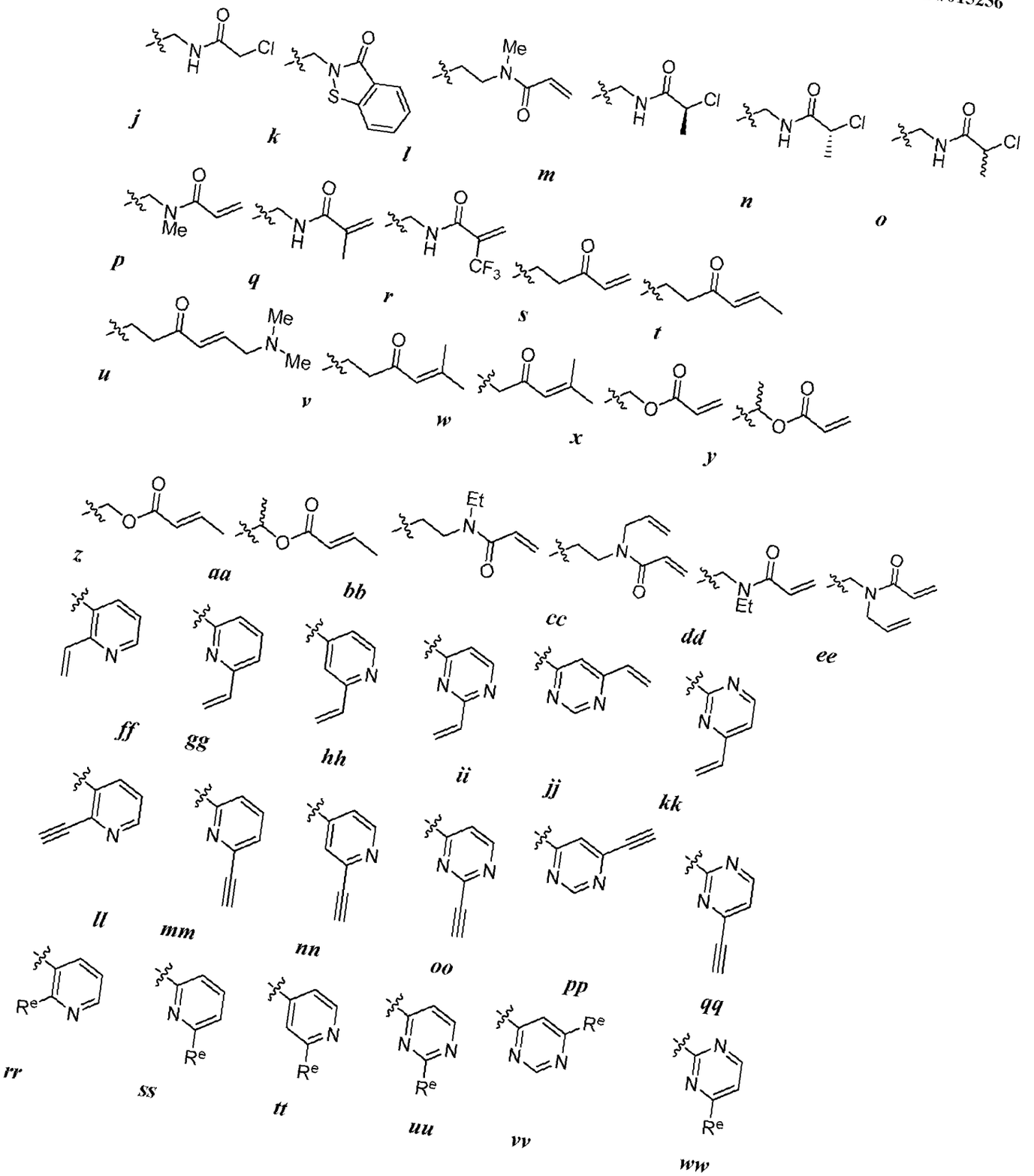
Table 2: Exemplary R^1 Groups

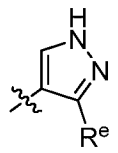


a *b* *c* *d*

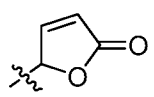


e *f* *g* *h* *i*

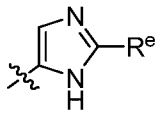

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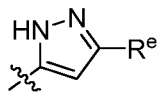
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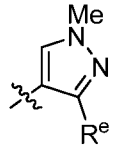
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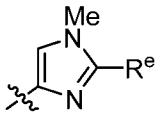
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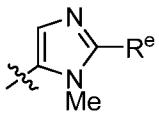
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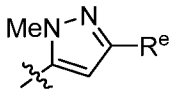
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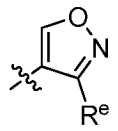
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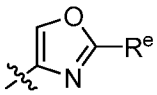
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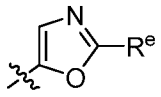
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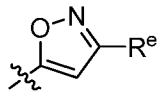
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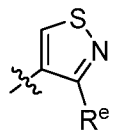
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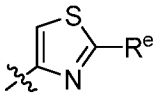
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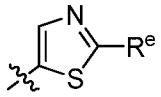
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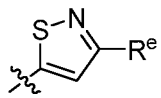
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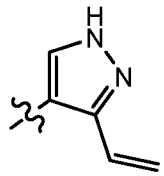
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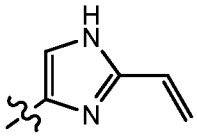
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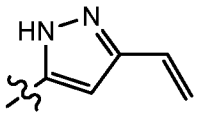
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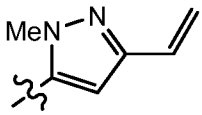
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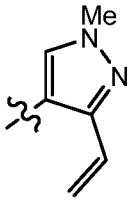


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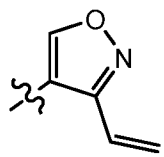


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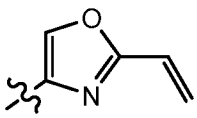




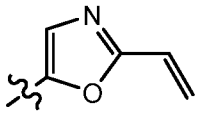
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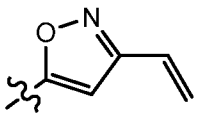
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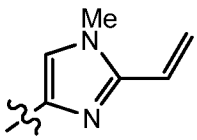
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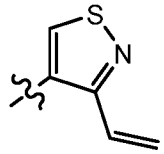
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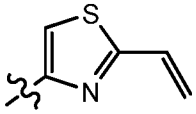
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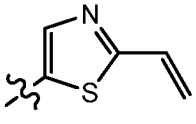
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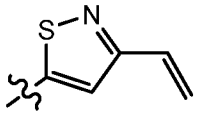
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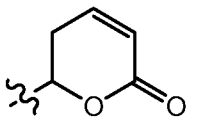
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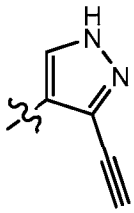
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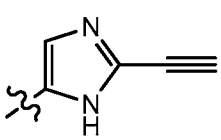
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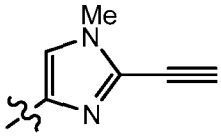
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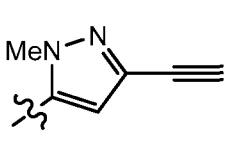
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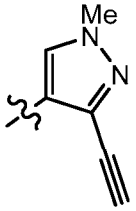
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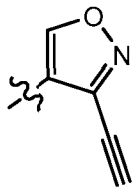
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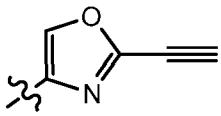
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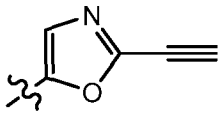
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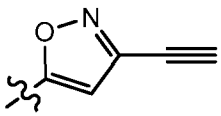
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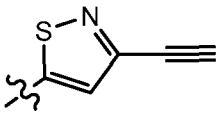
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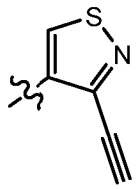
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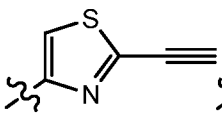
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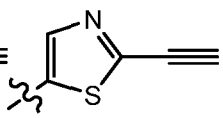
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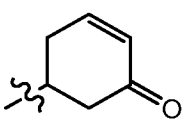
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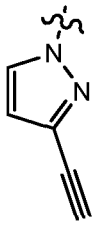
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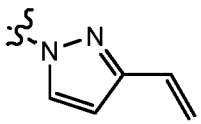
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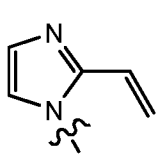
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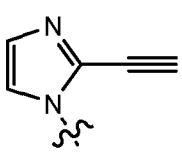
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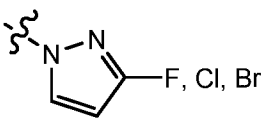
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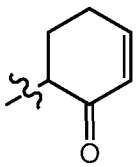
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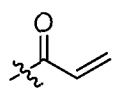
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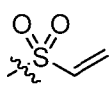
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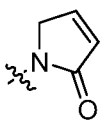
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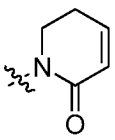
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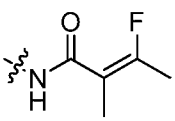
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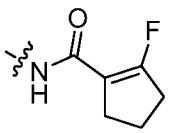
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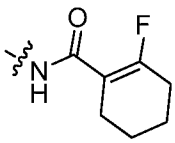
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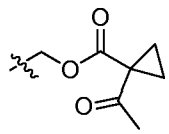
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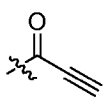
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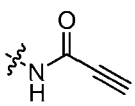
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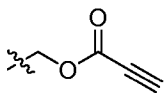
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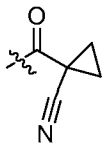
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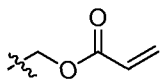
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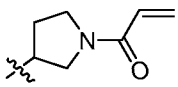
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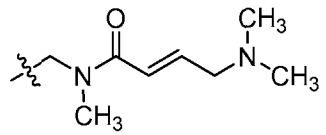
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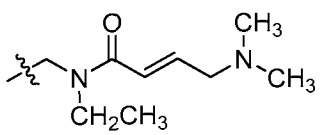
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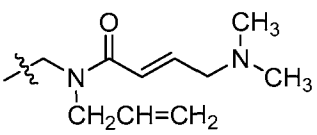
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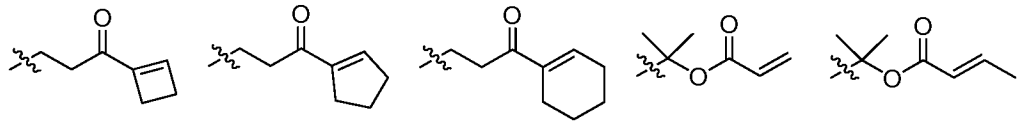
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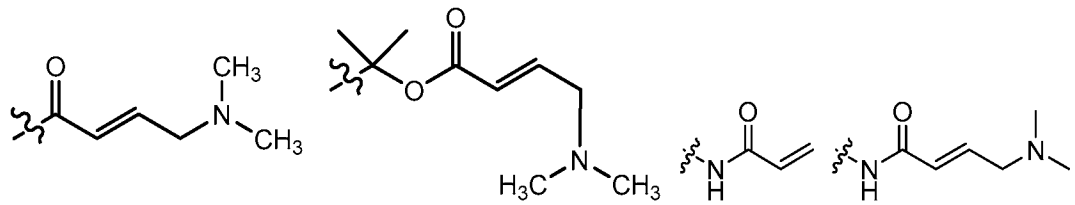
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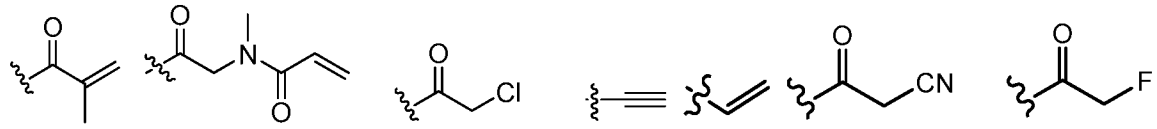
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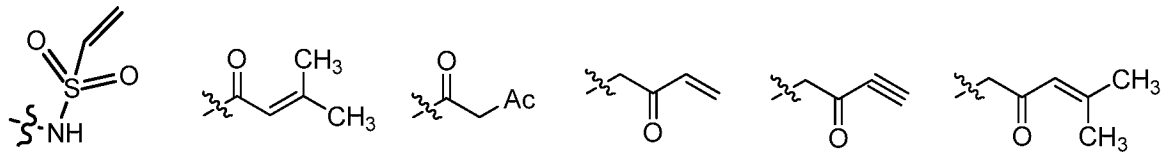
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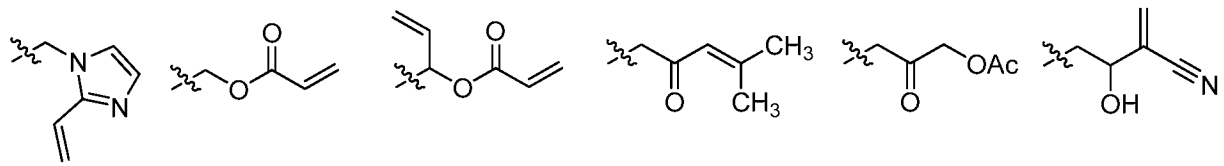
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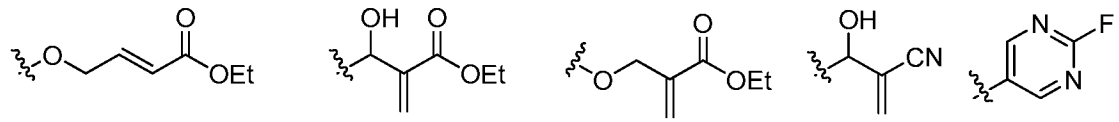
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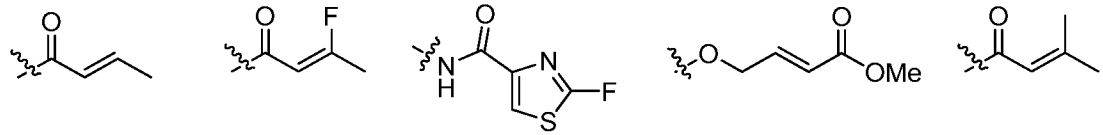
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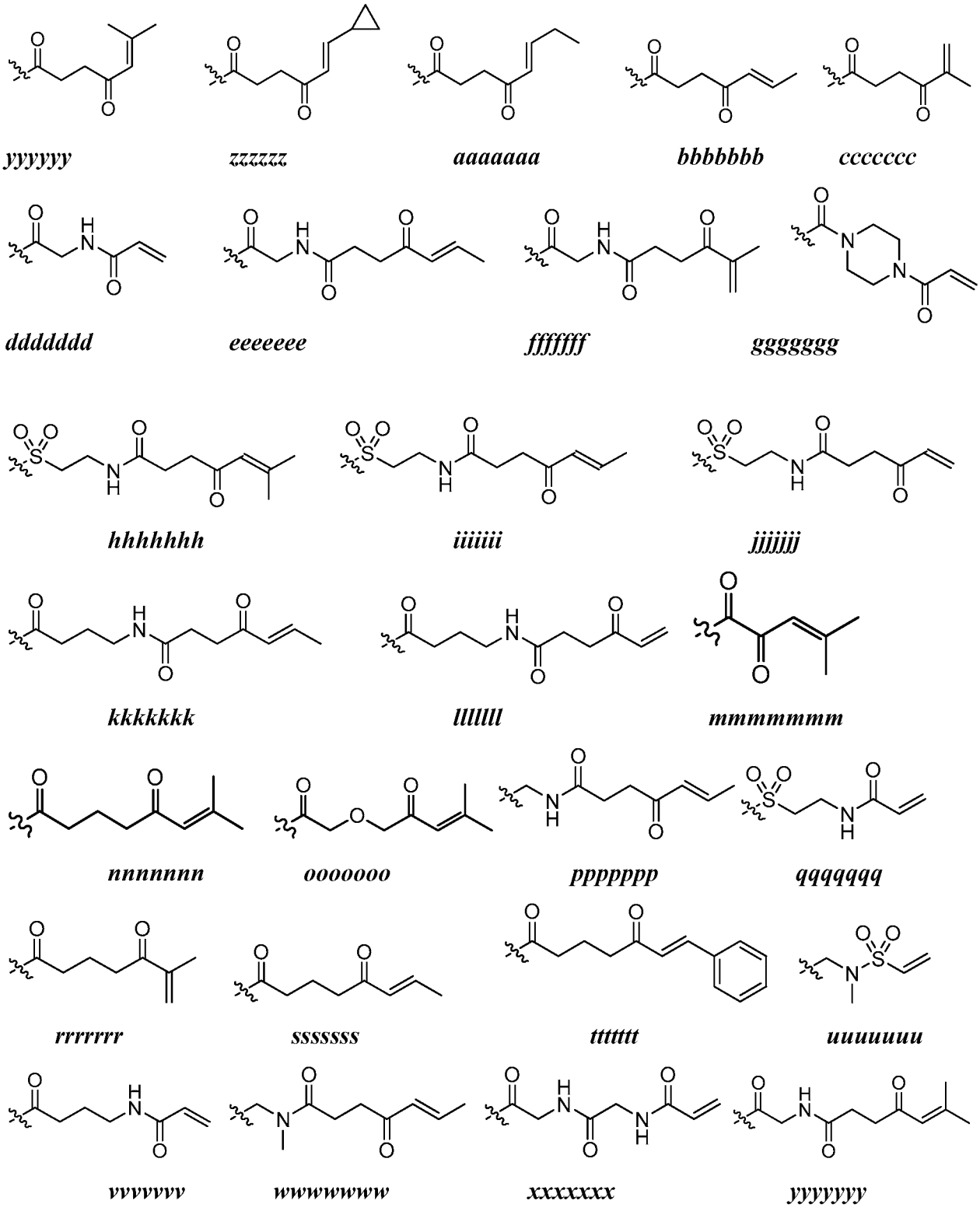
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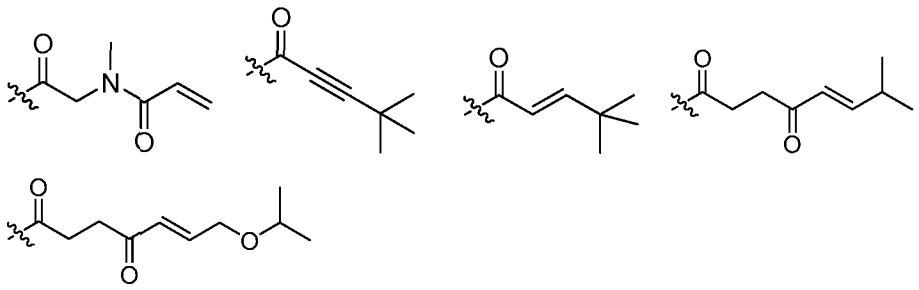


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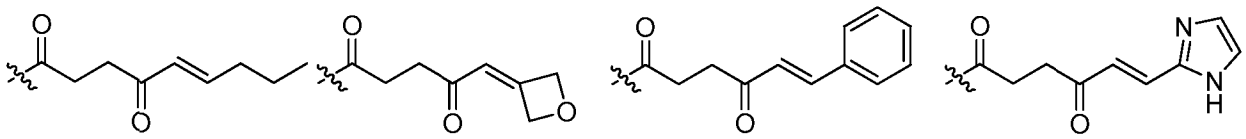


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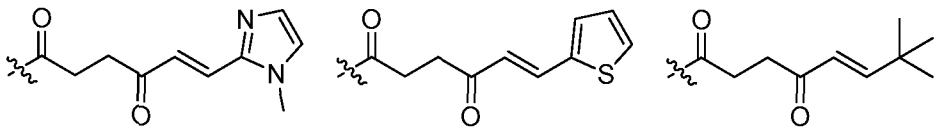

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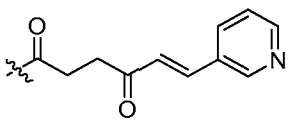


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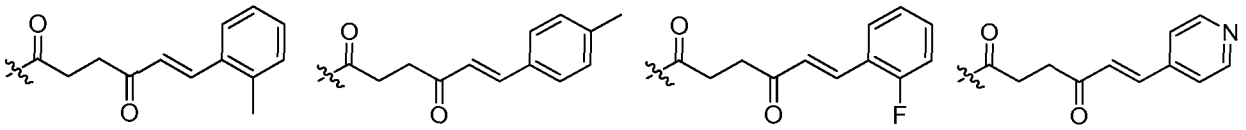
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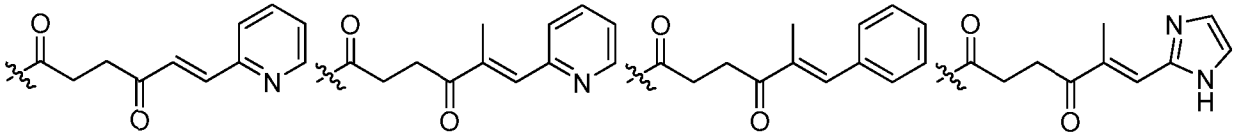


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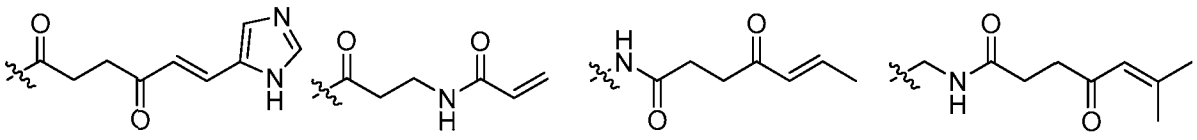
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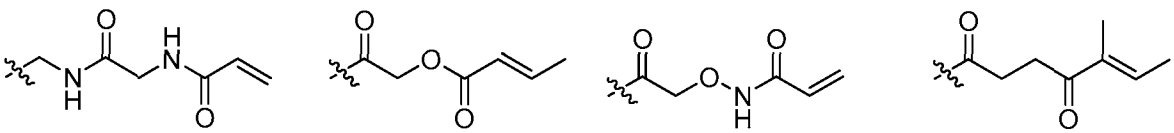
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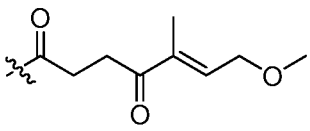
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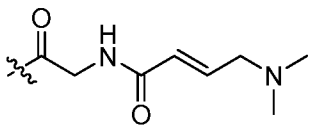
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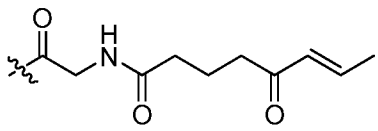
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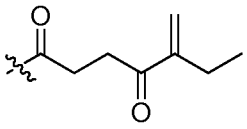
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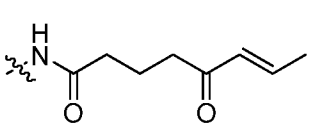
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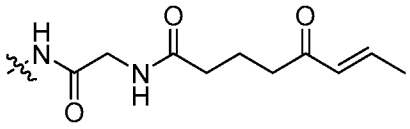
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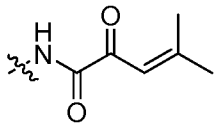
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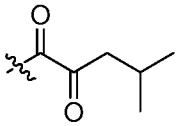
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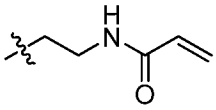
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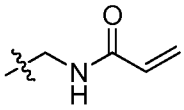
or *jjjjjjjjj*,

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

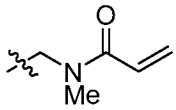
[00182] In certain embodiments, R^1 is selected from:



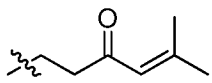
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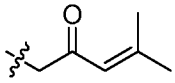
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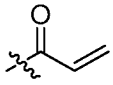
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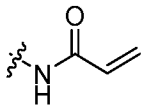
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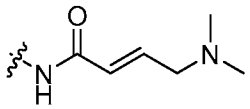
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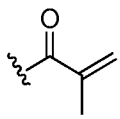
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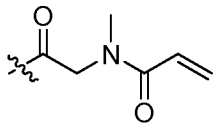
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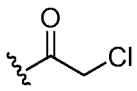
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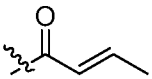
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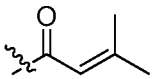
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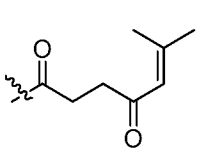
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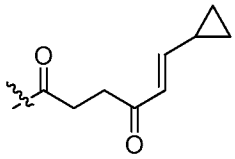
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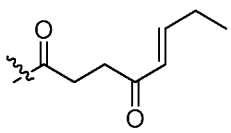
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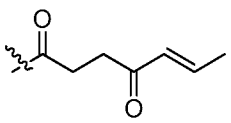
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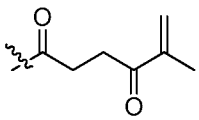
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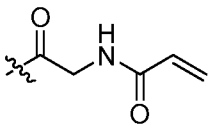
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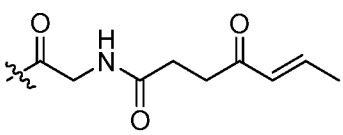
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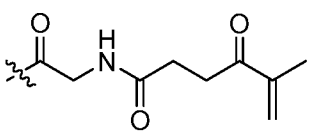
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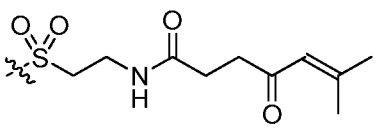
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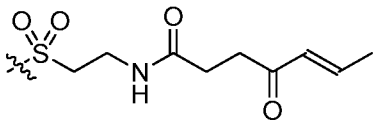
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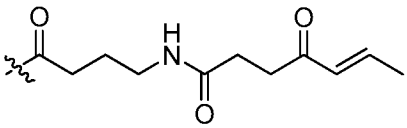
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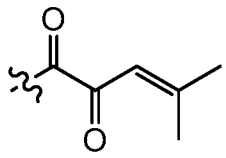
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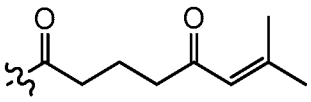
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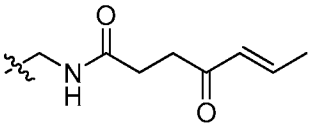
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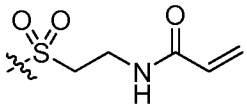
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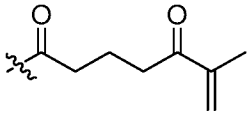
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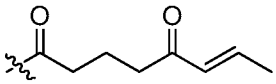
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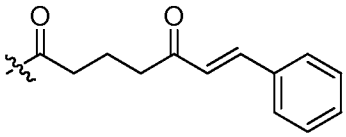
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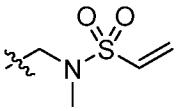
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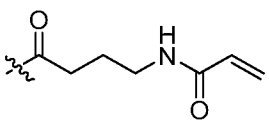
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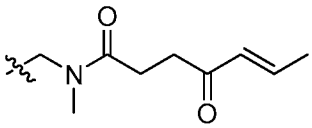
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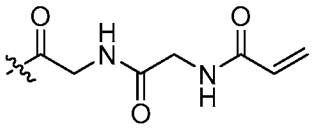
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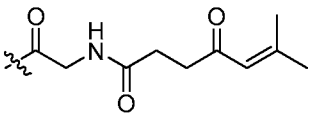
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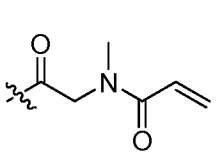
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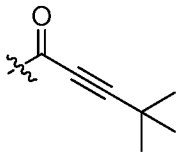


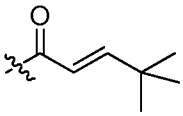
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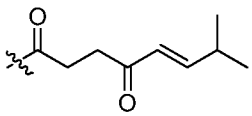


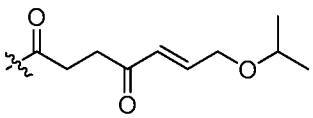
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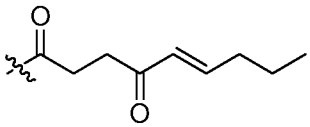
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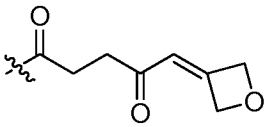
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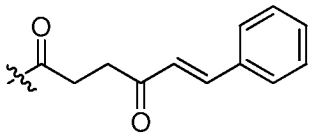
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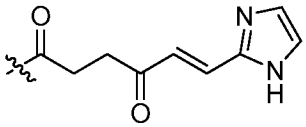
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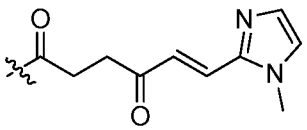


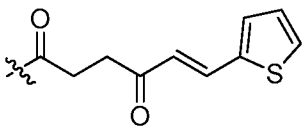
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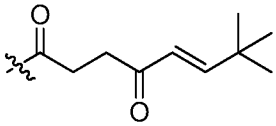
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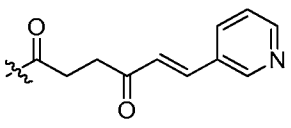
ggggggg

hhhhhhhh







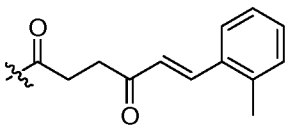


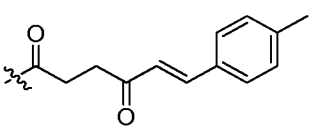
iiiiiiii

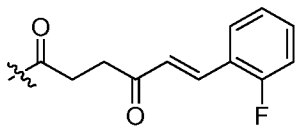
jjjjjjjj

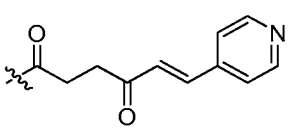
kkkkkkkk

lllllll

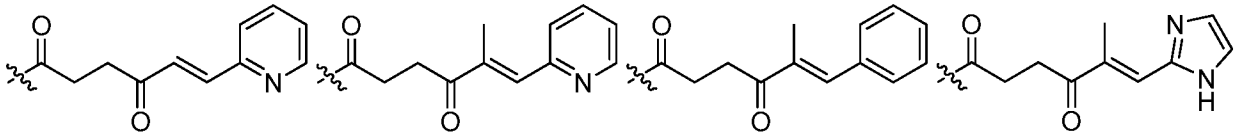




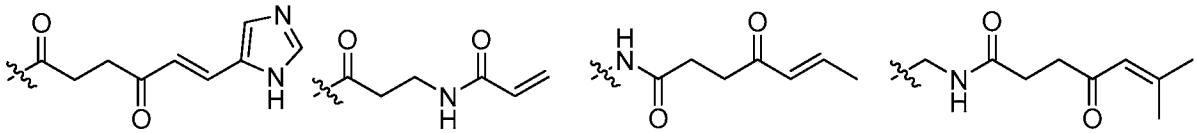




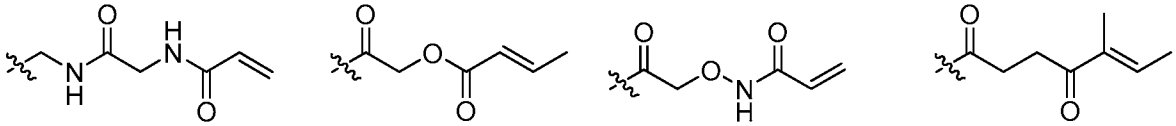
mmmmmmmm *nnnnnnnn* *oooooooo* *pppppppp*



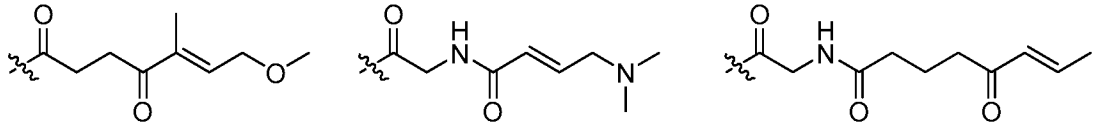
qqqqqqqq *rrrrrrrr* *ssssssss* *tttttttt*



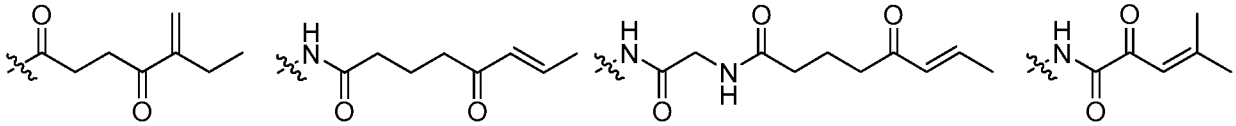
uuuuuuuu *vvvvvvvv* *wwwwwwww* *xxxxxxxx*



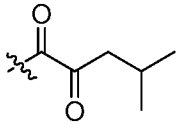
yyyyyyyy *zzzzzzzz* *aaaaaaaaa* *bbbbbbbbb*



ccccccccc *ddddddddd* *eeeeeeeee*

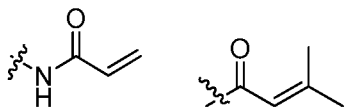


fffffffff *ggggggggg* *hhhhhhhhh* *iiiiiiii*

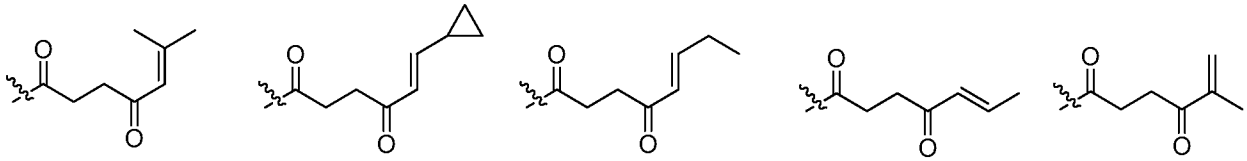


or *jjjjjjjjj*.

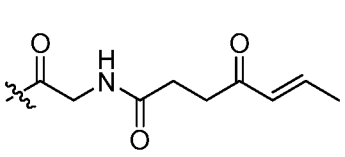
[00183] In certain embodiments, R^1 is selected from:



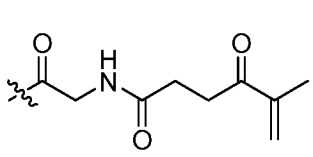
ttttt *xxxxxx*



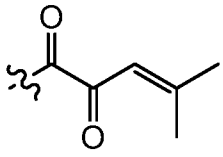
yyyyyy *zzzzzz* *aaaaaaa* *bbbbbbb* *ccccccc*



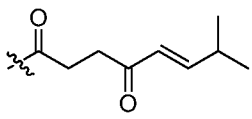
eeeeeee



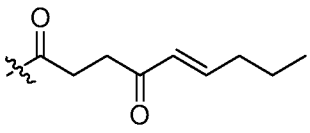
fffffff



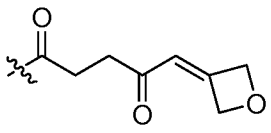
mmmmmmm



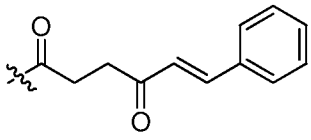
ccccccc



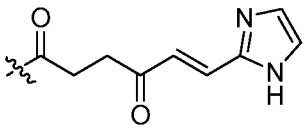
eeeeeeee



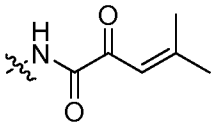
ffffffff



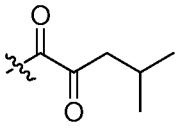
gggggggg



hhhhhhhh

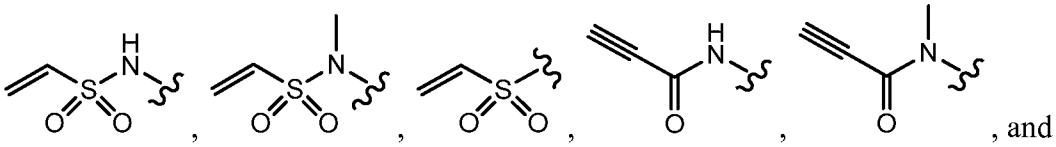


iiiiiiii



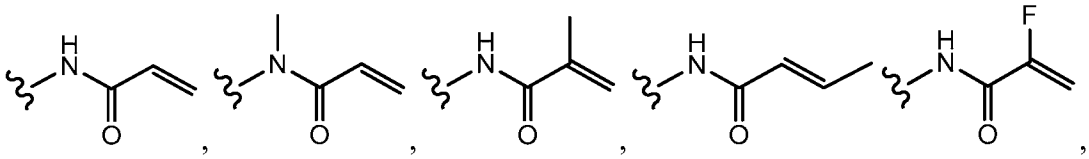
or *jjjjjjjjj*.

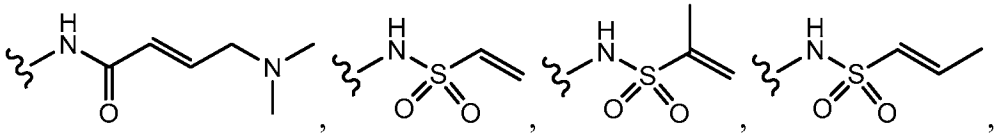
[00184] In certain embodiments, R^1 is selected from

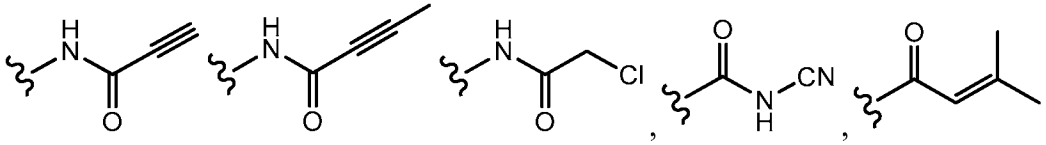


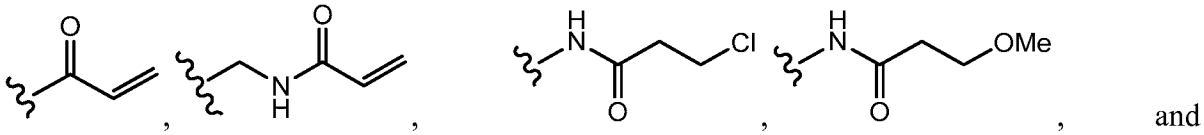
, and

[00185] In certain embodiments, R^1 is selected from:

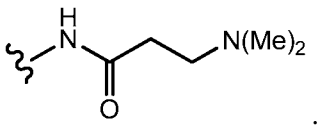








and

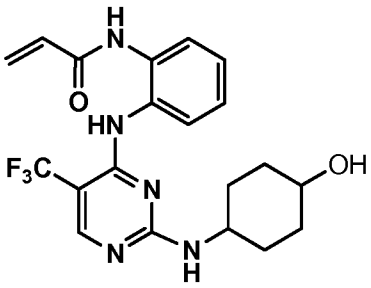


.

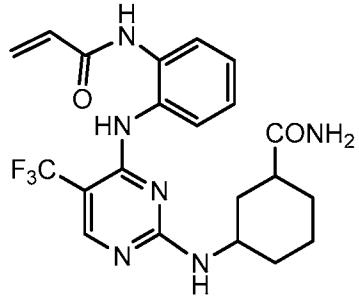
In some embodiments, R^1 is selected from those depicted in Table 3, below.

[00186] In certain embodiments, the invention provides a compound selected from the group consisting of those set forth in Table 3, below:

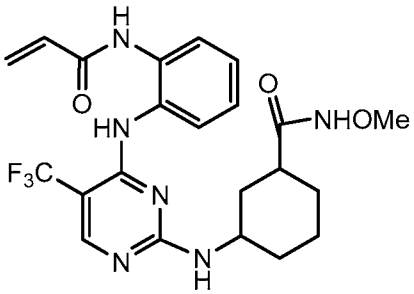
Table 3. Exemplary Compounds of Formula I



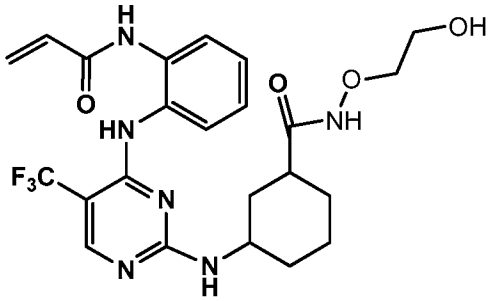
I-1



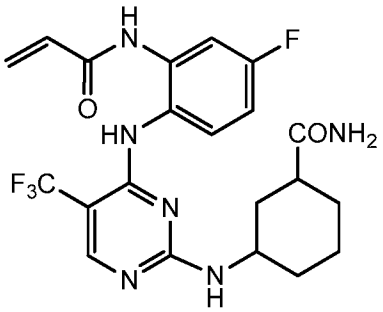
I-2



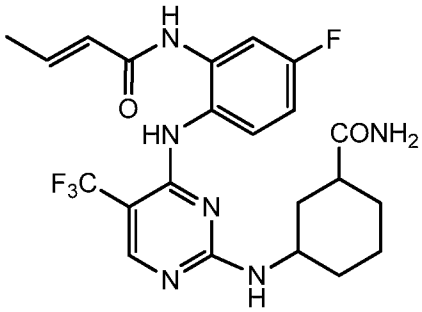
I-3



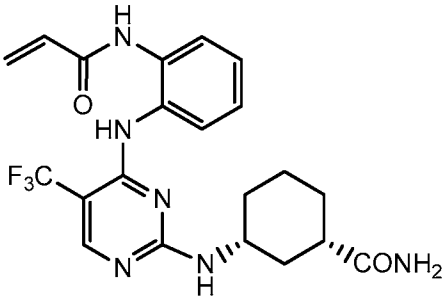
I-4



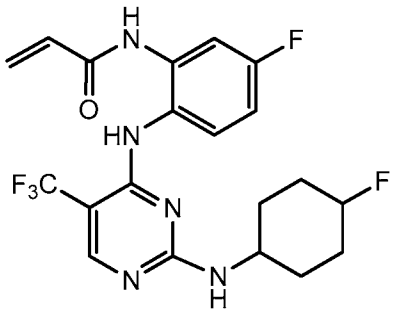
I-5



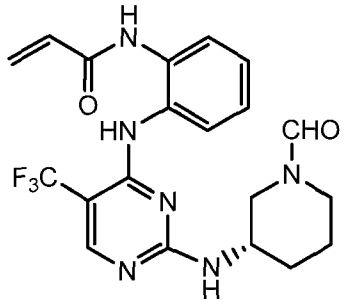
I-6



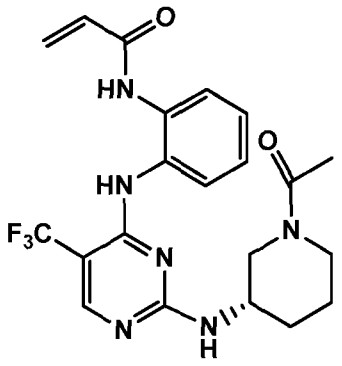
I-7



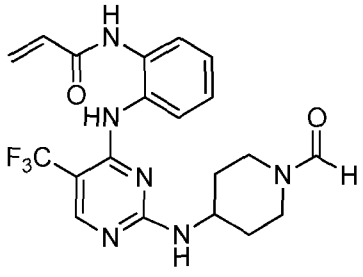
I-8



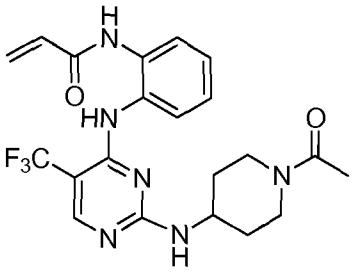
I-9



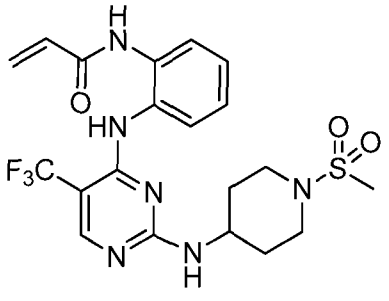
I-10



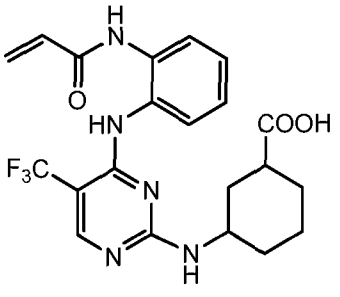
I-11



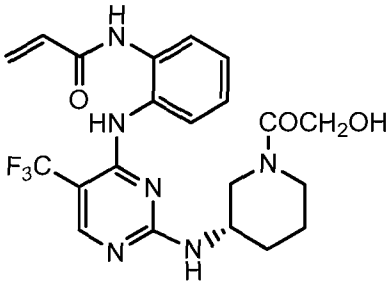
I-12



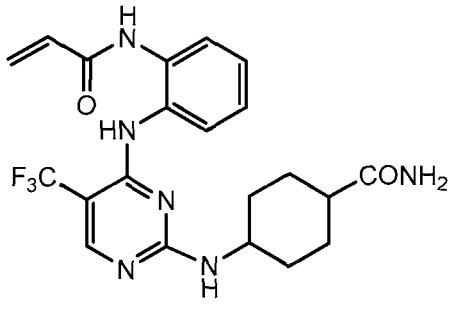
I-13



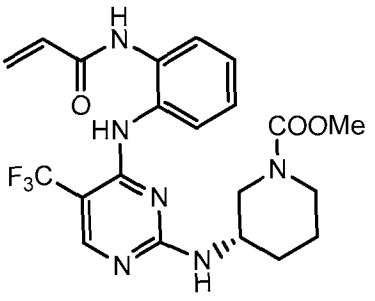
I-14



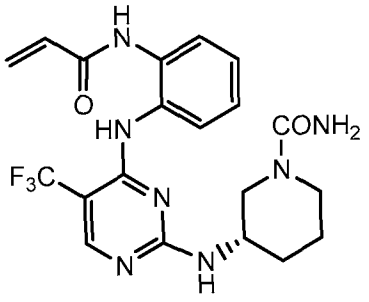
I-15



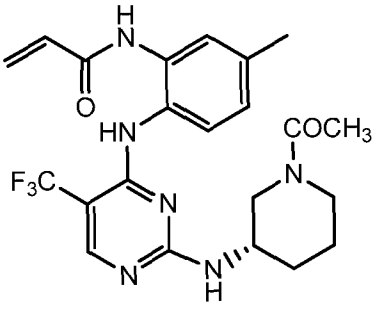
I-16



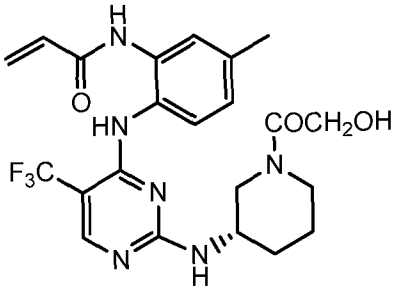
I-17



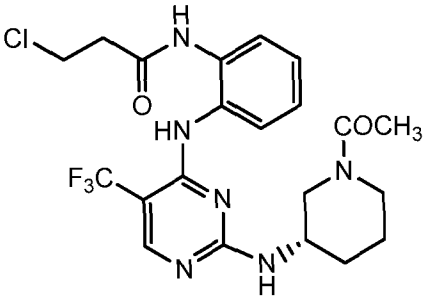
I-18



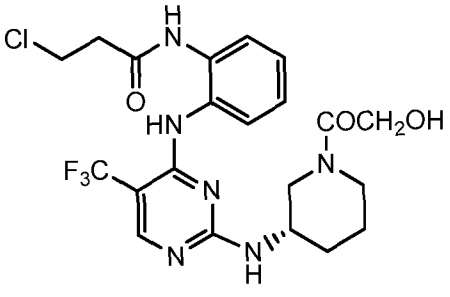
I-19



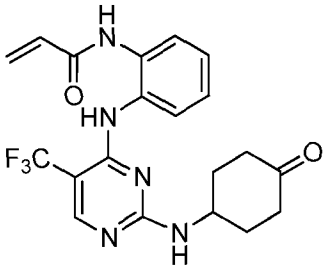
I-20



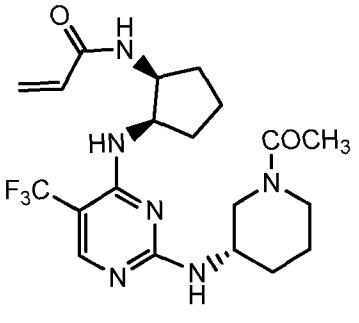
I-21



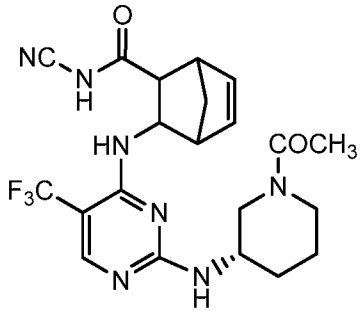
I-22



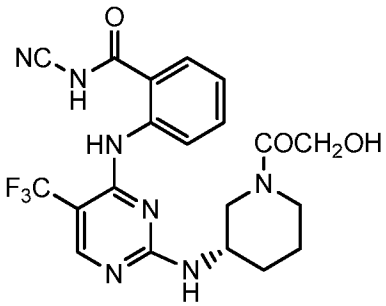
I-23



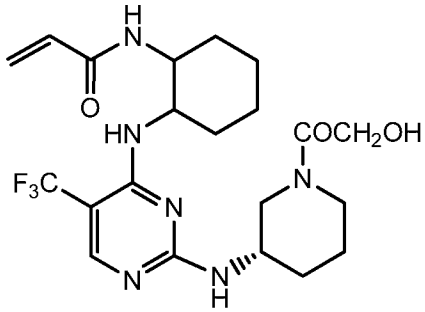
I-24



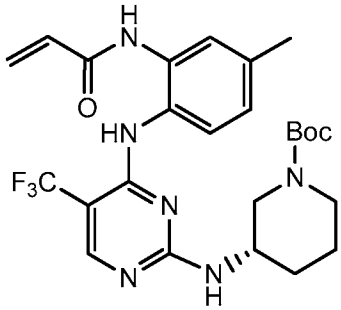
I-25



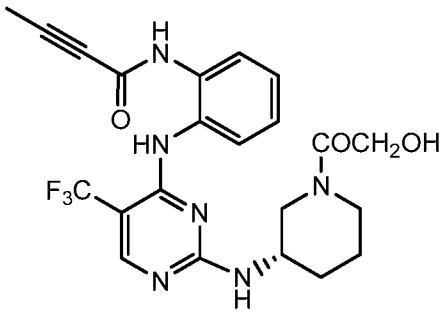
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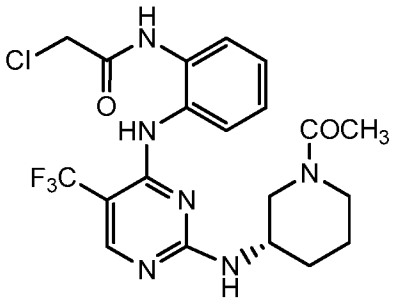
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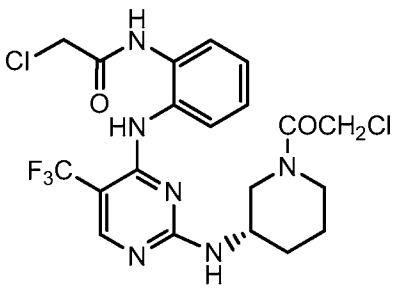
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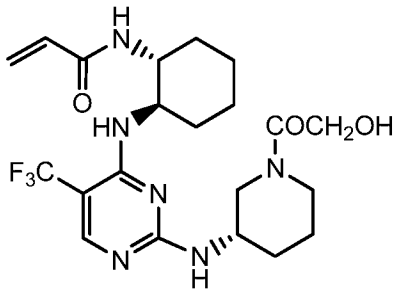
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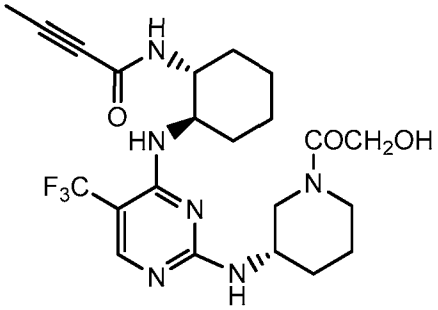
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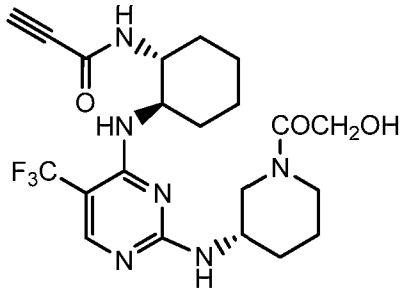
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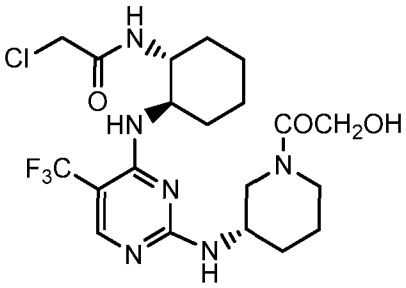
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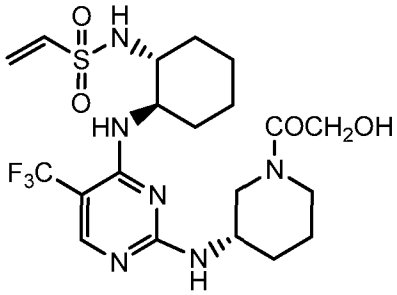
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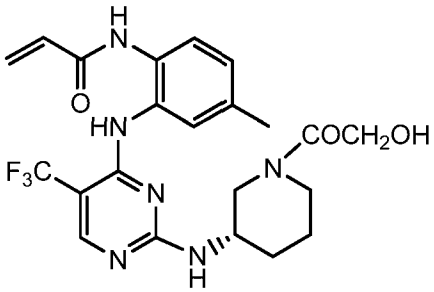
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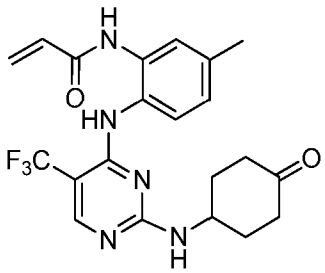
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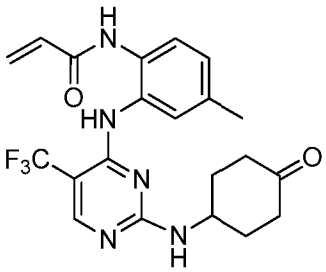
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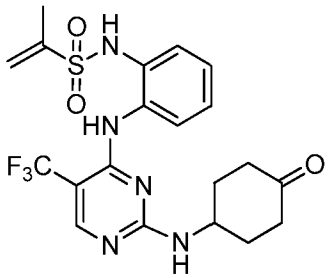
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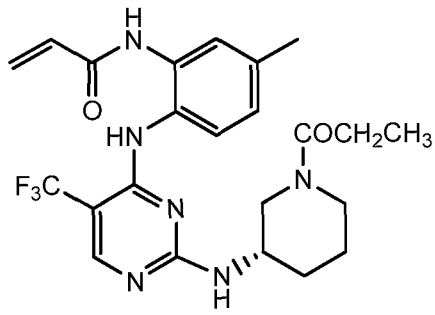
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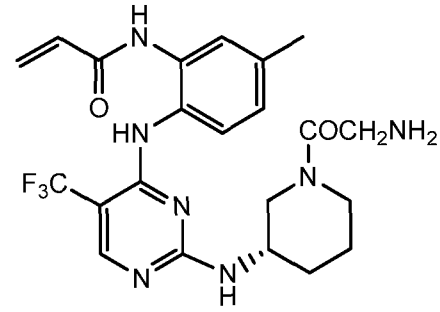
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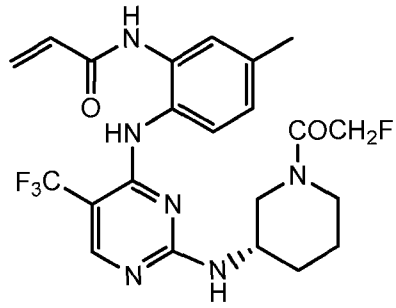
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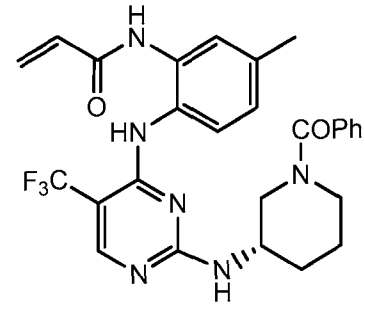
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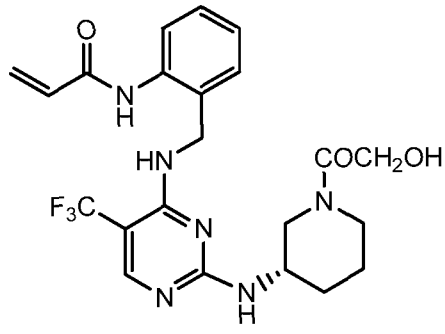
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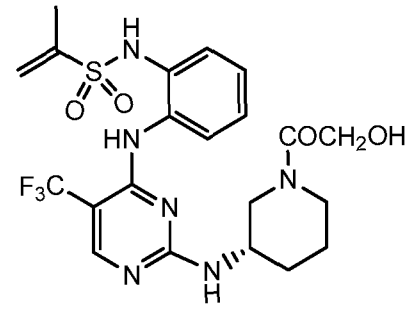
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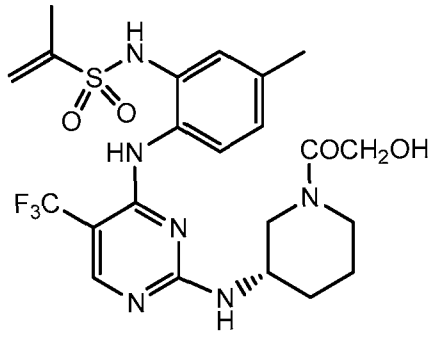
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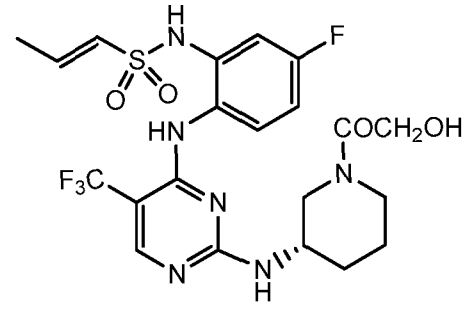
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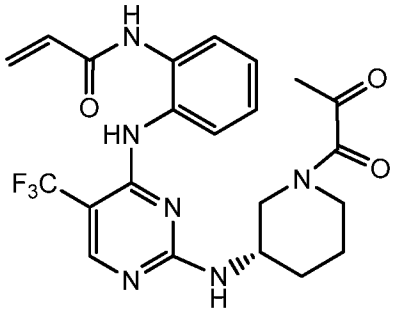
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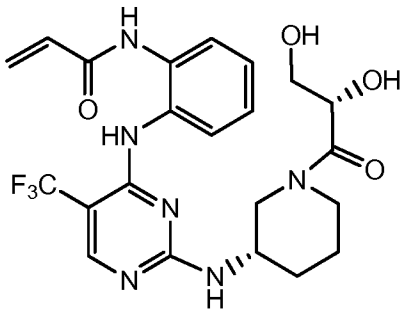
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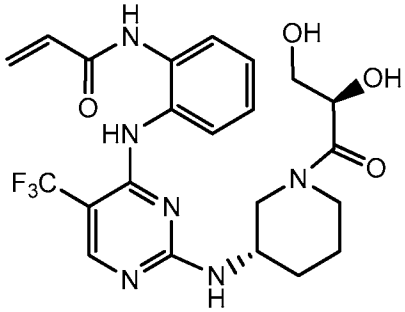
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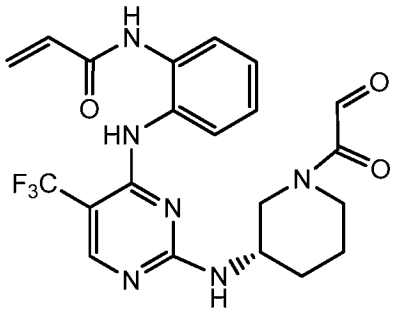
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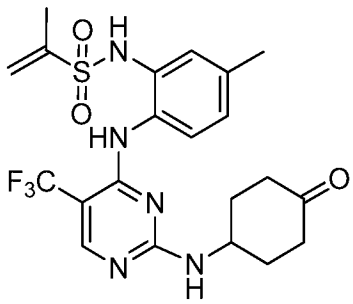
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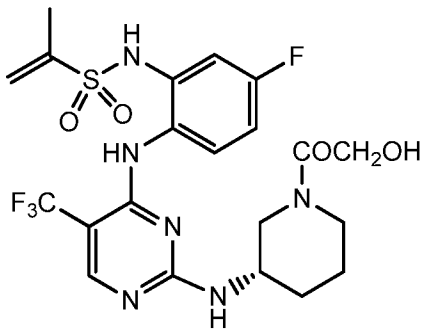
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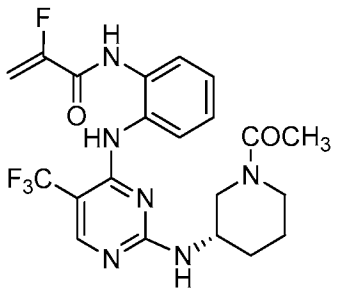
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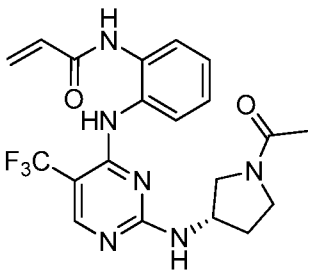
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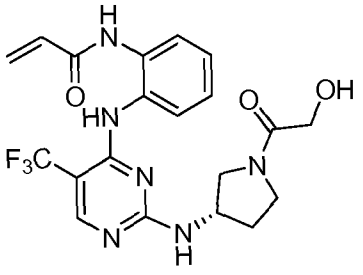
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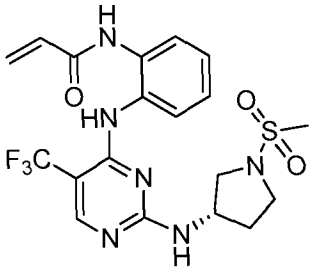
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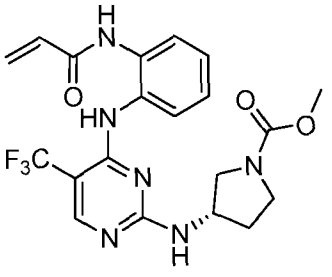
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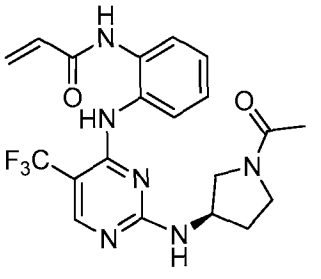
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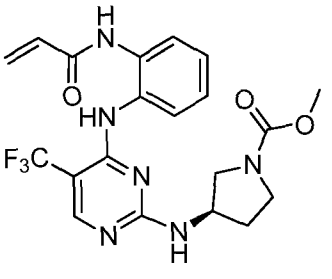
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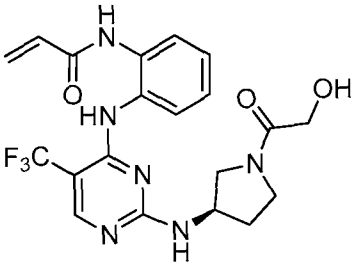
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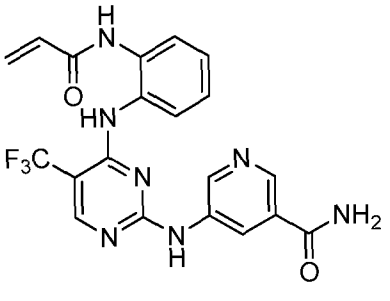
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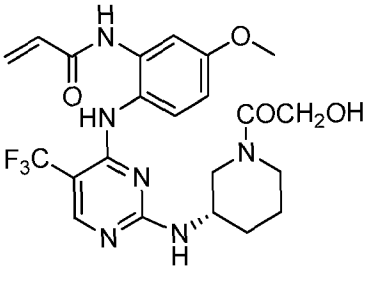
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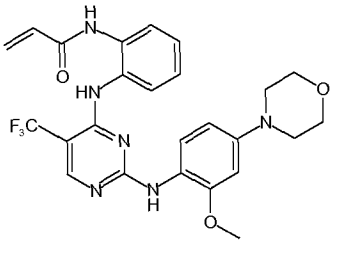
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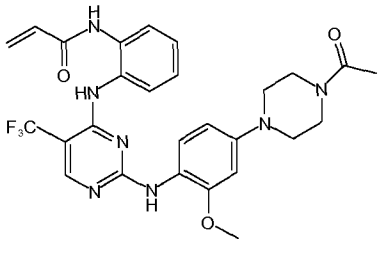


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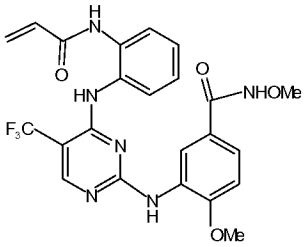


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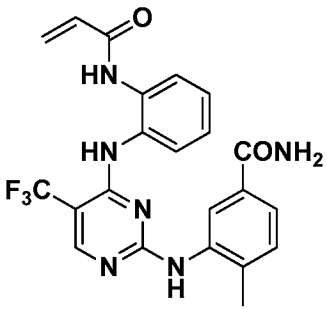




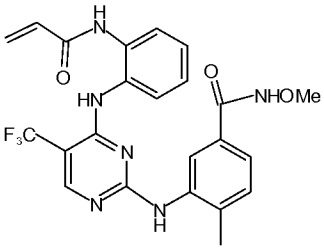
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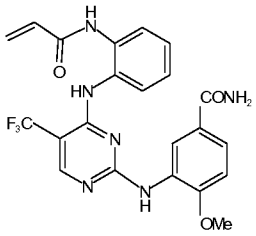
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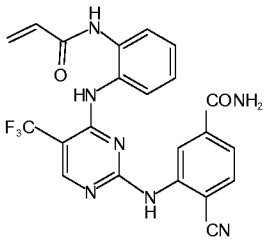
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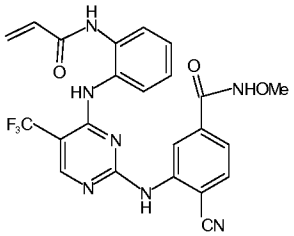
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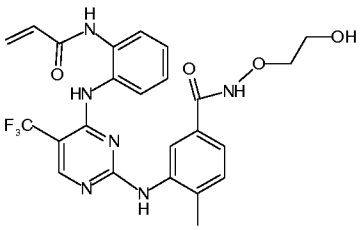
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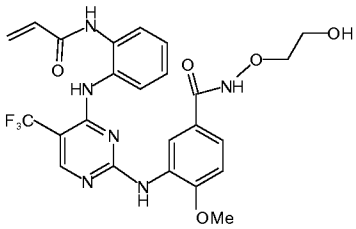
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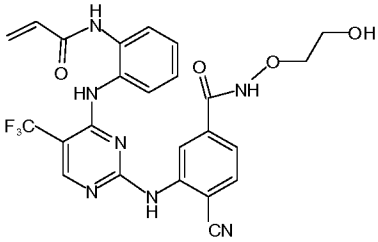
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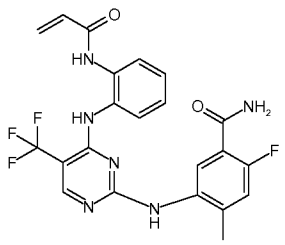
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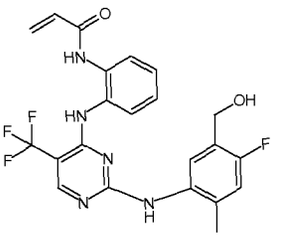
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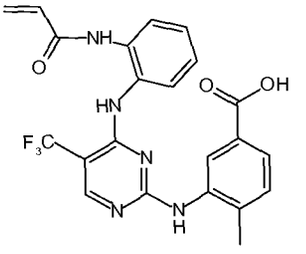
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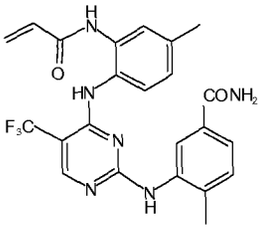
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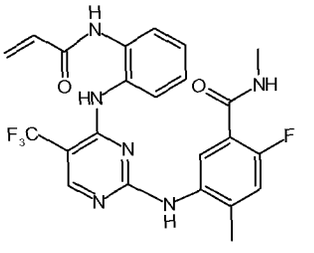
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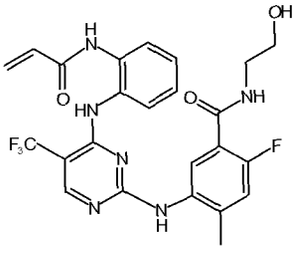
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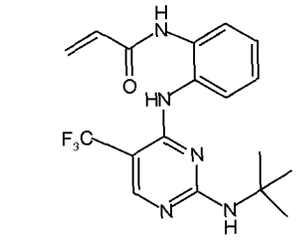
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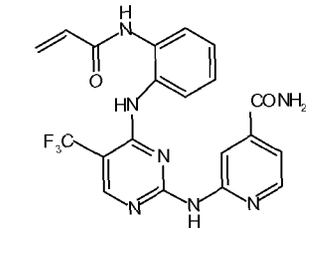
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I-80



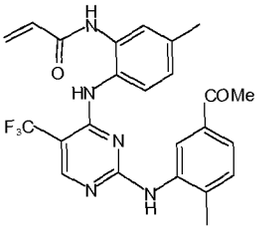
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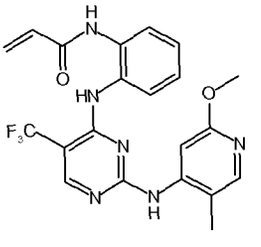
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I-83

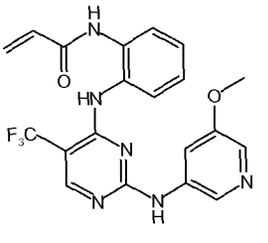
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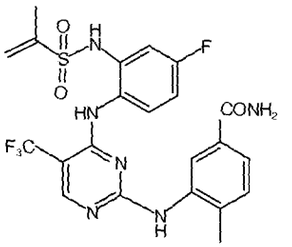


I-85

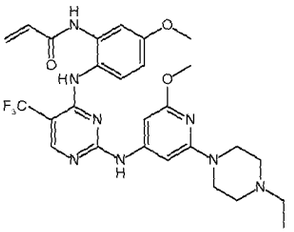


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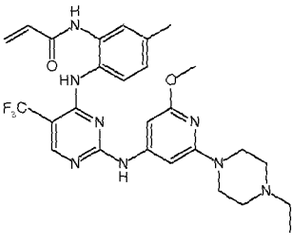




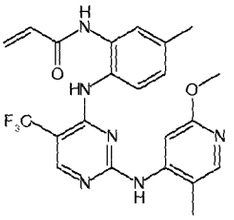
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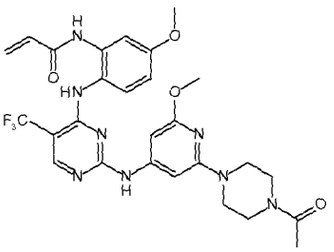
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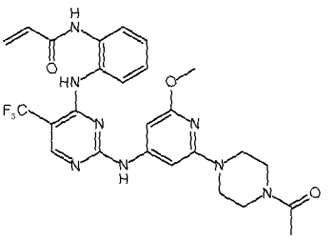
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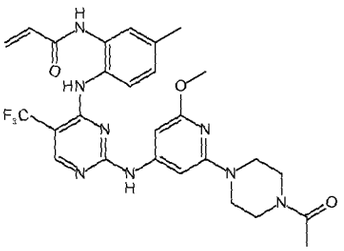
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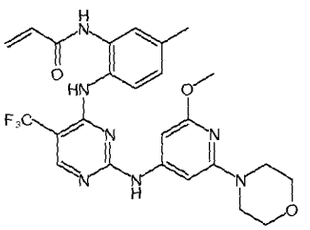
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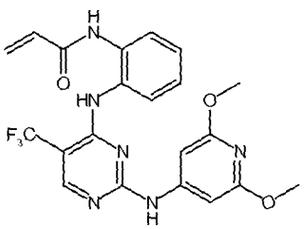
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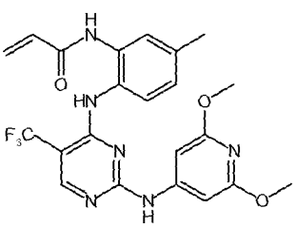
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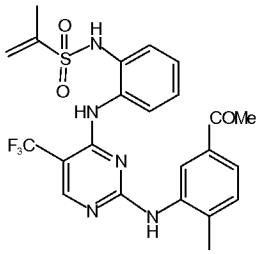
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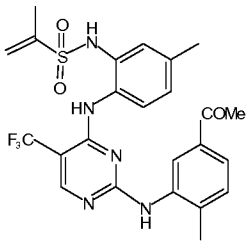
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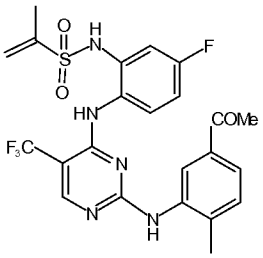
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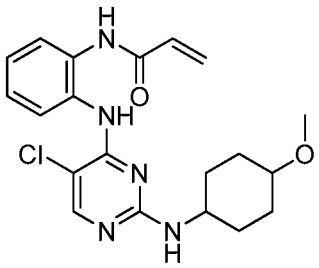
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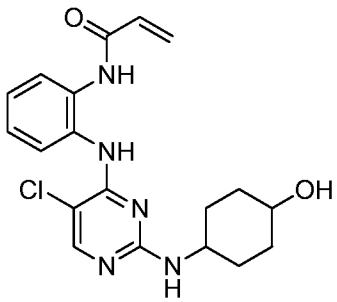
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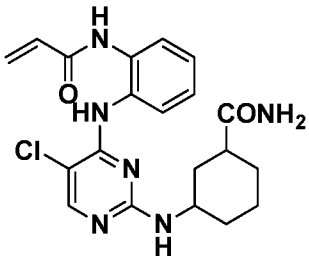
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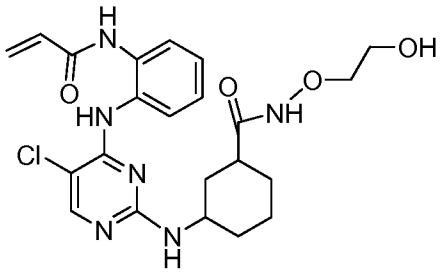
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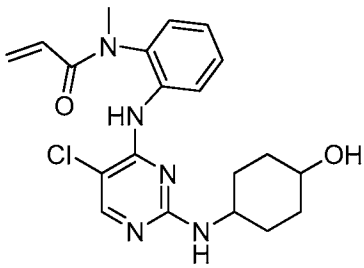
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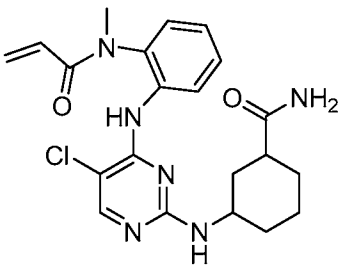
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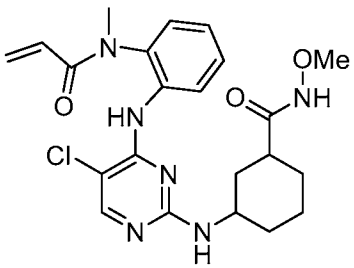
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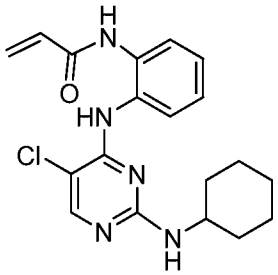
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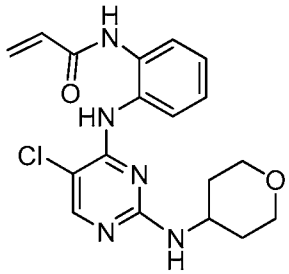
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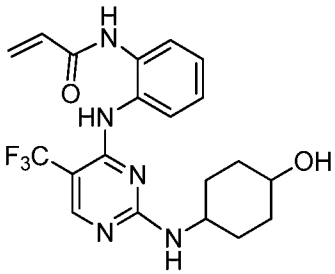
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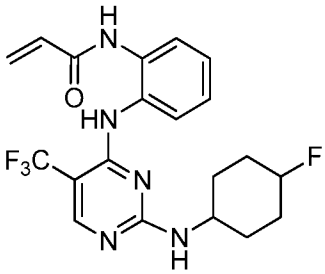
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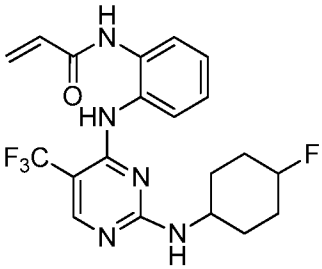
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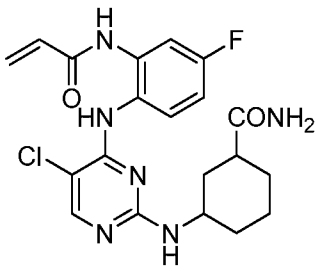
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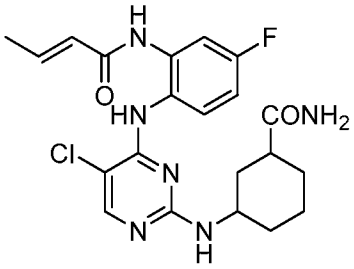
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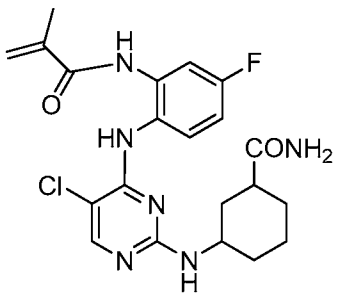
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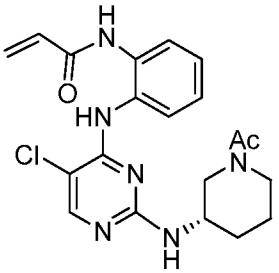
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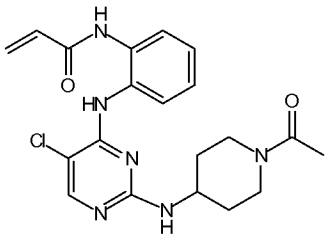


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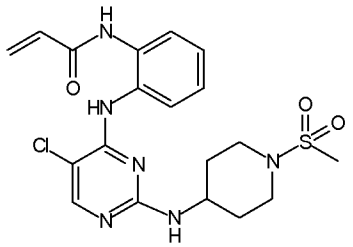


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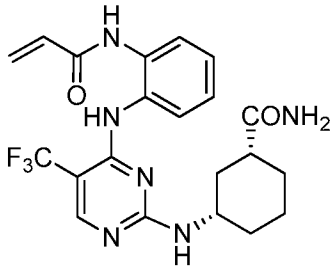




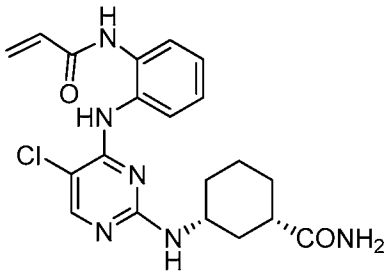
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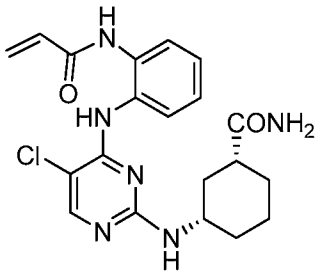
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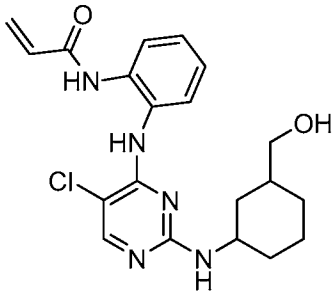
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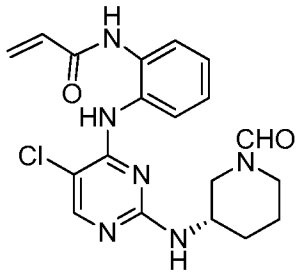
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I-119



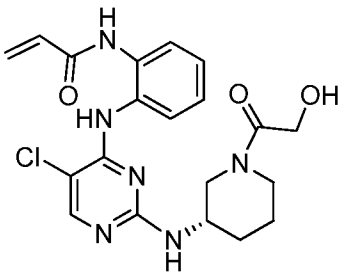
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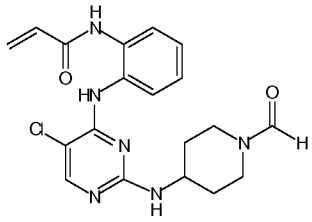
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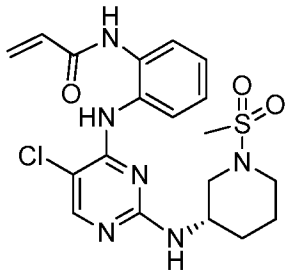
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I-123

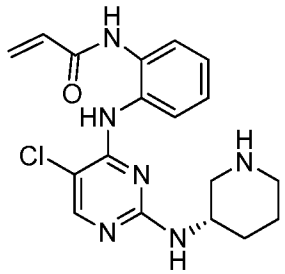


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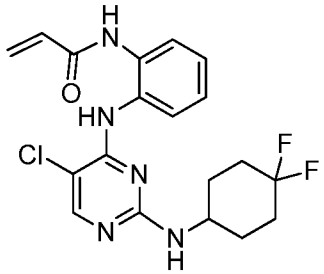




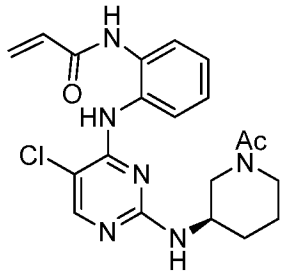
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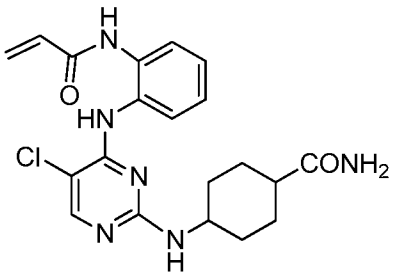
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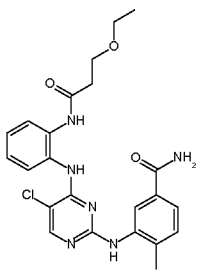
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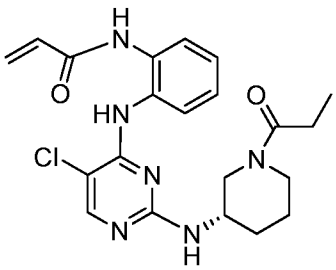
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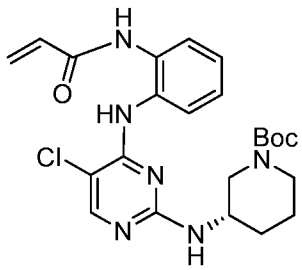
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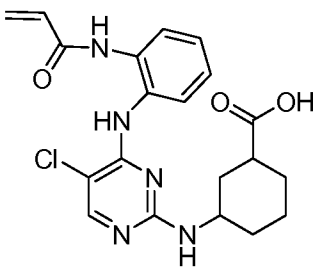
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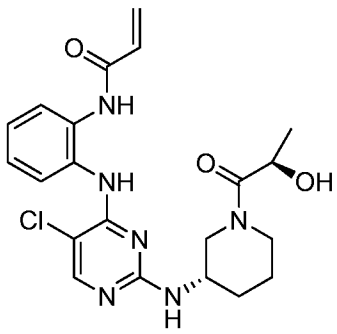


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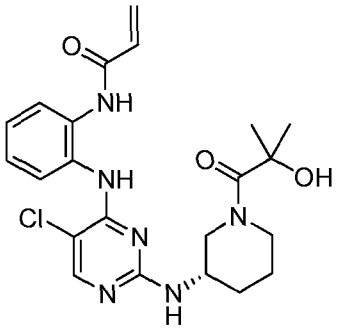


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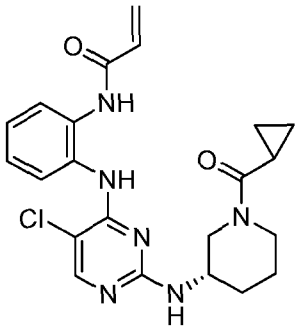




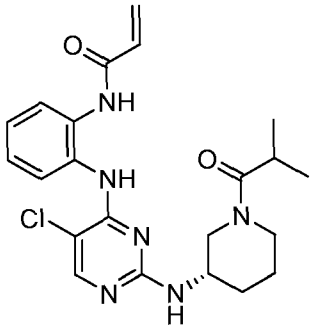
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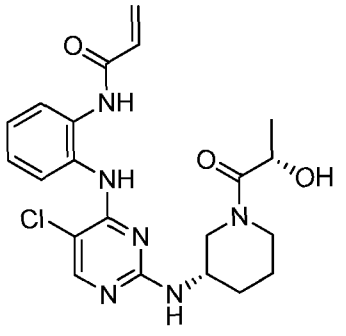
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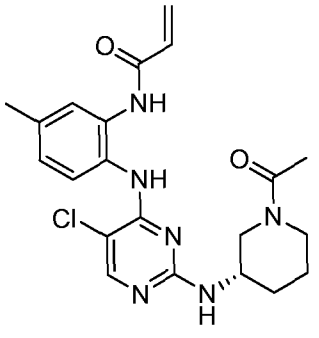
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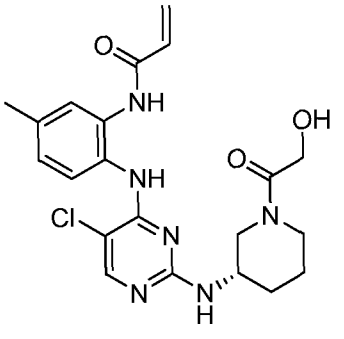
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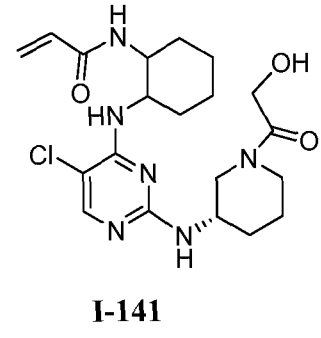
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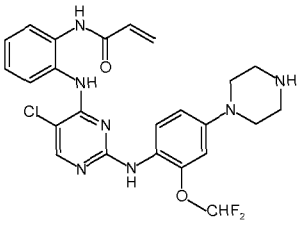
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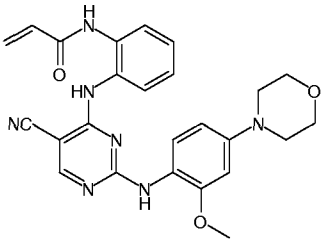


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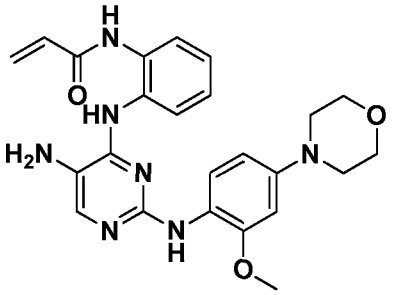
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I-142

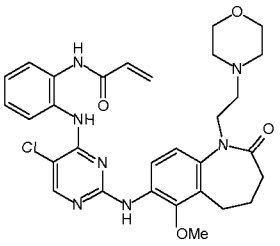




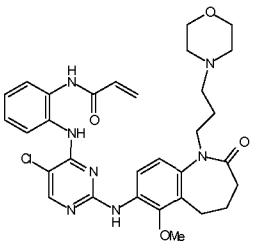
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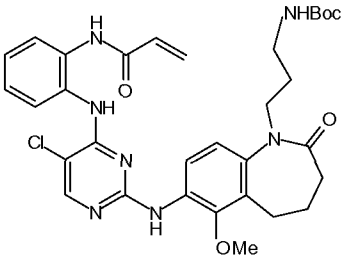
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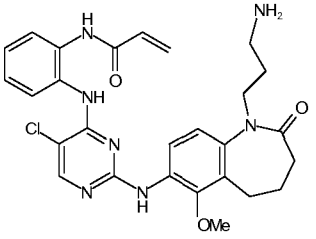
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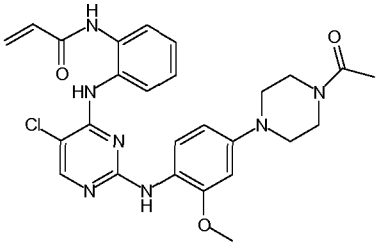
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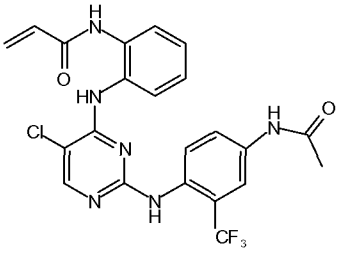
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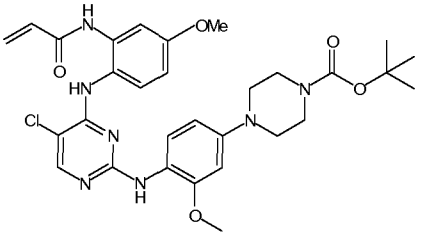
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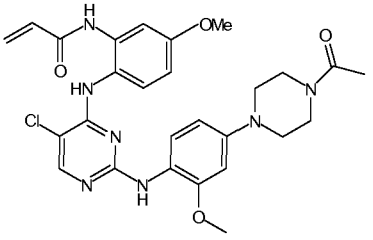
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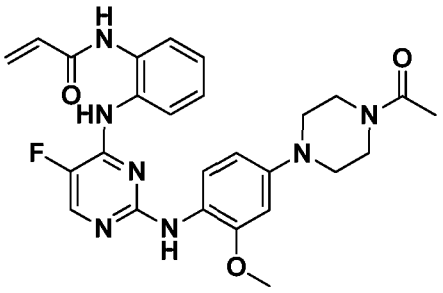
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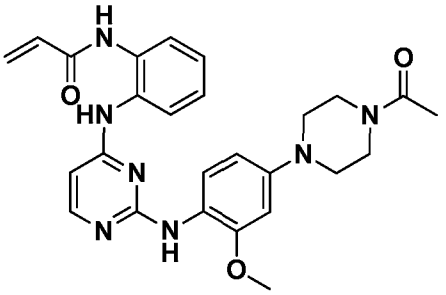
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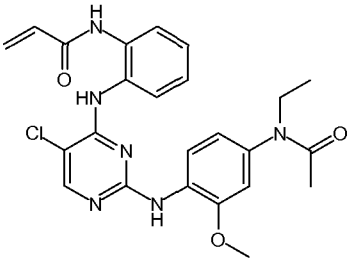
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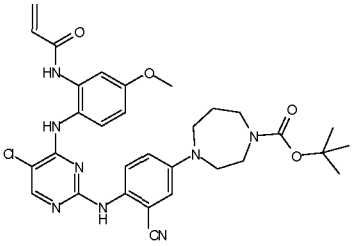
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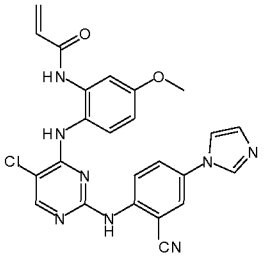
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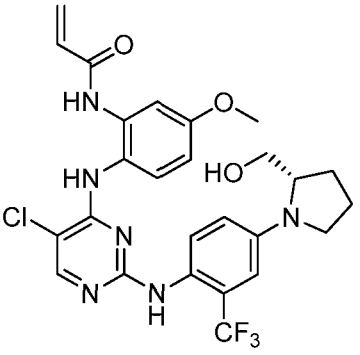
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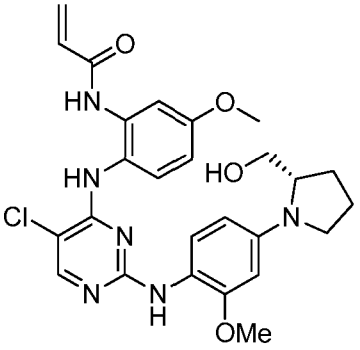
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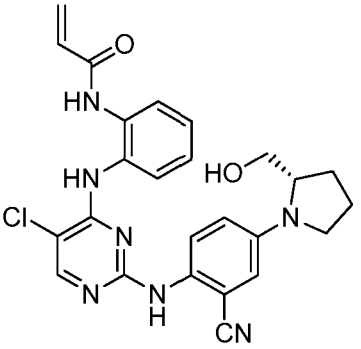
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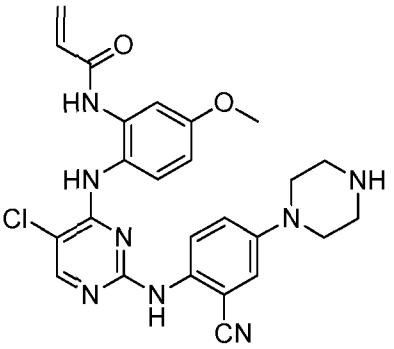
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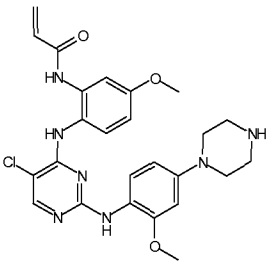
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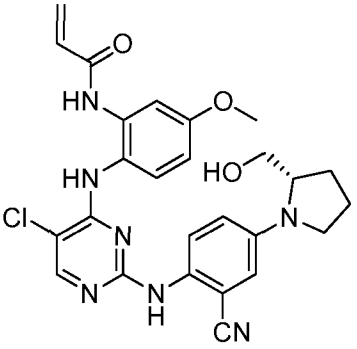
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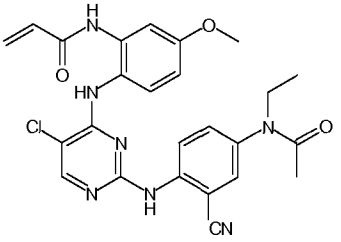
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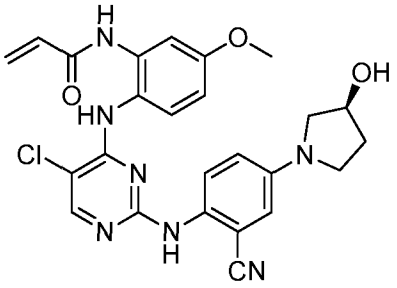
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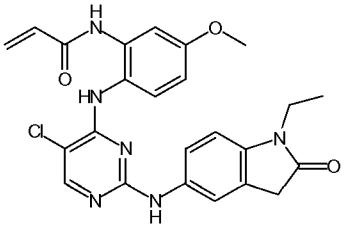
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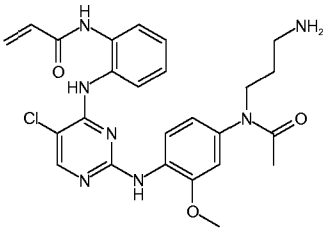
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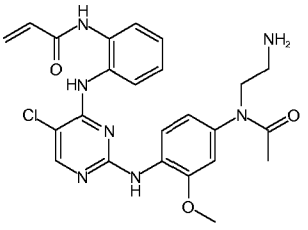
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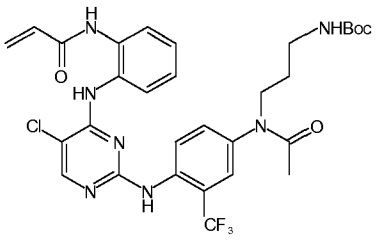
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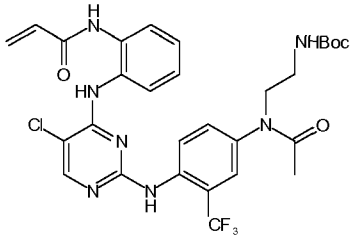
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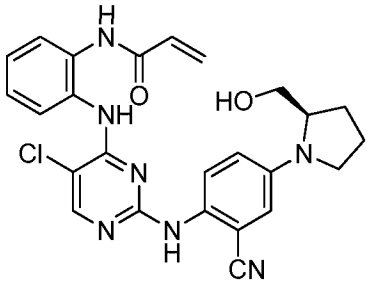
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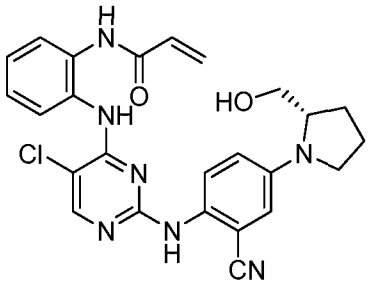
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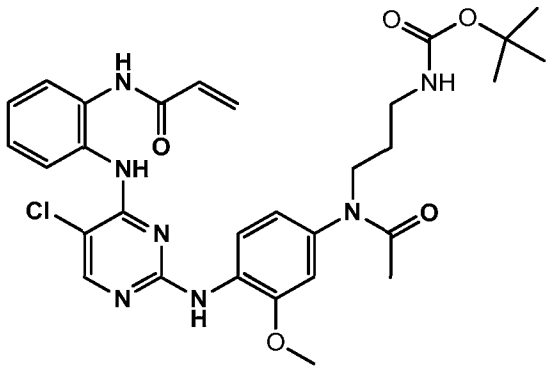
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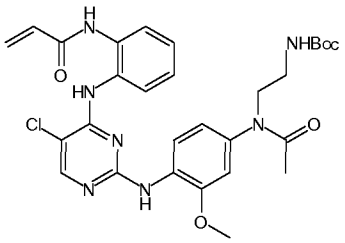
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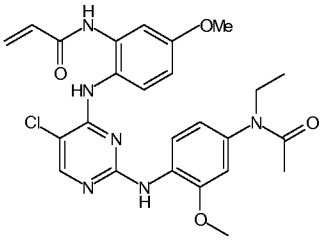
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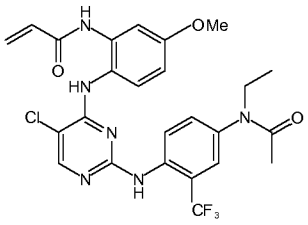
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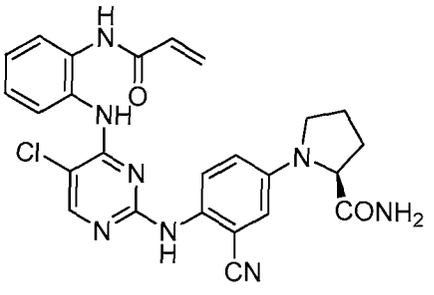
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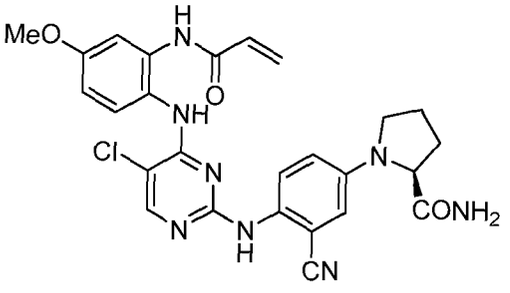
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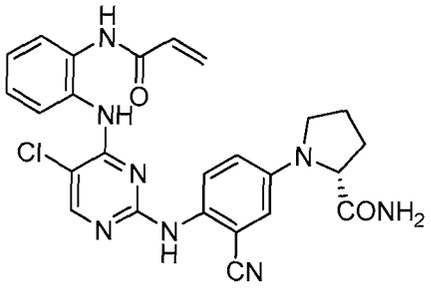
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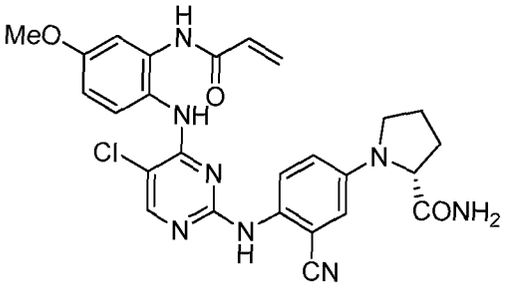
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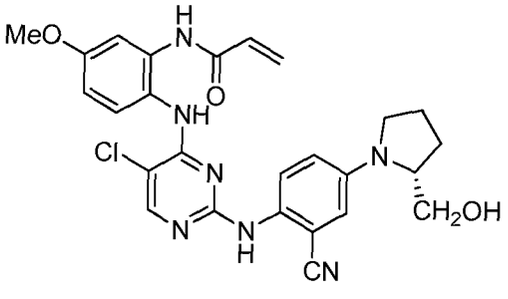
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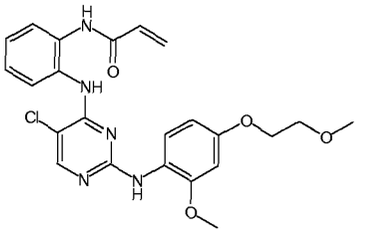
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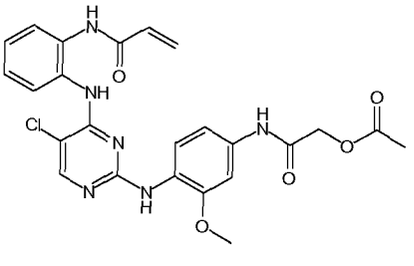
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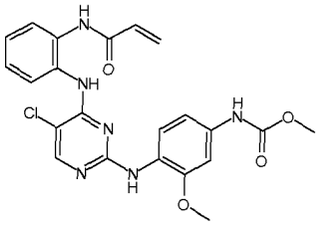
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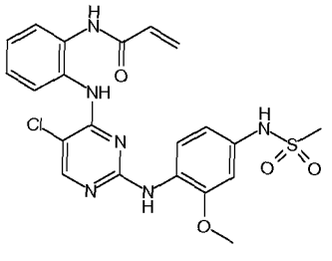
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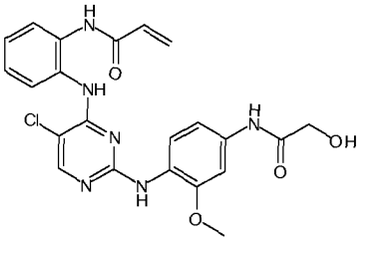


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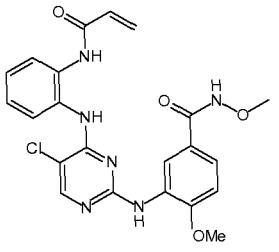


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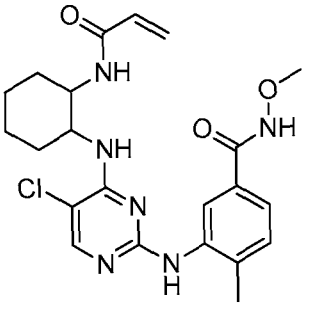




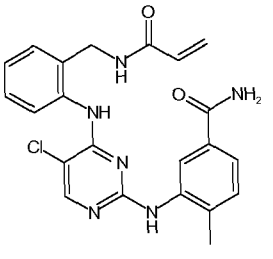
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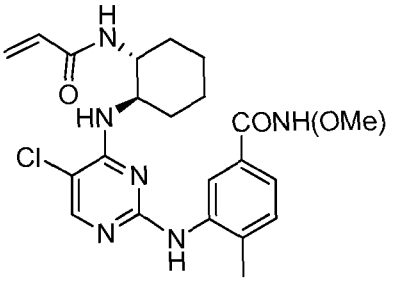
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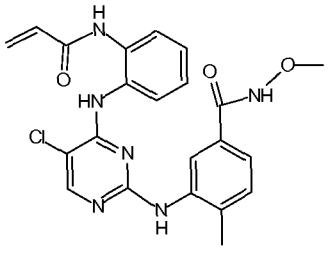
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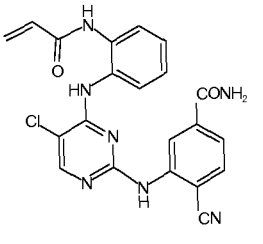
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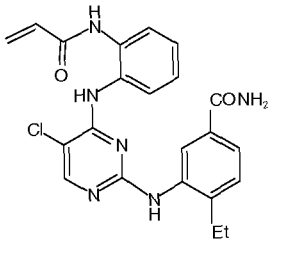
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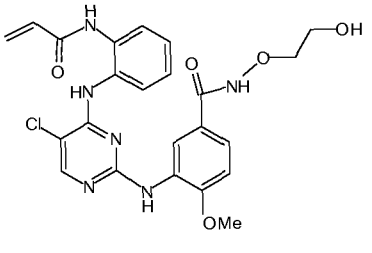
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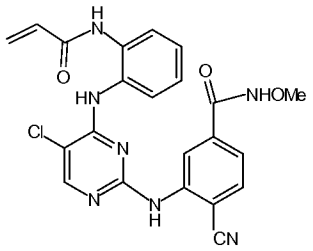


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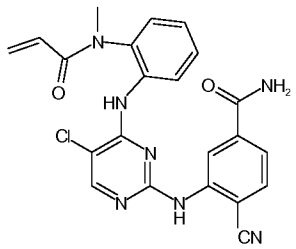
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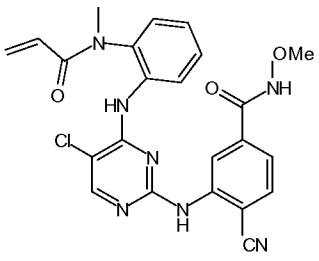




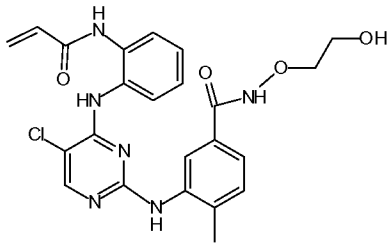
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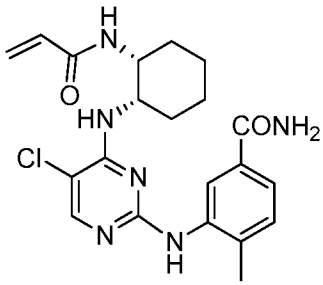
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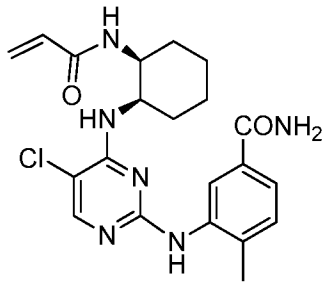
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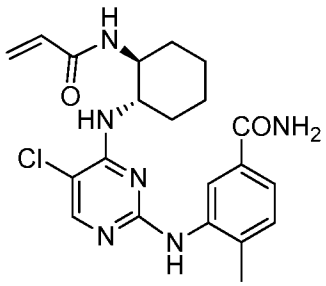
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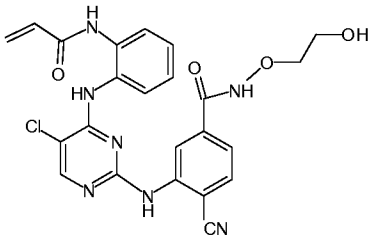
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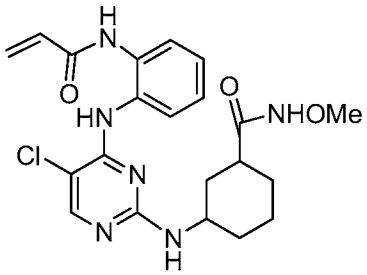
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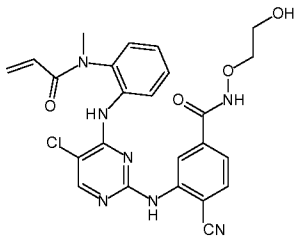


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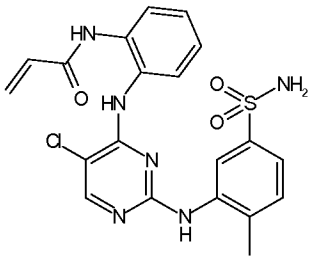


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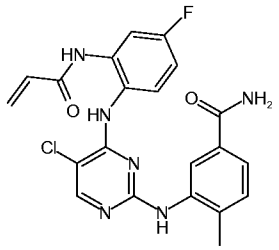




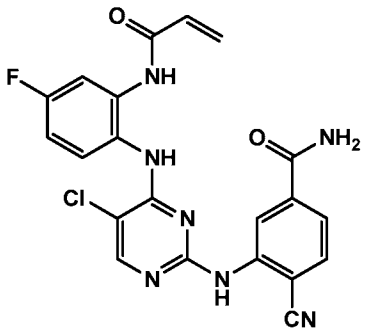
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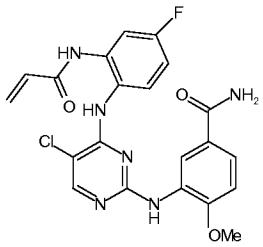
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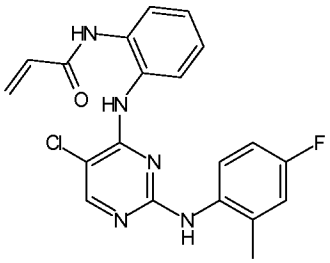
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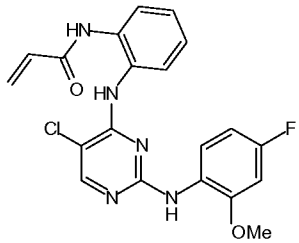
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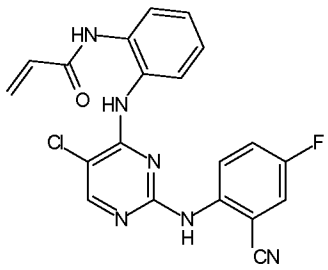
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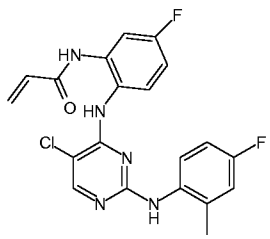
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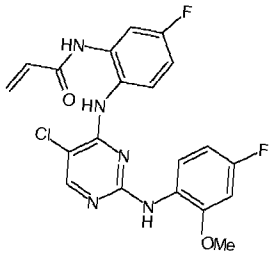


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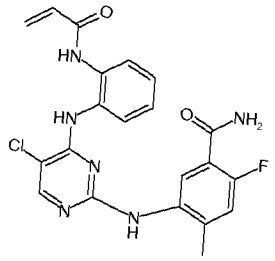


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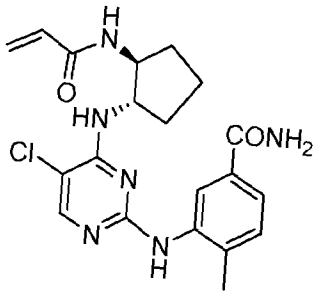
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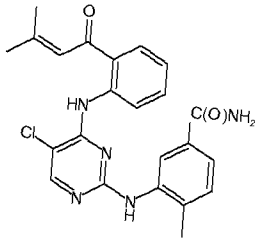
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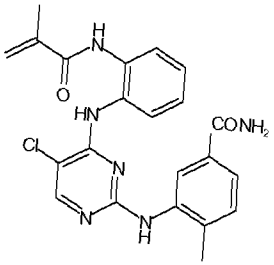
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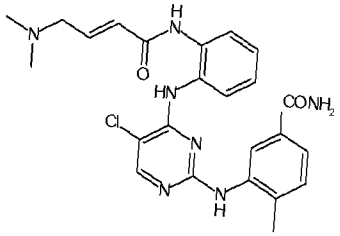
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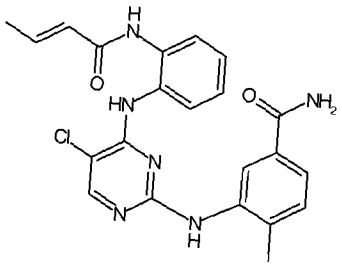
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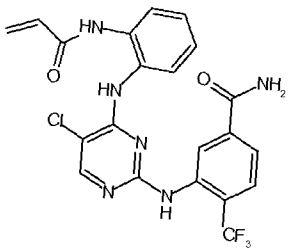
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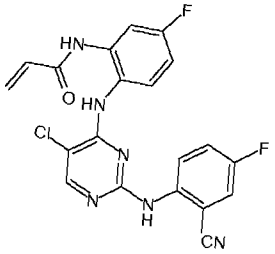
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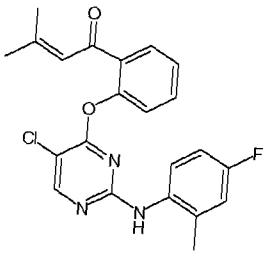
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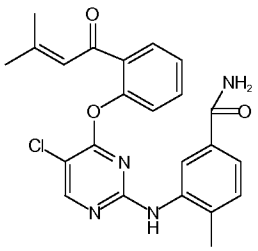
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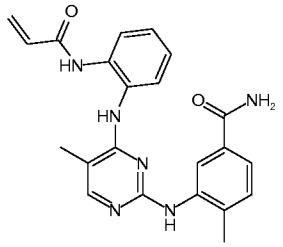
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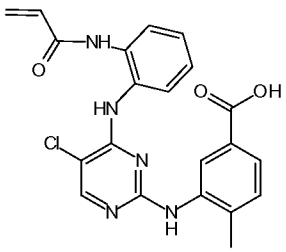
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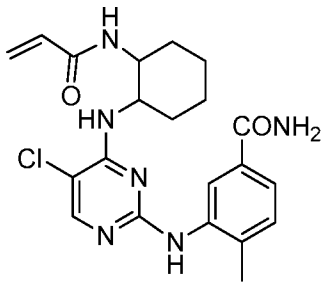
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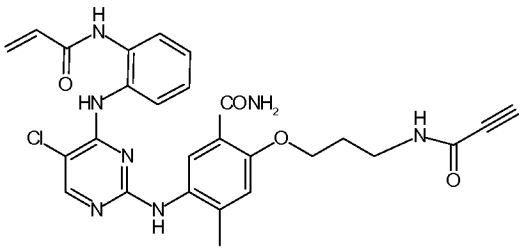
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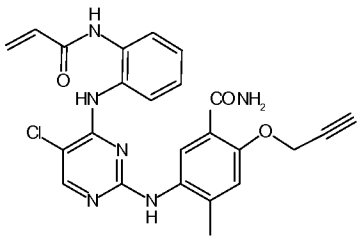
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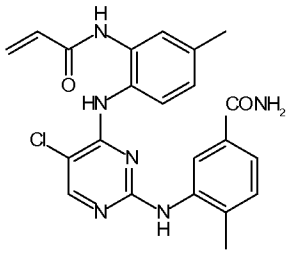
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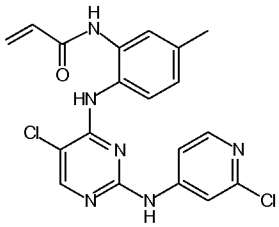
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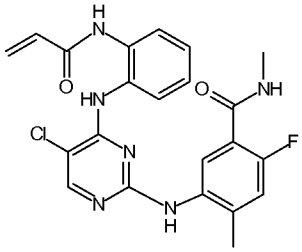
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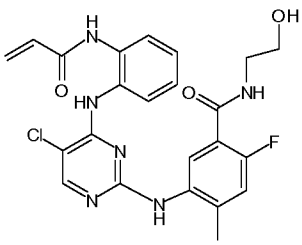
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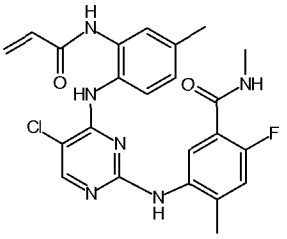
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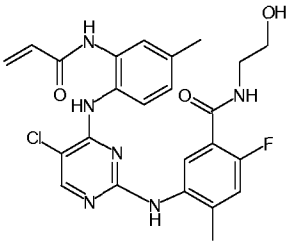
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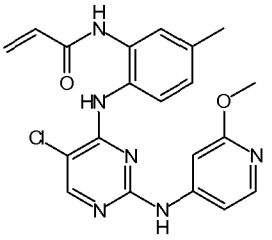
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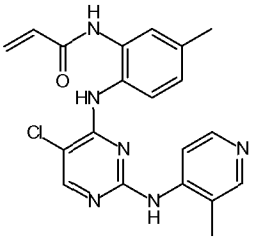
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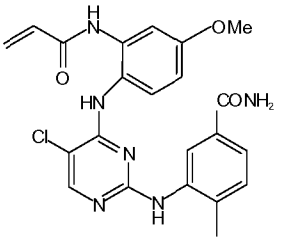
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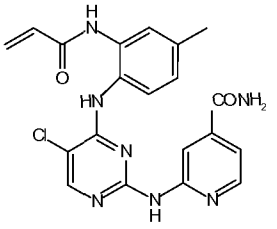
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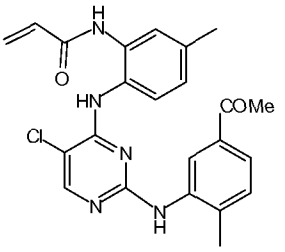
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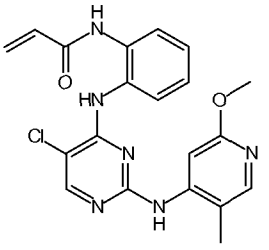
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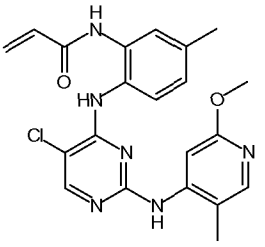
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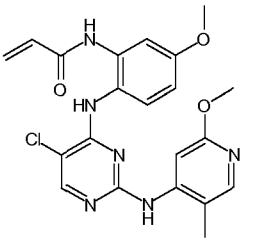
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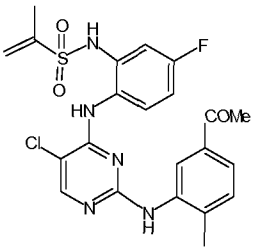
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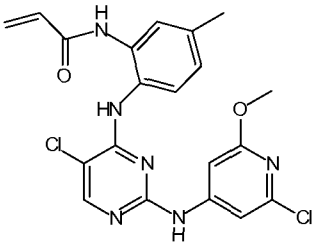
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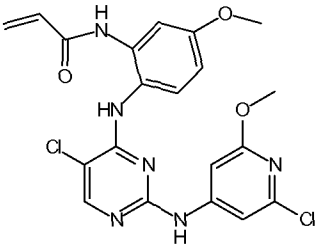
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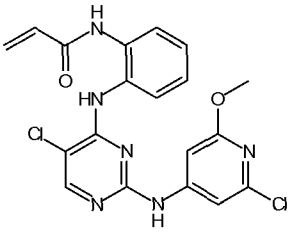
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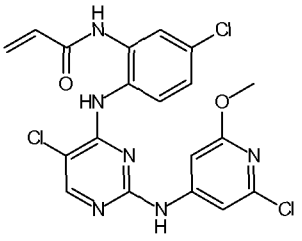
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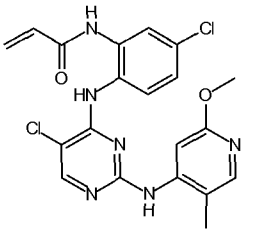
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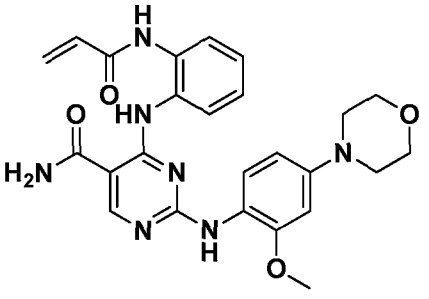
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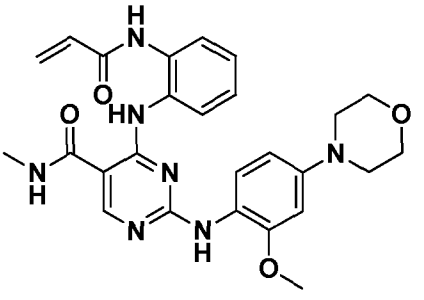
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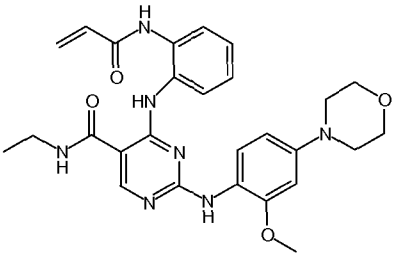
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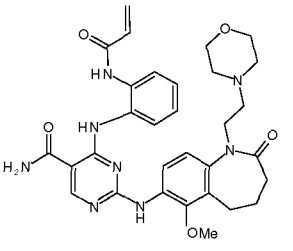
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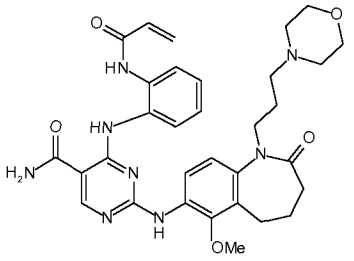
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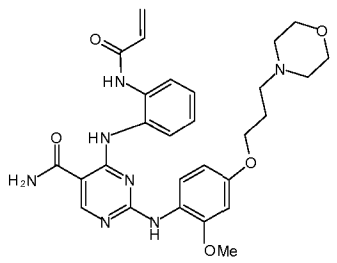
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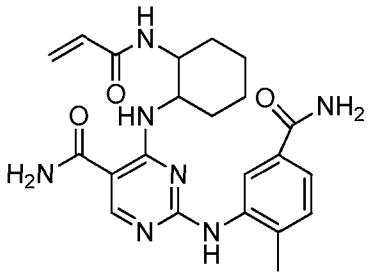
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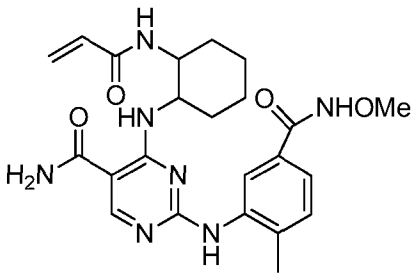
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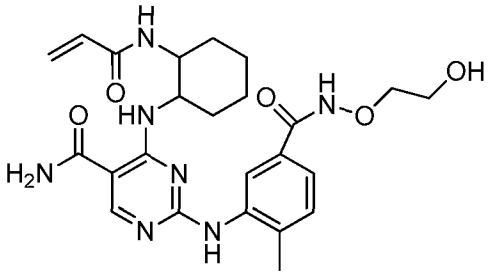
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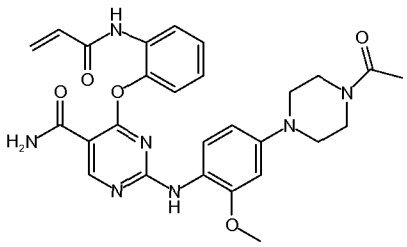
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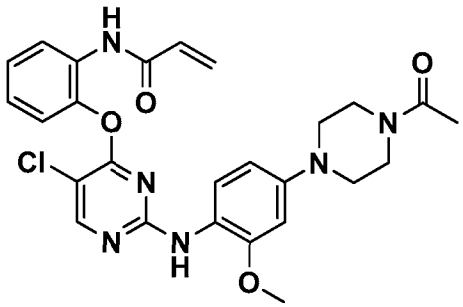
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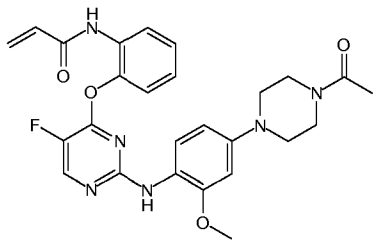
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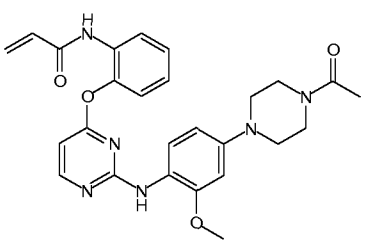
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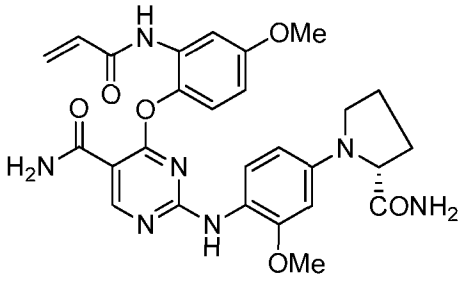


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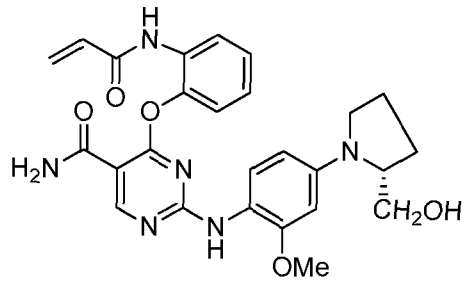


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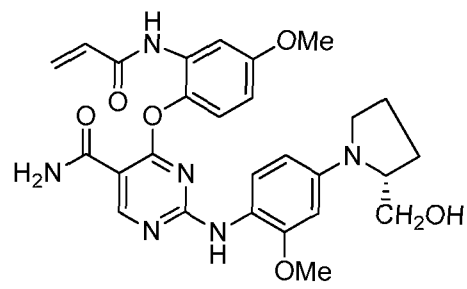




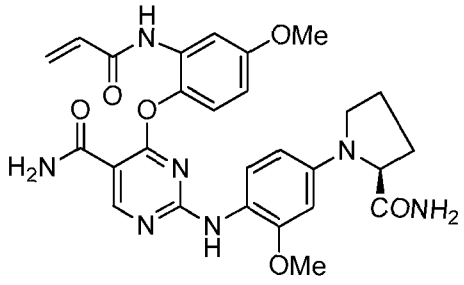
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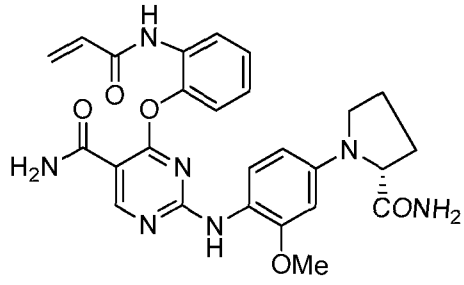
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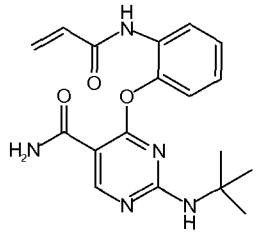
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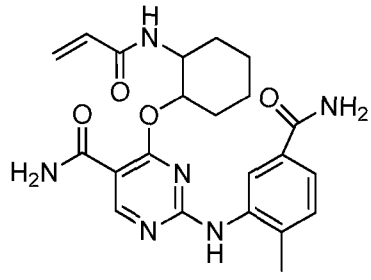
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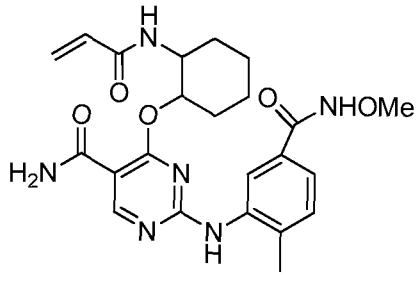
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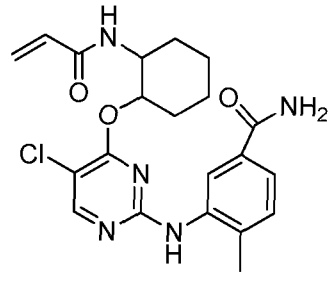
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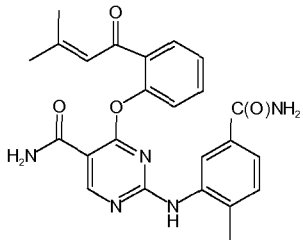
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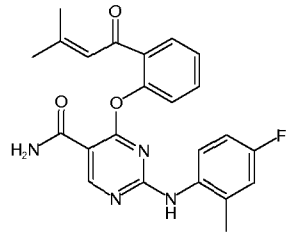
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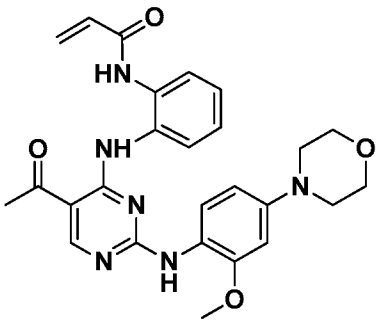
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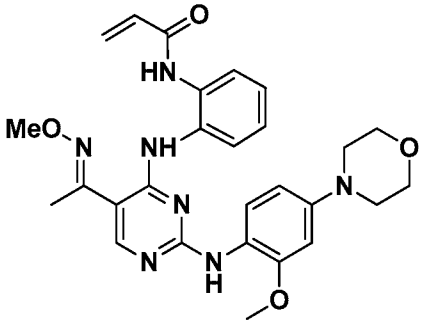
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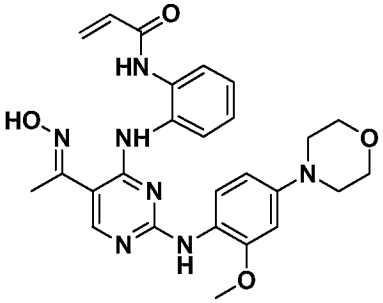
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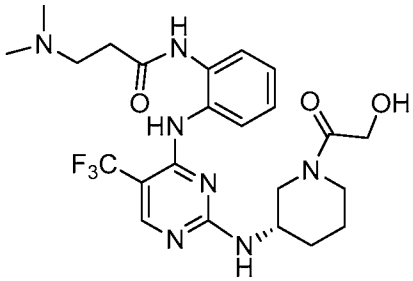
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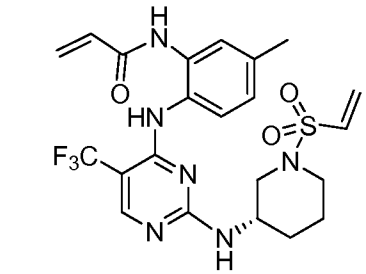
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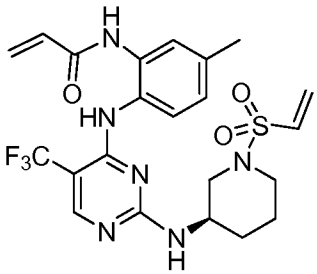
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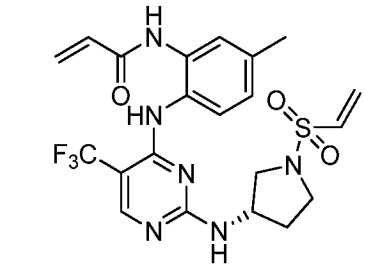
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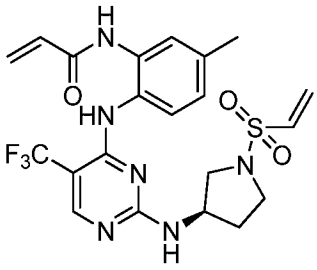
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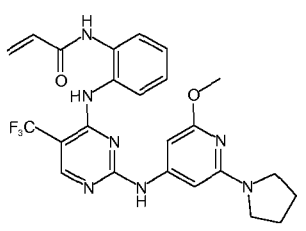


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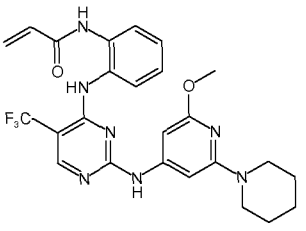


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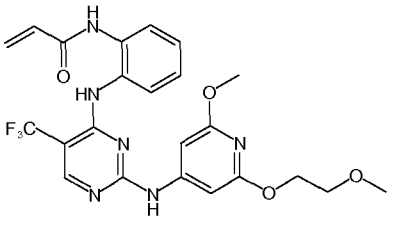
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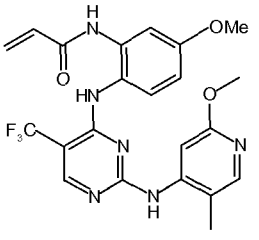
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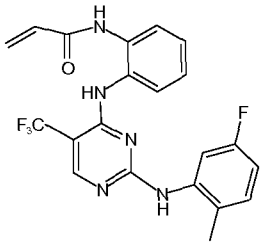
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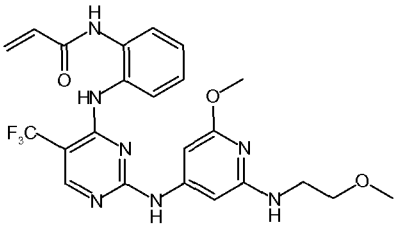
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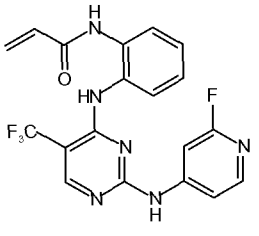
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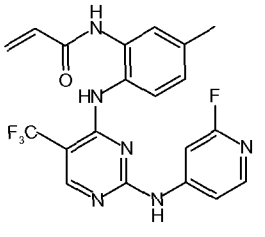
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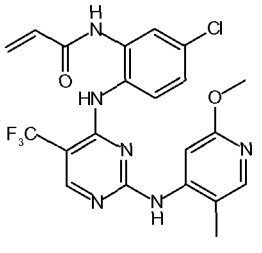
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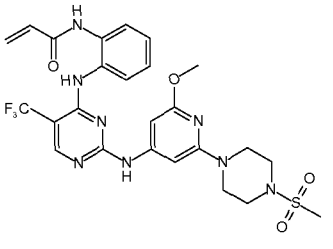
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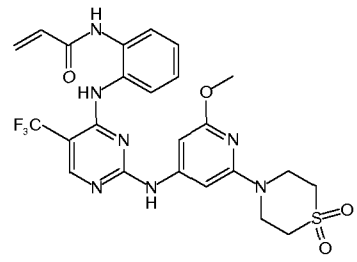
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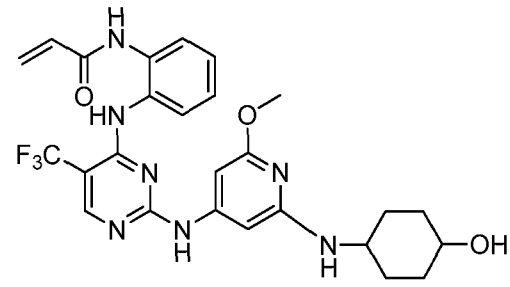
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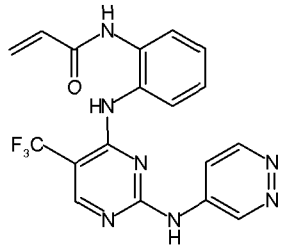
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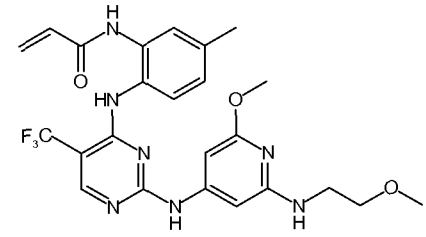
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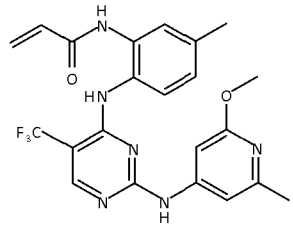
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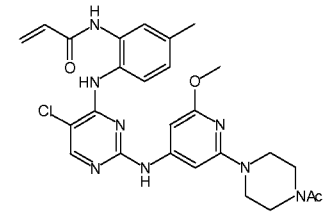
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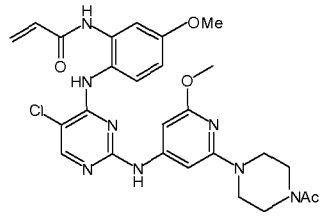
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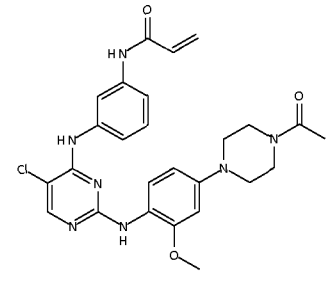
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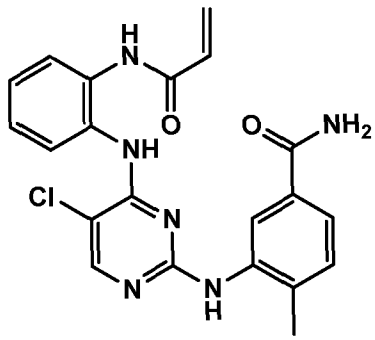
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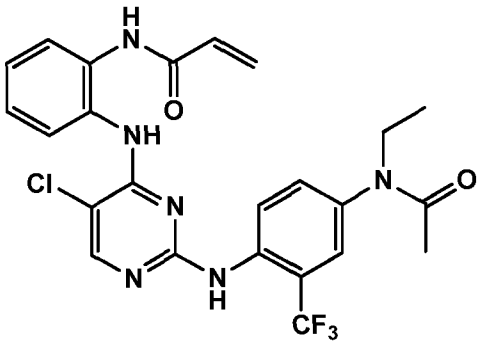
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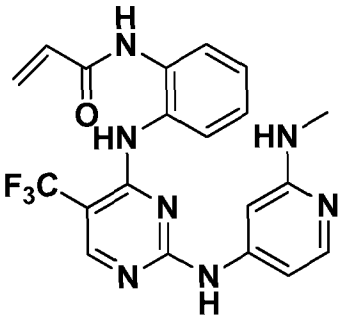
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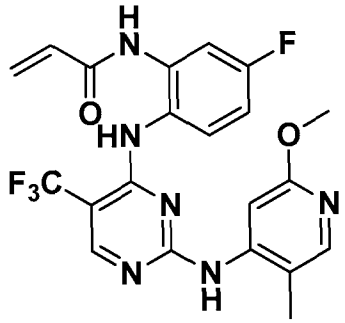
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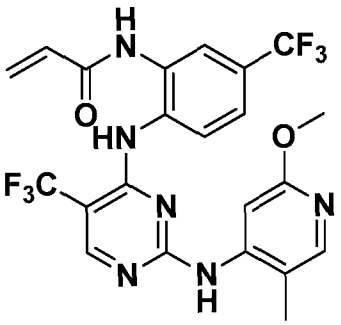
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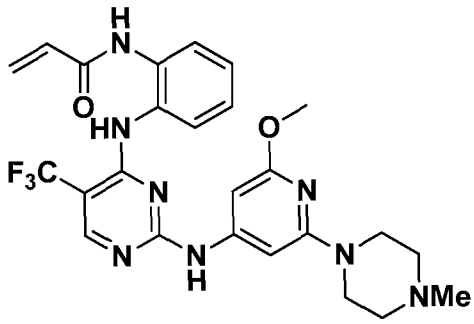
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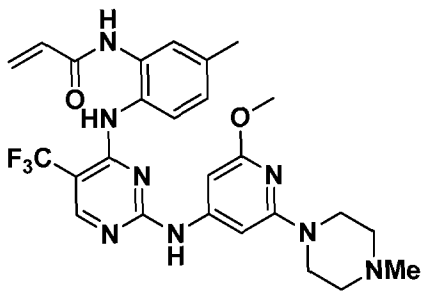
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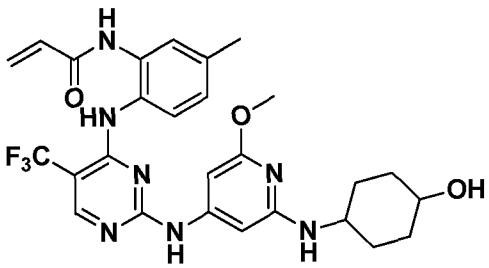
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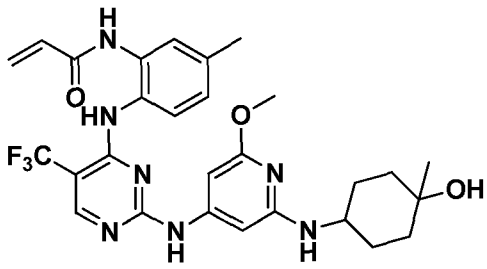
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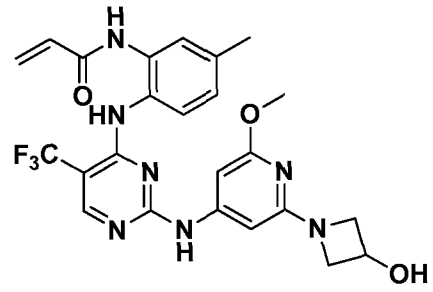
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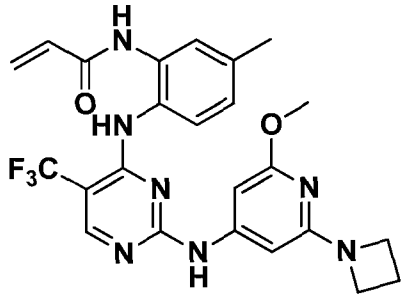
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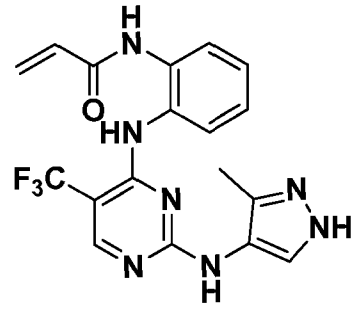
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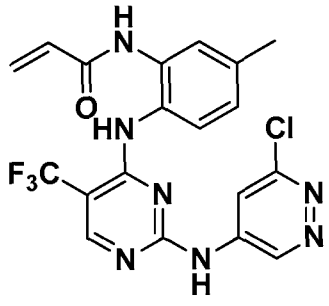
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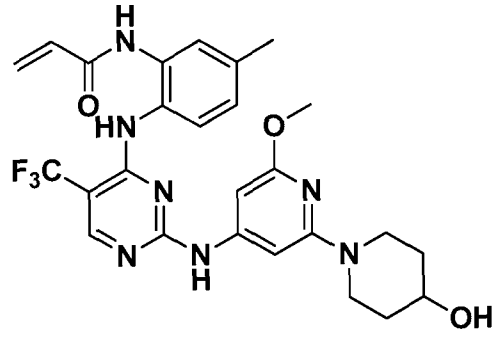
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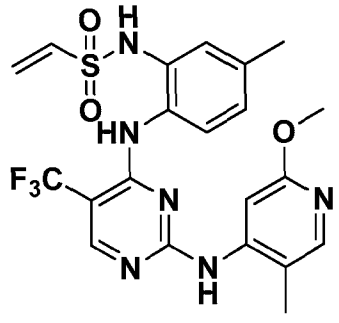
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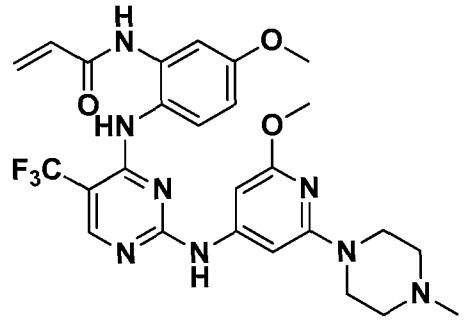
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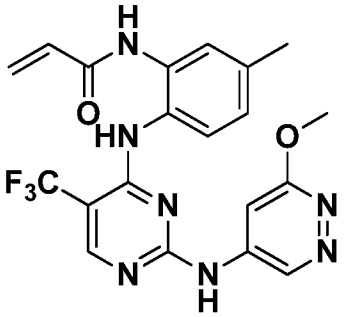
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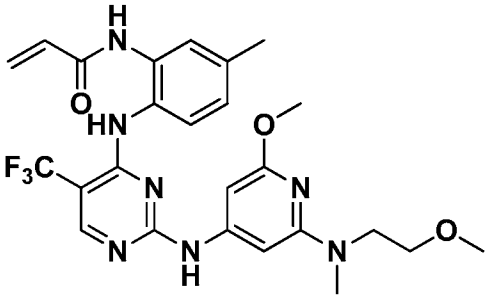
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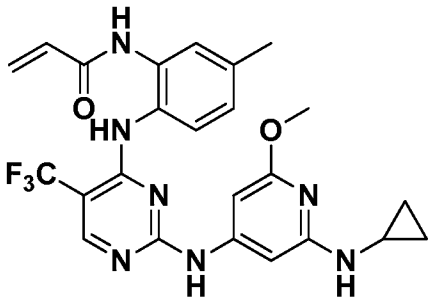
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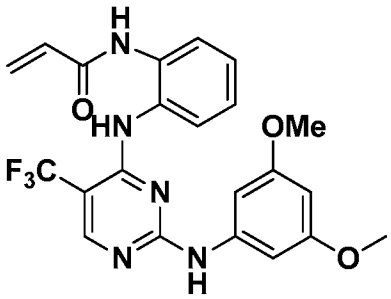
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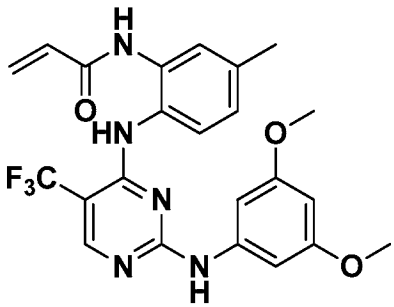
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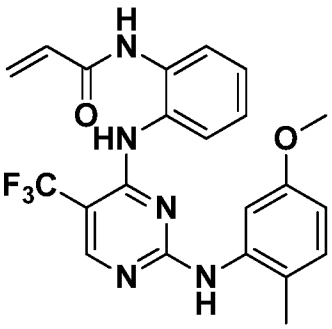
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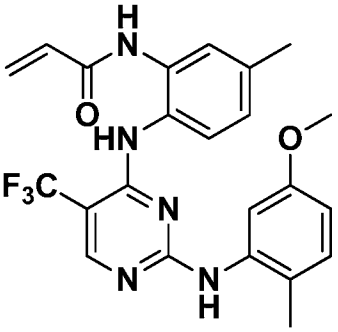
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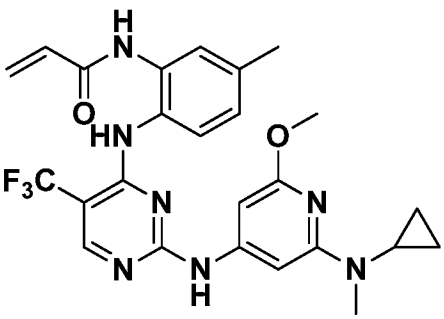
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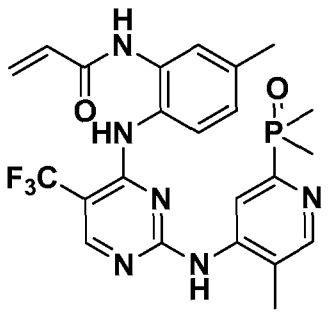
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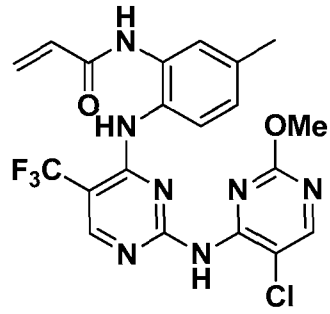
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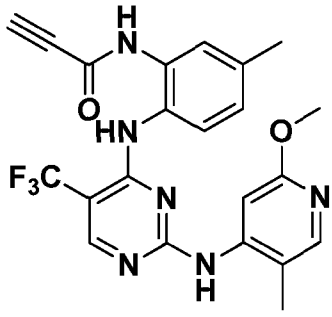
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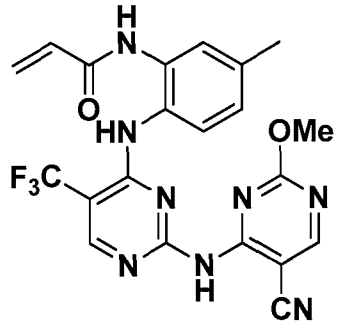
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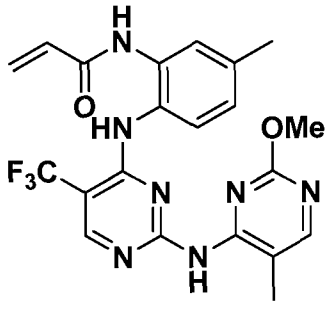
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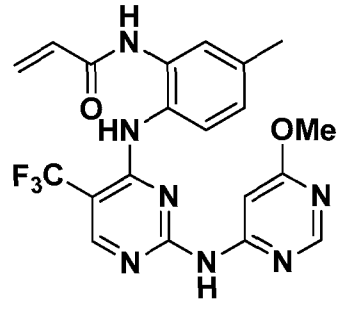
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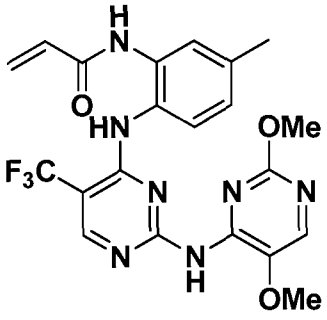
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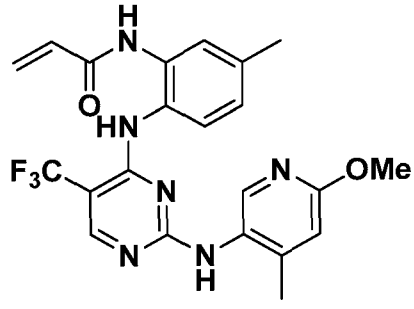
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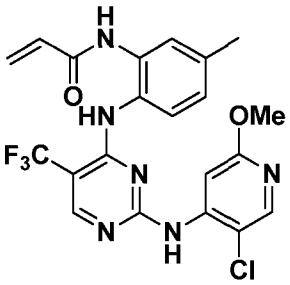
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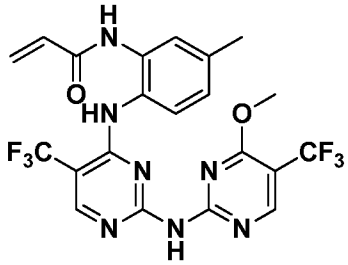
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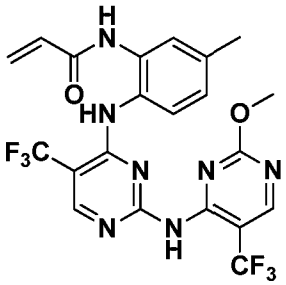
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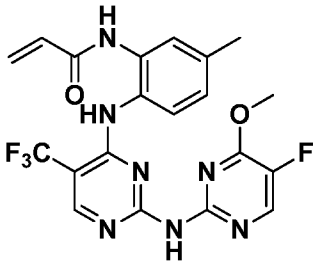
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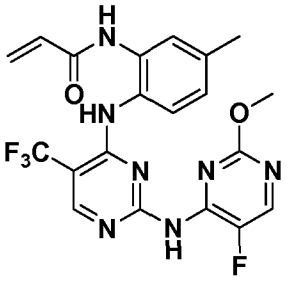
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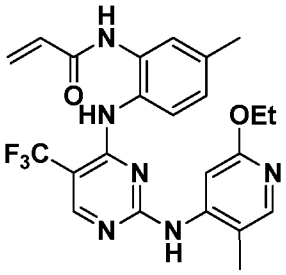
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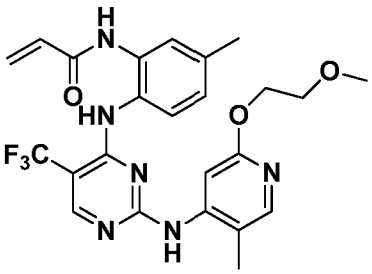
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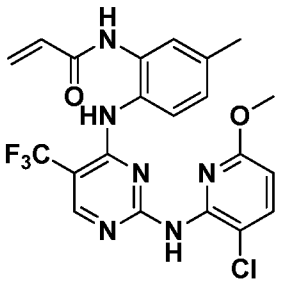
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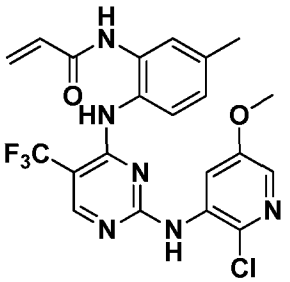
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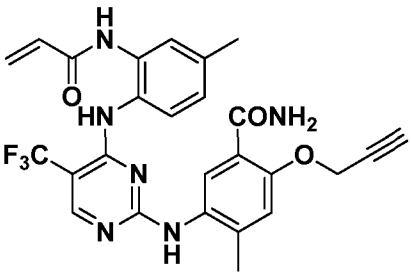


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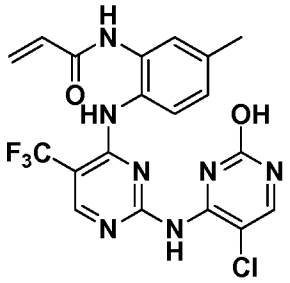


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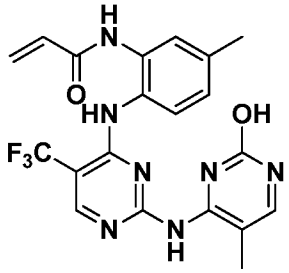




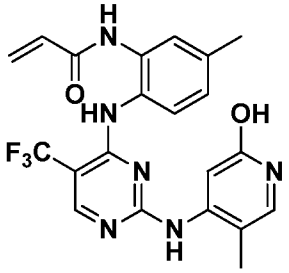
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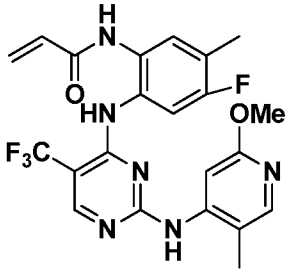
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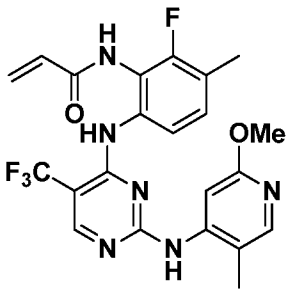
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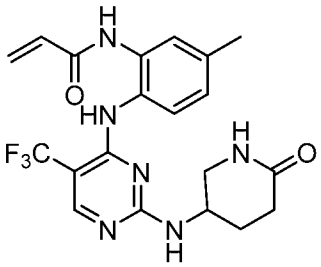
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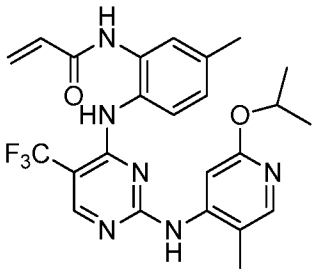


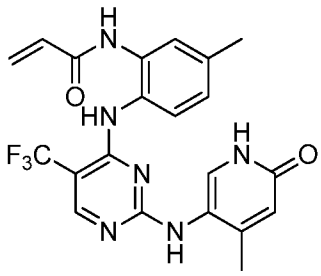
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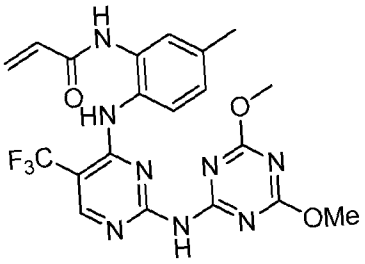
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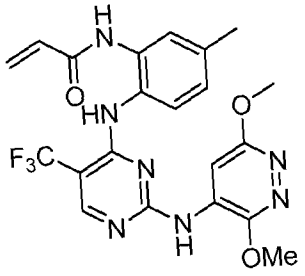


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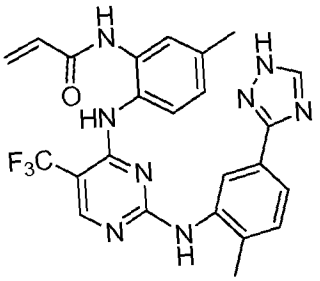
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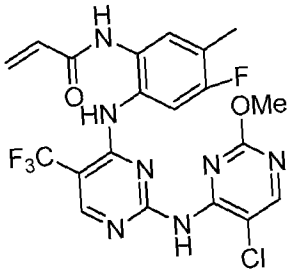
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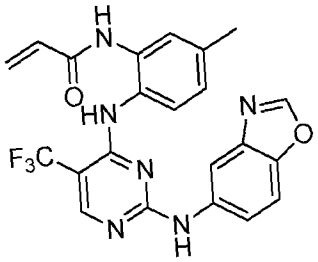
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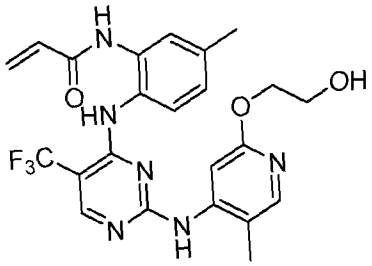
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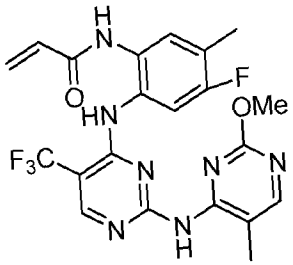
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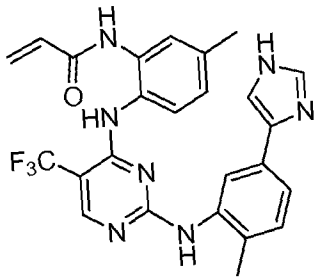
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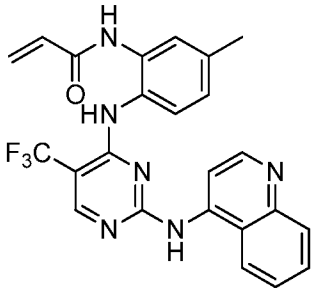
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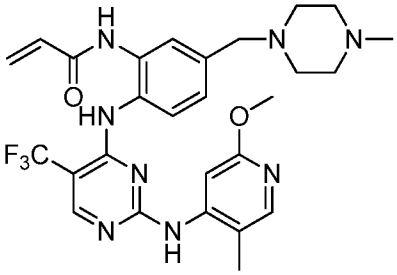
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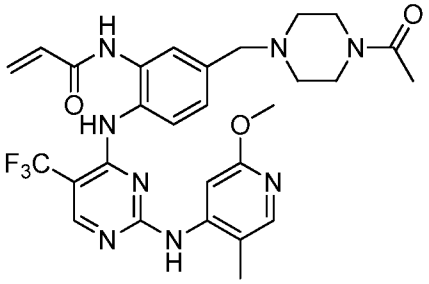
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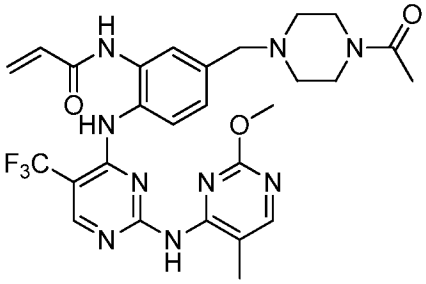
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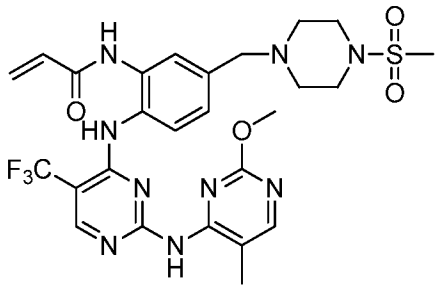
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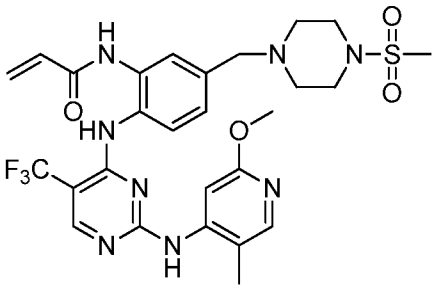
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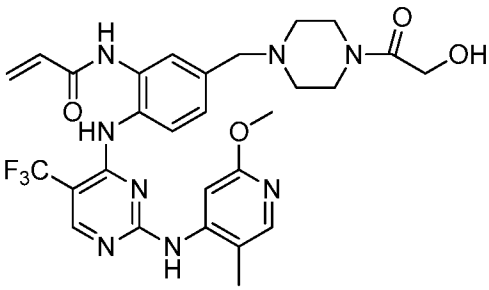
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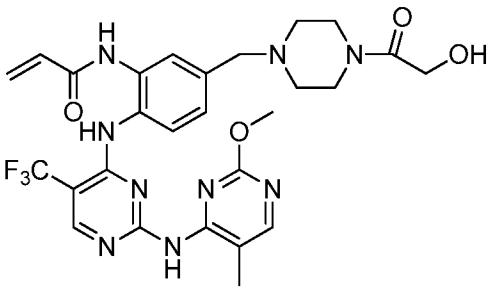
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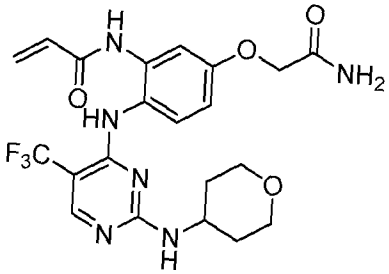
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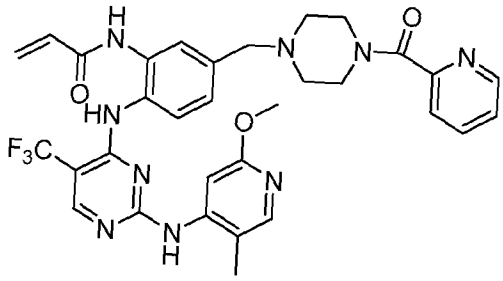
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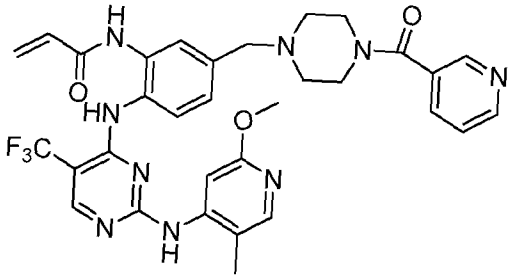
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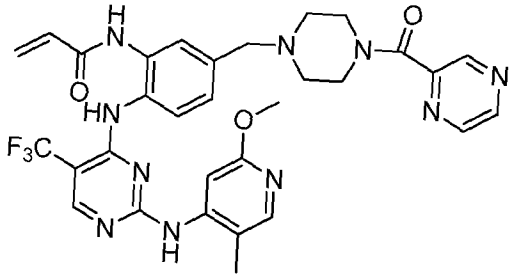
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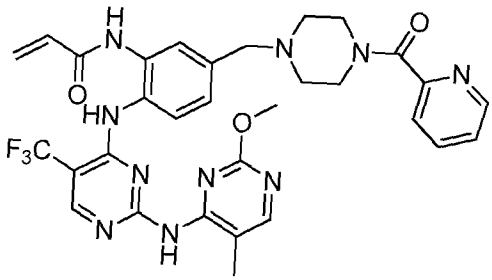
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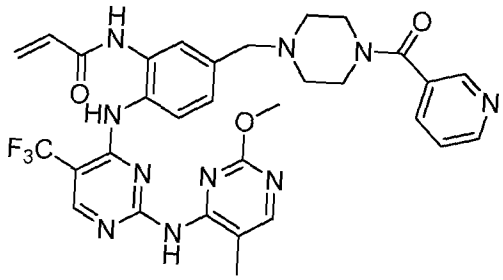
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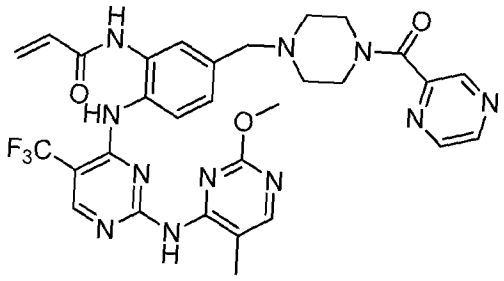
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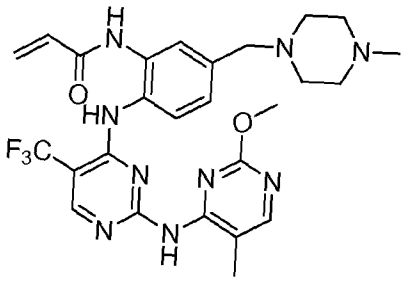
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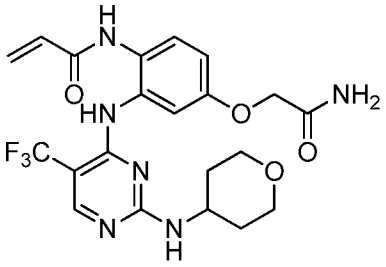
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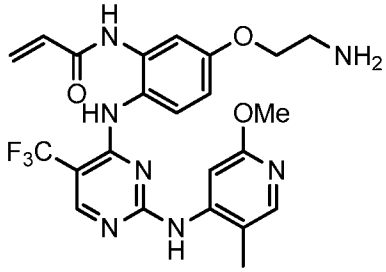
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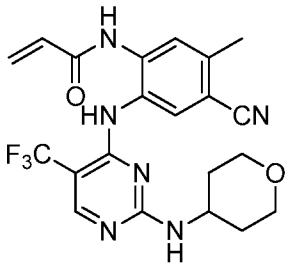
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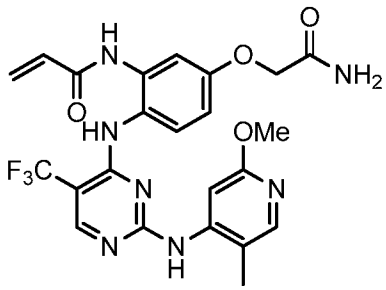
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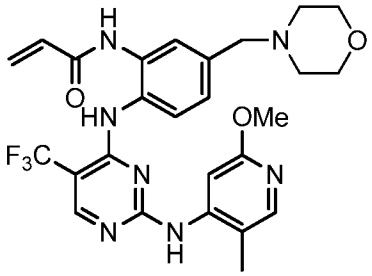
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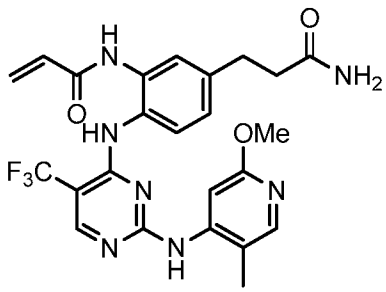
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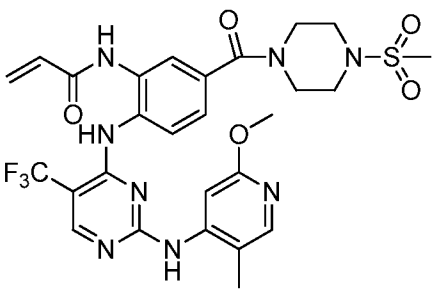
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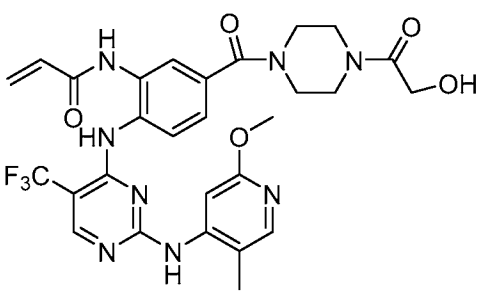
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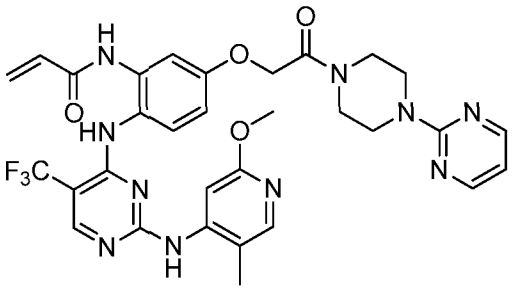
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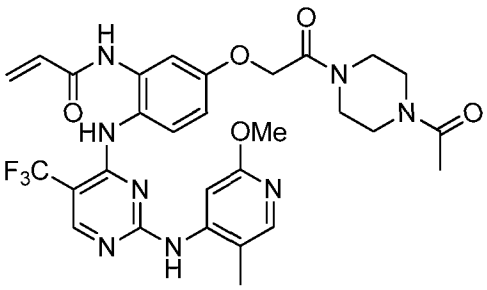
I-401



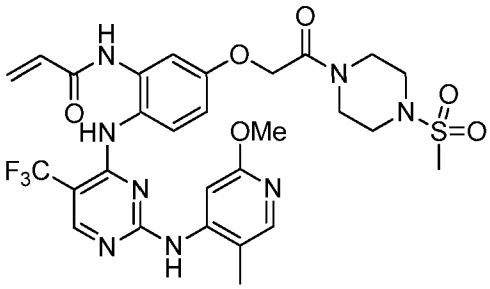
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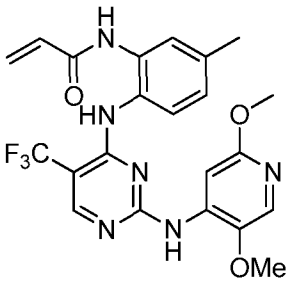
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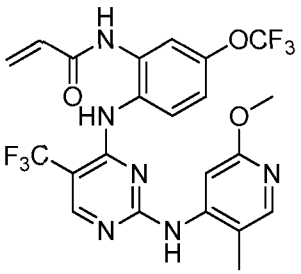
I-404



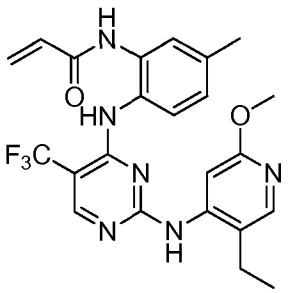
I-405



I-406

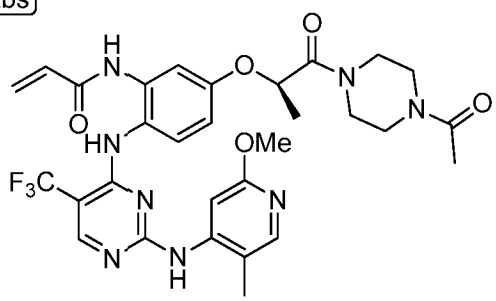


I-407



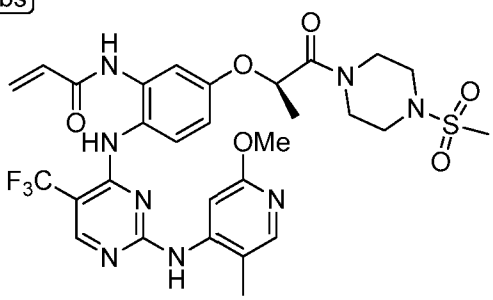
I-408

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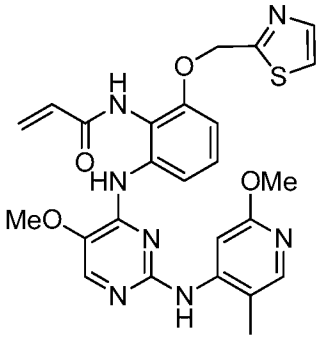


I-409

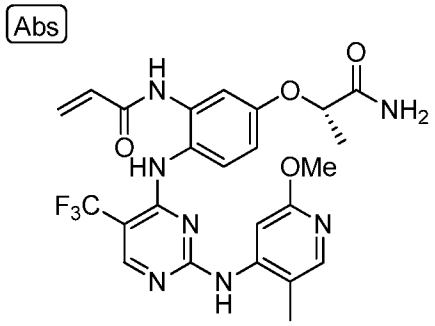
Abs



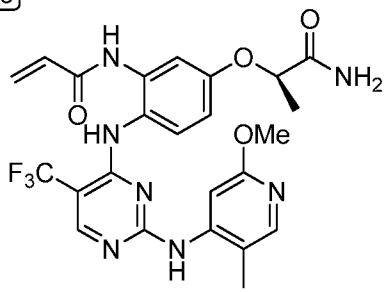
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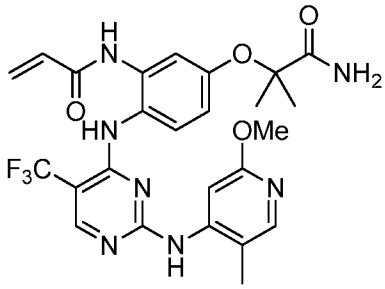
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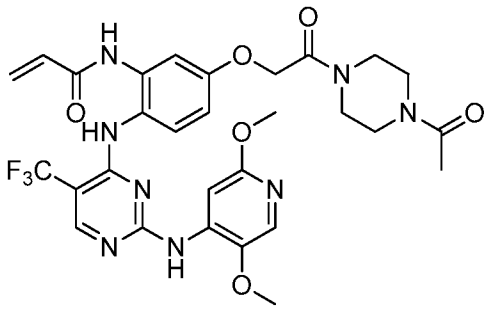
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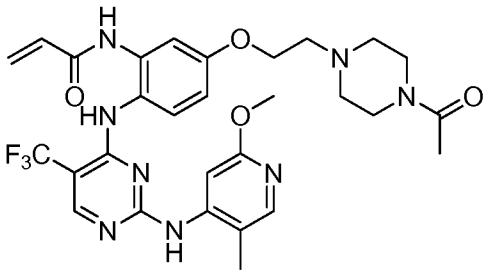
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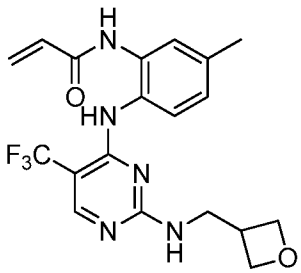
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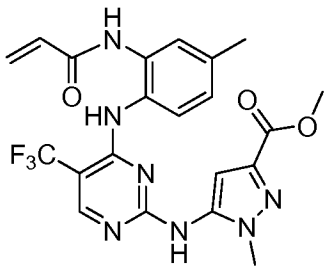
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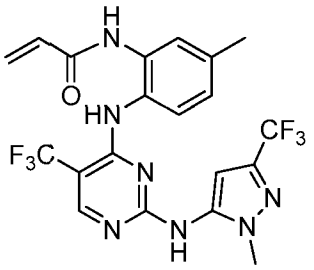
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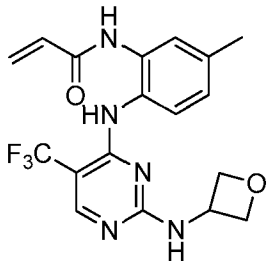
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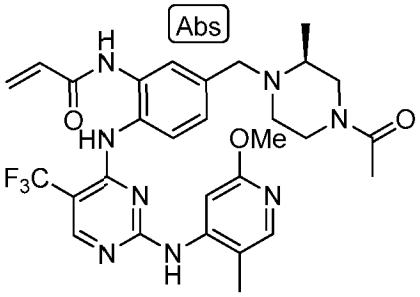
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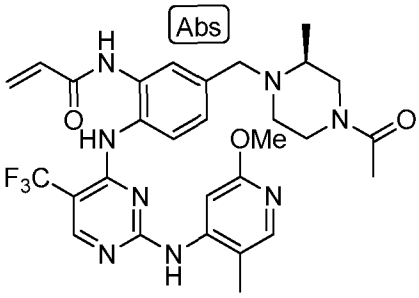
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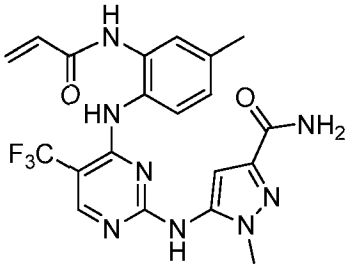
I-420



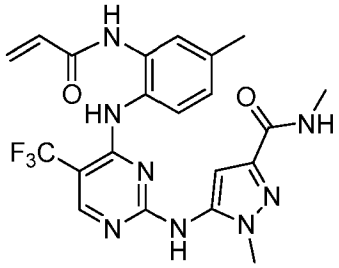
I-421



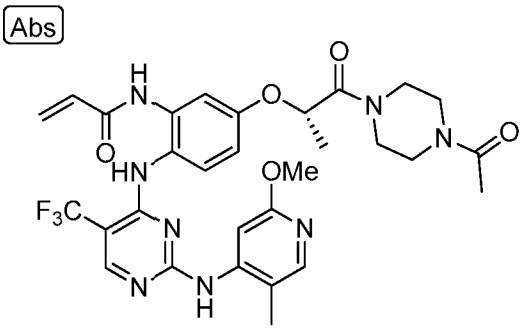
I-422



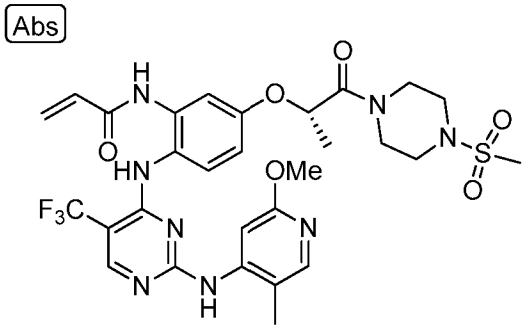
I-423



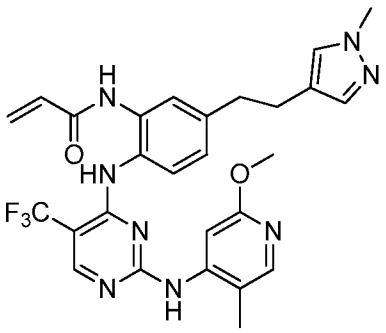
I-424



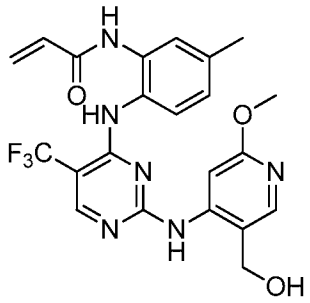
I-425



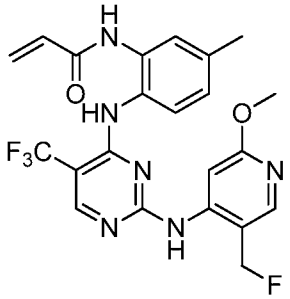
I-426



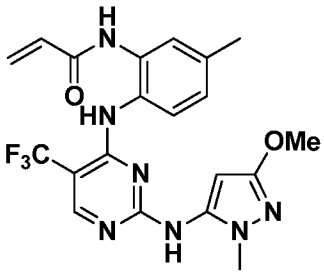
I-427



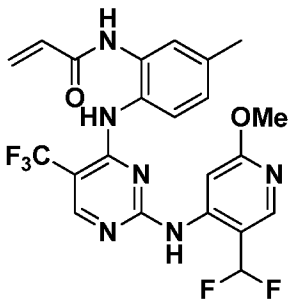
I-428



I-429



I-430

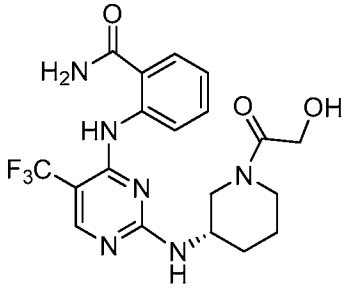


I-431

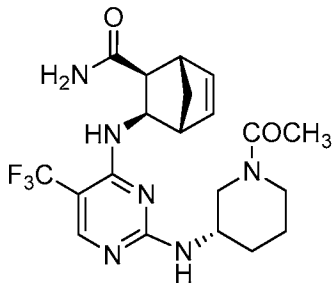
[00187] In some embodiments, the present invention provides a compound set forth in Table 3, above, or a pharmaceutically acceptable salt thereof.

[00188] Other compounds contemplated by the invention are selected from those depicted in Table 4, below:

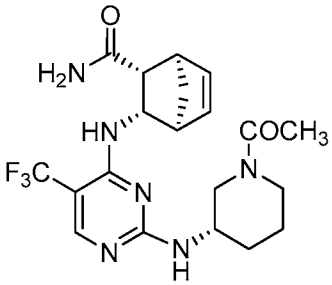
Table 4: Additional Exemplary Compounds



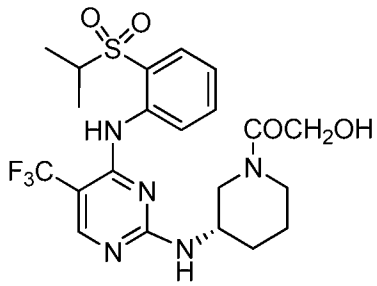
I-307



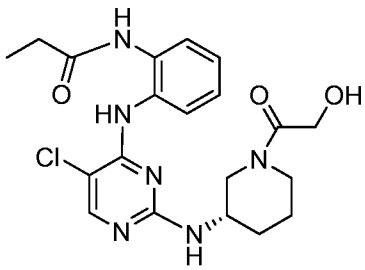
I-308



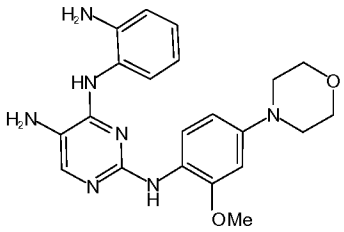
I-309



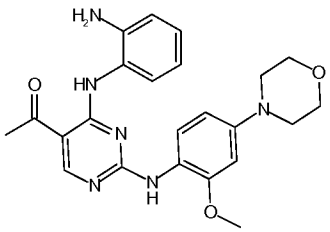
I-310



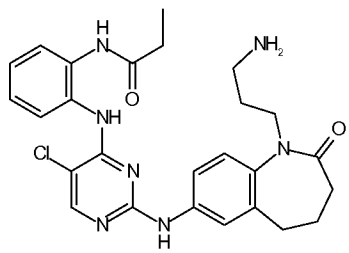
I-311



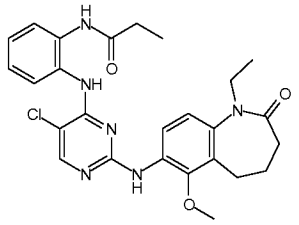
I-312



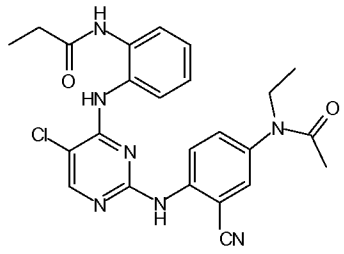
I-313



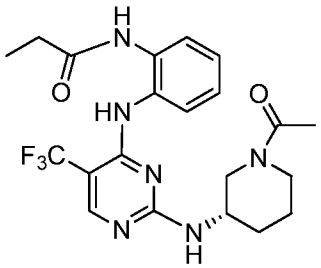
I-314



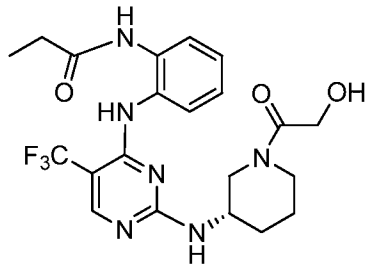
I-315



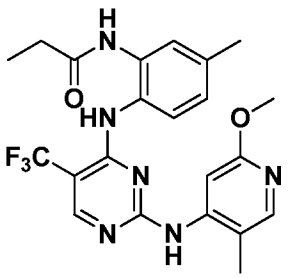
I-316



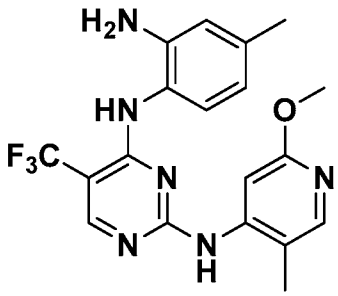
I-317



I-318



I-352



I-353

[00189] Compounds according to the invention can be conjugated to biological molecules, such as antibodies or other biological carriers. In certain embodiments, the present invention provides a conjugate comprising one or both of ERK1 and ERK2 kinase having a cysteine residue, Cys183 (ERK1) and/or Cys166 (ERK2), wherein the Cys183 and/or Cys166 is covalently, and irreversibly, bonded to an inhibitor, such that inhibition of the kinase is maintained. Cys166 of ERK2 is the same positional amino acid as Cys183 of ERK1. Thus, the below discussion regarding Cys183 of ERK1 also applies to Cys166 of ERK2 (and *vice versa*).

[00190] In certain embodiments, the present invention provides a conjugate of the formula **A**:

Cys183–modifier–inhibitor moiety

A

wherein:

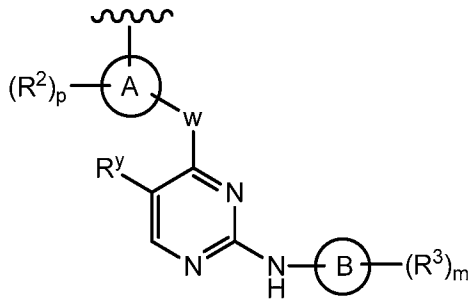
the Cys183 is Cys183 of ERK1;

the modifier is a bivalent group resulting from covalent bonding of a warhead group with the Cys183 of ERK1 kinase;

the warhead group is a functional group capable of covalently binding to Cys183; and

the inhibitor moiety is a moiety that binds in the ATP binding site of the ERK1 kinase.

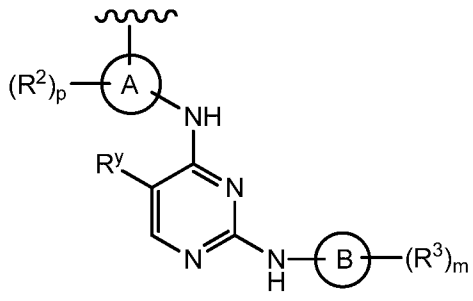
[00191] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **I-*i***:



I-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where W is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, W, m and p, of formula **I-*i*** is as defined for formula **I** above and as defined and described in embodiments herein. In some embodiments, each of Ring A, Ring B, R^2, R^3, R^y, W, m and p, of formula **I-*i*** is as defined for formula **I'** above and as defined and described in embodiments herein.

[00192] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **I-a-*i***:

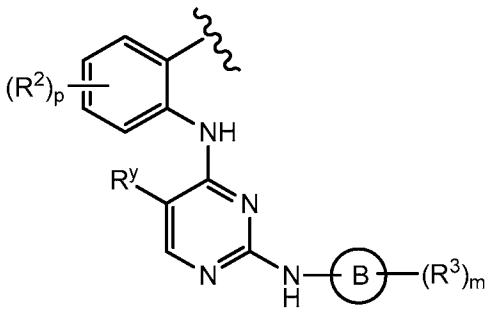


I-a-*i*

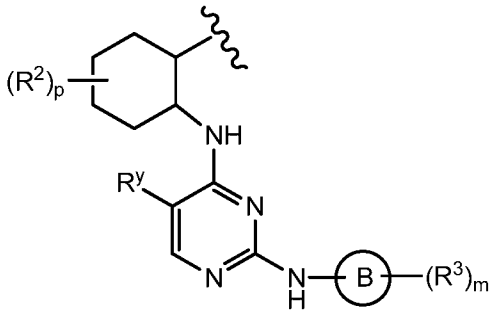
wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, m

and p, of formula **I-a-*i*** is as defined for formula **I-a** above and as defined and described in embodiments herein.

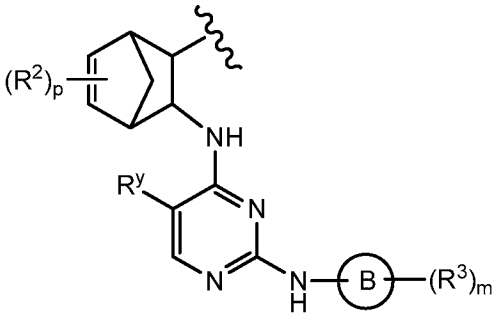
[00193] In certain embodiments, the inhibitor moiety of conjugate **A** is any one of formulae **I-b-*i***, **I-c-*i***, **I-d-*i***, and **I-e-*i***:



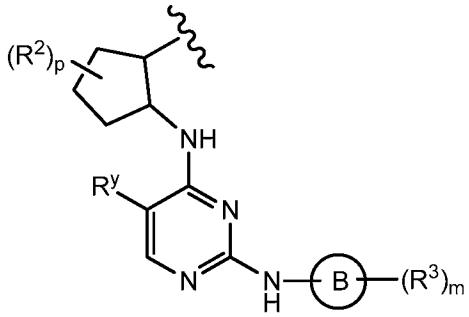
I-b-*i*



I-c-*i*



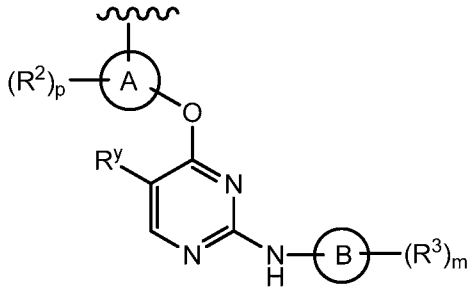
I-d-*i*



I-e-*i*

wherein each wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein each of Ring B, R^2, R^3, R^y, m and p, of formulae **I-b-*i***, **I-c-*i***, **I-d-*i***, and **I-e-*i*** is as defined for formulea **I-b**, **I-c**, **I-d**, and **I-e** above and as defined and described in embodiments herein.

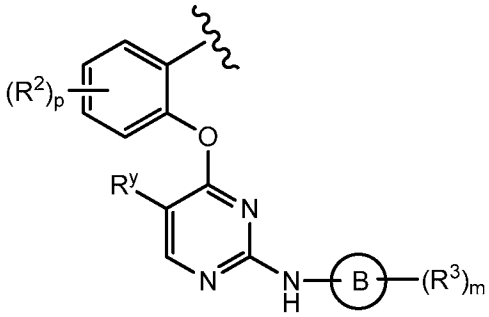
[00194] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **I-f-*i***:



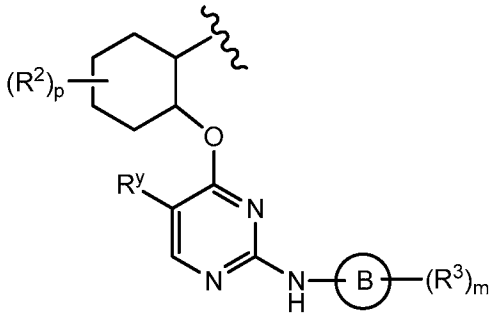
I-f-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, m and p, of formula **I-f-*i*** is as defined for formula **I-f** above and as defined and described in embodiments herein.

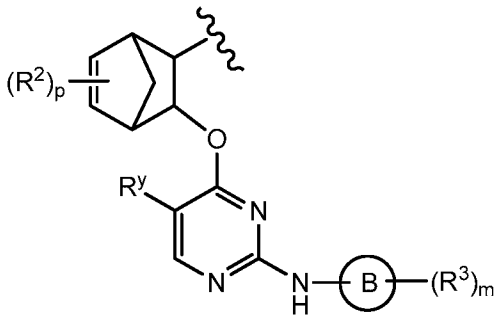
[00195] In certain embodiments, the inhibitor moiety of conjugate **A** is of any one of formulae **I-g-*i***, **I-h-*i***, **I-j-*i***, and **I-k-*i***:



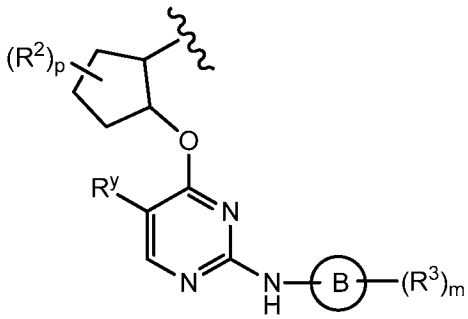
I-g-*i*



I-h-*i*



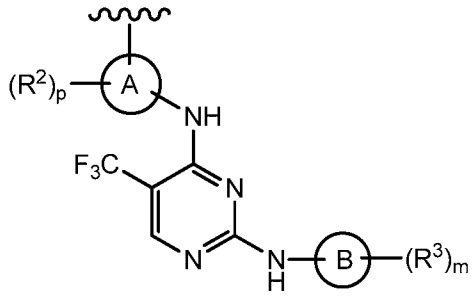
I-j-*i*



I-k-*i*

wherein each wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein each of Ring B, R^2, R^3, R^y, m and p, of formulae **I-g-*i***, **I-h-*i***, **I-j-*i***, and **I-k-*i***: is as defined for formula **I-g**, **I-h**, **I-j**, and **I-k** above and as defined and described in embodiments herein.

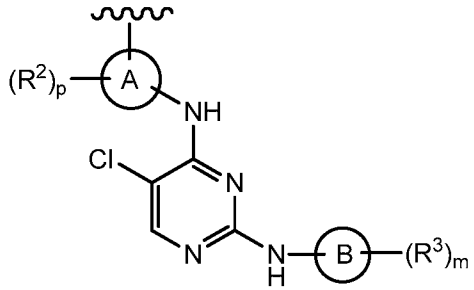
[00196] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **II-*i***:



II-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **II-*i*** is as defined for formula **II** above and as defined and described in embodiments herein.

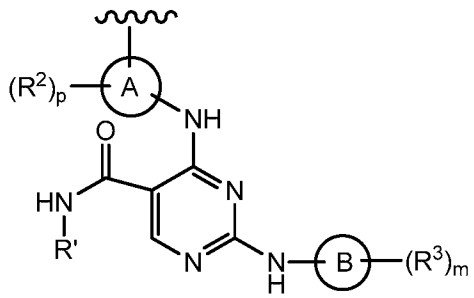
[00197] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **III-*i***:



III-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **III-*i*** is as defined for formula **III** above and as defined and described in embodiments herein.

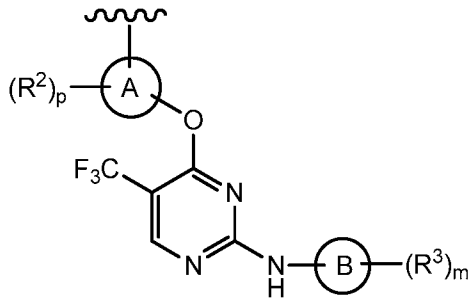
[00198] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **IV-*i***:



IV-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, R', m and p, of formula **IV-*i*** is as defined for formula **IV** above and as defined and described in embodiments herein.

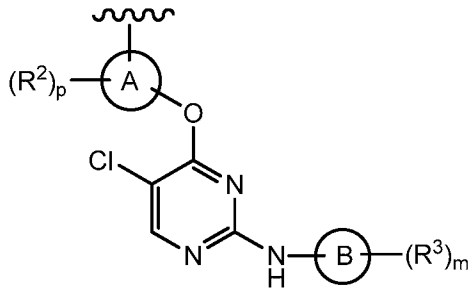
[00199] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **V-*i***:



V-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **V-*i*** is as defined for formula **V** above and as defined and described in embodiments herein.

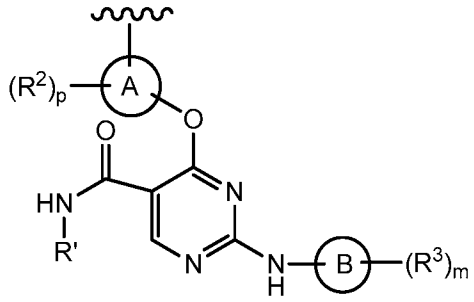
[00200] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **VI-*i***:



VI-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **VI-*i*** is as defined for formula **VI** above and as defined and described in embodiments herein.

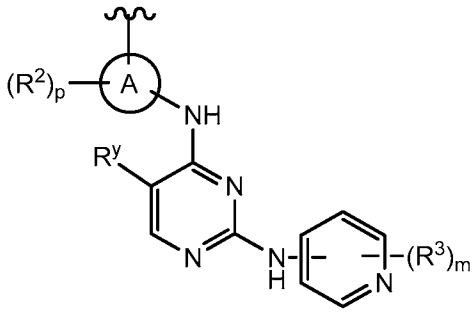
[00201] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **VII-*i***:



VII-*i*

wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, R', m and p, of formula **VII-*i*** is as defined for formula **VII** above and as defined and described in embodiments herein.

[00202] In certain embodiments, the inhibitor moiety of conjugate **A** is of formula **VIII-*i***:



VIII-*i*

[00203] wherein the wavy bond indicates the point of attachment to Cys183 of conjugate **A** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, m and p, of formula **VIII-*i*** is as defined for formula **VIII** above and as defined and described in embodiments herein.

[00204] In certain embodiments, the present invention provides a conjugate of the formula **B**:

Cys166–modifier–inhibitor moiety

B

wherein:

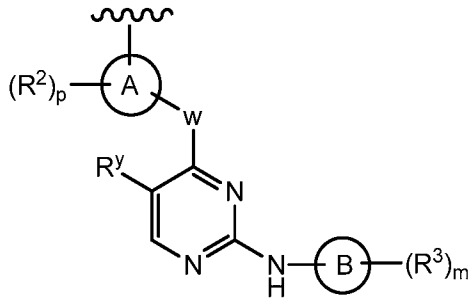
the Cys166 is Cys166 of ERK2;

the modifier is a bivalent group resulting from covalent bonding of a warhead group with the Cys166 of ERK2 kinase;

the warhead group is a functional group capable of covalently binding to Cys166; and

the inhibitor moiety is a moiety that binds in the ATP binding site of the ERK2 kinase.

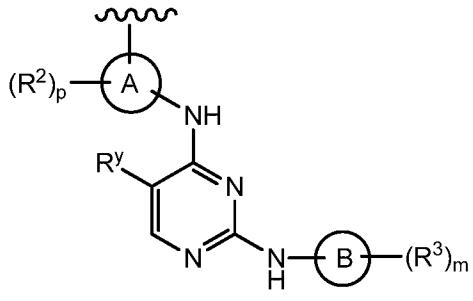
[00205] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **I-*i***:



I-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where W is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, W, m and p, of formula **I-*i*** is as defined for formula **I** above and as defined and described in embodiments herein. In some embodiments, each of Ring A, Ring B, R^2, R^3, R^y, W, m and p, of formula **I-*i*** is as defined for formula **I'** above and as defined and described in embodiments herein.

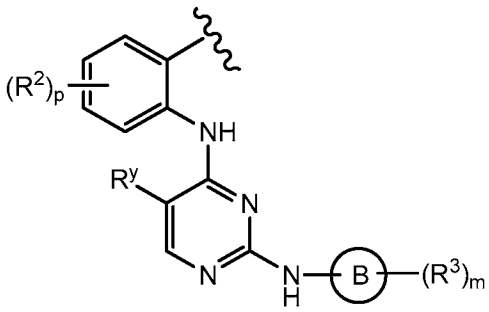
[00206] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **I-a-*i***:



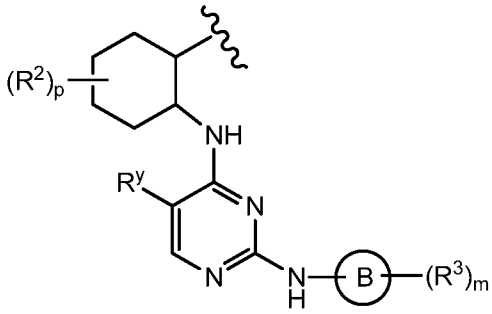
I-a-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, m and p, of formula **I-a-*i*** is as defined for formula **I-a** above and as defined and described in embodiments herein.

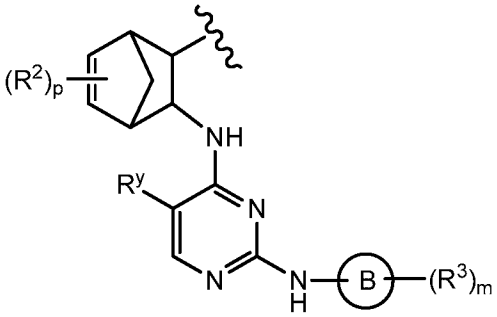
[00207] In certain embodiments, the inhibitor moiety of conjugate **B** is any one of formulae **I-b-*i***, **I-c-*i***, **I-d-*i***, and **I-e-*i***:



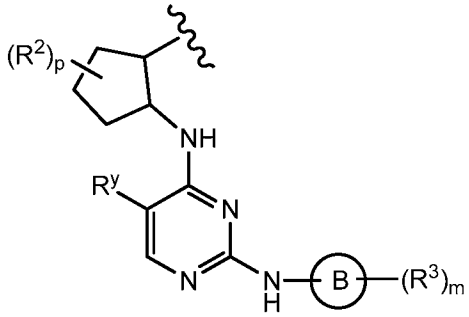
I-b-*i*



I-c-*i*



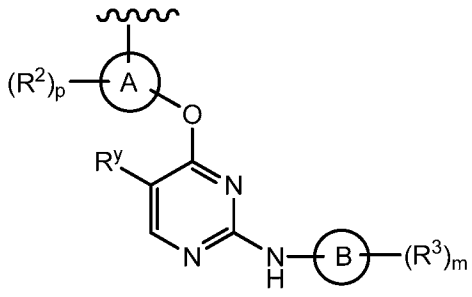
I-d-*i*



I-e-*i*

wherein each wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein each of Ring B, R^2, R^3, R^y, m and p, of formulae **I-b-*i***, **I-c-*i***, **I-d-*i***, and **I-e-*i*** is as defined for formula **I-b**, **I-c**, **I-d**, and **I-e** above and as defined and described in embodiments herein.

[00208] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **I-f-*i***:

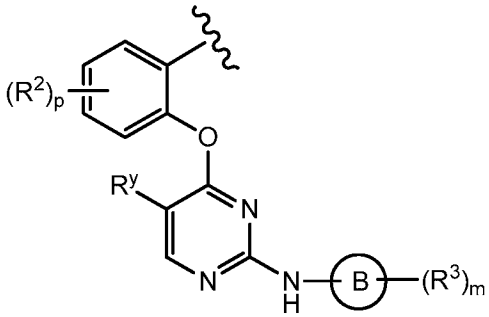


I-f-*i*

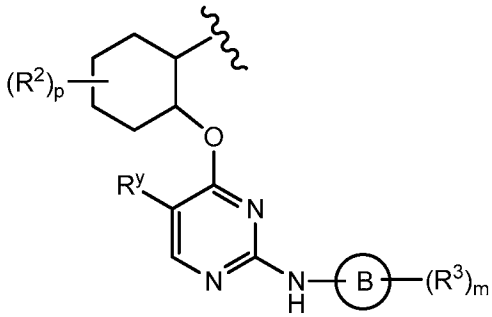
wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, R^y, m and

p, of formula **I-f-*i*** is as defined for formula **I-f** above and as defined and described in embodiments herein.

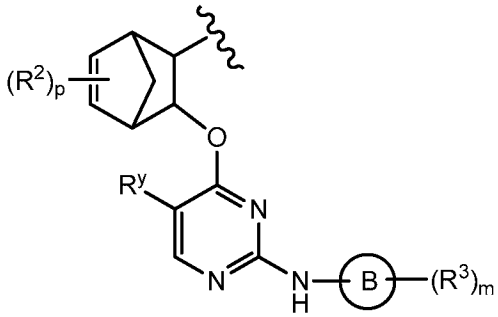
[00209] In certain embodiments, the inhibitor moiety of conjugate **B** is of any one of formulae **I-g-*i***, **I-h-*i***, **I-j-*i***, and **I-k-*i***:



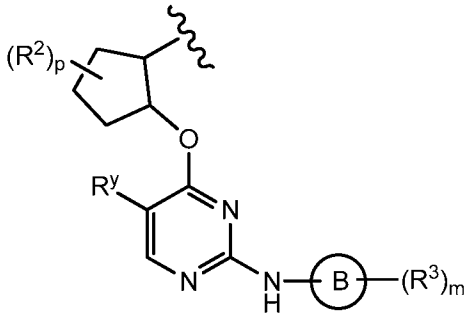
I-g-*i*



I-h-*i*



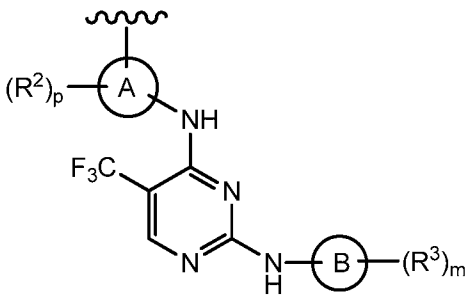
I-j-*i*



I-k-*i*

wherein each wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein each of Ring B, R^2, R^3, R^y, m and p, of formulae **I-g-*i***, **I-h-*i***, **I-j-*i***, and **I-k-*i***: is as defined for formula **I-g**, **I-h**, **I-j**, and **I-k** above and as defined and described in embodiments herein.

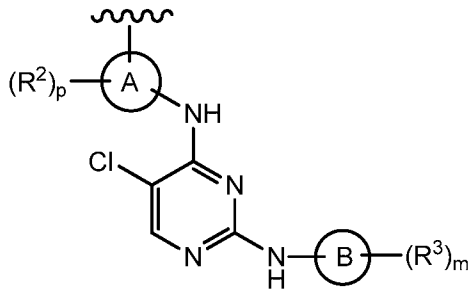
[00210] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **II-*i***:



II-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **II-*i*** is as defined for formula **II** above and as defined and described in embodiments herein.

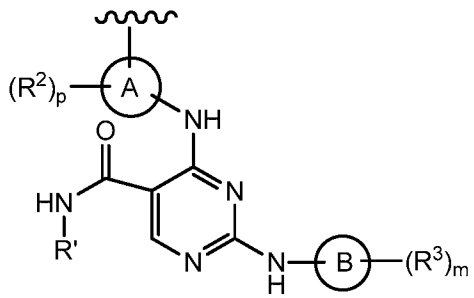
[00211] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **III-*i***:



III-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **III-*i*** is as defined for formula **III** above and as defined and described in embodiments herein.

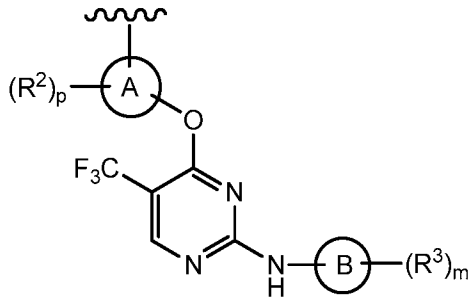
[00212] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **IV-*i***:



IV-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, Ring B, R^2, R^3, R', m and p, of formula **IV-*i*** is as defined for formula **IV** above and as defined and described in embodiments herein.

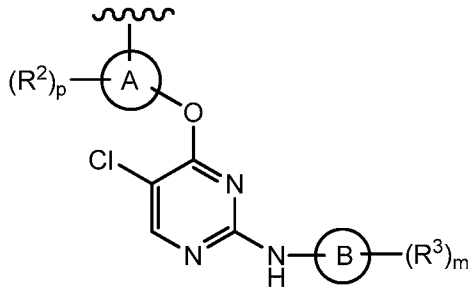
[00213] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **V-*i***:



V-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **V-*i*** is as defined for formula **V** above and as defined and described in embodiments herein.

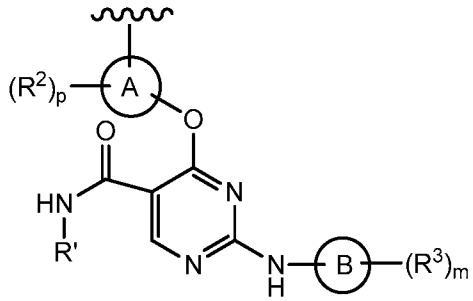
[00214] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **VI-*i***:



VI-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, m and p, of formula **VI-*i*** is as defined for formula **VI** above and as defined and described in embodiments herein.

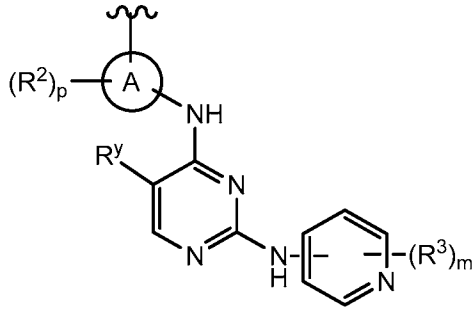
[00215] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **VII-*i***:



VII-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where O is attached; and wherein each of Ring A, Ring B, R^2, R^3, R', m and p, of formula **VII-*i*** is as defined for formula **VII** above and as defined and described in embodiments herein.

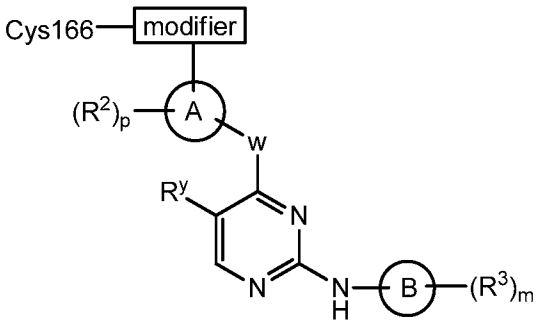
[00216] In certain embodiments, the inhibitor moiety of conjugate **B** is of formula **VIII-*i***:



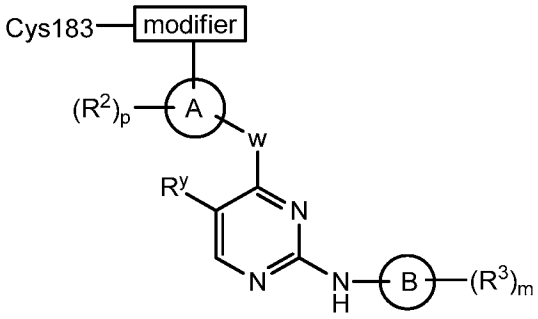
VIII-*i*

wherein the wavy bond indicates the point of attachment to Cys166 of conjugate **B** via the modifier, wherein when Ring A is a five or six member ring, then the wavy bond is attached to an atom adjacent to where NH is attached; and wherein each of Ring A, R^2, R^3, R^y, m and p, of formula **VIII-*i*** is as defined for formula **VIII** above and as defined and described in embodiments herein.

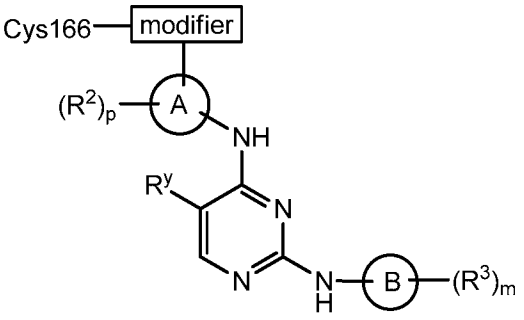
[00217] In certain embodiments, the present invention provides a conjugate of any of the formulae below:



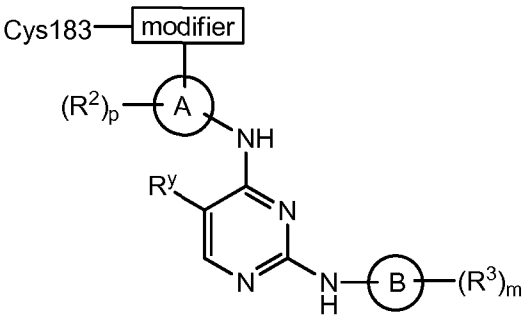
I-*i*-m



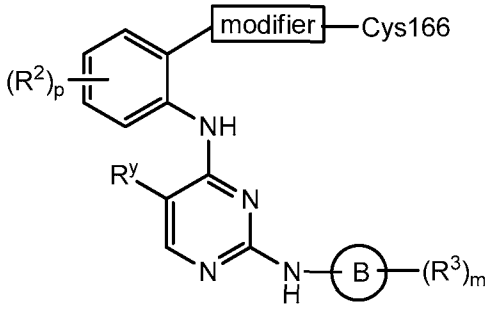
I-*i*-n



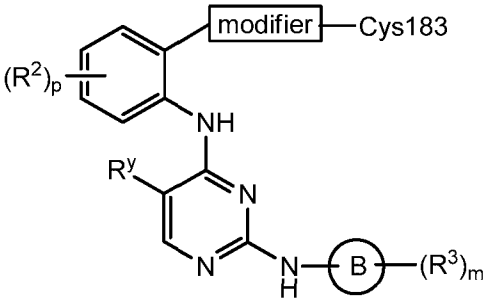
I-a-*i*-m



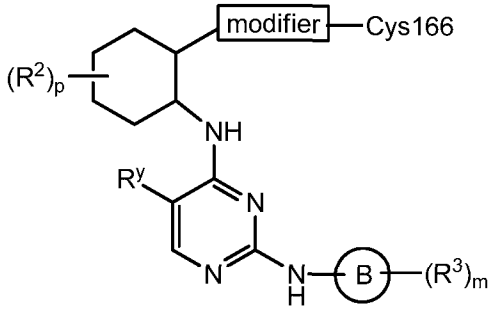
I-a-*i*-n



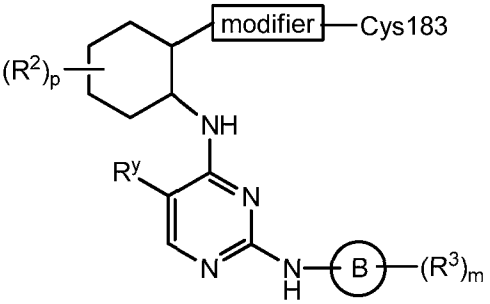
I-b-*i*-m



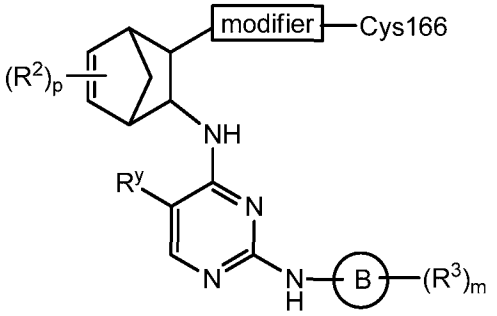
I-b-*i*-n



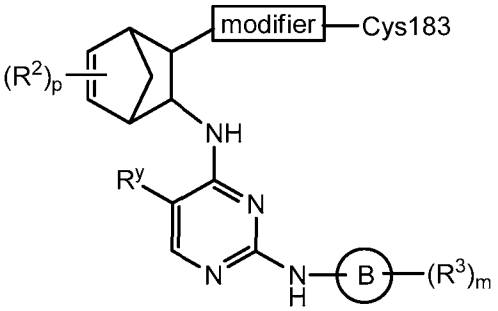
I-c-*i*-m



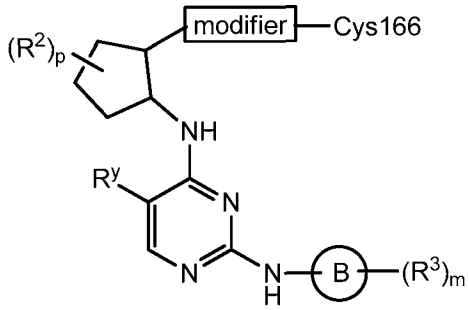
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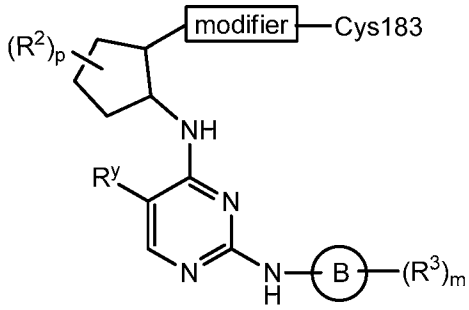
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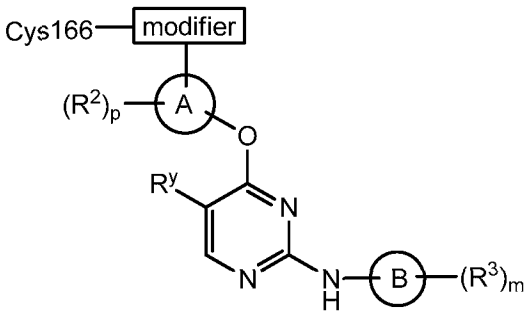
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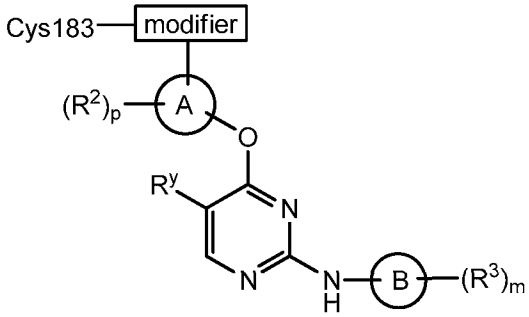
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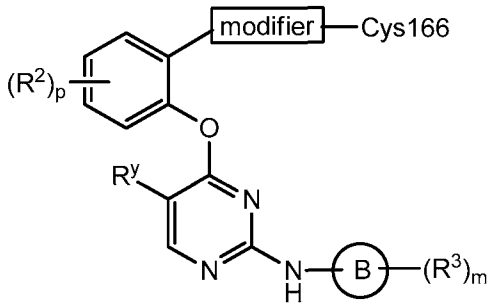
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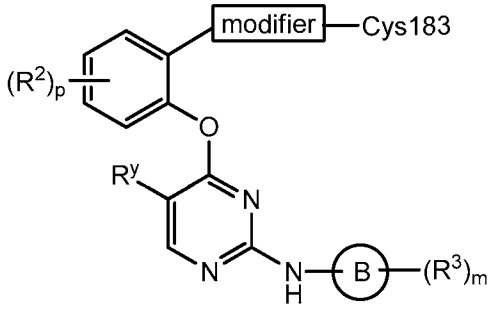
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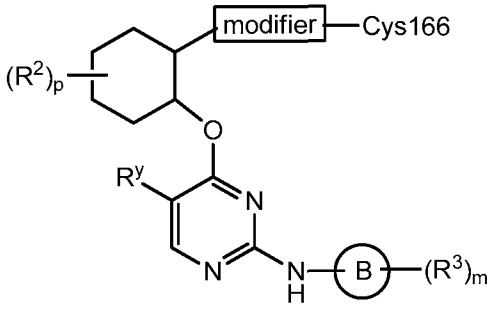
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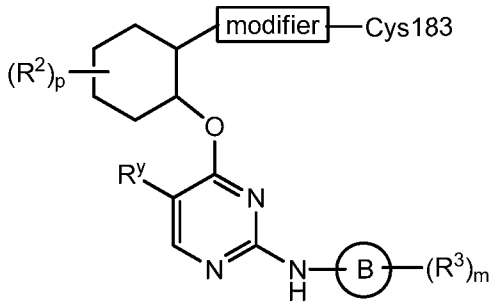
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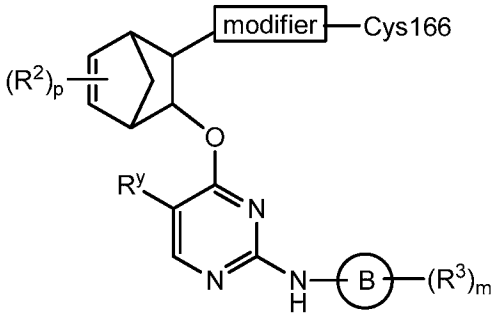
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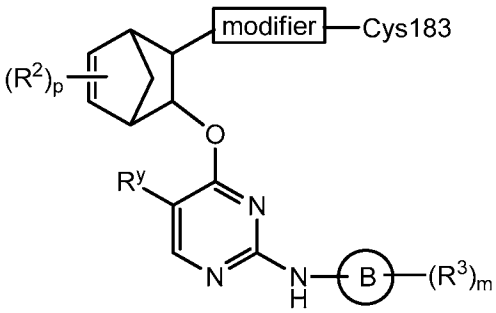
I-h-*i*-m



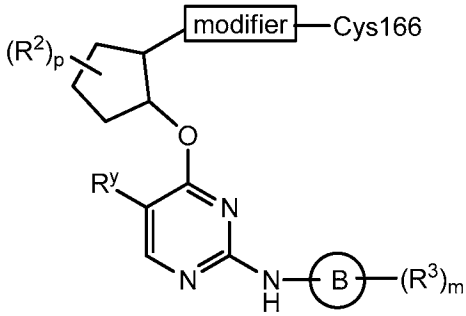
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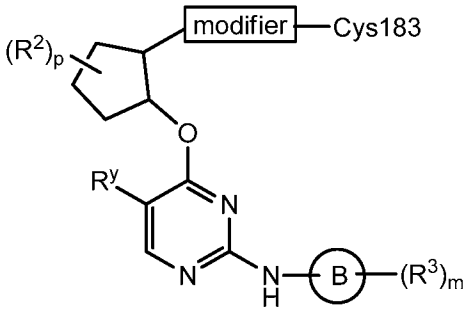
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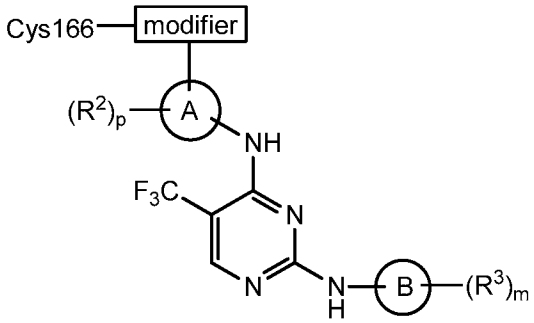
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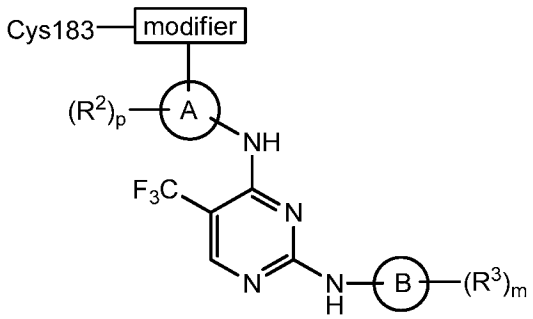
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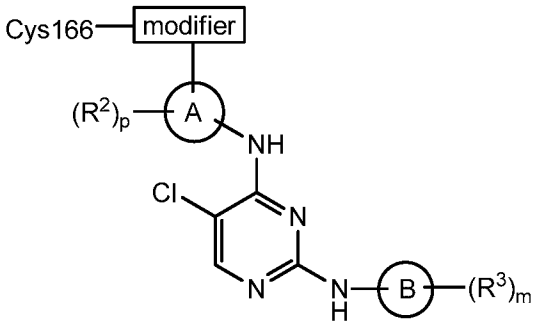
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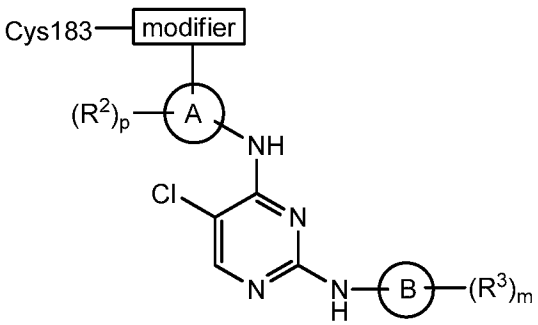
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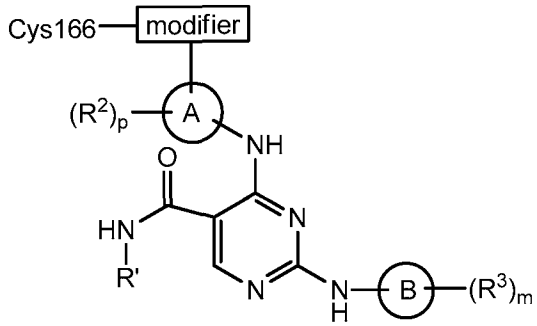
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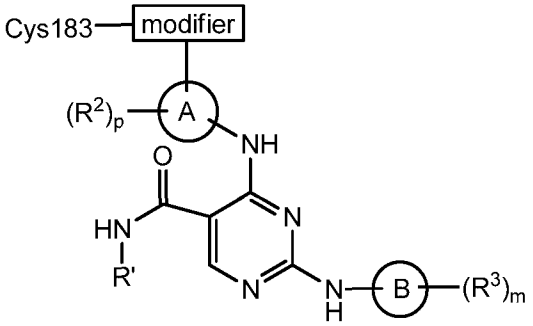
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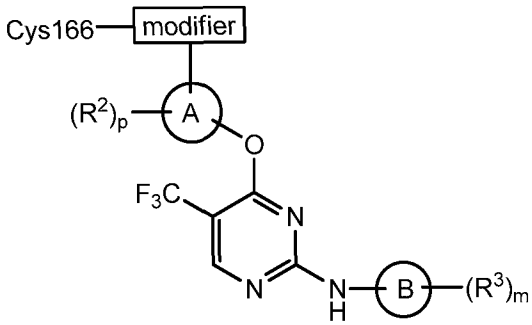
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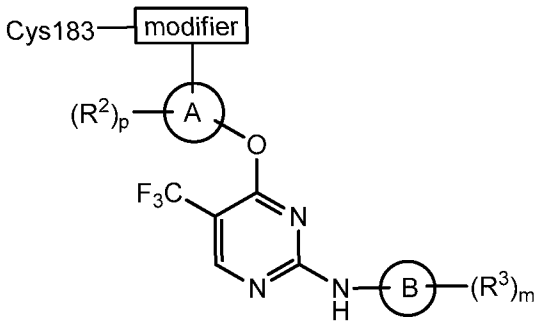
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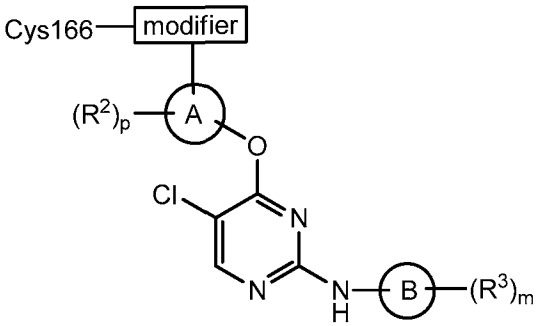
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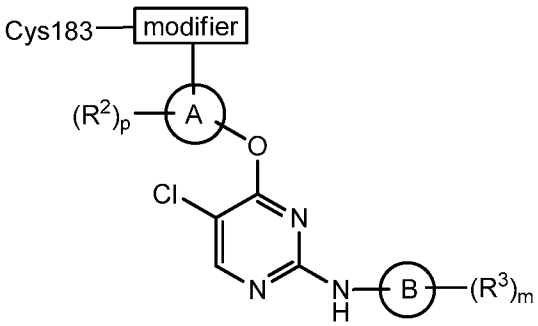
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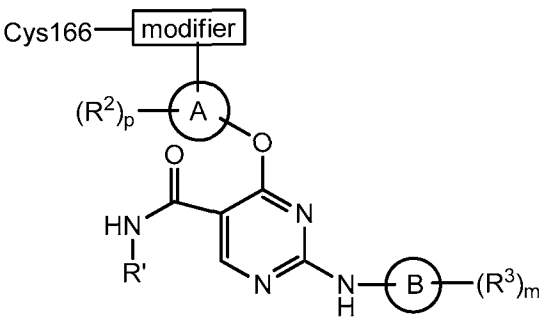
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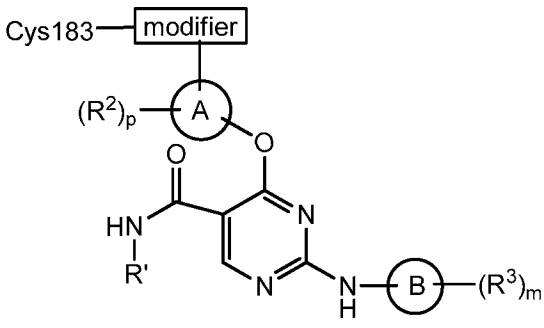
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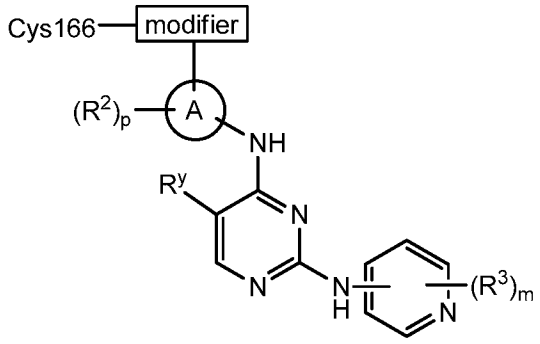
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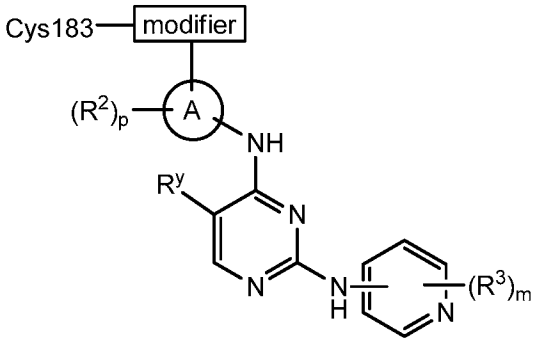
VII-*i*-m



VII-*i*-n



VIII-*i*-m

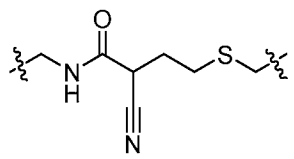


VIII-*i*-n

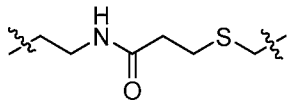
wherein each of Cys183, Cys166, Modifier, Ring A, Ring B, R^2, R^3, R^y, W, m and p, with respect to the above formulae is as defined and described in embodiments herein for formulae **I**, **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, **I-l**, **II**, **III**, **IV**, **V**, **VI**, **VII** and **VIII**. In some embodiments, each of Ring A, Ring B, R^2, R^3, R^y, W, m and p, with respect to the above formulae is as defined and described in embodiments herein for formula **I'**. In some embodiments, when Ring A is a five or six member ring, then modifier is attached to an atom adjacent to where W, N, or O is attached.

[00218] In other embodiments, the modifier moiety of any of conjugate described above is selected from those set forth in Table 5, below. Exemplary modifiers further include any bivalent group resulting from covalent bonding of a warhead moiety found in Table 1 or Table 2 with a cysteine of the kinases recited herein. It will be understood that the exemplary modifiers below are shown as conjugated to the sulfhydryl of CysX.

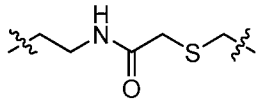
Table 5. Exemplary Modifiers Conjugated to Cys 183 or Cys166:



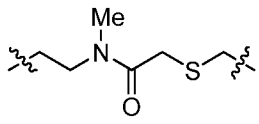
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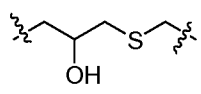
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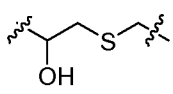
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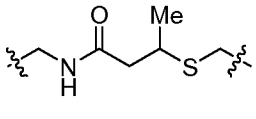
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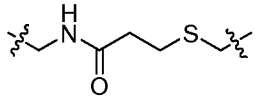
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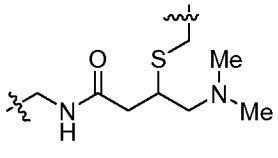
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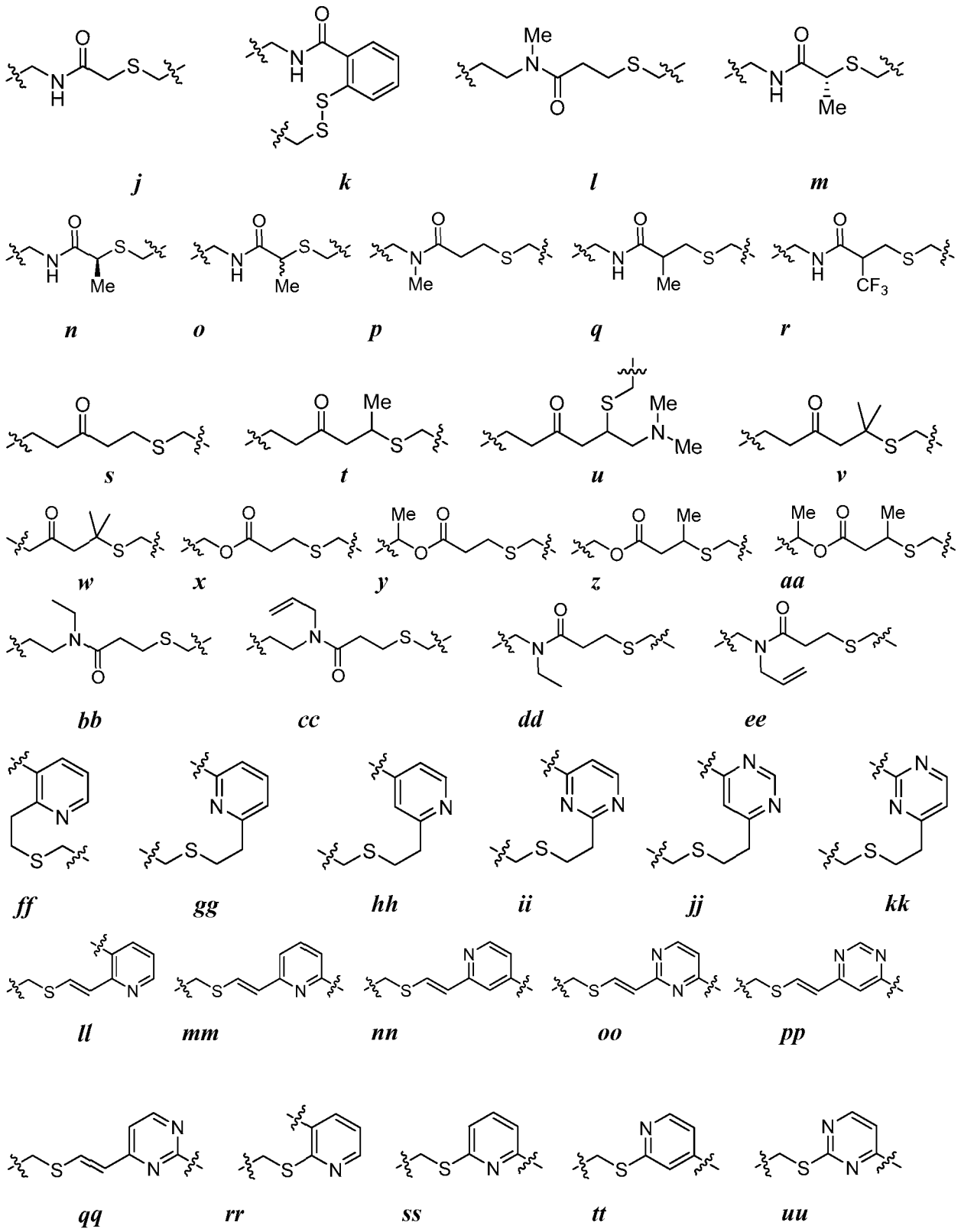
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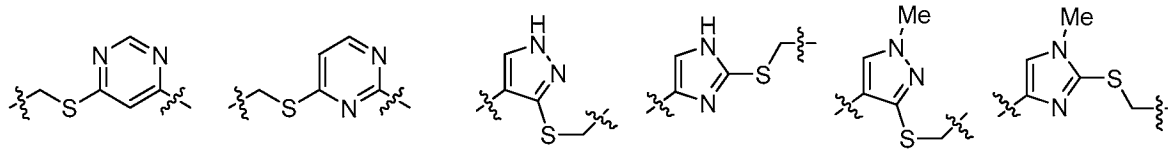


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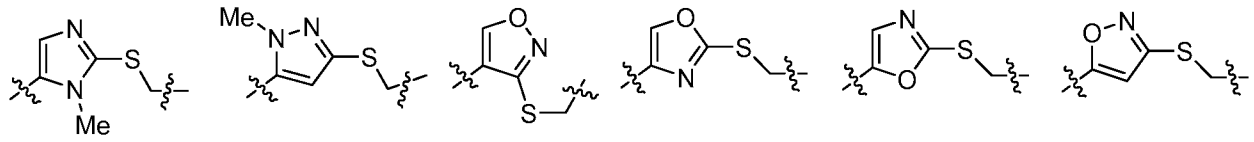


i

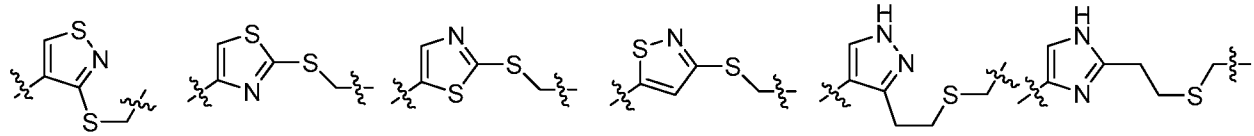

j
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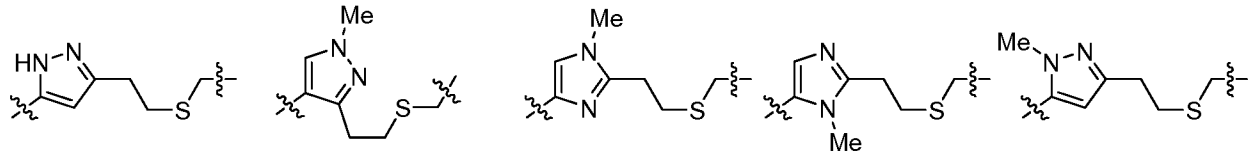
vv *ww* *xx* *yy* *zz* *aaa*



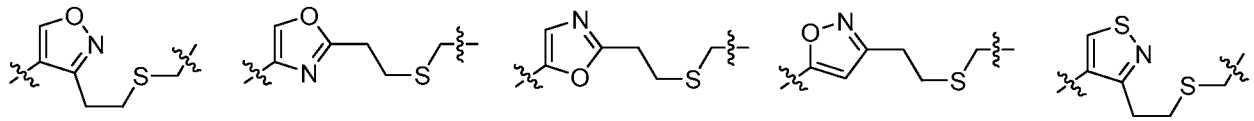
bbb *ccc* *ddd* *eee* *fff* *ggg*



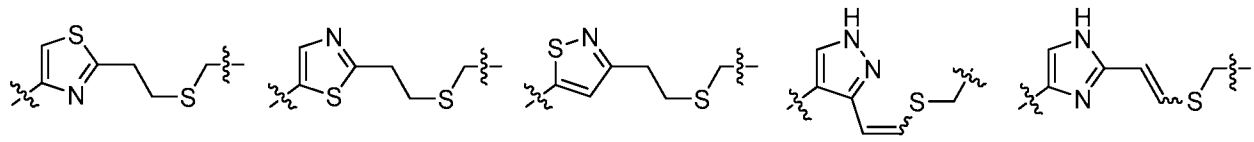
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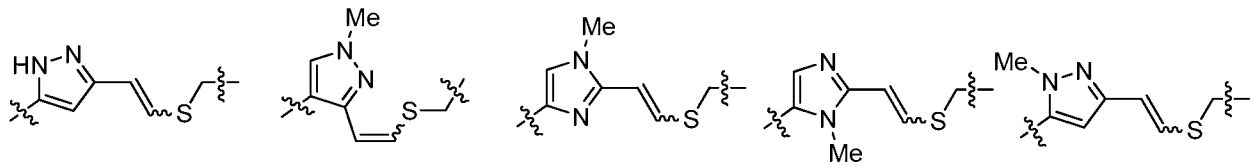
nnn *ooo* *ppp* *qqq* *rrr*



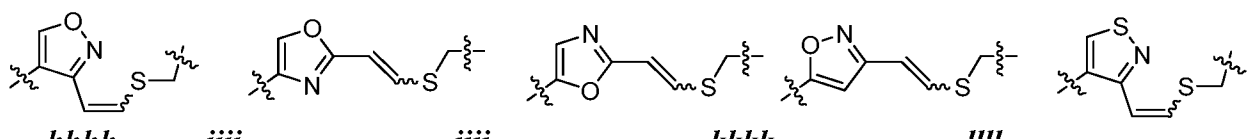
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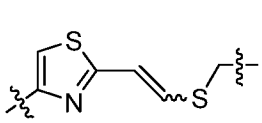
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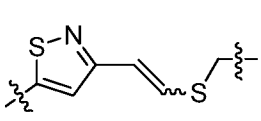
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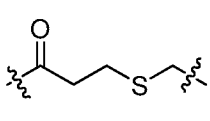
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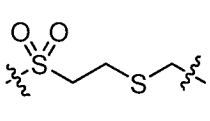
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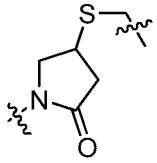
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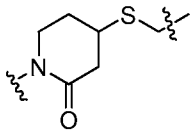
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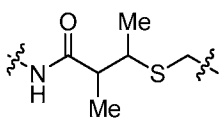
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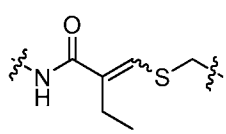
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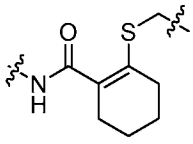
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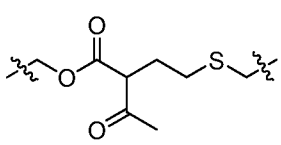
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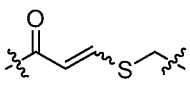
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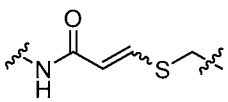
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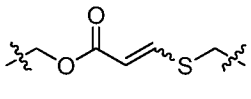
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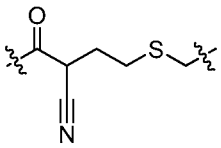
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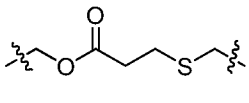
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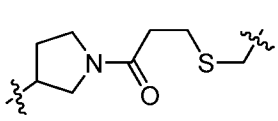
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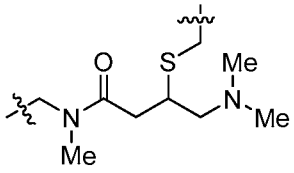
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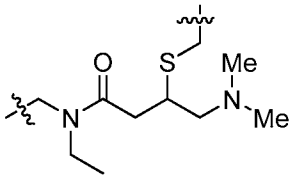
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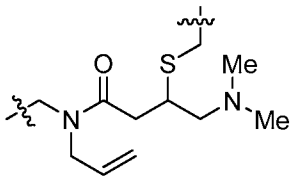
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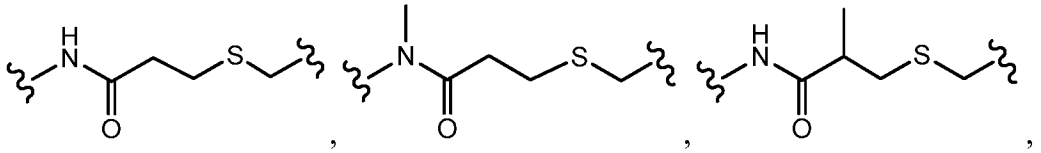
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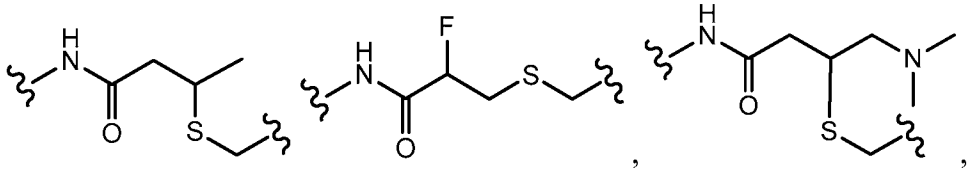
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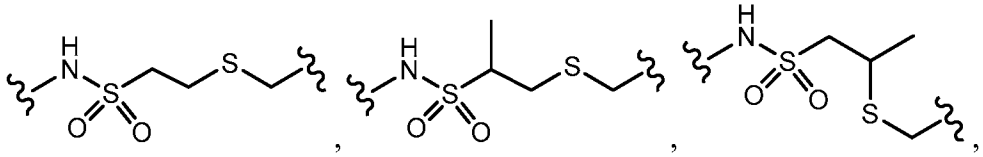
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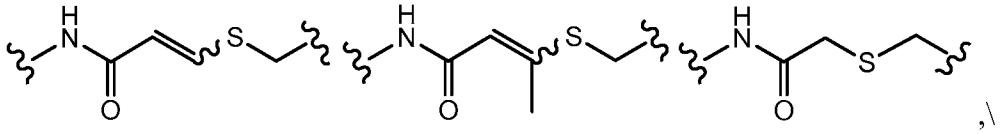
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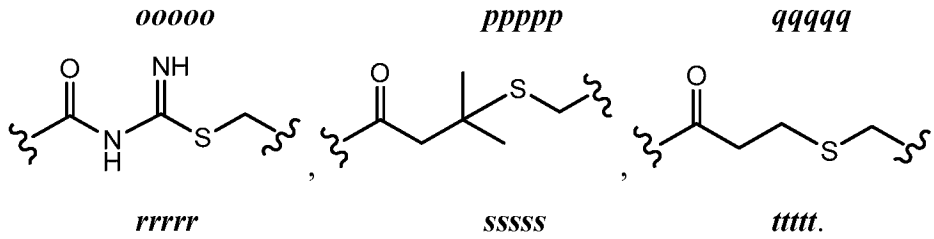


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4. Uses, Formulation and Administration

Pharmaceutically acceptable compositions

[00219] 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. In certain embodiments, the amount of compound in compositions of this invention is such that it is effective to measurably inhibit one or both of ERK1 and ERK2, 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.

[00220] The term "patient," as used herein, means an animal, preferably a mammal, and most preferably a human.

[00221] 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.

[00222] 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.

[00223] As used herein, the term "inhibitorily active metabolite or residue thereof" means that a metabolite or residue thereof is also an inhibitor of one or both of ERK1 and ERK2, or a mutant thereof.

[00224] 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.

[00225] 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.

[00226] 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.

[00227] Alternatively, pharmaceutically acceptable compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient that is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

[00228] 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.

[00229] 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.

[00230] 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.

[00231] 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.

[00232] 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.

[00233] Most preferably, pharmaceutically acceptable compositions of this invention are formulated for oral administration. Such formulations may be administered with or without food. In some embodiments, pharmaceutically acceptable compositions of this invention are administered without food. In other embodiments, pharmaceutically acceptable compositions of this invention are administered with food.

[00234] 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.

[00235] 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

[00236] Compounds and compositions described herein are generally useful for the inhibition of kinase activity of one or more enzymes.

[00237] Examples of kinases that are inhibited by the compounds and compositions described herein and against which the methods described herein are useful include one or both of ERK1 and ERK2, or a mutant thereof.

[00238] The activity of a compound utilized in this invention as an inhibitor of one or both of an ERK1 and ERK2 kinase, 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 one or both of activated ERK1 and ERK2 kinase, or a mutant thereof. Alternate *in vitro* assays quantitate the ability of the test compound to bind to one or both of ERK1 and ERK2. Test compound binding may be measured by radiolabeling the test compound prior to binding, isolating one or both of the compound / ERK1 complex and the compound / ERK2 complex, and determining the amount of radiolabel bound. Alternatively, test compound binding may be determined by running a competition experiment where test compounds are incubated with one or both of ERK1 and ERK2 kinase bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of one or both of ERK1 and ERK2, or a mutant thereof, are also set forth in the Examples below.

[00239] Without wishing to be bound by any particular theory, it is believed that a provided compound comprising a warhead moiety is more effective at inhibiting one or both of ERK1 and ERK2, or a mutant thereof, as compared to a corresponding compound wherein the R^1 moiety of any of the formulae herein is instead a non-warhead group or is completely absent (i.e., is hydrogen). For example, a compound of any of the formulae herein is more effective at inhibition of one or both of ERK1 and ERK2, or a mutant thereof, as compared to a corresponding compound wherein the R^1 moiety of any of the formulae herein is instead a non-warhead moiety or is absent.

[00240] A provided compound comprising a warhead moiety, as disclosed above, is more potent with respect to an IC_{50} against one or both of ERK1 and ERK2, or a mutant thereof, than a corresponding compound wherein the R^1 moiety of any of the formulae herein is instead a non-warhead moiety or is absent. Such comparative potency can be determined by standard time-dependent assay methods, such as those described in detail in the Examples section, *infra*. In certain embodiments, a compound of any of the formulae herein is measurably more potent than a corresponding compound of any of the formulae herein wherein the R^1 moiety is a non-warhead moiety or is absent. In some embodiments, a compound of any of the formulae herein is measurably more potent, wherein such potency is observed after about 1 minute, about 2 minutes, about 5 minutes, about 10 minutes, about 20 minutes, about 30 minutes, about 1 hour, about 2 hours, about 3 hours, about 4 hours, about 8 hours, about 12 hours, about 16 hours, about 24 hours, or about 48 hours, than a corresponding compound of any of the formulae herein

wherein the R^1 moiety of formula is a non-warhead moiety or is absent. In some embodiments, a compound of any of the formulae herein is any of about 1.5 times, about 2 times, about 5 times, about 10 times, about 20 times, about 25 times, about 50 times, about 100 times, or even about 1000 times more potent than a corresponding compound of any of the formulae herein wherein the R^1 moiety is a non-warhead moiety or is absent.

ERK1 and ERK2 Kinase

[00241] As described generally above, the compounds of the invention are useful as inhibitors of ERK protein kinases. ERK is one of the key components in the RAS-RAF-MEK-ERK MAPK pathway. As a downstream target, ERK inhibitors are believed to be able to overcome drug resistance from K-RAS and B-RAF mutations, as well as toxicity from RAF and MEK inhibitors. Kinase selectivity was achieved through silencing the selective Cys in a combination of the interactions between the covalent inhibitors of the invention and unique amino acids in the ATP binding pocket. Targeting the selective Cys provides for prolonged pharmacodynamics in silencing ERK activity, as well as potential lower doses in cancer treatment, compared to reversible inhibitors.

[00242] In one embodiment, the compounds and compositions of the invention are inhibitors of one or both of ERK1 and ERK2 protein kinases and thus, without wishing to be bound by any particular theory, the compounds and compositions are particularly useful for treating or lessening the severity of a disease, condition, or disorder where activation of one or both of ERK1 and ERK2 protein kinases is implicated in the disease, condition, or disorder. When activation of one or both of ERK1 and ERK2 protein kinases is implicated in a particular disease, condition, or disorder, the disease, condition, or disorder may also be referred to as “a disease, disorder, or condition mediated by one or both of ERK1 and ERK2”, or alternatively as an "ERK1- or ERK2-mediated disease", condition, or disease symptom. Accordingly, in another aspect, the present invention provides a method for treating or lessening the severity of a disease, condition, or disorder where activation of one or both of ERK1 and ERK2 protein kinases is implicated in said disease, condition, or disorder.

[00243] The activity of a compound utilized in this invention as an inhibitor of one or both of ERK1 and ERK2 protein kinases 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 or ATPase activity of one or both of activated ERK1 and ERK2 protein kinases. Alternate in vitro assays quantitate

the ability of the test compound to bind to one or both of ERK1 and ERK2 protein kinases. Test compound binding may be measured by radiolabelling the test compound prior to binding, isolating one or both of the test compound/ERK1 complex and test compound/ERK2 complex, and determining the amount of radiolabel bound. Alternatively, test compound binding may be determined by running a competition experiment where new test compounds are incubated with one or both of ERK1 and ERK2 protein kinases bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of one or both of ERK1 and ERK2, or a mutant thereof, are also set forth in the Examples below.

[00244] The term "measurably inhibit", as used herein means a measurable change in one or both of ERK1 and ERK2 protein kinase activity between a sample comprising said composition, and one or both of an ERK1 and ERK2 protein kinase and an equivalent sample comprising one or both of ERK1 and ERK2 protein kinase in the absence of said composition. Such measurements of protein kinase activity are known to one of ordinary skill in the art and include those methods set forth herein below.

[00245] According to another embodiment, the invention relates to a method of inhibiting one or both of ERK1 and ERK2 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.

[00246] Diseases, disorders, or conditions treated by the compounds of the invention include cancer, an autoimmune disorder, a neurodegenerative or neurological disorder, liver disease, a cardiac disorder, schizophrenia, or a bone-related disorder, and are referred to herein as an ERK1- and/or ERK2-mediated disease, disorder, or condition.

[00247] Specifically, the present invention relates to a method of treating or lessening the severity of a disease, disorder, or condition selected from cancer, stroke, diabetes, hepatomegaly, cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases, wherein the method comprises administering to a patient in need thereof a composition according to the present invention. In certain embodiments, the cancer is a MAPK-mediated cancer.

[00248] In certain embodiments, the disease, disorder, or condition mediated by one or both of ERK1 and ERK2 includes, without limitation, cancer, stroke, diabetes, hepatomegaly,

cardiovascular disease including cardiomegaly, Alzheimer's disease, cystic fibrosis, viral disease, autoimmune diseases, atherosclerosis, restenosis, psoriasis, allergic disorders including asthma, inflammation, neurological disorders and hormone-related diseases. In some embodiments, the the ERK1- and/or ERK2-mediated disease, disorder, or condition is a cancer selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute lymphoblastic leukemia. According to another embodiment, the present invention relates to a method of treating a cancer selected from breast, ovary, cervix, prostate, testis, genitourinary tract, esophagus, larynx, glioblastoma, neuroblastoma, stomach (gastric), skin, keratoacanthoma, lung, epidermoid carcinoma, large cell carcinoma, small cell carcinoma, lung adenocarcinoma, bone, colon, adenoma, pancreas, adenocarcinoma, thyroid, follicular carcinoma, undifferentiated carcinoma, papillary carcinoma, seminoma, melanoma, sarcoma, bladder carcinoma, liver carcinoma and biliary passages, kidney carcinoma, myeloid disorders, lymphoid disorders, Hodgkin's, hairy cells, buccal cavity and pharynx (oral), lip, tongue, mouth, pharynx, small intestine, colon-rectum, large intestine, rectum, brain and central nervous system, and leukemia. In some embodiments, the present invention relates to a method of treating CNS tumors. In certain embodiments, a CNS tumor is a glioblastoma or glioblastoma multiforme (GBM). In some embodiments, the present invention relates to a method of treating stomach (gastric) and esophageal tumors and cancers.

[00249] In some embodiments, the ERK1- and/or ERK2-mediated disease, disorder, or condition is a cancer selected from carcinoma, lymphoma, blastoma, sarcoma, and leukemia. In some embodiments, a sarcoma is a soft tissue sarcoma. In some embodiments, a lymphoma is non-hodgkins lymphoma. More particular examples of such cancers include adenocarcinoma;

adenoma; adrenocortical cancer; bladder cancer; bone cancer; brain cancer; breast cancer; cancer of the buccal cavity; cervical cancer; colon cancer; colorectal cancer; endometrial or uterine carcinoma; epidermoid carcinoma; esophogeal cancer; eye cancer; follicular carcinoma; gallbladder cancer; gastrointestinal cancer; cancer of the genitourinary tract; glioblastoma; hairy cell carcinoma; various types of head and neck cancer; hepatic carcinoma; hepatocellular cancer; Hodgkin's disease; keratoacanthoma; kidney cancer; large cell carcinoma; cancer of the large intestine; laryngeal cancer; liver cancer; lung cancer, such as, for example, adenocarcinoma of the lung, small-cell lung cancer, squamous carcinoma of the lung, non-small cell lung cancer; melanoma and nonmelanoma skin cancer; lymphoid disorders; myeloproliferative disorders, such as, for example, polycythemia vera, essential thrombocythemia, chronic idiopathic myelofibrosis, myeloid metaplasia with myelofibrosis, chronic myeloid leukemia (CML), chronic myelomonocytic leukemia, chronic eosinophilic leukemia, chronic lymphocytic leukemia (CLL), hypereosinophilic syndrome, systematic mast cell disease, atypical CML, or juvenile myelomonocytic leukemia; multiple myeloma; neuroblastoma; ovarian cancer; papillary carcinoma; pancreatic cancer; cancer of the peritoneum; prostate cancer, including benign prostatic hyperplasia; rectal cancer; salivary gland carcinoma; sarcoma; seminoma; squamous cell cancer; small cell carcinoma; cancer of the small intestine; stomach cancer; testicular cancer; thyroid cancer; undifferentiated carcinoma; and vulval cancer. In particular embodiments, the treated cancer is melanoma, breast cancer, colon cancer, or pancreatic cancer.

[00250] In certain embodiments, the cancer is selected from the group consisting of: melanoma, pancreatic cancer, thyroid cancer, colorectal cancer, lung cancer, breast cancer, ovarian cancer, and leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute myeloid leukemia. In some embodiments, a leukemia is an acute leukemia. In certain embodiments, a leukemia is acute lymphoblastic leukemia.

[00251] In certain embodiments, the invention provides a method for overcoming drug resistance to Raf and Mek inhibitors, comprising the step of administering to said patient an inhibitor compound of one or both of ERK1 and ERK2.

[00252] 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.

[00253] 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.

[00254] 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 is administered after one or more symptoms have developed. In other embodiments, treatment is administered in the absence of symptoms. For example, treatment is 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 is also continued after symptoms have resolved, for example to prevent or delay their recurrence.

[00255] The compounds and compositions, according to the method of the present invention, are administered using any amount and any route of administration effective for treating or lessening the severity of a disorder provided above. 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.

[00256] 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 are 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.

[00257] 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.

[00258] 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.

[00259] 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.

[00260] 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.

[00261] 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.

[00262] 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.

[00263] 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.

[00264] 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.

[00265] 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.

[00266] 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.

[00267] According to another embodiment, the invention relates to a method of inhibiting one or both of ERK 1 and ERK2 kinase, 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 one or both of ERK1 and ERK2 kinase, 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.

[00268] 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.

[00269] Inhibition of one or both of ERK1 and ERK2, 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.

[00270] 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.

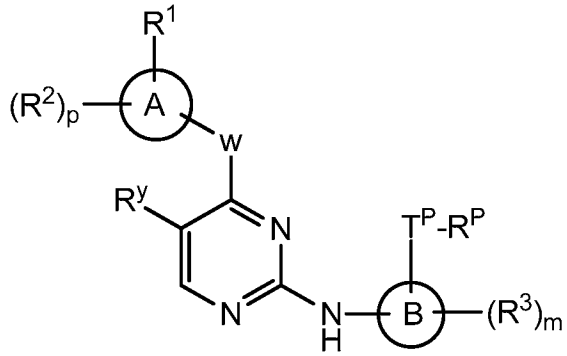
[00271] According to another embodiment, the invention relates to a method of inhibiting one or both of ERK1 and ERK2 kinase, or a mutant thereof, activity in a patient comprising the step of administering to said patient a compound of the present invention, or a composition comprising said compound. According to certain embodiments, the invention relates to a method of irreversibly inhibiting one or both of ERK1 and ERK2 kinase, 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 certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 166 of ERK2. In certain embodiments, the activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1 and Cys 166 of ERK2. In other embodiments, the present invention provides a method for

treating a disease, disorder, or condition mediated by one or both of ERK1 and ERK2 kinase, 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.

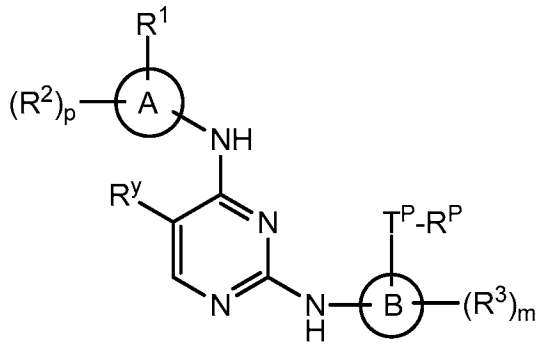
5. Probe Compounds

[00272] In certain aspects, a compound of the present invention is 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 any formulae as described herein, a detectable moiety, and a tethering moiety that attaches the inhibitor to the detectable moiety.

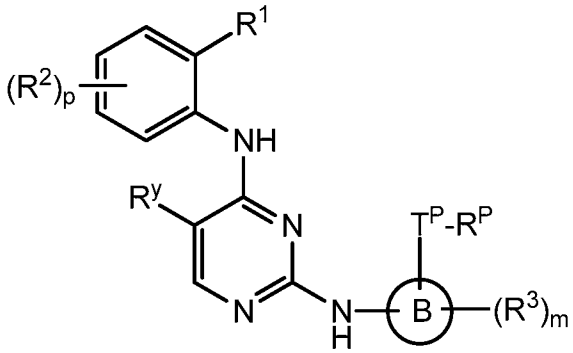
[00273] In some embodiments, such probe compounds of the present invention comprise a provided compound of any formulae as described herein, tethered to a detectable moiety, R^P, by a bivalent tethering moiety, - T^P-. In certain embodiments, a provided probe compound is selected from any of following formulae:



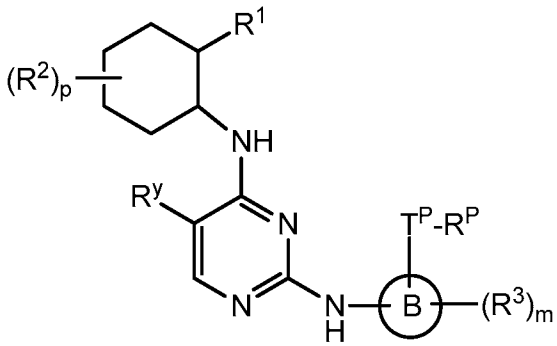
I-p



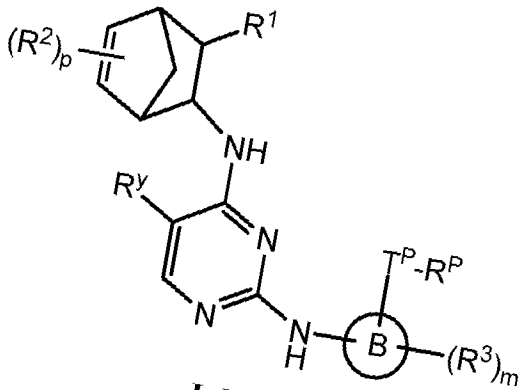
I-a-p



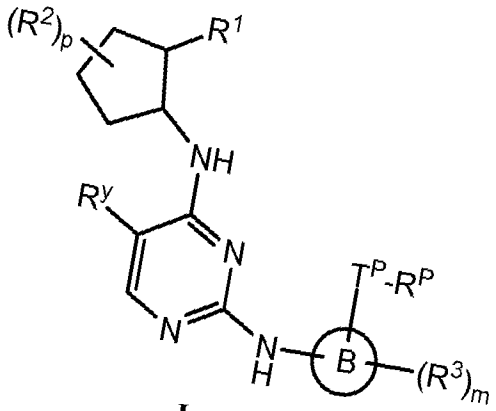
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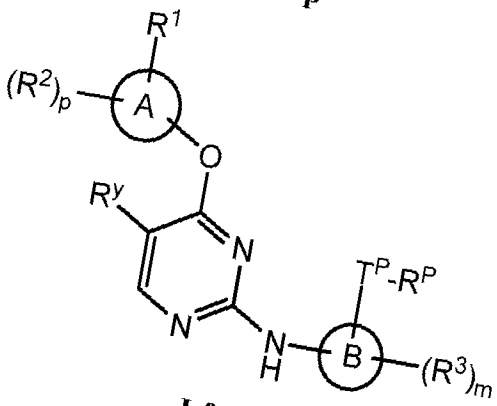
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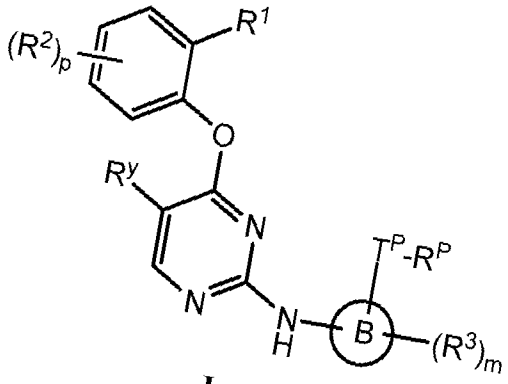
I-d-p



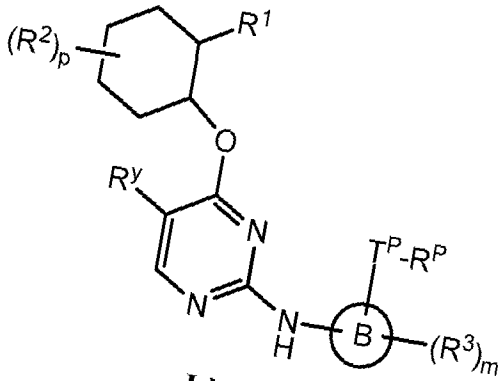
I-e-p



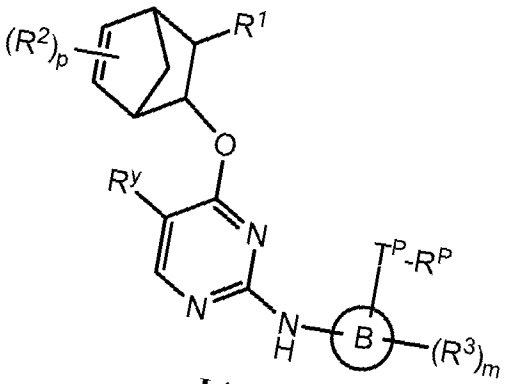
I-f-p



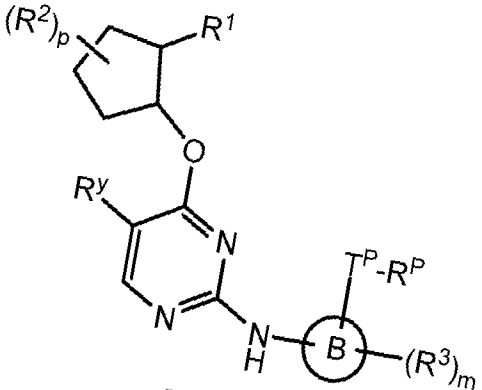
I-g-p



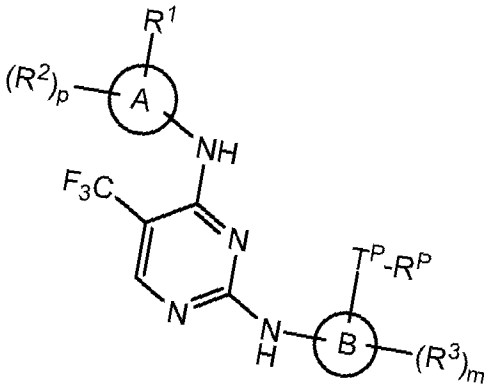
I-h-p



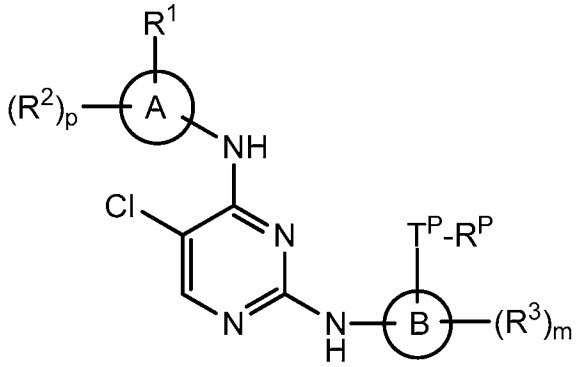
I-j-p



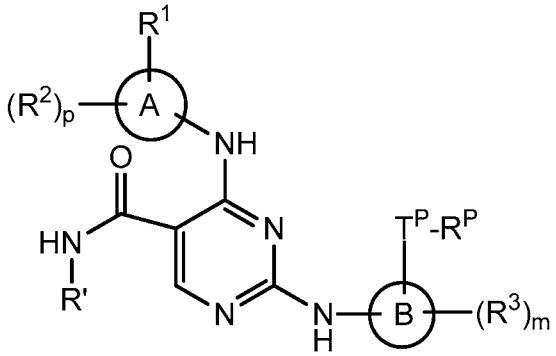
I-k-p



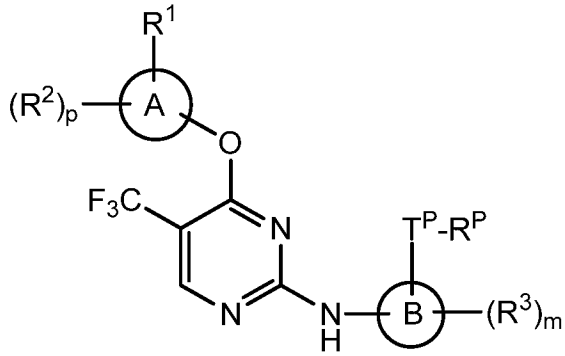
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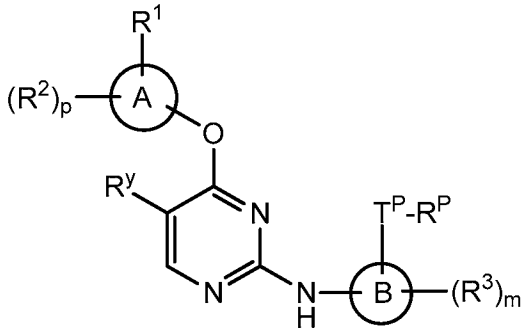
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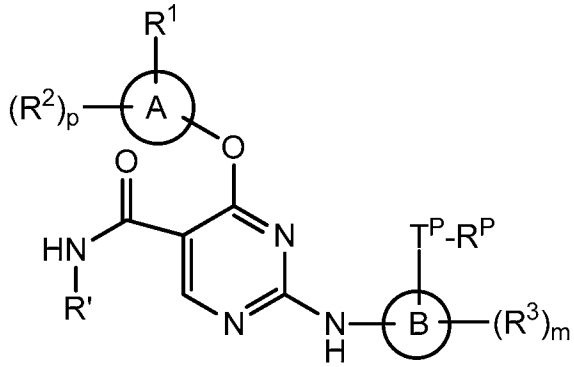
IV-p



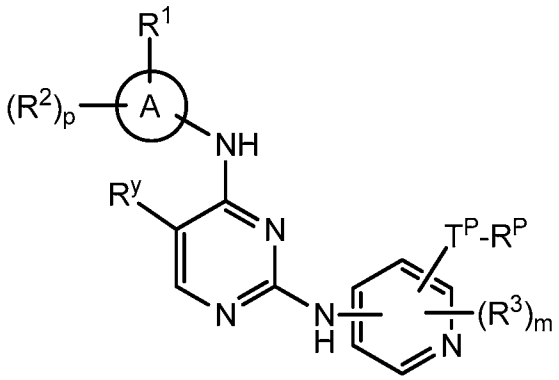
V-p



VI-p



VII-p and



VIII-p

wherein each of Ring A, Ring B, R^1, R^2, R^3, R^y, W, m and p, with respect to the formulae above, is as defined and described in embodiments herein, T^P is a bivalent tethering moiety; and R^P is a detectable moiety. In some embodiments, when Ring A is a five or six member ring, then R^1 is attached to an atom adjacent to where W, N, or O is attached.

[00274] In some embodiments, R^P is a detectable moiety selected from a primary label or a secondary label. In certain embodiments, R^P 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.

[00275] 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).

[00276] 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 are 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, which are signal generating reporter groups which can be detected without further modifications. Detectable moities are analyzed by methods. Exemplary methods are 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.

[00277] 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 includes streptavidin-enzyme conjugates. For antigen labels, secondary intermediates 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.

[00278] 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.

[00279] 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) are also used as mass-tags. Stable isotopes (e.g., ^{13}C, ^{2}H, ^{17}O, ^{18}O, and ^{15}N) are also used as mass-tags.

[00280] 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).

[00281] The term "chromophore," as used herein, refers to a molecule which absorbs light of visible wavelengths, UV wavelengths or IR wavelengths.

[00282] The term "dye," as used herein, refers to a soluble, coloring substance which contains a chromophore.

[00283] 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.

[00284] 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.

[00285] 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.

[00286] 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.

[00287] 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.

[00288] The term "photoisomerizable moiety," as used herein, refers to a group wherein upon illumination with light changes from one isomeric form to another.

[00289] 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.

[00290] 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.

[00291] 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).

[00292] One of ordinary skill in the art will recognize that a detectable moiety is 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 are directly attached to a provided compound or *via* a tethering moiety, such as a bivalent saturated or unsaturated hydrocarbon chain.

[00293] 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).

[00294] In some embodiments, the detectable moiety, R^P, 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.

[00295] In some embodiments, R^P is biotin or an analog thereof. In certain embodiments, R^P is biotin. In certain other embodiments, R^P is biotin sulfoxide.

[00296] In another embodiment, R^P 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.

[00297] As described generally above, a provided probe compound comprises a tethering moiety, - T^P-, that attaches the irreversible inhibitor to the detectable moiety. As used herein, the term "tether" or "tethering moiety" refers to any bivalent chemical spacer. Exemplary tethers are 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.

[00298] In some embodiments, the tethering moiety, - T^P-, 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.

[00299] 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.

[00300] In some embodiments, a tethering moiety, - T^P-, 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.

[00301] In some embodiments, examples of hydrophilic polymers, for use in tethering moiety –T^P-, include, but are not limited to: polyalkyl ethers and alkoxy-capped analogs thereof (e.g.,

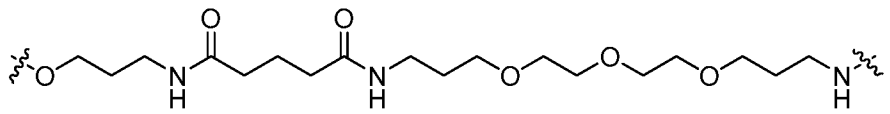
polyoxyethylene glycol, polyoxyethylene/propylene glycol, and methoxy or ethoxy-capped analogs thereof, polyoxyethylene glycol, the latter is also known as polyethylene glycol or PEG); polyvinylpyrrolidones; polyvinylalkyl ethers; polyoxazolines, polyalkyl oxazolines and polyhydroxyalkyl oxazolines; 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. Exemplary forms are 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.

[00302] 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. Exemlary ranges are 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, 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

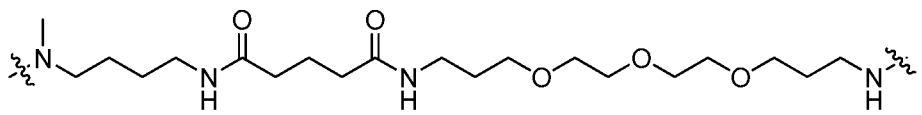
polymer is between about 100 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is between about 1,000 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is between about 5,000 Da and 40,000 Da. In some embodiments, the molecular weight of the polymer is 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. Exemplary ranges are 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.

[00303] One of ordinary skill in the art will appreciate that when – T^P-R^P is attached to a compound of the formulae herein.

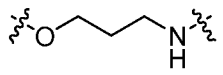
[00304] In certain embodiments, the tethering moiety, - T^P-, has one of the following structures:



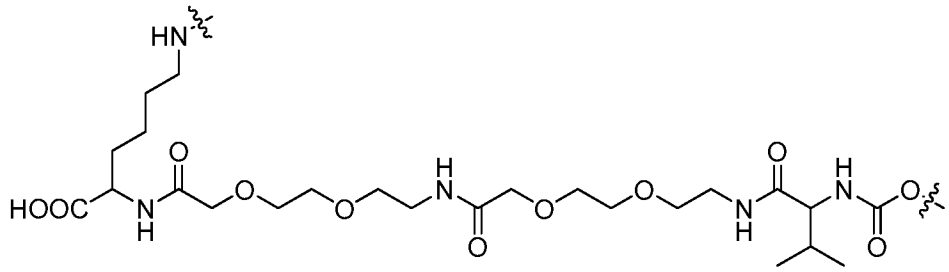
[00305] In some embodiments, the tethering moiety, - T^P-, has the following structure:



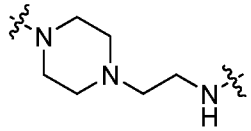
[00306] In other embodiments, the tethering moiety, - T^P-, has the following structure:



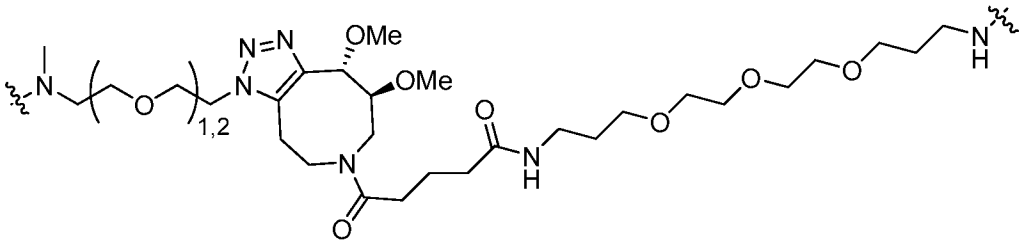
[00307] In certain other embodiments, the tethering moiety, - T^P-, has the following structure:



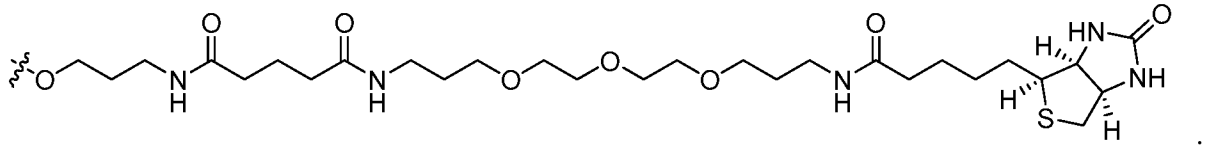
[00308] In yet other embodiments, the tethering moiety, - T^P-, has the following structure:



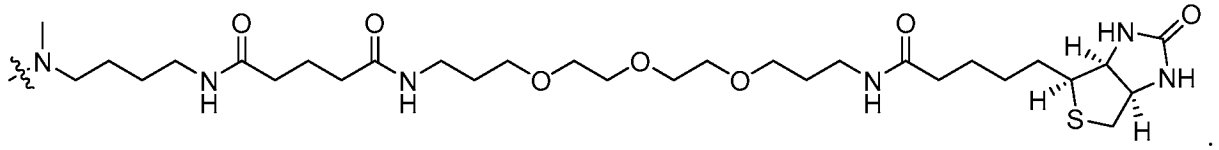
[00309] In some embodiments, the tethering moiety, - T^P-, has the following structure:



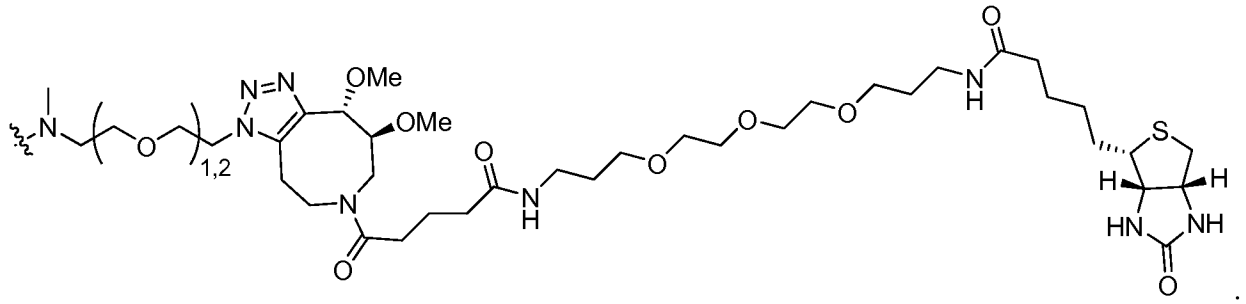
[00310] In some embodiments, - T^P-R^P is of the following structure:



[00311] In other embodiments, - T^P-R^P is of the following structure:

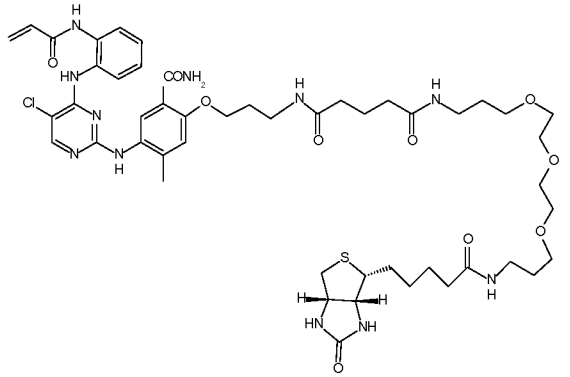


[00312] In certain embodiments, - T^P-R^P is of the following structure:

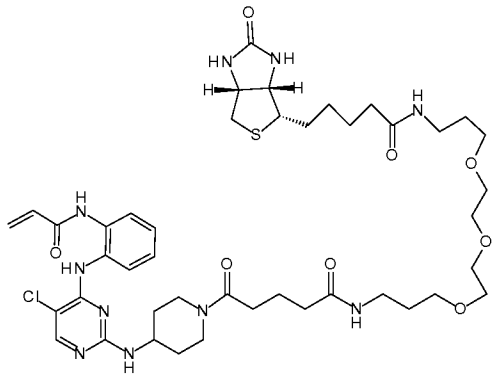


[00313] In some embodiments, a probe compound is derived from any compound described herein.

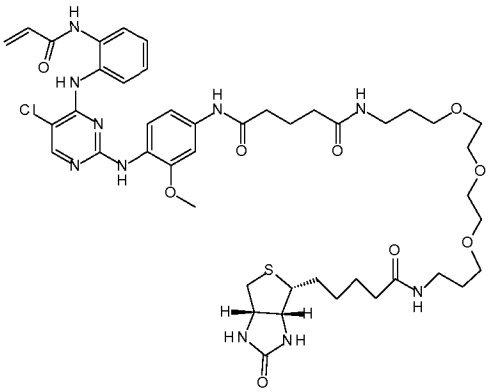
[00314] In certain embodiments, the probe compound is one of the following structures:



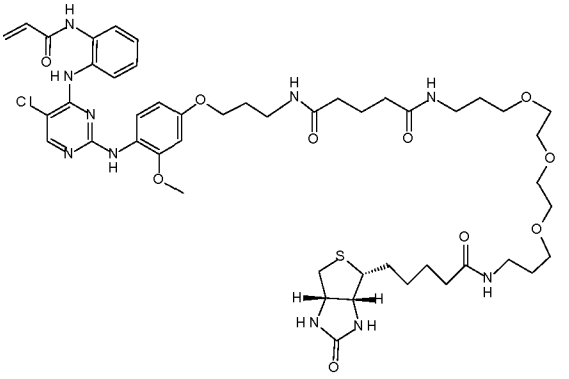
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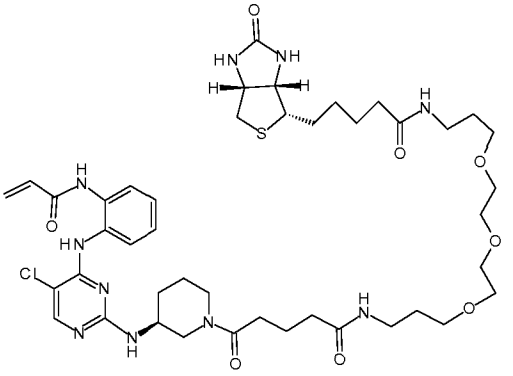
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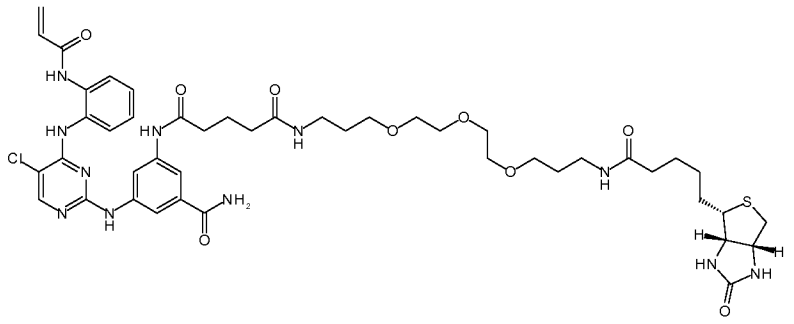
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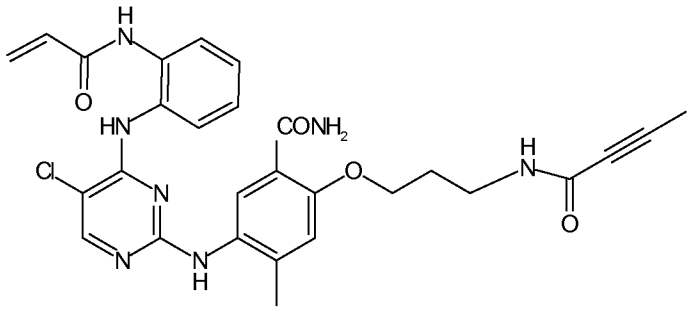
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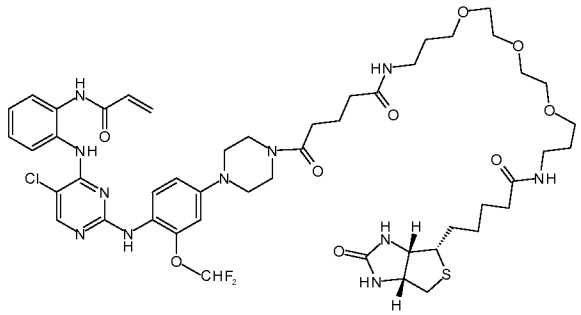
I-303



I-304



I-305 and



I-306

[00315] It will be appreciated that many – T^P-R^P 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.

[00316] In some embodiments, analogous probe structures to the ones exemplified above are prepared using click-ready inhibitor moieties and click-ready – T^P-R^P moieties, as described herein.

[00317] 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.

[00318] 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 any of the formulae presented herein) 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 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 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 formulae presented herein 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 formulae presented herein to decrease occupancy of the protein kinase.

[00319] 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.

[00320] In some embodiments, the protein kinase to be modified is one or both of ERK1 and ERK2.

[00321] In some embodiments, the probe compound comprises the irreversible inhibitor for which occupancy is being determined.

[00322] 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.

[00323] 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.

[00324] 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.

[00325] 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.

[00326] 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.

[00327] 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.

[00328] In certain embodiments, the probe compound is detected by binding to avidin, streptavidin, neutravidin, or captavidin.

[00329] 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.

[00330] 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.

[00331] 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.

[00332] 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 any of the formulae presented herein, 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

[00333] As depicted in the Examples below, in certain exemplary embodiments, compounds were 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.

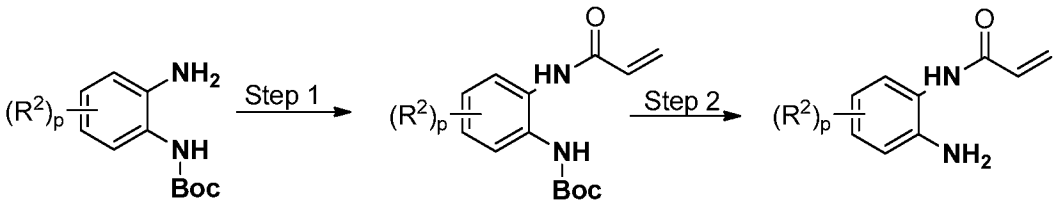
[00334] Enantioenriched compounds of the invention were prepared in enantioenriched form using chiral starting materials, or were separated after reaction with a racemic starting material, using chiral chromatography. For compounds prepared as racemic or diastereomeric mixtures, the single isomers can be prepared in optically pure form by either employing chiral starting materials or performing chiral chromatography.

[00335] Compound numbers utilized in the Examples below correspond to compound numbers set forth the Tables provided, *supra*.

General Methods for Preparing Certain Intermediates

[00336] Scheme IA, below, depicts a general method for preparing certain intermediates for preparing compounds of formula **I**, wherein Ring A is phenyl and R^2 and p are as defined and described herein. At Step 1, intermediate *i* can be treated with acryloyl chloride (or other reagent suitable for introducing the acryloyl moiety) to form intermediate *ii*. As depicted in Step 2, the BOC protecting group can then be removed by treating *ii* with a suitable acid to form common intermediate *iii*. One of ordinary skill in the art will recognize that the depicted BOC protecting group can be replaced with other suitable amine protecting groups and then removed via suitable deprotection methods known in the art.

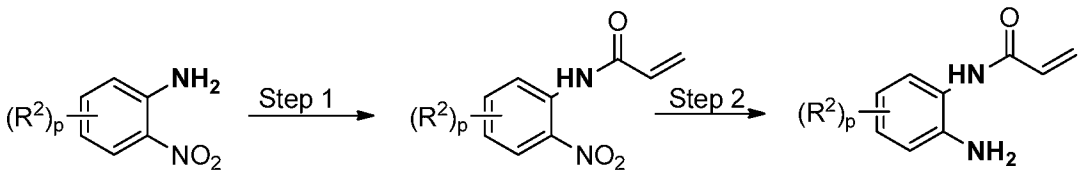
Scheme IA:



i *ii* *iii*

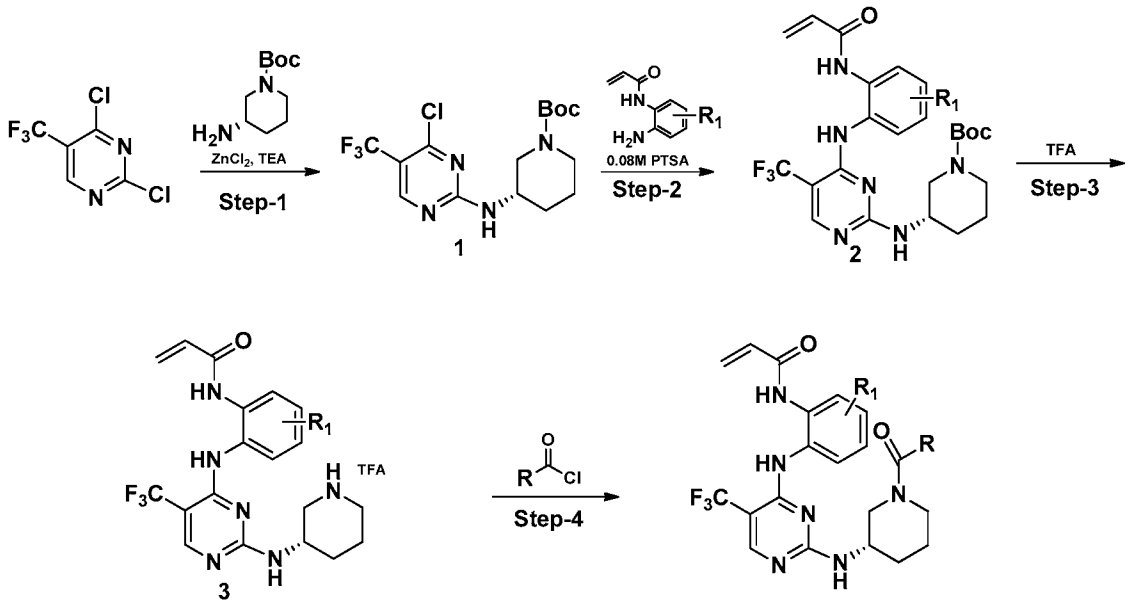
[00337] Scheme IB, below, depicts an alternate general method for preparing certain intermediates for preparing compounds of formula **I**, wherein Ring A is phenyl and R^2 and p are as defined and described herein. At Step 1, intermediate *iv* can be treated with acryloyl chloride (or other reagent suitable for introducing the acryloyl moiety) to form intermediate *v*. At Step 2, the nitro moiety of intermediate *v* can then be reduced to an amine to form common intermediate *iii*. One of ordinary skill in the art will recognize that the reduction step can be achieved in a variety of ways, including treatment of intermediate *v* with Zn/NH_4Cl to form common intermediate *iii*.

Scheme IB:

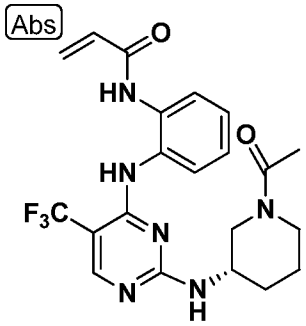


iv *v* *iii*

[00338] **Method A** was used to first introduce aliphatic cyclic amine at the C-2 position of 5-CF_3-2,4-dichloropyrimidine, followed by introduction of warhead-bearing intermediates at the C-4 position. The general synthetic approach is depicted in **Example 1** below.



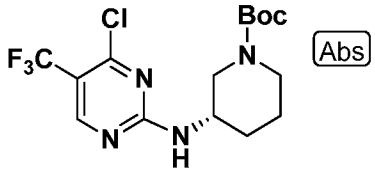
Example 1



I-10

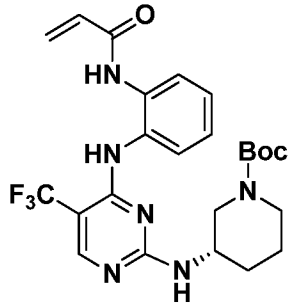
[00339] (S)-N-(2-(2-(1-acetylpiperidin-3-ylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide: The title compound was prepared according to the steps and intermediates as described below.

Step 1: (S)-tert-butyl 3-((4-chloro-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (Intermediate 1)



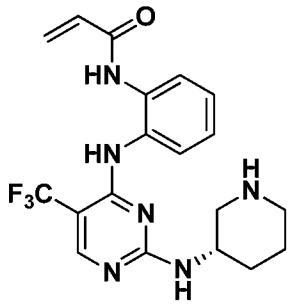
[00340] To a solution of 2,4-dichloro-5-(trifluoromethyl)pyrimidine (5g, 23mmol) in dichloroethane: t-butanol (50 ml, 1:1) was added dry zinc chloride (3.7 g, 27 mmol) and triethylamine (2.52 g, 25 mmol), and the mixture was stirred at rt for 1h (pH should not be >7). To this mixture, (S)-tert-butyl 3-aminopiperidine-1-carboxylate (4.9 g, 25 mmol) was added and stirring continued at rt for 16h. TLC showed formation of the major compound (0.2 Rf) and a minor other isomer (0.25 Rf) and ~10% starting material in 15% EtOAc: hexane solvent system. Solvents were evaporated, and crude was diluted with ice cold water (50 mL) and stirred for 5 min at rt to get a pale yellow gummy mass. The crude pale yellow gummy mass (6 g) was taken in 60 mL hexane and stirred for 10min at rt to get a solid which was immediately filtered to get the pure desired compound (5 g, 57%). MS m/z: 381.1 (ES+, M+H).

Step 2: (S)-tert-butyl 3-(4-(2-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)piperidine-1-carboxylate (Intermediate 2)



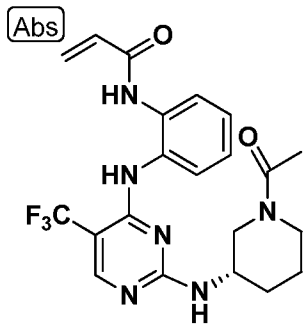
[00341] To a solution of (S)-tert-butyl 3-((4-chloro-5-(trifluoromethyl)pyrimidin-2-ylamino)piperidine-1-carboxylate (3.5 g, 9.21 mmol) in 0.04 M PTSA in 1, 4-dioxane (50 ml) was added N-(2-aminophenyl)acrylamide (2.79 g, 10.13 mmol, TFA salt), and the mixture was stirred at rt for 16h. TLC showed completion of starting material. (TLC system: 5% methanol in dichloromethane, $\mathbf{R_f}$ = 0.3). 1,4-dioxane was evaporated, and the crude was diluted with water (2×30 mL), extracted with ethyl acetate (50 mL), and washed with saturated sodium bicarbonate solution (2×20 mL). The organic layer was dried over sodium sulfate and concentrated to the crude (4.7 g), which was purified by silica gel column chromatography using 1% MeOH/DCM as eluents to obtain the title compound as a off white solid (3 g, 64%). MS m/z: 507.3 (ES+, M+H).

Step 3: (S)-N-(2-(2-(piperidin-3-ylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino) phenyl)acrylamide (Intermediate 3)



[00342] To a solution of (S)-tert-butyl 3-(4-(2-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)piperidine-1-carboxylate (3 g) in DCM (30 ml) was added trifluoroacetic acid (5 ml) at 0°C for 10 min and stirred at rt for 2h. TLC showed completion of starting material. (TLC system: 15% methanol in dichloromethane, $\mathbf{R_f}$ = 0.2). The reaction mixture was concentrated, and the crude was co-distilled with DCM (3x 20 mL) and washed with diethyl ether (2x10 mL) to obtain (S)-N-(2-(2-(piperidin-3-ylamino)-5-(trifluoromethyl) pyrimidin-4-ylamino)phenyl)acrylamide as an off white solid. (3 g, 97%). MS: m/z = 407.1 (ES+, M+H).

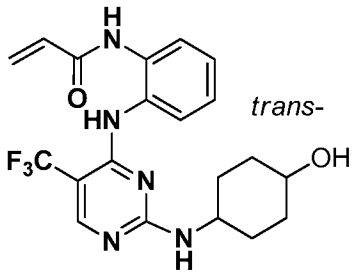
Step 4: (S)-N-(2-(2-(1-acetylpiperidin-3-ylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide



[00343] To a solution of **intermediate 3** (1.5 g, 2.88 mmol) in DCM (15 ml) was added triethylamine (0.291 g, 8.653 mmol) and acetyl chloride (0.216 g, 2.884 mmol) at 0°C, and the mixture was stirred at rt for 30 min. TLC showed completion of starting material. (TLC System: 5% Methanol in dichloromethane ($\mathbf{R_f}$ = 0.4). [Alternatively, acetic anhydride was used in place of acetyl chloride to provide the title compound.] The reaction mixture was diluted with water (2×30 mL), and extracted with DCM (2x30 mL). The organic layer was dried over sodium sulphate and concentrated to get the crude compound (1.1 g) which was purified by prep-HPLC

to obtain the desired compound (430 mg, 35%). MS m/z: 449.6 (ES+, M+1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.21-1.27 (m, 1H), 1.38-1.67 (m, 2H), 1.67-1.70 (t, 1H), 1.83-1.89 (br s, 1H), 1.94-1.96 (d, 1H, J = 8.01Hz), 2.01 (s, 1H), 2.64-2.68 (m, 1H), 2.86-2.96 (m, 1H), 3.49-3.59 (m, 1H), 3.62-3.96 (m, 1H), 3.96-4.14 (m, 1H), 5.78-5.80 (d, 1H, J = 10.1Hz), 6.27-6.31 (d, 1H, J = 16.9Hz), 6.40-6.50 (dd, 1H), 7.18-7.29 (m, 3H), 7.42-7.48 (m, 1H), 7.7-7.8 (m, 1H), 8.14-8.24 (m, 1H), 8.20 (s, 2H), 10.30 (s, 1H).

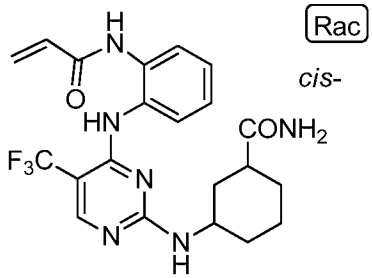
Example 2



I-1

[00344] Trans-N-(2-((2-((4-hydroxycyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-1** was prepared in a manner similar to Example 1, substituting *trans*-4-aminocyclohexanol for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 422.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.01-1.07 (m, 2H), 1.15-1.22 (m, 4H), 1.74 (br s, 4H), 4.47-4.48 (d, 1H), 5.78-5.81 (d, 1H, J=10.1Hz), 6.27-6.32 (d, 1H, J=17Hz), 6.42-6.46 (dd, 1H, J=6.8Hz and J=17Hz), 7.20-7.27 (m, 3H), 7.36-7.38 (d, 1H, J=7.1Hz), 7.74-7.76 (m, 1H), 8.11 (s, 2H), 10.31 (s, 1H).

Example 3

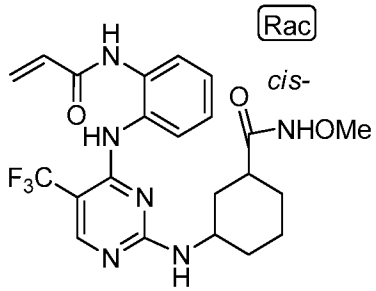


I-2

[00345] Rac-cis-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexanecarboxamide. Compound **I-2** was prepared in a manner similar to Example 1, substituting *cis*-3-aminocyclohexanecarboxamide for (S)-tert-butyl 3-

aminopiperidine-1-carboxylate: MS m/z 449.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.0-1.3 (m, 5H), 1.50-1.78 (m, 4H), 2.0 (t, 1H), 3.40 (s, 1H), 5.77-5.81 (m, 1H), 6.28-6.32 (m, 1H), 6.42-6.49 (m, 1H), 6.62-6.65 (d, 1H, J = 11.8Hz), 7.13-7.23 (m, 2H), 7.25-7.29 (m, 2H), 7.47-7.49 (d, 1H, J = 7.78Hz), 7.74-7.46 (d, 1H, J = 7.82Hz), 8.12 (s, 1H), 10.3 (s, 1H).

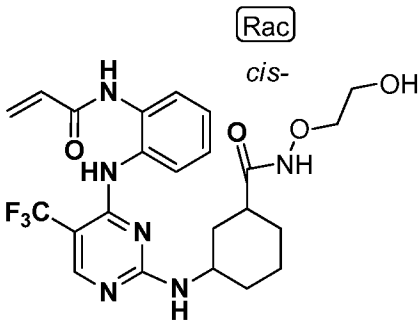
Example 4



I-3

[00346] Rac-cis-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-methoxycyclohexanecarboxamide: Compound **I-3** was prepared in a manner similar to Example 1, substituting cis-3-amino-N-methoxycyclohexanecarboxamide for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 479.4 (ES+, M+H). ^{1}H NMR (CD_3OD) δ 1.31-1.43 (m, 5H), 1.71-1.74 (d, 1H, J=9Hz), 1.82-2.05 (m, 4H), 3.38 (m, 1H), 3.63 (s, 3H), 3.86-3.88 (m, 1H), 5.82-5.84 (d, 1H, J=8Hz), 6.39-6.46 (m, 2H), 7.28-7.39 (m, 3H), 7.73-7.74 (d, 1H, J=6.98Hz), 8.08 (s, 1H).

Example 5

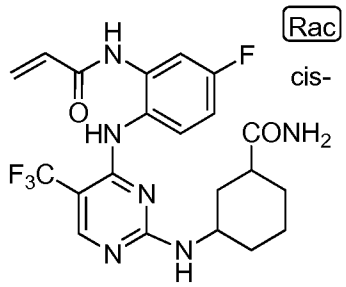


I-4

[00347] Rac-cis-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)cyclohexanecarboxamide: Compound **I-4** was prepared in a manner similar to Example 1, substituting cis-3-amino-N-(2-hydroxyethoxy)cyclohexanecarboxamide for (S)-tert-butyl 3-aminopiperidine-1-carboxylate.

MS m/z: 509.2 (ES+, M+H). ^{1}H NMR (CD_3OD) δ 1.20-1.23 (m, 1H), 1.31-1.44 (m, 4H), 1.41-1.44 (m, 1H), 1.73-1.75 (m, 2H), 1.91-1.96 (m, 4H), 1.96-2.0 (m, 1H), 3.79-3.82 (m, 2H), 3.88-3.98(m, 2H), 5.82-7.83 (d, 1H, J=7.8Hz), 6.43-6.46 (m, 2H), 7.28-7.39 (m, 3H), 7.73-7.74 (m, 1H), 8.08 (s, 1H).

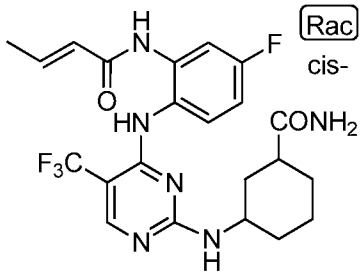
Example 6



I-5

[00348] Rac-cis-3-((4-((2-acrylamido-4-fluorophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexanecarboxamide: Compound **I-5** was prepared in a manner similar to Example 1, substituting cis-3-aminocyclohexanecarboxamide for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 467.5 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.08-1.14 (m, 1H), 1.16-1.23 (m, 2H), 1.23-1.29 (m, 2H), 1.66-1.74 (m, 4H), 1.97-2.01 (m, 1H), 5.78-5.82 (dd, 1H, J=1.6, 11.8Hz), 6.25-6.31 (d, 1H, J=6.6, 15Hz), 6.42-6.49 (dd, 1H, J=10, 16.8Hz), 6.62-6.64 (d, 1H, J=10.3Hz), 7.08-7.16 (m, 2H), 7.26-7.29 (dd, 1H, J=2.8, 10Hz), 7.45-7.47 (d, 1H, J=7.7Hz), 7.61-7.67 (m, 1H), 8.0 (s, 1H), 10.20 (s, 1H).

Example 7

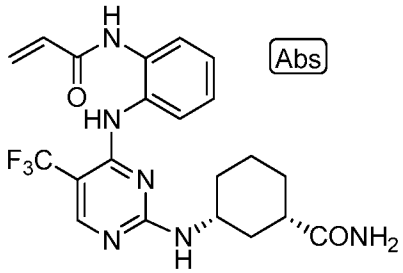


I-6

[00349] Rac-(E)-3-((4-((2-(but-2-enamido)-4-fluorophenyl)amino)-5-(trifluoromethyl) pyrimidin-2-yl)amino)-*cis*-cyclohexanecarboxamide: Compound **I-6** was prepared in a manner similar to Example 1, substituting *cis*-3-aminocyclohexanecarboxamide for (S)-tert-butyl

3-aminopiperidine-1-carboxylate, and (E)-N-(2-amino-5-fluorophenyl)but-2-enamide for N-(2-aminophenyl)acrylamide. MS m/z: 481.4 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 0.98-1.18 (m, 3H), 1.23-1.32 (m, 2H), 1.65-1.74 (m, 4H), 1.85-1.87 (d, 3H, J=6.6Hz), 2.01-2.11 (m, 1H), 6.12-6.16 (d, 1H, J=15.4Hz), 6.62-6.64 (d, 1H, J=11.Hz), 6.83-6.87 (m, 1H), 7.05-7.16 (m, 3H), 7.22-7.24 (m, 1H), 7.44-7.46 (d, 1H, J=7.7Hz), 7.62-7.65 (m, 1H), 8.11 (s, 1H), 9.99 (s, 1H).

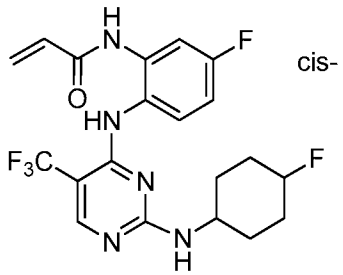
Example 8



I-7

[00350] (1S,3R)-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl) amino)cyclohexanecarboxamide: Compound **I-7** was prepared in a manner similar to Example 1, substituting (1S, 3R)-3-aminocyclohexanecarboxamide for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 449.2 (ES+, M+H).

Example 9

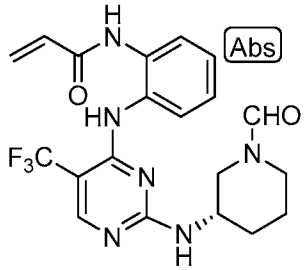


I-8

[00351] N-(5-fluoro-2-((2-((cis-4-fluorocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-8** was prepared in a manner similar to Example 1, substituting cis-4-fluorocyclohexanamine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 442.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.3-1.6 (m, 6H), 1.82-1.85 (br s, 2H), 4.67 (s, 0.5H), 4.79 (s, 0.5H), 5.79-5.81 (dd, J = 1.5, 10.2 Hz, 1H), 6.28(d, J = 17.1 Hz, 1H), 6.42-6.49 (dd, J = 10.1,

17.0 Hz, 1H), 7.02-7.11 (m, 1H), 7.29-7.31 (dd, J = 7.13, 9.75 Hz, 1H), 7.47 (d, J = 7.1 Hz, 1H), 7.62-7.65 (m, 1H), 8.08 (s, 1H), 8.12 (s, 1H), 10.15 (br s, 1H).

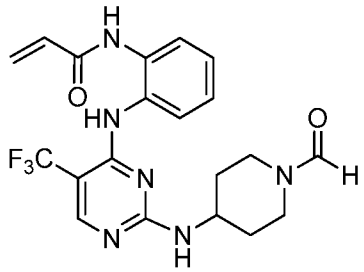
Example 10



I-9

[00352] (S)-N-(2-((2-((1-formylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-9** was prepared in a manner similar to Example 1, substituting formic acid, HATU, and DIPEA for acetic chloride in amide bond formation. MS m/z: 435.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.21-1.28 (m, 2H), 1.42-1.54 (m, 1H), 1.60-1.75 (m, 1H), 1.79-1.9 (m, 1H), 2.63-2.66 (m, 1H), 2.71-3 (m, 1H), 3.45-3.62 (m, 1H), 3.81-4 (m, 1H), 5.79 (d, J = 11.0 Hz, 1H), 6.29 (d, J = 17.0 Hz, 1H), 6.41-6.48 (dd, J = 10.1, 16.9 Hz, 1H), 7.18-7.34 (m, 3H), 7.54-7.58 (m, 1H), 7.68-7.7 (m, 1H), 8.01-8.04 (m, 1H), 8.15-8.22 (m, 2H), 10.26-10.32 (m, 1H).

Example 11

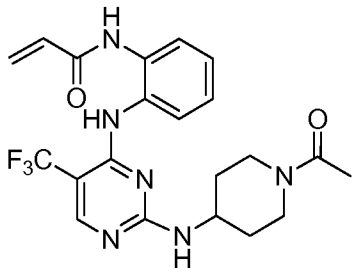


I-11

[00353] N-(2-((2-((1-formylpiperidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-11** was prepared in a manner similar to Example 1, substituting tert-butyl-4-aminopiperidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting formic acid, HATU, and DIPEA for acetic chloride in final amide bond formation step. MS m/z: 435.4 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.14-1.17 (m, 1H), 1.21-1.22 (m, 1H), 1.27-1.34 (m, 1H), 1.73-1.79 (m, 2H), 2.9 (t, J = 13.9 Hz, 1H), 3.56 (m, 1H), 3.62-3.65 (d, J = 12.8 Hz, 1H), 4.08 (d, J = 12.7 Hz, 1H), 5.8 (d, J = 10.0 Hz, 1H), 6.3 (d, J =

16.9 Hz, 1H), 6.42-6.49 (dd, J = 10.0, 16.9 Hz, 1H), 7.22 (d, J = 6.8 Hz, 1H), 7.29 (d, J = 7.2 Hz, 2H), 7.58 (d, J = 6.8 Hz, 1H), 7.67-7.74 (dd, J = 7.8, 21.4 Hz, 1H), 7.94 (s, 1H), 8.15-8.21 (m, 2H), 10.27 (d, J = 14.5 Hz, 1H).

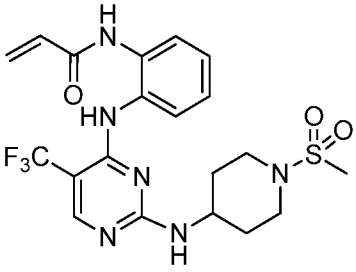
Example 12



I-12

[00354] N-(2-((2-((1-acetylpiperidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-12** was prepared in a manner similar to Example 1, substituting tert-butyl 4-aminopiperidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 449.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.1-1.4 (m, 2H), 1.69-1.77 (m, 2H), 1.95 (s, 3H), 2.40-2.43 (m, 1H), 2.88 (t, J = 12.0 Hz, 1H), 3.5 (br s, 1H), 3.75 (d, J = 12.8 Hz, 1H), 4.25 (t, J = 13.8 Hz, 1H), 5.8 (d, J = 10.1 Hz, 1H), 6.3 (d, J = 17 Hz, 1H), 6.42-6.49 (dd, J = 10.1, 16.9 Hz, 1H), 7.2-7.3 (m, 1H), 7.26-7.29 (m, 2H), 7.53 (d, J = 6.7 Hz, 1H), 7.68-7.74 (dd, J = 7.7, 19.4 Hz, 1H), 8.14-8.2 (m, 2H), 10.26 (d, J = 16.8 Hz, 1H) Mixture of rotamers.

Example 13

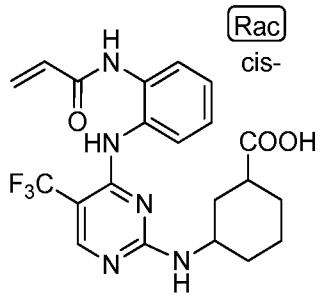


I-13

[00355] N-(2-((2-((1-(methylsulfonyl)piperidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-13** was prepared in a manner similar to Example 1, substituting tert-butyl 4-aminopiperidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate and substituting MsCl for acetic chloride. MS m/z: 485.5 (ES+, M+H). 1H NMR (DMSO-d6) δ 1.41-1.5 (m, 2H), 1.81-1.89 (m, 2H), 2.59-2.66 (m, 1H), 2.59-2.66 (m, 1H), 2.78-

2.83 (m, 1H), 2.85 (s, 3H), 3.5 (d, J = 11.5 Hz, 2H), 5.8 (d, J = 9.7 Hz, 1H), 6.3 (d, J = 16.7 Hz, 1H), 6.42-6.48 (m, 1H), 7.2-7.24 (m, 1H), 7.29-7.33 (m, 2H), 7.54 (d, J = 6.5 Hz, 1H), 7.67-7.75 (dd, J = 8.2, 20.5 Hz, 1H), 8.15-8.2 (m, 2H), 10.29 (d, J = 13 Hz, 1H) Mixture of rotamers.

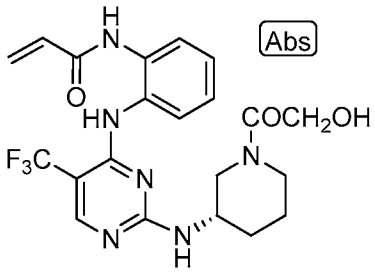
Example 14



I-14

[00356] Rac-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl) amino)-cis-cyclohexanecarboxylic acid: Compound **I-14** was prepared in a manner similar to Example 1, substituting *cis*—tert-butyl-3-aminocyclohexanecarboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and final deprotection of t-butyl ester with 50% TFA in DCM. MS m/z: 450.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.10-1.22 (m, 5H), 1.68-1.77 (m, 3H), 1.95-2.00 (m, 2H), 5.78-7.80 (d, 1H, J=10Hz), 6.26-6.31 (dd, 1H, J=5.9, 16.5Hz), 6.42-6.49 (dd, 1H, J=9.8, 16.7Hz), 7.15-7.25 (m, 3H), 7.48-7.50 (d, 1H, J=7Hz), 7.72-7.75 (m, 1H), 8.11 (s, 1H), 10.28 (s, 1H).

Example 15

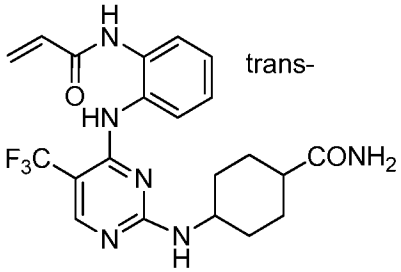


I-15

[00357] (S)-N-(2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-15** was prepared in a manner similar to Example 1, substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 465.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.24-1.45 (br s, 1H), 1.45-1.67 (br s, 1H), 1.67-1.70 (d, 1H, J = 13.3Hz), 1.80-1.83 (d, 1H, J = 11.45Hz), 2.78-2.89 (m,

2H), 3.45-3.51 (m, 2H), 3.65-3.75 (m, 1H), 4.04-4.08 (d, 2H, J = 10.0 Hz), 4.44-4.48 (d, 1H, J = 16.4 Hz), 5.78-5.80 (d, 1H, J = 10.2 Hz), 6.27-6.32 (d, 1H, J = 16.7 Hz), 6.41-6.48 (dd, 1H, J=10.1, 16.0Hz), 7.20-7.27 (m, 3H), 7.54 (br s, 1H), 7.68-7.04 (m, 1H), 8.16-8.23 (m, 2H), 10.28 (s, 1H).

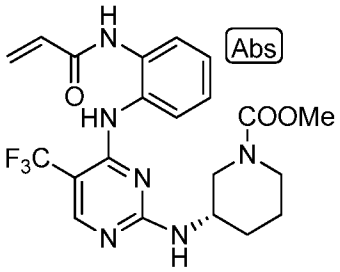
Example 16



I-16

[00358] 4-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-trans-cyclohexanecarboxamide: Compound **I-16** was prepared in a manner similar to Example 1, substituting trans-4-aminocyclohexanecarboxamide for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 449.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.13-1.22 (m, 4H), 1.30-1.4 (m, 1H), 1.69-1.71 (d, 2H, J=9.8Hz), 1.81-1.83 (d, 2H, J=10.4Hz), 1.94- 2.0 (m, 1H), 5.78-7.81 (d, 1H, J=10.1Hz), 6.26-6.32 (dd, 1H, J= 7.2, 16.9Hz), 6.43-6.49 (dd, 1H, J= 10.1, 16.8Hz), 6.63 (br s, 1H), 7.15 (br s, 1H), 7.21-7.28 (m, 3H), 7.38-7.40 (d, 1H, J= 7.6Hz), 7.74-7.77 (m, 1H), 8.11 (s, 1H), 10.28 (s, 1H).

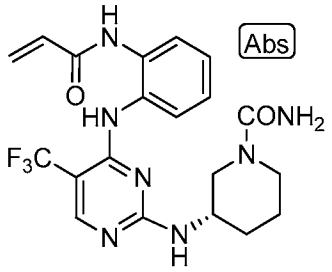
Example 17



I-17

[00359] (S)-Methyl 3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino) piperidine-1-carboxylate: Compound **I-17** was prepared in a manner similar to Example 1, substituting $ClCOOCH_3$ for acetic chloride. MS m/z: 465.2 (ES+, M+H).

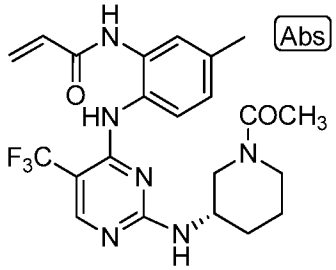
Example 18



I-18

[00360] (S)-3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)piperidine-1-carboxamide: Compound **I-18** was prepared in a manner similar to Example 1, substituting TMSNCO for acetic chloride. MS m/z: 450.2 (ES+, M+H).

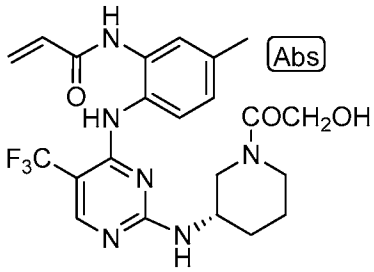
Example 19



I-19

[00361] (S)-N-(2-((2-((1-Acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-19** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 463.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.22 (br s, 1H), 1.42 (br s, 2H), 1.67-1.79 (m, 1H), 1.84 (br s, 1H), 1.92-2.01(m, 1H), 2.31(s, 3H), 2.5-2.8 (m, 1H), 2.8-3.04 (m, 1H), 3.49 (s, 3H), 3.96-4.13 (m, 1H), 5.76-5.79 (dd, J=1.4, 10.2Hz, 1H), 6.28 (d, J=16.8Hz, 1H), 6.4-6.47(dd, J=10.2, 16.9Hz, 1H), 6.97-7.08 (m, 2H), 7.40-7.68 (m, 2H), 7.91-8.23 (m, 2H), 10.26 (br s, 1H).

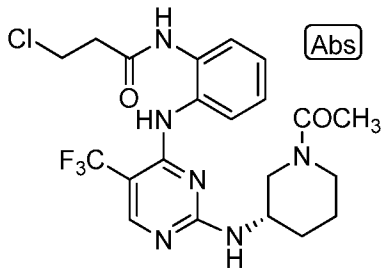
Example 20



I-20

[00362] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-20** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 479.5 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.47 (m, 1H), 1.67 (m, 1H), 1.83-1.86 (m, 2H), 2.31 (s, 3H), 2.81 (m, 1H), 3.42-3.44 (m, 2H), 3.63-3.67 (m, 2H), 4.01-4.08 (m, 2H), 4.24 (br s, 1H), 4.45 (br s, 1H), 5.76-5.79 (d, J = 10.0 Hz, 1H), 6.26-6.30 (d, J = 16.9 Hz, 1H), 6.40-6.47 (dd, J = 10.0, 17.0 Hz, 1H), 7.02 (s, 1H), 7.07-7.09 (d, J = 7.0 Hz, 1H), 7.90-8.29 (m, 2H), 8.13-8.22 (m, 2H), 10.27 (s, 1H).

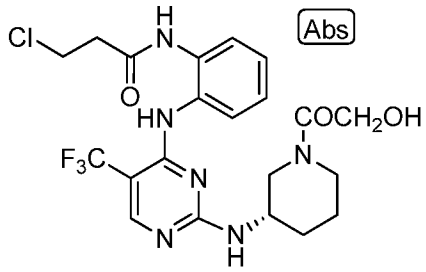
Example 21



I-21

[00363] (S)-N-(2-((2-((1-Acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-3-chloropropanamide: Compound **I-21** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-3-chloropropanamide for N-(2-aminophenyl)acrylamide. MS m/z: 485.6 (ES+, M+H). ^1H NMR (CD_3OD) δ 1.59 (m, 1H), 1.63-1.64 (m, 2H), 1.77 (m, 1H), 1.97 (m, 1H), 2.13 (s, 2H), 2.80-2.90 (m, 3H), 3.32-3.34 (m, 1H), 3.65 (m, 2H), 3.85-3.88 (m, 3H), 4.88 (br s, 1H), 7.34-7.41 (m, 3H), 7.62-7.66 (t, J = 8.4 Hz, 1H), 8.28-8.30 (d, J = 6.0 Hz, 1H).

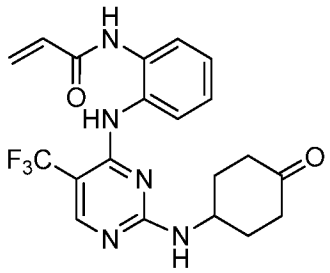
Example 22



I-22

[00364] (S)-3-Chloro-N-(2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)propanamide: Compound **I-22** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-3-chloropropanamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 501.5 (ES+, M+H). ^{1}H NMR (CD_3OD) δ 1.47 (m, 1H), 1.60-1.67 (m, 1H), 1.76 (m, 1H), 1.85-2.0 (m, 1H), 2.89 (br s, 2H), 2.95-3.10 (m, 1H), 3.40-3.57 (m, 2H), 3.69 (br s, 1H), 3.87 (t, J=5.2Hz, 4H), 4.25 (s, 1H), 7.30-7.47 (m, 3H), 7.62 (d, J=5.8Hz, 1H), 8.29 (s, 1H).

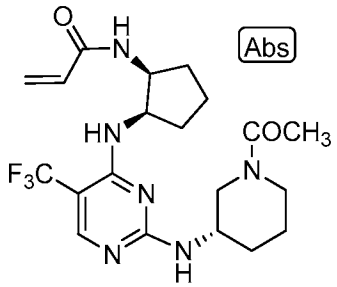
Example 23



I-23

[00365] N-(2-((2-((4-Oxocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-23** was prepared in a manner similar to Example 1, substituting 4-aminocyclohexanone for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z 420.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.62-1.66 (m, 2H), 1.95-2.09 (m, 2H), 2.21-2.32 (m, 3H), 2.48-2.49 (m, 1H), 3.77 (m, 1H), 5.80 (d, J=10.3Hz, 1H), 6.30 (d, J=16.6Hz,1H), 6.42-6.49 (dd, J=10.2, 17.1Hz, 1H), 7.19-7.29 (m, 4H), 7.60 (d, J=6.5Hz, 1H), 7.65-7.79 (m, 1H), 8.10-8.25 (m, 2H), 10.28 (d, J=16Hz, 1H). Mixture of Rotamers.

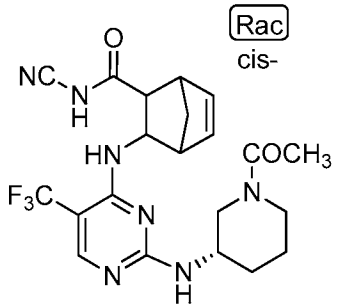
Example 24



I-24

[00366] N-((1S,2S)-2-((2-(((S)-1-Acetylpiperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)cyclopentyl)acrylamide: Compound **I-24** was prepared in a manner similar to Example 1, substituting N-((1S,2S)-2-aminocyclopentyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 441.2 (ES+, M+H).

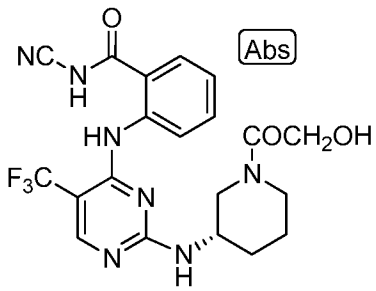
Example 25



I-25

[00367] Rac-3-((2-(((S)-1-acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)-cis-amino)-N-cyanobicyclo[2.2.1]hept-5-ene-2-carboxamide: Compound **I-25** was prepared in a manner similar to Example 1, substituting cis-3-amino-N-cyanobicyclo[2.2.1]hept-5-ene-2-carboxamide for N-(2-aminophenyl)acrylamide. MS m/z: 464.1 (ES+, M+H).

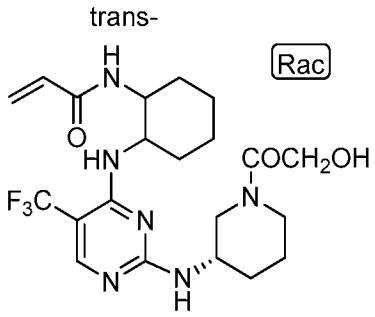
Example 26



I-26

[00368] (S)-N-Cyano-2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)benzamide: Compound **I-26** was prepared in a manner similar to Example 1, substituting 2-amino-N-cyanobenzamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 464.5 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.42-1.58 (m, 2H), 1.74-176 (m, 1H), 1.89-2.06 (m, 1H), 2.85-2.95 (m, 2H), 3.75-4.08 (m, 3H), 4.08 (s, 2H), 4.47 (br s, 1H), 7.29 (br s, 1H), 7.39 (br s, 1H), 7.60 (d, J =7.5 Hz, 1H), 7.72 (d, J =6 Hz, 1H), 7.88 (br s, 1H), 7.96 (d, J = 7.7 Hz, 1H), 8.36 (br s, 1H), 12.38 (br s, 1H).

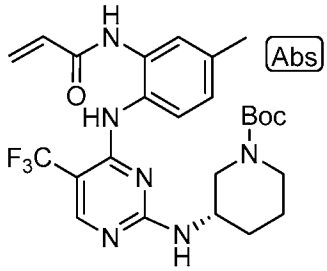
Example 27



I-27

[00369] Rac-N-(2-((2-(((R)-1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-trans-cyclohexyl)acrylamide: Compound **I-27** was prepared in a manner similar to Example 1, substituting N-trans-2-aminocyclohexylacrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 471.6 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.12-1.37 (m, 4H), 1.40-1.59 (m, 2H), 1.60-1.78 (m, 3H), 1.80-1.89 (m, 1H), 1.91-1.98 (m, 1H), 2.12-2.19 (m, 1H), 2.70-2.82 (m, 1H), 2.83-3.0 (m, 1H), 3.52-3.61 (m, 1H), 3.63-3.72 (m, 1H), 3.75-3.95 (m, 2H), 3.95-4.19 (m, 2H), 4.2-4.6 (m, 2H), 5.52-5.58 (m, 1H), 6.0-6.25 (m, 2H), 6.37 (d, J=32.1Hz, 1H), 7.11-7.47 (m, 1H), 7.95-8.18 (m, 2H). Mixture of diastereomers.

Example 28

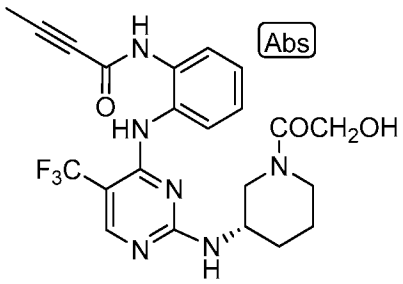


I-28

[00370] (S)-tert-Butyl 3-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl) pyrimidin-2-yl)amino)piperidine-1-carboxylate: Compound **I-28** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 519.5 (ES-, M–H). ^1H NMR (DMSO-d_6) δ 1.22-1.27 (m, 3H), 1.35 (s, 9H), 1.66-1.7 (m, 2H), 2.27 (s, 3H), 2.27-2.29 (m, 1H), 3.36 (br s, 1H), 3.51-3.90 (m, 2H), 5.78 (d, J=10.0Hz, 1H), 6.26-6.31 (d, J=16.8Hz, 1H), 6.4-6.47 (dd, J=10.1, 16.8Hz,

1H), 7.05-7.09 (m, 2H), 7.42-7.52 (m, 1H), 6.63 (d, J=6.3Hz, 1H), 7.95-8.19 (m, 2H), 10.20 (d, J=33.1Hz, 1H). Mixture of Rotamers

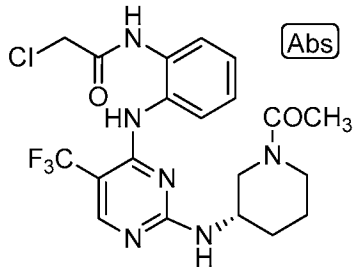
Example 29



I-29

[00371] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)but-2-ynamide: Compound **I-29** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)but-2-ynamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 477.5 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.22 (m, 1H), 1.67-1.74 (m, 1H), 1.79-1.85 (m, 1H), 2.03 (s, 3H), 2.70-2.95 (m, 2H), 3.38 (m, 2H), 3.60-3.86 (m, 2H), 4.04-4.11 (m, 2H), 4.45-4.49 (m, 1H), 7.18-7.30 (m, 3H), 7.56 (br s, 1H), 7.67 (m, 1H), 7.76 (d, J=6.7Hz, 1H), 7.89 (br s, 1H), 8.18 (s, 1H), 8.24 (d, J=13.4 Hz, 1H), 10.66 (br s, 1H).

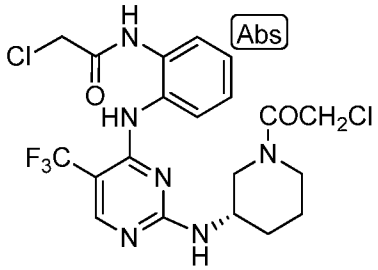
Example 30



I-30

[00372] (S)-N-(2-((2-((1-Acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-chloroacetamide Compound **I-30** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-2-chloroacetamide for N-(2-aminophenyl) acrylamide. MS m/z: 471.0 (ES+, M+H).

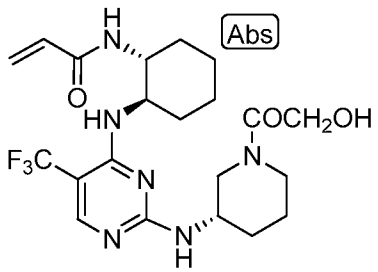
Example 31



I-31

[00373] (S)-2-Chloro-N-(2-((2-((1-(2-chloroacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acetamide: Compound **I-31** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-2-chloroacetamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2Cl$ for acetic chloride. MS m/z: 505.1 (ES+, M+H).

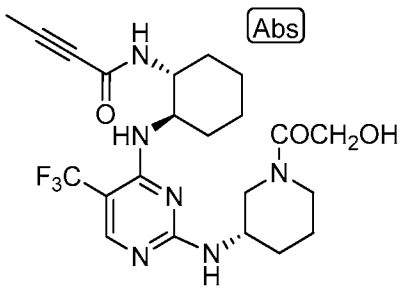
Example 32



I-32

[00374] N-((1R,2R)-2-((2-(((S)-1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)cyclohexyl)acrylamide: Compound **I-32** was prepared in a manner similar to Example 1, substituting N-((1R,2R)-2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 471.6 (ES+, M+H).

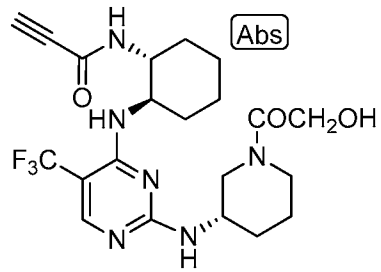
Example 33



I-33

[00375] N-((1R,2R)-2-((2-(((S)-1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)cyclohexyl)but-2-ynamide: Compound **I-33** was prepared in a manner similar to Example 1, substituting N-((1R,2R)-2-aminocyclohexyl)but-2-ynamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 483.2 (ES+, M+H).

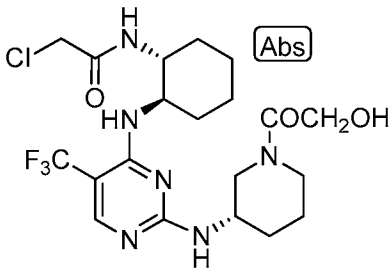
Example 34



I-34

[00376] N-((1R,2R)-2-((2-(((S)-1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)cyclohexyl)propiolamide: Compound **I-34** was prepared in a manner similar to Example 1, substituting N-((1R,2R)-2-aminocyclohexyl)propiolamide for N-((1R,2R)-2-aminocyclohexyl)but-2-ynamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 469.2 (ES+, M+H).

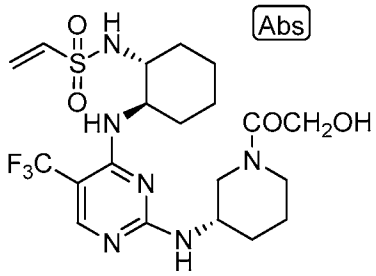
Example 35



I-35

[00377] 2-Chloro-N-((1R,2R)-2-((2-(((S)-1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)cyclohexyl)acetamide: Compound **I-35** was prepared in a manner similar to Example 1, substituting N-((1R,2R)-2-aminocyclohexyl)-2-chloroacetamide for N-((1R,2R)-2-aminocyclohexyl)but-2-ynamide, and substituting $ClCOCH_2OAc$ for acetic chloride followed by hydrolysis with aqueous LiOH. MS m/z: 493.1 (ES+, M+H).

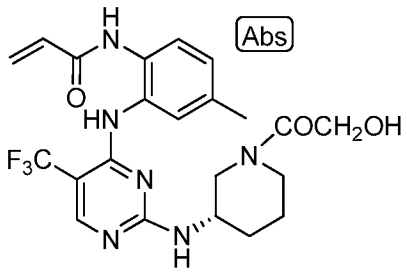
Example 36



I-36

[00378] N-((1R,2R)-2-((2-(((S)-1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)cyclohexyl)ethenesulfonamide: Compound **I-36** was prepared in a manner similar to Example 1, substituting N-((1R,2R)-2-aminocyclohexyl)ethenesulfonamide for N-((1R,2R)-2-aminocyclohexyl)but-2-ynamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 507.2 (ES+, M+H).

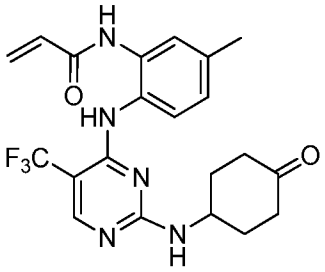
Example 37



I-37

[00379] (S)-N-(2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-4-methylphenyl)acrylamide: Compound **I-37** was prepared in a manner similar to Example 1, substituting N-(2-amino-4-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 478.1 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.22 (m, 1H), 1.40-1.55 (m, 1H), 1.70 (m, 1H), 1.84 (m, 1H), 2.26 (s, 3H), 2.72-2.88 (m, 1H), 2.95 (m, 1H), 3.35-3.45 (m, 1H), 3.54 (m, 1H), 3.64-3.70 (m, 1H), 3.83-3.96 (m, 1H), 4.04 (br s, 1H), 4.25-4.39 (m, 1H), 5.75 (d, J=10.1Hz, 1H), 6.26-6.30 (dd, J=8.4, 16.2Hz, 1H), 6.39-6.46 (dd, J=10.3, 16.2Hz, 1H), 6.98-7.04 (m, 1H), 7.09-7.20 (m, 1H), 7.45-7.65 (m, 1H), 8.16-8.23 (m, 2H), 10.27 (d, J=21.4Hz, 1H). Mixture of Rotamers.

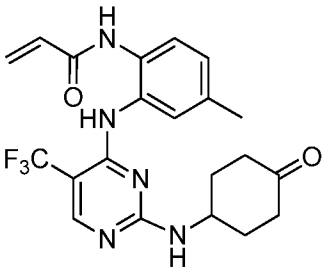
Example 38



I-38

[00380] N-(5-Methyl-2-((2-((4-oxocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide Compound **I-38** was prepared in a manner similar to Example 1, substituting 4-aminocyclohexanone for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 434.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.64 (br s, 2H) 1.99 (br s, 3H), 2.20 (s, 3H), 2.29 (br s, 3H), 3.77 (s, 1H), 5.78 (d, J = 10.1 Hz, 1H), 6.28 (d, J = 17 Hz, 1H), 6.41-6.47(dd, J =10.1, 16.8 Hz, 1H), 7.08 (br s, 2H), 7.53-7.57 (m, 1H), 7.63-7.65 (m, 1H), 8.13 (br s, 1H), 8.20 (br s, 1H), 10.2 (br s, 1H).

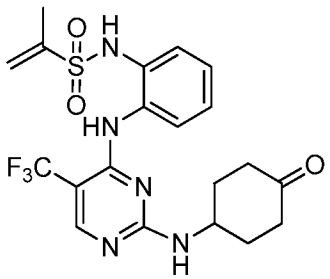
Example 39



I-39

[00381] N-(4-Methyl-2-((2-((4-oxocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-39** was prepared in a manner similar to Example 1, substituting 4-aminocyclohexanone for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-4-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 434.6 (ES+, M+H). ^{1}H NMR (CD_3OD) δ 1.69-1.79 (m, 2H), 2.15 (br s, 2H), 2.33-2.39 (br s, 4H), 2.41 (s, 3H), 3.95 (br s, 1H), 5.79-5.82 (dd, J = 2.4, 9.2 Hz, 1H), 6.37-6.44 (m, 2H), 7.09-7.12 (dd, J = 1.1, 6.7 Hz, 1H), 7.21-7.27 (dd, J = 8, 17 Hz, 1H), 7.54 (s, 1H), 8.12 (s, 1H).

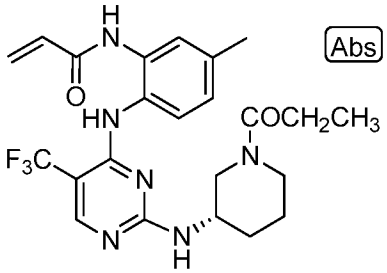
Example 40



I-40

[00382] N-(2-((2-((4-Oxocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)prop-1-ene-2-sulfonamide: Compound **I-40** was prepared in a manner similar to Example 1, substituting 4-aminocyclohexanone for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-aminophenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide. MS m/z: 470.5 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 1.66-1.73 (m, 2H), 2.04 (s, 3H), 2.06 (br s, 2H), 2.22-2.32 (br s, 4H), 3.84 (br s, 1H), 5.61 (s, 1H), 5.67 (s, 1H), 7.08-7.13 (m, 2H), 7.29-7.21 (m, 1H), 7.73 (d, J = 6 Hz, 1H), 7.98 (d, J = 8 Hz, 1H), 8.16-8.24 (m, 1H), 8.31 (s, 1H), 9.48 (d, J= 14.0Hz, 1H). Mixture of Rotamers.

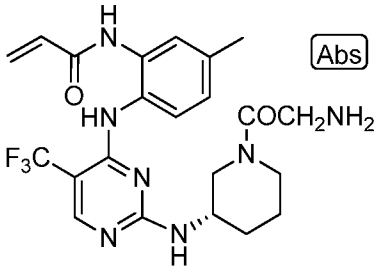
Example 41



I-41

[00383] (S)-N-(5-Methyl-2-((2-((1-propionylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-41** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $CH_3CH_2CO_2H$, HATU and DIPEA for acetic chloride in final amide bond formation step. MS m/z: 477.2 (ES+, M+H).

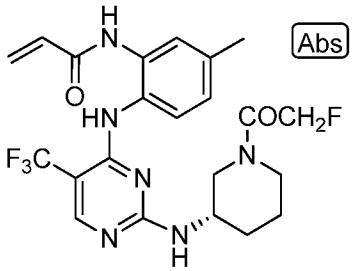
Example 42



I-42

[00384] (S)-N-(2-((2-((1-(2-Aminoacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-42** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, substituting N-Boc-glycine, HATU and DIPEA for acetic chloride in final amide bond formation step, followed by Boc-deprotection with TFA. MS m/z: 478.3 (ES+, M+H).

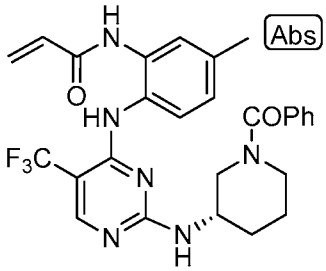
Example 43



I-43

[00385] (S)-N-(2-((2-((1-(2-Fluoroacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-43** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-fluoroacetic acid, HATU and DIPEA for acetic chloride in final amide bond formation step. MS m/z: 481.4 (ES+, M+H).

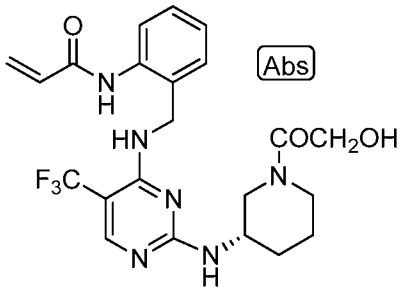
Example 44



I-44

[00386] (S)-N-(2-((2-((1-Benzoylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-44** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting benzoic acid, HATU and DIPEA for acetic chloride in final amide bond formation step. MS m/z: 525.2 (ES+, M+H).

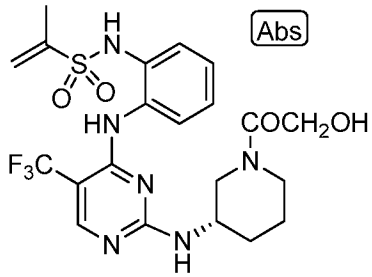
Example 45



I-45

[00387] (S)-N-(2-(((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)methyl)phenyl)acrylamide: Compound **I-45** was prepared in a manner similar to Example 1, substituting N-(2-(aminomethyl)phenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 479.3 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.22 (m, 1H), 1.32-1.34 (m, 2H), 1.45 (m, 1H), 1.67-1.89 (m, 2H), 2.87 (m, 2H), 3.34-3.39 (m, 1H), 3.63 (m, 1H), 3.99-4.06 (m, 2H), 4.41-4.50 (m, 1H), 4.56-4.59 (m, 1H), 5.74 (d, J=9.2Hz, 1H), 6.24 (d, J=16.2Hz, 1H), 6.52-6.59 (m, 1H), 7.08-7.36 (m, 5H), 7.43-7.51 (m, 1H), 8.01-8.12 (m, 1H), 9.55 (d, J=33Hz, 1H). Mixture of Rotamers

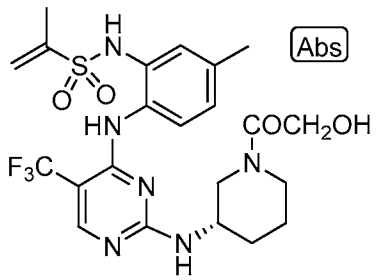
Example 46



I-46

[00388] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)prop-1-ene-2-sulfonamide: Compound **I-46** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 515.5 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.48 (m, 1H), 1.69 (m, 1H), 1.83-1.89 (m, 1H), 2.04 (s, 3H), 2.87-2.95 (m, 2H), 3.42-3.51 (m, 2H), 3.66-3.77 (m, 2H), 4.07-4.12 (m, 2H), 4.30 (s, 1H), 5.62 (s, 1H), 5.68 (s, 1H), 7.13-7.19 (m, 2H), 7.24-7.30 (m, 1H), 7.81 (s, 1H), 7.90-8.29 (m, 1H), 8.33 (s, 1H), 8.55-8.59 (m, 1H), 9.47 (d, J= 8.3Hz, 1H). Mixture of Rotamers.

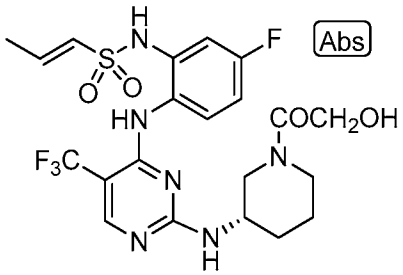
Example 47



I-47

[00389] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)prop-1-ene-2-sulfonamide: Compound **I-47** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 529.5 (ES+, M+H). ^1H NMR (DMSO-d_6) δ 1.47 (m, 1H), 1.69 (m, 1H), 1.86-1.89 (m, 1H), 2.02 (s, 3H), 2.25 (s, 3H), 2.83-2.93 (m, 2H), 3.51 (m, 2H), 3.65-3.77 (m, 2H), 4.05-4.08 (m, 2H), 4.45 (s, 1H), 5.65 (s, 1H), 5.89 (s, 1H), 6.92 (m, 2H), 7.80 (s, 1H), 7.90-8.29 (m, 1H), 8.08-8.29 (m, 2H), 9.38 (d, J= 22.0Hz, 1H). Mixture of Rotamers.

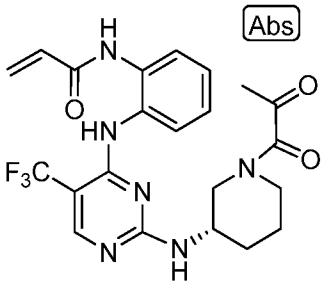
Example 48



I-48

[00390] (S,E)-N-(5-Fluoro-2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)prop-1-ene-1-sulfonamide: Compound **I-48** was prepared in a manner similar to Example 1, substituting (E)-N-(2-amino-5-fluorophenyl)prop-1-ene-1-sulfonamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 575.2 (ES+, M+H).

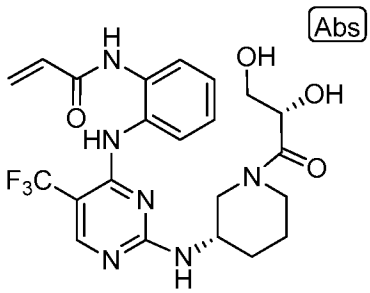
Example 49



I-49

[00391] (S)-N-(2-((2-((1-(2-Oxopropanoyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-49** was prepared in a manner similar to Example 1, substituting $CH_3COCOOH$, HATU and DIPEA for acetic chloride in the final amide formation step. MS m/z: 477.1 (ES+, M+H).

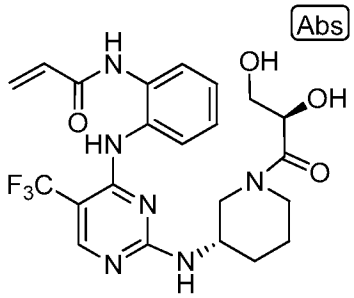
Example 50



I-50

[00392] N-(2-((2-(((S)-1-((S)-2,3-Dihydroxypropanoyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-49** was prepared in a manner similar to Example 1, substituting (S)-2,3-dihydroxypropanoic acid, HATU and DIPEA for acetic chloride in the final amide formation step. MS m/z: 495.2 (ES+, M+H).

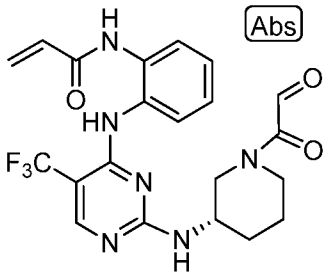
Example 51



I-51

[00393] N-(2-((2-(((S)-1-((R)-2,3-Dihydroxypropanoyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide Compound **I-51** was prepared in a manner similar to Example 1, substituting (R)-2,3-dihydroxypropanoic acid, HATU and DIPEA for acetic chloride in the final amide formation step. MS m/z: 495.2 (ES+, M+H).

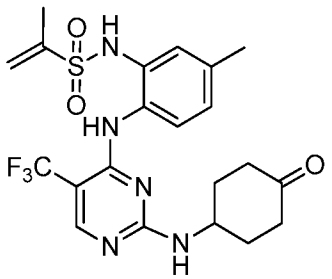
Example 52



I-52

[00394] (S)-N-(2-((2-((1-(2-Oxoacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-52** was prepared in a manner similar to Example 1, substituting (R)-2,3-dihydroxypropanoic acid for acetic acid, followed by oxidizative-cleavage with $NaIO_4$. MS m/z: 463.1 (ES+, M+H).

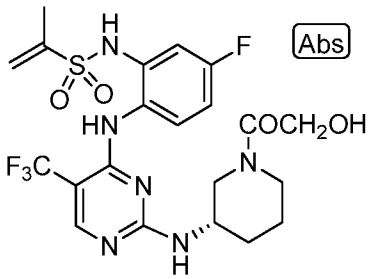
Example 53



I-53

[00395] N-(5-Methyl-2-((2-((4-oxocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)prop-1-ene-2-sulfonamide: Compound **I-53** was prepared in a manner similar to Example 1, substituting 4-aminocyclohexanone for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-methylphenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide. MS m/z: 484.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.65 (m, 2H), 2.02 (s, 6H), 2.25 (br s, 7H), 3.84 (br s, 1H), 5.62 (s, 1H), 5.66 (s, 1H), 6.92 (s, 1H), 7.11 (d, J = 8 Hz, 1H), 7.69 (d, J = 6 Hz, 1H), 7.81 (d, J = 8 Hz, 1H), 8.22-8.29 (m, 2H), 9.40 (s, 1H).

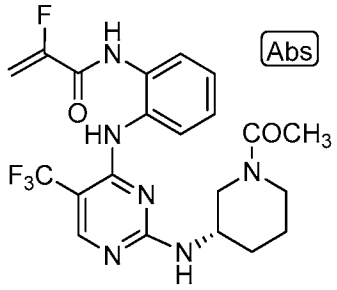
Example 54



I-54

[00396] (S)-N-(5-Fluoro-2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)prop-1-ene-2-sulfonamide: Compound **I-54** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-fluorophenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ and LiOH for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 533.5 (ES+, M+H). ^{1}H NMR: (DMSO-d_6) δ 1.46 (m, 1H), 1.68 (m, 1H), 1.89 (m, 1H), 2.03 (s, 3H), 2.88-2.90 (m, 2H), 3.30 (m, 1H), 3.64 (m, 1H), 3.64-3.76 (m, 2H), 4.06-4.09 (m, 2H), 4.46 (s, 1H), 5.65 (s, 1H), 5.69 (s, 1H), 6.94-7.12 (m, 2H), 7.61 (d, J = 7.1 Hz, 1H), 7.90-8.29 (br s, 1H), 8.21-8.29 (m, 2H), 9.6 (s, 1H).

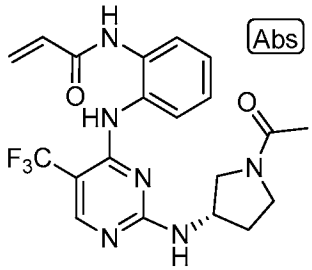
Example 55



I-55

[00397] (S)-N-(2-((2-((1-Acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-fluoroacrylamide: Compound **I-55** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-2-fluoroacrylamide for N-(2-aminophenyl) acrylamide. MS m/z: 467.1 (ES+, M+H).

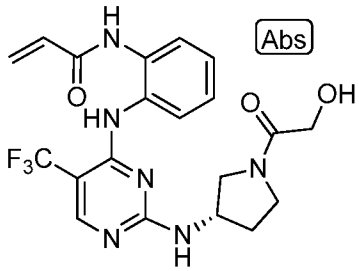
Example 56



I-56

[00398] (S)-N-(2-((2-((1-Acetylpyrrolidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-56** was prepared in a manner similar to Example 1, substituting (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 435.1 (ES+, M+H).

Example 57

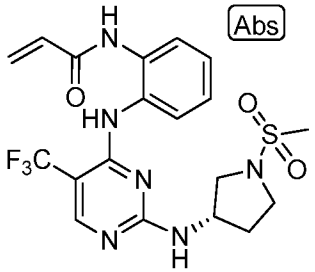


I-57

[00399] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)pyrrolidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide Compound **I-57** was prepared in a

manner similar to Example 1, substituting (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 451.1 (ES+, M+H).

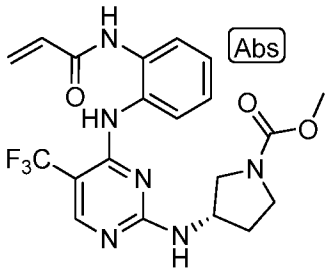
Example 58



I-58

(S)-N-(2-((2-((1-(Methylsulfonyl)pyrrolidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-58** was prepared in a manner similar to Example 1, substituting (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting MsCl for acetic chloride. MS m/z: 471.1 (ES+, M+H).

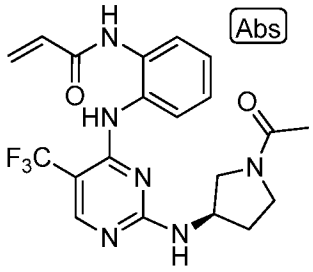
Example 59



I-59

[00400] (S)-methyl 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl) pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate: Compound **I-59** was prepared in a manner similar to Example 1, substituting (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting $ClCOOCH_3$ for acetic chloride. MS m/z: 451.1 (ES+, M+H).

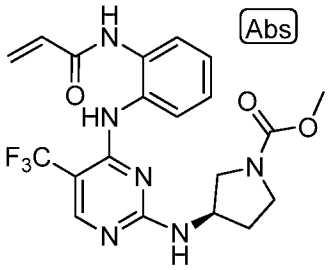
Example 60



I-60

[00401] (R)-N-(2-((2-((1-Acetylpyrrolidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-60** was prepared in a manner similar to Example 1, substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate. MS m/z: 435.2 (ES+, M+H).

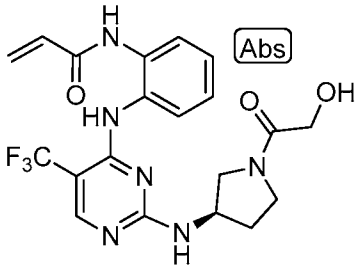
Example 61



I-61

[00402] (R)-Methyl 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate: Compound **I-61** was prepared in a manner similar to Example 1, substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting $ClCOOCH_3$ for acetic chloride. MS m/z: 435.2 (ES+, M+H).

Example 62

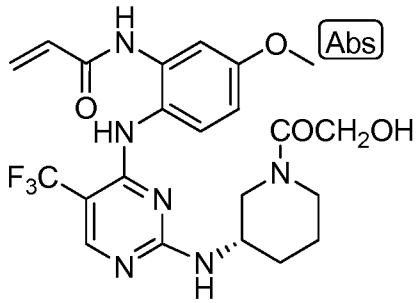


I-62

[00403] (R)-N-(2-((2-((1-(2-Hydroxyacetyl)pyrrolidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-62** was prepared in

a manner similar to Example 1, substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 451.1 (ES+, M+H).

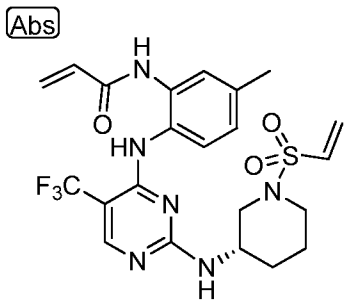
Example 63



I-64

[00404] (S)-N-(2-((2-((1-(2-Hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-64** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting $ClCOCH_2OAc$ for acetic chloride, followed by hydrolysis with aqueous LiOH. MS m/z: 495.2 (ES+, M+H).

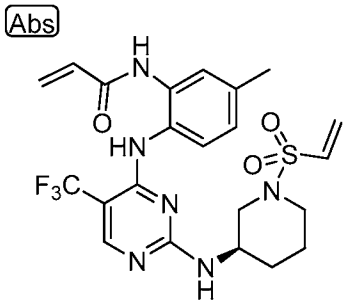
Example 64



I-277

[00405] (S)-N-(5-Methyl-2-((5-(trifluoromethyl)-2-((1-(vinylsulfonyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-277** was prepared in a manner similar to Example 1, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-chloroethansulfonyl chloride for acetic chloride. MS m/z: 511.1 (ES+, M+H).

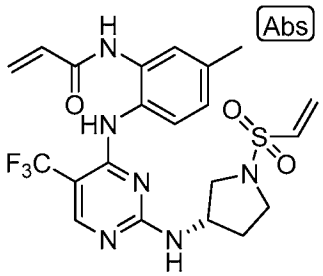
Example 65



I-278

[00406] (R)-N-(5-Methyl-2-((5-(trifluoromethyl)-2-((1-(vinylsulfonyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-278** was prepared in a manner similar to Example 1, substituting (R)-tert-butyl 3-aminopiperidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-chloroethansulfonyl chloride for acetic chloride. MS m/z: 511.1 (ES+, M+H).

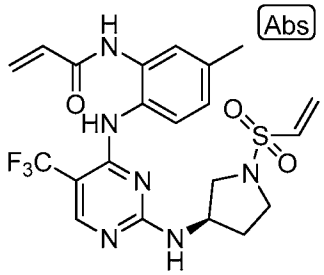
Example 66



I-279

[00407] (S)-N-(5-Methyl-2-((5-(trifluoromethyl)-2-((1-(vinylsulfonyl)pyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-279** was prepared in a manner similar to Example 1, substituting (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-chloroethansulfonyl chloride for acetic chloride. MS m/z: 497.1 (ES+, M+H).

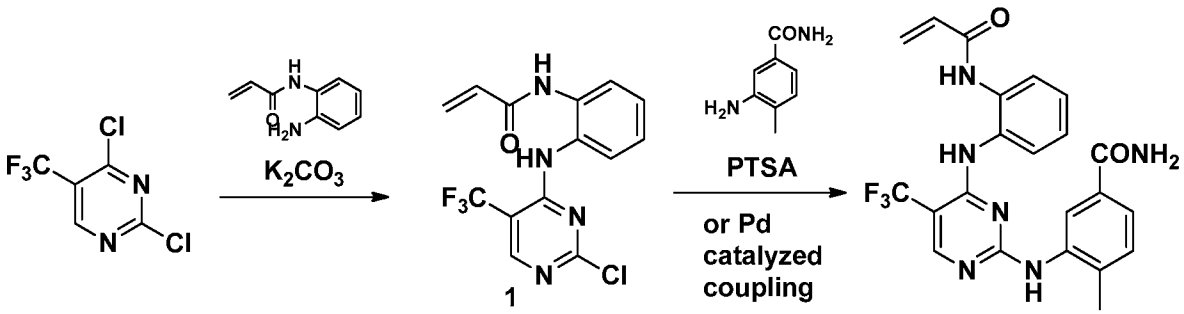
Example 67



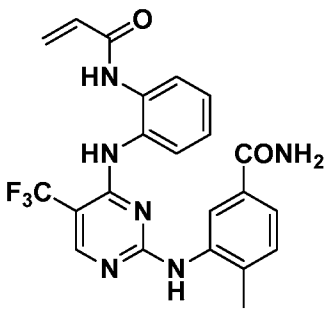
I-280

[00408] (R)-N-(5-Methyl-2-((5-(trifluoromethyl)-2-((1-(vinylsulfonyl)pyrrolidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-280** was prepared in a manner similar to Example 1, substituting (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-chloroethansulfonyl chloride for acetic chloride. MS m/z: 497.1 (ES+, M+H).

[00409] Method B first introduces the aniline at the C-4 positioin of the pyrimidine system, followed by the coupling of a second aniline or aliphatic amine group at the pyrimidine C-2 position. General reaction sequences are described below.



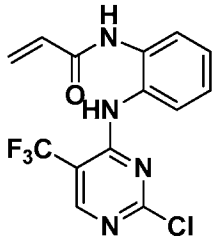
Example 68



I-68

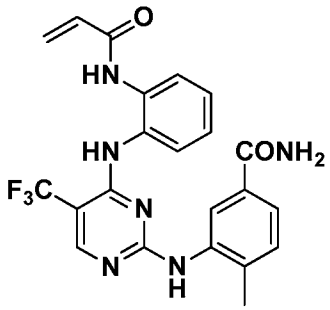
[00410] 3-(4-(2-Acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-4-methylbenzamide: The title compound was prepared according to the steps and intermediates described below.

Step 1: N-(2-(2-Chloro-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide (Intermediate 1)



[00411] To a stirred solution of N-(2-aminophenyl) acrylamide (3.6 g, 22.2 mmol) in dimethyl acetamide (25 mL) was added potassium carbonate (6.34 g, 46.0 mmol) at rt, and the mixture was stirred for 15min. To this reaction mixture, 2,4-dichloro-5-trifluoromethylpyrimidine (4.8 g, 22.2 mmol) was added, and the stirring continued at 60 °C for 1h. TLC showed completion of starting material and formation of two isomers (TLC system: 30% ethyl acetate/hexane). The reaction mixture was diluted with water (2x50 mL) and extracted with EtOAc (2x100 mL). The organic layer was dried over sodium sulfate and concentrated to get the crude (7 g). This crude was purified by silica gel column chromatography using 20% ethyl acetate/hexane and subsequently purified by prep-HPLC to get desired **intermediate 1** as a white solid (1.1 g, 14%). MS: m/z 343.1 (ES+, M+H).

Step 2: Acid catalyzed coupling method: 3-(4-(2-Acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-4-methylbenzamide

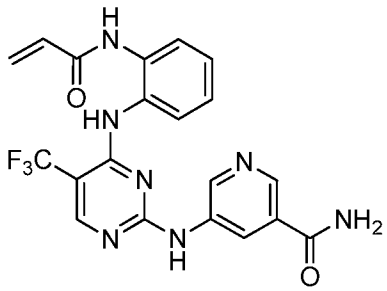


[00412] To a solution of **Intermediate 1** (1g, 2.923 mmol) in 0.04 M PTSA solution in 1,4-Dioxane (20 mL) was added 3-amino-4-methylbenzamide (526 mg, 3.5076 mmol), and the mixture was stirred at 95 °C for 16h. TLC showed completion of starting material. (TLC system:

10% Methanol/DCM, (R_f): 0.6). The reaction mixture was directly absorbed on silica gel and purified by column chromatography using 4% methanol/DCM as eluents. The resulting off-white solid was stirred in a mixture of DCM: EtOAc: Diethyl Ether (10 mL:10 mL:30 mL) for 10min, then filtered and dried under vacuum to obtain 596 mg of the desired compound (44%). ^{1}HNMR (400 MHz, DMSO-d_6) δ 2.15 (s, 3H), 5.78-5.81 (dd, 1H, J= 1.9, 10.0Hz), 6.26-6.31 (dd, 1H, J= 2.0, 17.0 Hz), 6.40-6.46 (dd, 1H, J= 10.0, 16.9 Hz), 7.02-7.09 (m, 2H), 7.13-7.15 (d, 1H, J= 7.5Hz), 7.19-7.21 (dd, 1H, J= 7.9Hz), 7.32 (br s, 1H), 7.57-7.59 (dd, 1H, J= 1.6, 7.6Hz), 7.66-7.68 (d, 1H, J= 8Hz), 7.88-7.91 (d, 2H, J= 11.4Hz), 8.21 (s, 1H), 8.27 (s, 1H), 9.12 (br s, 1H) 10.3 (s, 1H). MS: m/z 457.3 (ES+, M+H).

[00413] Step 2: Pd-catalyzed coupling method: 3-(4-(2-Acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-4-methylbenzamide. Alternatively, Step 2 was carried out as follows: To a solution of 3-amino-4-methylbenzamide (20 mg, 0.13 mmol), **Intermediate 1** (34 mg, 0.10 mmol), and Na_2CO_3 (44 mg, 0.40 mmol) in 1 mL of degassed tert-amyl alcohol, was added tris-dibenzylamino dipalladium (5.0 mg, 5.5 μmol) and Dave Phos (7.5 mg). The mixture was degassed and purged again with argon, then heated at 100 °C for 1h. LC-MS confirmed the completion of the reaction. After EtOAc/water workup, the residue was purified by column chromatograph on silica get, using heptanes/EtOAc gradient system, giving pale white solid 23 mg (50%). MS: m/z 457.3 (ES+, M+H).

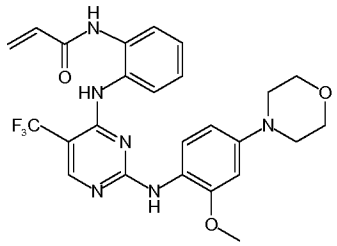
Example 69



I-63

5-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)nicotinamide: Compound **I-63** was prepared in a manner similar to Example 68, substituting 5-aminonicotinamide for 3-amino-4-methylbenzamide. MS m/z: 444.1 (ES+, M+H).

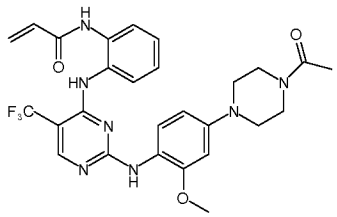
Example 70



I-65

[00414] N-(2-((2-((2-Methoxy-4-morpholinophenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-65** was prepared in a manner similar to Example 68, substituting 2-methoxy-4-morpholinoaniline for 3-amino-4-methylbenzamide**:** MS m/z 515.3 (ES+, M+H).

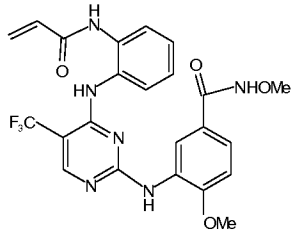
Example 71



I-66

[00415] N-(2-((2-((4-(4-Acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-66** was prepared in a manner similar to Example 68, substituting 1-(4-(4-amino-3-methoxyphenyl) piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide**:** MS m/z 556.2 (ES+, M+H). ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H), 3.03-3.05 (m, 2H), 3.09-3.11 (m, 2H), 3.55-3.58 (m, 4H), 3.75 (s, 3H), 5.77-5.80 (dd, 1H, J=1.8, 10.0Hz), 6.26-6.31 (m, 2H), 6.41-6.47 (dd, 1H, J=10.0, 16.8Hz), 6.60 (d, 1H, J=2.4Hz), 7.21-7.28 (m, 3H), 7.36-7.38 (dd, 1H, J=8.5Hz), 7.67-7.68 (d, 1H, J=6Hz), 8.16 (s, 1H), 8.21-8.23 (d, 2H, J=9.7Hz), 10.28 (s, 1H).

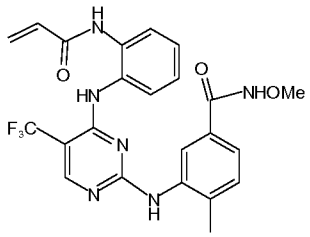
Example 72



I-67

[00416] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N,4-dimethoxybenzamide. Compound **I-67** was prepared in a manner similar to Example 68, substituting 3-amino-N,4-dimethoxybenzamide for 3-amino-4-methylbenzamide: MS m/z 503.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.69 (s, 3H), 3.79 (s, 3H), 5.77-5.80 (dd, 1H, J=1.9, 10Hz), 6.26-6.31 (dd, 1H, J=1.9, 17.0Hz), 6.40-6.47 (dd, 1H, J=2.0, 17.0Hz), 7.05-7.11 (m, 3H), 7.17-7.19 (d, 1H, J=7.33Hz), 7.50-7.52 (dd, 1H, J=1.9, 7.5 Hz), 7.65-7.67 (d, 1H, J=7.5Hz), 7.93 (s, 1H), 8.27-8.30 (d, 2H, J=14.6Hz), 8.60 (s, 1H), 10.3 (s, 1H), 11.51 (s, 1H).

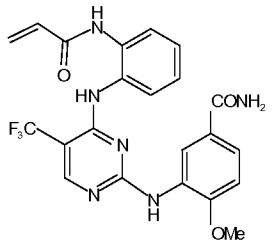
Example 73



I-69

[00417] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-methoxy-4-methylbenzamide. Compound **I-69** was prepared in a manner similar to Example 68, substituting 3-amino-N-methoxy-4-methylbenzamide for 3-amino-4-methylbenzamide: MS m/z 487.4 (ES+, M+H); 1HNMR (DMSO-d_6) δ 2.16 (s, 3H), 3.70 (s, 3H), 5.78-7.81 (dd, 1H, J=1.9, 10.0Hz), 6.26-6.31 (dd, 1H, J=1.9, 16.9Hz), 6.40-6.47 (dd, 1H, J=10, 16.9Hz), 7.0 (br s, 1H), 7.08-7.10 (d, 1H, J=7.0Hz), 7.14-7.16 (d, 1H, J=7.0Hz), 7.22-7.24 (d, 1H, J=8.0 Hz), 7.44-7.47 (dd, 1H, J=1.6, 7.8Hz), 7.62-7.64 (d, 1H, J=8Hz), 7.75 (s, 1H), 8.23 (s, 1H), 8.28 (s, 1H), 9.14 (s, 1H) 10.3 (s, 1H), 11.65 (s, 1H).

Example 74

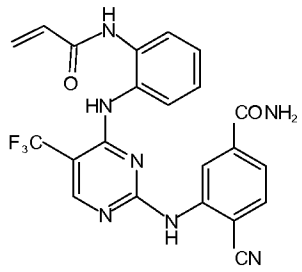


I-70

[00418] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methoxybenzamide. Compound **I-70** was prepared in a manner similar to Example 68,

substituting 3-amino-4-methoxybenzamide for 3-amino-4-methylbenzamide: MS m/z 473.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.78 (s, 3H), 5.77-5.80(dd, 1H, J=1.9, 10.0Hz), 6.26-6.31 (dd, 1H, J=2.0, 17.0 Hz), 6.40-6.47 (dd, 1H, J=10.0 17.0 Hz), 7.03-7.05 (d, 1H, J=8.7Hz), 7.09-7.12 (m, 2H), 7.16-7.18 (m, 2H), 7.67-7.70 (m, 2H), 7.76 (s, 1H), 8.02 (s, 1H), 8.24 (s, 1H), 8.29 (s, 1H), 8.62 (br s, 1H), 10.29 (s, 1H).

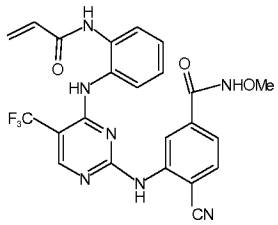
Example 75



I-71

[00419] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-cyanobenzamide. Compound **I-71** was prepared in a manner similar to Example 68, substituting 3-amino-4-cyanobenzamide for 3-amino-4-methylbenzamide: MS m/z 468.1 (ES+, M+H); ^{1}H NMR (DMSO-d_6) δ 5.78-5.81 (dd, 1H, J=1.9,10.0 Hz), 6.27-6.32 (dd, 1H, J=2.0, 16.0 Hz), 6.40-6.47 (dd, 1H,J=10.0, 16.9Hz), 7.07-7.15 (m, 2H), 7.18-7.20 (dd, 1H, J=1.5, 7.8Hz), 7.62-7.66 (m, 2H), 7.70-7.72 (dd, 1H, J=1.5, 7.8Hz), 7.81-7.83 (d, 1H, J=8Hz), 7.96 (s, 1H), 8.14 (br s, 1H), 8.35-8.38 (d, 2H, J=9Hz), 9.88 (s, 1H), 10.32 (s, 1H).

Example 76

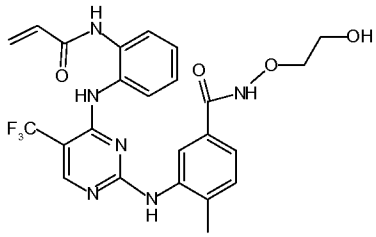


I-72

[00420] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-cyano-N-methoxybenzamide. Compound **I-72** was prepared in a manner similar to Example 68, substituting 3-amino-4-cyano-N-methoxybenzamide for 3-amino-4-methylbenzamide: MS m/z 498.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 3.83 (s, 3H), 5.81-5.84 (dd, 1H, J=3.2, 8.59Hz), 6.38-

6.49 (m, 2H), 7.16-7.29 (m, 3H), 7.55-7.57 (d, 1H, J=8.8Hz), 7.58-7.60 (d, 1H, J=7.8Hz), 7.70-7.72 (d, 1H, J=8Hz), 8.01(d, 1H, J=1.36Hz), 8.32 (s, 1H).

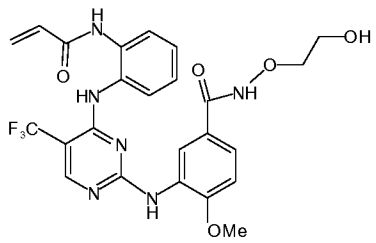
Example 77



I-73

[00421] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)-4-methylbenzamide. Compound **I-73** was prepared in a manner similar to Example 68, substituting 3-amino-N-(2-hydroxyethoxy)-4-methylbenzamide for 3-amino-4-methylbenzamide**:** MS m/z 517.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.16 (s, 3H), 3.60 (q, 2H, J=10.3, 16.9Hz), 3.90-3.93 (t, 2H, J=5.6Hz), 4.75 (t, 1H, J=5.7Hz), 5.78-5.81 (dd, 1H, J=2.0, 10.0Hz), 6.26-6.31 (dd, 1H, J=2.0, 17.0 Hz), 6.40-6.50 (dd, 1H, J=10.1, 17.0 Hz), 6.99 (br s, 1H), 7.06-7.10 (t, 1H, J=7.8, 14.5Hz), 7.14-7.16 (d, 1H, J=7.8Hz), 7.22-7.24 (d, 1H, J=8Hz), 7.46-7.49 (dd, 1H, J=1.6, 7.9Hz), 7.62-7.64 (d, 1H, J=8.2Hz), 7.77 (s, 1H), 8.23 (s, 1H), 8.28 (s, 1H), 9.15 (s, 1H) 10.3 (s, 1H), 11.68 (s, 1H).

Example 78

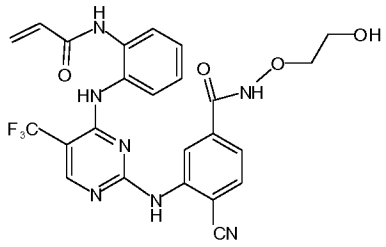


I-74

[00422] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)-4-methoxybenzamide. Compound **I-74** was prepared in a manner similar to Example 68, substituting 3-amino-N-(2-hydroxyethoxy)-4-methoxybenzamide for 3-amino-4-methylbenzamide**:** MS m/z 533.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.58-3.59 (d, 2H, J=4.8Hz), 3.80 (s, 3H), 3.90-3.91 (m, 2H), 4.75 (m, 1H), 5.77-7.80 (dd, 1H, J=1.9, 10.0 Hz), 6.21-6.31 (dd, 1H, J=1.9, J=17.0 Hz), 6.40-6.47 (dd, 1H, J=10.0, 17.0 Hz), 7.07-7.19 (m, 4H),

7.52-7.55 (d, 1H, J=2.0, 8.5Hz), 7.65-7.67 (d, 1H, J=8.4Hz), 7.95 (s, 1H), 8.27 (s, 1H), 8.30 (s, 1H), 8.61 (s, 1H), 10.3 (s, 1H), 11.55 (s, 1H).

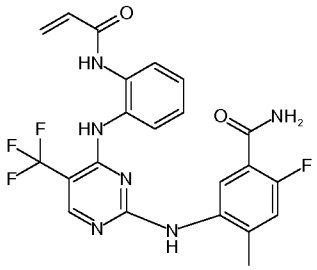
Example 79



I-75

[00423] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-cyano-N-(2-hydroxyethoxy)benzamide. Compound **I-75** was prepared in a manner similar to Example 68, substituting 3-amino-4-cyano-N-(2-hydroxyethoxy)benzamide for 3-amino-4-methylbenzamide**:** MS m/z 528.2 (ES+, M+H); 1HNMR (CD_3OD) δ 3.79-3.81 (t, 2H, , J=4.7, 9.1Hz), 4.10 (m, 2H), 5.81-5.84 (dd, 1H, J=3.2, 8.6 Hz), 6.38-6.49 (m, 2H), 7.15-7.25 (m, 2H), 7.28-7.30 (d, 1H, J=6.6Hz), 7.55-7.60 (m, 2H), 7.70-7.72 (d, 1H, J=8Hz), 8.0 (s, 1H), 8.32 (s, 1H).

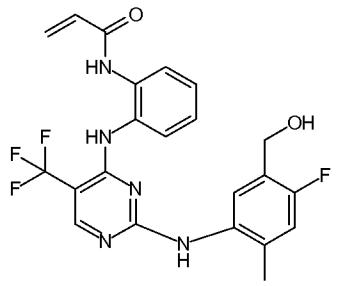
Example 80



I-76

[00424] 5-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-4-methylbenzamide. Compound **I-76** was prepared in a manner similar to Example 68, substituting 5-amino-2-fluoro-4-methylbenzamide for 3-amino-4-methylbenzamide**:** MS m/z 475.1 (ES+, M+H).

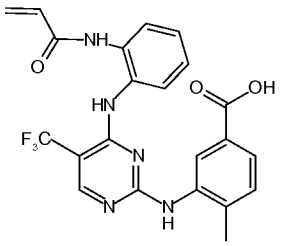
Example 81



I-77

[00425] N-(2-((2-((4-Fluoro-5-(hydroxymethyl)-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-77** was prepared in a manner similar to Example 68, substituting (5-amino-2-fluoro-4-methylphenyl)methanol for 3-amino-4-methylbenzamide**:** MS m/z 462.2 (ES+, M+H).

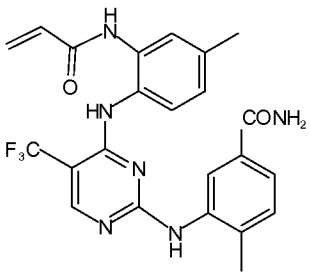
Example 82



I-78

[00426] 3-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methylbenzoic acid. Compound **I-78** was prepared in a manner similar to Example 68, substituting 3-amino-4-methylbenzoic acid for 3-amino-4-methylbenzamide: MS m/z 458.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.16 (s, 3H), 5.77-5.80 (dd, 1H, J=1.9, 10.0Hz), 6.26-6.31 (dd, 1H, J=1.9, 17 Hz), 6.40-6.47 (dd, 1H, J=10, 17Hz), 7.08 (br s, 1H), 7.10-7.16 (t, 1H, J= 7 Hz), 7.24-7.26 (d, 1H, J=7.9Hz), 7.60-7.62 (dd, 2H, J=1.5, 7.8Hz), 7.86 (s, 1H), 8.21 (s, 1H), 8.28 (s, 1H), 9.13(s, 1H), 10.28 (s, 1H), 12.81 (s, 1H).

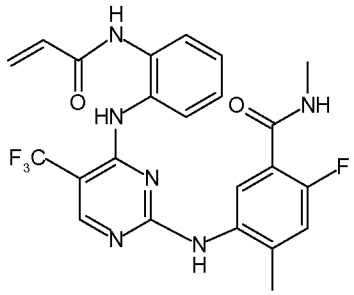
Example 83



I-79

[00427] 3-((4-((2-Acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methylbenzamide. Compound **I-79** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 471.2 (ES+, M+H).

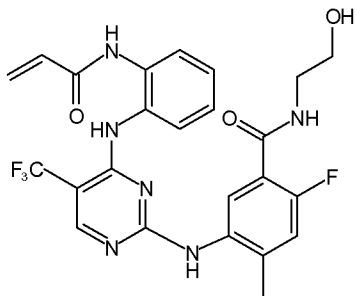
Example 84



I-80

[00428] 5-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-N,4-dimethylbenzamide. Compound **I-80** was prepared in a manner similar to Example 68, substituting 5-amino-2-fluoro-N,4-dimethylbenzamide for 3-amino-4-methylbenzamide. MS m/z 489.2 (ES+, M+H).

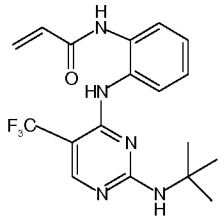
Example 85



I-81

[00429] 5-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-2-fluoro-N-(2-hydroxyethyl)-4-methylbenzamide. Compound **I-81** was prepared in a manner similar to Example 68, substituting 5-amino-2-fluoro-N-(2-hydroxyethyl)-4-methylbenzamide for 3-amino-4-methylbenzamide. MS m/z 519.1 (ES+, M+H).

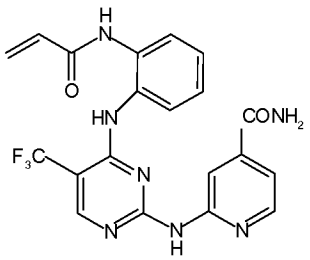
Example 86



I-82

[00430] N-(2-((2-(tert-Butylamino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-82** was prepared in a manner similar to Example 68, substituting 2-methylpropan-2-amine for 3-amino-4-methylbenzamide**:** MS m/z 380.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.10-1.31 (s, 9H), 5.77-5.80 (dd, 1H, J=1.9, 10 Hz), 6.26-6.31 (dd, 1H, J=1.8, 16.8Hz), 6.41-6.48 (dd, 1H, J=10, 17Hz), 7.02 (br s, 1H), 7.24-7.29 (m, 3H), 7.56 (br s, 1H), 8.02 (br s, 1H), 8.10 (br s, 1H), 10.28(s, 1H).

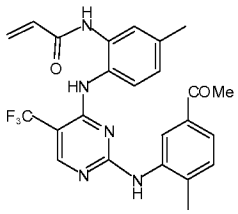
Example 87



I-83

[00431] 2-((4-((2-Acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)isonicotinamide. Compound **I-83** was prepared in a manner similar to Example 68, substituting 2-aminoisonicotinamide for 3-amino-4-methylbenzamide. MS m/z 443.3 (ES+, M+H).

Example 88

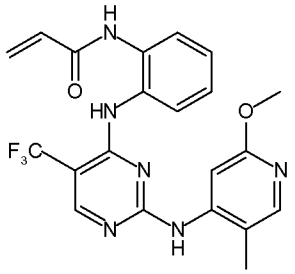


I-84

[00432] N-(2-((2-((5-Acetyl-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-84** was prepared in a manner similar to

Example 68, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-methylbenzamide: MS m/z 470.5 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.21 (s, 6H), 2.38 (m, 3H), 5.76-5.79 (dd, J = 1.9, 10.0 Hz, 1H), 6.25-6.30 (dd, J = 1.9, 16.9 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 16.9 Hz, 1H), 6.71 (br s, 1H), 6.99 (s, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.38 (d, J = 7.4 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.84 (d, J = 1.4 Hz, 1H), 8.12 (s, 1H), 8.26 (s, 1H), 9.11 (s, 1H), 10.21 (s, 1H).

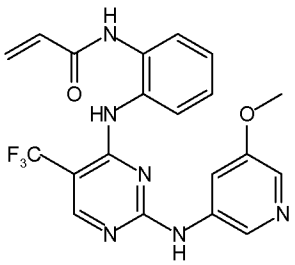
Example 89



I-85

N-(2-((2-((2-Methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-85** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 443.3 (ES+, M+H).

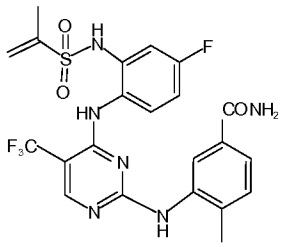
Example 90



I-86

[00433] N-(2-((2-((5-Methoxypyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-86** was prepared in a manner similar to Example 68, substituting 5-methoxypyridin-3-amine for 3-amino-4-methylbenzamide. MS m/z 431.1 (ES+, M+H).

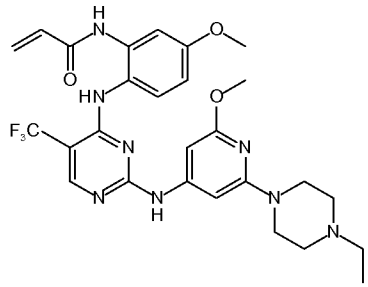
Example 91



I-87

[00434] 3-((4-((4-Fluoro-2-(1-methylvinylsulfonamido)phenyl)amino)-5-(trifluoromethyl) pyrimidin-2-yl)amino)-4-methylbenzamide. Compound **I-87** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-fluorophenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide**:** MS m/z 525.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.99 (s, 3H), 2.16 (s, 3H), 5.62 (s, 1H), 5.68 (s, 1H), 6.85 (d, J = 9.3 Hz, 2H), 7.23 (d, J = 7.9 Hz, 1H), 7.31 (s, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.69-7.73 (dd, J = 6.5, 8.7 Hz, 1H), 7.81 (s, 1H), 7.89 (s, 1H), 8.20 (s, 1H), 8.34 (s, 1H), 9.24 (s, 1H), 9.59 (s, 1H).

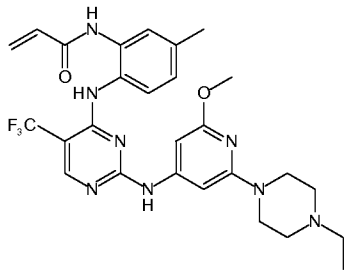
Example 92



I-88

[00435] N-(2-((2-((2-(4-Ethylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide. Compound **I-88** was prepared in a manner similar to Example 68, substituting 2-(4-ethylpiperazin-1-yl)-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 573.1 (ES+, M+H).

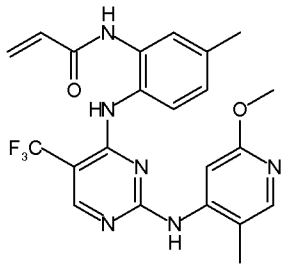
Example 93



I-89

N-(2-((2-((2-(4-Ethylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-89** was prepared in a manner similar to Example 68, substituting 2-(4-ethylpiperazin-1-yl)-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 557.1 (ES+, M+H).

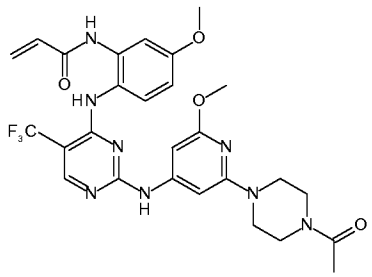
Example 94



I-90

[00436] N-(2-((2-((2-Methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-90** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 459.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 3H), 2.32 (s, 3H), 3.75 (s, 3H), 5.78 (dd, 1H, J = 2.0, 10.0 Hz), 6.28 (dd, 1H, J = 2.0, 16.8 Hz), 6.45 (dd, 1H, J = 10.6, 16.8 Hz), 7.09 (br t, 3 H, J = 8.0 Hz), 7.50 (d, 1H, J = 8.4 Hz), 7.79 (s, 1H), 8.36 (s, 2H), 8.72 (s, 1H), 10.25 (s, 1H).

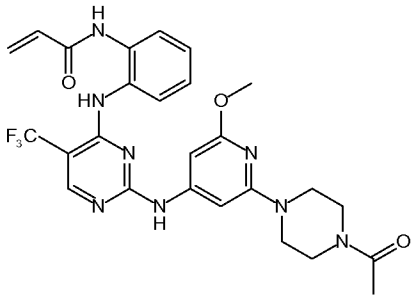
Example 95



I-91

[00437] N-(2-((2-((2-(4-Acetylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide. Compound **I-91** was prepared in a manner similar to Example 68, substituting 1-(4-(4-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 587.2 (ES+, M+H).

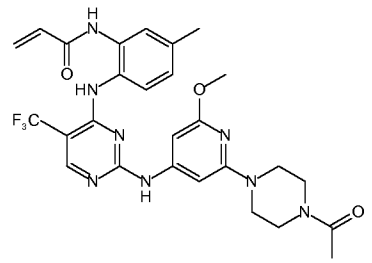
Example 96



I-92

[00438] N-(2-((2-((2-(4-Acetylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide. Compound **I-92** was prepared in a manner similar to Example 68, substituting 1-(4-(4-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide. MS m/z 557.3 (ES+, M+H).

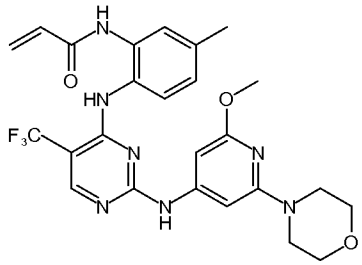
Example 97



I-93

N-(2-((2-((2-(4-Acetylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-93** was prepared in a manner similar to Example 68, substituting 1-(4-(4-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 571.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.02 (s, 3H), 2.33 (s, 3H), 3.12 (br s, 2H), 3.46 (br s, 4H), 3.74 (s, 3H), 5.78 (dd, 1H, J = 2.0, 10.0 Hz), 6.28 (30, 1H, J = 2.0, 16.8 Hz), 6.45 (m, 3H), 7.10 (d, 1H, J = 8.4 Hz), 7.15 (s, 1H), 7.50 (d, 1H, J = 8.4 Hz), 8.36 (d, 2H, J = 9.6 Hz), 9.70 (s, 1H), 10.30 (s, 1H)

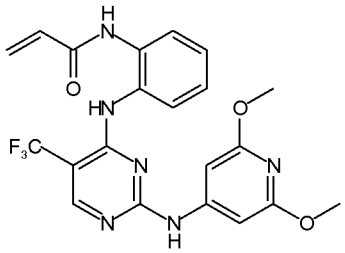
Example 98



I-94

[00439] N-(2-((2-((2-Methoxy-6-morpholinopyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-94** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-morpholinopyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 530.2 (ES+, M+H).

Example 99

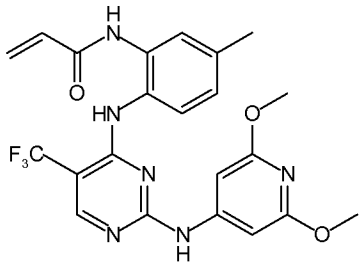


I-95

[00440] N-(2-((2-((2,6-Dimethoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-95** was prepared in a manner similar to Example 68,

substituting 2,6-dimethoxypyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 461.1 (ES+, M+H).

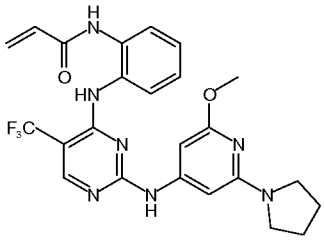
Example 100



I-96

[00441] N-(2-((2-((2,6-Dimethoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-96** was prepared in a manner similar to Example 68, substituting 2,6-dimethoxypyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 475.1 (ES+, M+H).

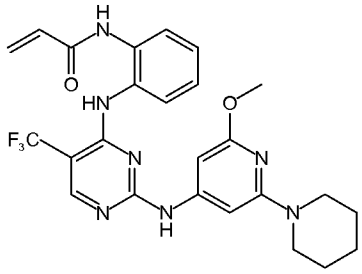
Example 101



I-281

[00442] N-(2-((2-((2-Methoxy-6-(pyrrolidin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-281** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-(pyrrolidin-1-yl)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 500.7 (ES+, M+H).

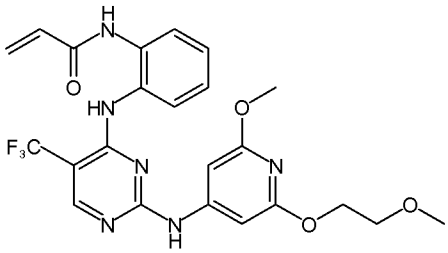
Example 102



I-282

[00443] N-(2-((2-((2-Methoxy-6-(piperidin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-282** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-(piperidin-1-yl)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 514.2 (ES+, M+H).

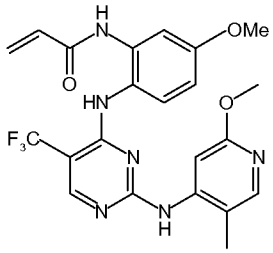
Example 103



I-283

[00444] N-(2-((2-((2-Methoxy-6-(2-methoxyethoxy)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-283** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-(2-methoxyethoxy)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 505.2 (ES+, M+H).

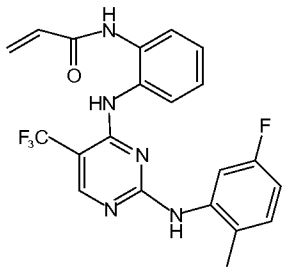
Example 104



I-284

[00445] N-(5-Methoxy-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-284** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 475.3 (ES+, M+H).

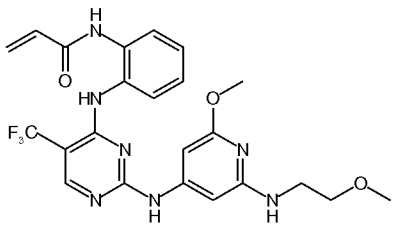
Example 105



I-285

N-(2-((2-((5-Fluoro-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-285** was prepared in a manner similar to Example 68, substituting 5-fluoro-2-methylaniline for 3-amino-4-methylbenzamide. MS m/z 432.2 (ES+, M+H).

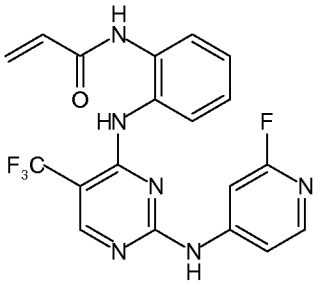
Example 106



I-286

N-(2-((2-((2-Methoxy-6-((2-methoxyethyl)amino)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-286** was prepared in a manner similar to Example 68, substituting 6-methoxy-N^2-(2-methoxyethyl)pyridine-2,4-diamine for 3-amino-4-methylbenzamide. MS m/z 504.2 (ES+, M+H).

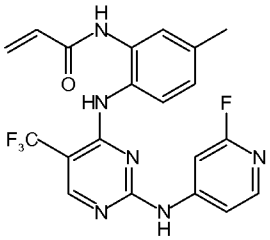
Example 107



I-287

[00446] N-(2-((2-((2-Fluoropyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-287** was prepared in a manner similar to Example 68, substituting 2-fluoropyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 419.1 (ES+, M+H).

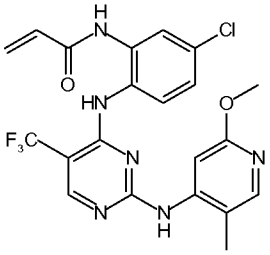
Example 108



I-288

[00447] N-(2-((2-((2-Fluoropyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-288** was prepared in a manner similar to Example 68, substituting 2-fluoropyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 479.6 (ES+, M+H).

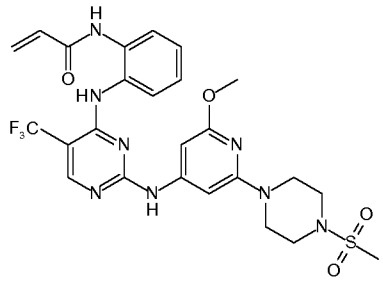
Example 109



I-289

N-(5-Chloro-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-289** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-chlorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 593.2 (ES+, M+H).

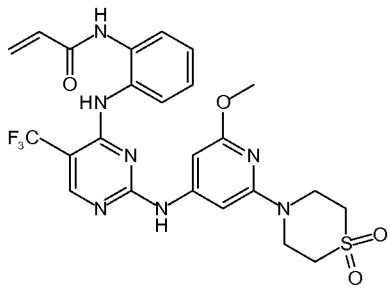
Example 110



I-290

[00448] N-(2-((2-((2-Methoxy-6-(4-(methylsulfonyl)piperazin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-290** was prepared in a manner similar to Example 68, substituting tert-butyl 4-(4-amino-6-methoxypyridin-2-yl)piperazine-1-carboxylate for 3-amino-4-methylbenzamide, followed by deprotection with TFA and reaction with MsCl. MS m/z 514.2 (ES+, M+H).

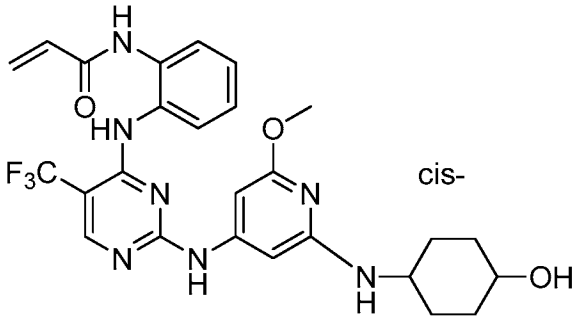
Example 111



I-291

[00449] N-(2-((2-((2-(1,1-Dioxidothiomorpholino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-291** was prepared in a manner similar to Example 68, substituting 4-(4-amino-6-methoxypyridin-2-yl)thiomorpholine 1,1-dioxide for 3-amino-4-methylbenzamide. MS m/z 595.1 (ES+, M+H).

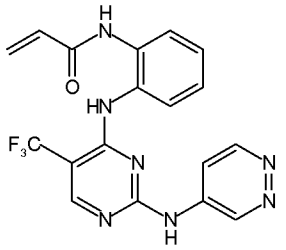
Example 112



I-292

N-(2-((2-((2-((cis-4-Hydroxycyclohexyl)amino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylimidamide. Compound **I-292** was prepared in a manner similar to Example 68, substituting Cis-4-((4-amino-6-methoxypyridin-2-yl)amino)cyclohexanol for 3-amino-4-methylbenzamide. MS m/z 544.2 (ES+, M+H).

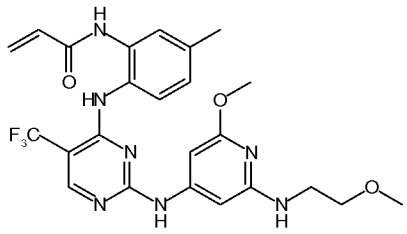
Example 113



I-293

[00450] N-(2-((2-(Pyridazin-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-293** was prepared in a manner similar to Example 68, substituting pyridazin-4-amine for 3-amino-4-methylbenzamide. MS m/z 404.2 (ES+, M+H).

Example 114

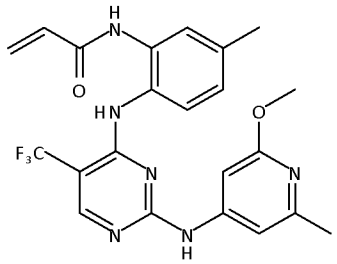


I-294

N-(2-((2-((2-methoxy-6-((2-methoxyethyl)amino)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-294** was prepared in a manner similar to Example 68, substituting 6-methoxy-N^2-(2-

methoxyethyl)pyridine-2,4-diamine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 518.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.48 (s, 3H), 3.25 (s, 3H), 3.65 (s, 3H), 5.78 (dd, 1H, J = 2.0, 10.0 Hz), 5.82 (br s, 1H), 6.10 (br s, 1H), 6.25 (s, 1H), 6.28 (dd, 1H, J = 2.0, 16.8 Hz), 6.45 (dd, 1H, J = 10.6, 16.8 Hz), 7.14 (s, 1 H), 7.50 (d, 1H, J = 8.4 Hz), 8.30 (d, 1H, J = 8.0 Hz), 8.33 (s, 1H), 9.62 (s, 1H), 10.25 (s, 1H).

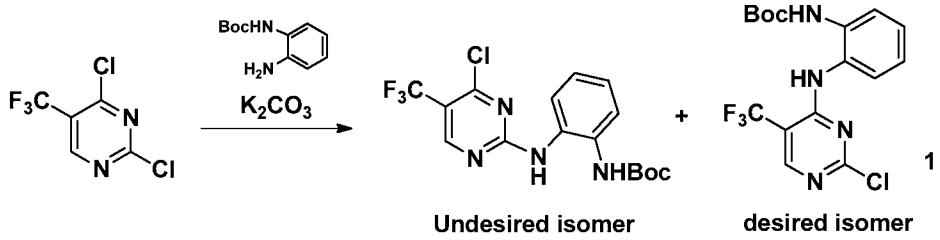
Example 115

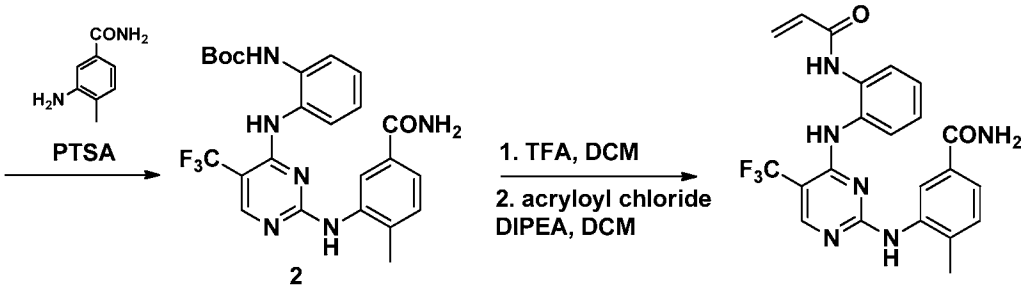


I-295

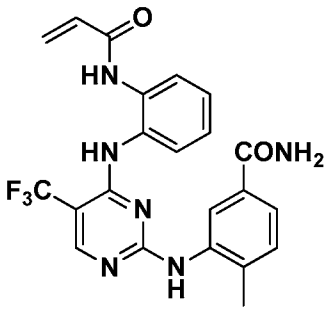
[00451] N-(2-((2-((2-methoxy-6-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-295** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 459.2 (ES+, M+H). HCl-salt. 1H NMR (DMSO-d6) δ 2.22 (s, 3H), 2.34 (s, 3H), 3.75 (s, 3H), 5.78 (dd, 1H, J = 2.0, 10.0 Hz), 6.28 (dd, 1H, J = 2.0, 16.8 Hz), 6.45 (dd, 1H, J = 10.6, 16.8 Hz), 7.05 (s, 1 H), 7.16 (d, 1H, J = 8.4 Hz), 7.26 (s, 1 H), 7.47 (d, 1H, J = 8.4 Hz), 8.50 (s, 1H), 8.62 (s, 1H), 10.34 (s, 1H), 10.69 (br s, 1H).

[00452] Different from Method B, **Method C** introduces the Boc-protected aniline at the C4-position of CF_3-pyrimidine first, followed by the coupling of the second aniline or amine at the C2-position under basic conditions. After Boc-deprotection, final acryloylation was achieved via amide bond formation with acrylic acid or acryloyl chloride. The general synthetic approach is described below.





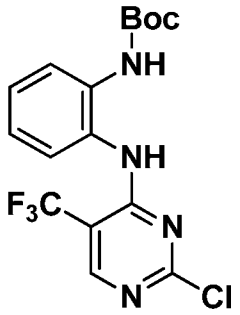
Example 116



I-68

[00453] 3-(4-(2-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-4-methylbenzamide: The title compound was prepared according to the steps and intermediates described below.

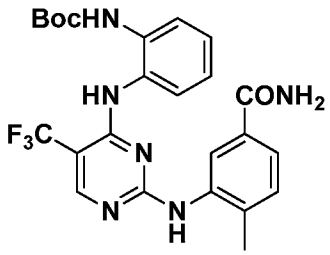
[00454] Step-1. tert-butyl (2-((2-chloro-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)carbamate (Intermediate 1): This intermediate was synthesized according to step-1 in example 2, using tert-butyl (2-aminophenyl)carbamate to react with 5-CF3-2,4-dichloropyrimidine.



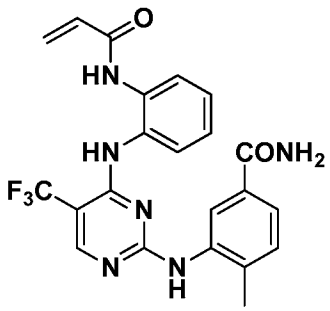
[00455] Desired isomer (intermediate 1): ^{1}HNMR (400 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.98 (s, 1H), 8.58 (s, 1H), 7.49 (d, 1H, J = 7.6 Hz), 7.37 (d, 1H, J = 7.6 Hz), 7.18-7.28 (m, 2H), 1.44 (s, 9H). LC-MS: m/z 389.3 (ES+, M+H).

[00456] Undesired isomers: 1HNMR (400 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.68 (s, 1H), 8.52 (s, 1H), 7.60 (d, 1H, J = 7.6 Hz), 7.42 (d, 1H, J = 7.6 Hz), 7.18 (t, 1H, J = 7.2 Hz), 7.10 (t, 1H, J = 7.2 Hz), 1.44 (s, 9H). LC-MS: m/z 389.3 (ES+, M+H).

[00457] Step-2. tert-butyl (2-((2-((5-carbamoyl-2-methylphenyl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)carbamate (Intermediate 2): This intermediate was synthesized according to step-2 in example 2, using 3-amino-4-methylbenzamide to react with the desired **intermediate 1** from Step-1. LC-MS: m/z = 503.2 (ES+, M+H)



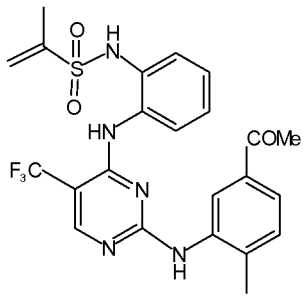
[00458] Step-3. 3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methylbenzamide.



[00459] To a solution of **Intermediate 2** (70 mg, 0.133 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL) and the reaction mixture was stirred at rt for 2h. TLC showed completion of starting material. After concentration, the resulting residue is ready to use for the following step. LC-MS: m/z = 403.1 (ES+, M+H)

[00460] To a solution of de-Boc intermediate obtained above in (1: 1) dichloromethane: tetrahydrofuran (5 mL) at -78°C was added acryloyl chloride (11.9 mg, 0.132 mmol). After stirring for 2h, TLC showed completion of starting material. The reaction mixture was quenched with ice-cold water (15 mL) and extracted with chloroform (3×10 mL). The organic layer was separated, dried over sodium sulfate and concentrated. The crude compound was purified by preparative TLC to obtain the title compound as a white solid (10 mg, 13%). ^{1}HNMR (400 MHz, DMSO-d6) δ 2.15 (s, 3H), 5.78-5.81 (dd, 1H, J= 1.9Hz and J= 10.0Hz), 6.26-6.31 (dd, 1H, J= 2.05Hz and J= 16.97Hz), 6.40-6.46 (dd, 1H, J= 10Hz and J= 16.9 Hz), 7.02-7.09 (m, 2H), 7.13-7.15 (d, 1H, J= 7.5Hz), 7.19-7.21 (dd, 1H, J= 7.9Hz), 7.32 (br s, 1H), 7.57-7.59 (dd, 1H, J= 1.6Hz and J= 7.6Hz), 7.66-7.68 (d, 1H, J= 8Hz), 7.88-7.91 (d, 2H, J= 11.38Hz), 8.21 (s, 1H), 8.27 (s, 1H), 9.12 (br s, 1H) 10.3 (s, 1H). MS m/z: m/z 457.3 (ES+).

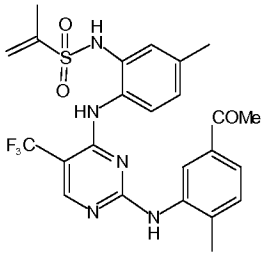
Example 117



I-97

[00461] N-(2-((2-((5-acetyl-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)prop-1-ene-2-sulfonamide. Compound **I-97** was prepared in a manner similar to Example 116, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-methylbenzamide, followed by deprotection with TFA and reaction with prop-1-ene-2-sulfonyl chloride. MS m/z 506.4 (ES+, M+H), 1H NMR (DMSO-d6) δ 2.05 (s, 3H), 2.23 (s, 3H), 2.44 (s, 3H), 5.56 (s, 1H), 5.68 (s, 1H), 6.87 (br s,1H), 7.01 (d, J = 3.6 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.68 (d, J = 1.69 Hz, 1H), 7.8 (br s, 1H), 7.85 (d, J =1.51 Hz, 1H), 8.32 (s, 1H), 8.37 (s, 1H), 9.35 (s, 1H), 9.45 (s, 1H).

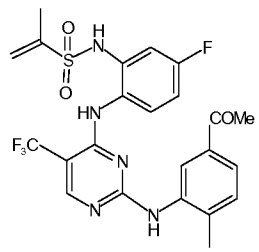
Example 118



I-98

[00462] N-(2-((2-((5-acetyl-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)prop-1-ene-2-sulfonamide. Compound **I-98** was prepared in a manner similar to Example 116, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-methylbenzamide, and substituting tert-butyl (2-amino-5-methylphenyl)carbamate for tert-butyl (2-aminophenyl)carbamate, followed by deprotection with TFA and reaction with 2-chloroethylsulfonyl chloride. MS m/z 520.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.02 (s, 3H), 2.17 (s, 3H), 2.22 (s, 3H), 2.42 (s, 3H), 5.57 (s, 1H), 5.66 (s, 1H), 6.71 (br s, 1H), 6.81 (s, 1H), 7.35 (d, J = 7.9 Hz, 1H), 7.55 (br s, 1H), 7.65 (dd, J = 1.6, 7.8 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 8.24 (s, 1H), 8.34 (s, 1H), 9.27 (s, 1H), 9.35 (s, 1H).

Example 119

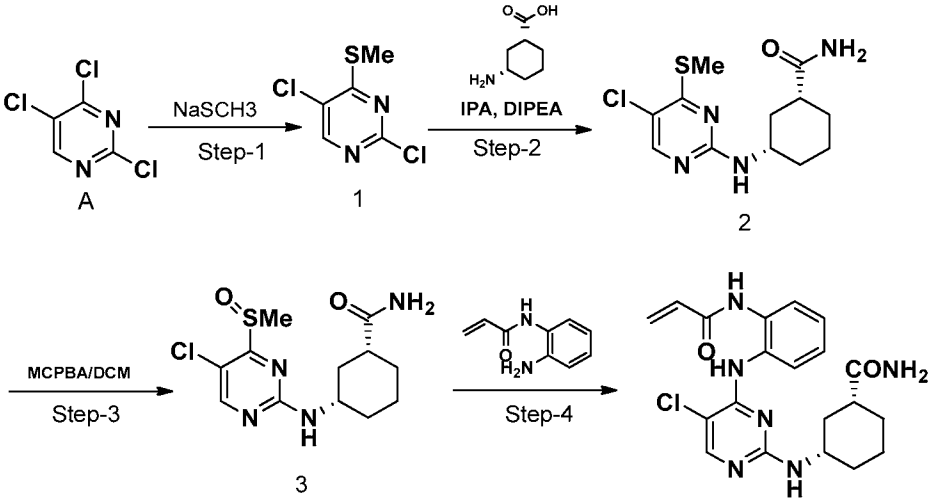


I-99

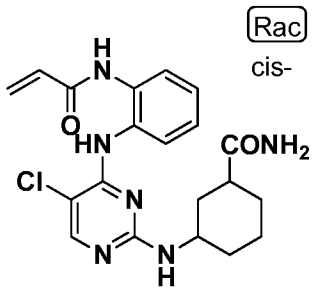
[00463] N-(2-((2-((5-acetyl-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-fluorophenyl)prop-1-ene-2-sulfonamide. Compound **I-98** was prepared in a manner similar to Example 116, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-methylbenzamide, and substituting tert-butyl (2-amino-5-fluorophenyl)carbamate for tert-butyl (2-aminophenyl)carbamate, followed by deprotection with TFA and reaction with 2-chloroethylsulfonyl chloride: MS m/z 524.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 2.19 (s, 3H), 2.42 (s, 3H), 5.67 (d, J = 10.84 Hz, 2H), 6.8 (br s, 1H), 6.89 (d, J = 7.7 Hz, 1H),

7.31 (d, J = 7.95 Hz, 1H), 7.55 (br s, 1H), 7.66 (dd, J = 1.67, 7.87 Hz, 1H), 7.77 (d, J = 1.37 Hz, 1H), 8.22 (s, 1H), 8.34 (s, 1H), 9.22 (s, 1H), 9.54 (s, 1H).

[00464] **Method D** was developed for preparation of a 5-chloro-2,4-diamino-pyrimidine analog with an aliphatic amine at the C-2 position of the pyrimidine system. This method uses thio-ether and sulfoxide intermediates, and applies the various acrylamide ring system in the final stage. The general practice of this method is described below.



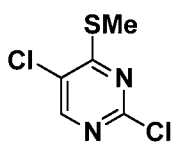
Example 120



I-102

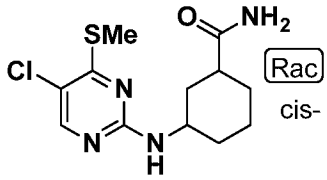
[00465] **Rac-cis-3-(4-(2-acrylamidophenylamino)-5-chloropyrimidin-2-ylamino)cyclohexane carboxamide:** The title compound was prepared according to the steps and intermediates as described below.

Step 1: 2,5-dichloro-4-(methylthio)pyrimidine (Intermediate 1)



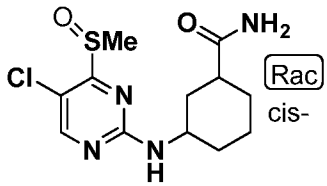
[00466] To a solution of 2,4,5-trichloropyrimidine (5 g, 27.32 mmol) in THF: water (1:1,40 mL), was added sodium thiomethoxide (2.15 g, 30.01 mmol) at 0 °C, and the mixture was stirred at rt for 4h. TLC showed completion of starting material and formation of a slightly polar spot (TLC system: hexane charred in iodine). The reaction mixture was concentrated, water (20 ml) was added, and the product was extracted with ethyl acetate (2x20 ml). The organic layer was dried over sodium sulfate and concentrated to afford the desired compound as a white solid (5 g, 94.8%). MS m/z: 195.2 (ES+, M+H).

Step 2: Rac-Cis-3-(5-chloro-4-(methylthio)pyrimidin-2-ylamino) cyclohexane carboxamide (Intermediate 2)



[00467] To a solution of **Intermediate 1** (2 g, 10.36 mmol) in isopropyl alcohol (10 mL), was added DIPEA (4.01 g, 31.08 mmol) and Cis-3-aminocyclohexanecarboxamide (2.2 g, 15.45 mmol) at room temperature and heated to 100 °C for 48h in a sealed tube. TLC showed completion of starting material and formation of a polar spot (TLC System: 10% ethyl acetate/hexane, **(R_f):** 0.1). After cooling down to room temperature, the mixture was concentrated, water (30 ml) was added, and the precipitated product was filtered, washed with pentane (20 ml) and dried to afford Cis-3-(5-chloro-4-(methylthio)pyrimidin-2-ylamino)cyclohexanecarboxamide as a white solid (2.2g, 70.9%). MS m/z: 301.1 (ES+, M+H).

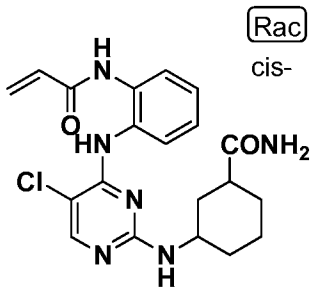
Step 3: Rac-Cis-3-(5-chloro-4-(methylsulfinyl)pyrimidin-2-ylamino) cyclohexane carboxamide (Intermediate 3)



[00468] To a stirred solution of **Intermediate 2** (1.9 g, 6.33 mmol) in dichloromethane: acetonitrile (700 mL), m-CPBA (1.19 g, 6.96 mmol) was added and stirred at rt for 1h. TLC showed completion of starting material and formation of a polar spot (TLC System: 10% methanol/chloroform, **(R_f):** 0.4). The reaction mixture was concentrated, diluted with dichloromethane (30 ml), and washed with saturated sodium bicarbonate solution (20 mL) and

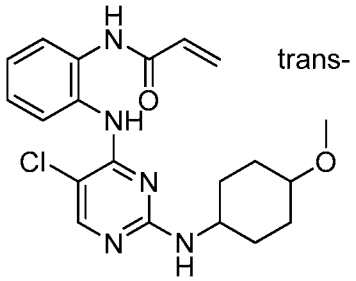
water (15 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The crude compound was purified by silica gel column chromatography with 1 to 1.5% methanol in chloroform as eluents to afford **Intermediate 3** as colorless gummy solid. (1.4 g, 70%). MS m/z: 317.1 (ES+, M+H).

Step 4: Rac-Cis-3-(4-(2-acrylamidophenylamino)-5-chloropyrimidin-2-ylamino) cyclohexane carboxamide



[00469] To a solution of **Intermediate 3** (1.4 g, 4.43 mmol) in 0.04 M PTSA/1,4-dioxane (12 mL, 0.106 mmol) was added N-(2-aminophenyl)acrylamide (1.72 g, 6.64 mmol), and the reaction mixture was stirred at 70 °C for 1h. After completion of the reaction (TLC System: 5% methanol/chloroform, **(R_f):** 0.5), the reaction mixture was concentrated and diluted with water (30 mL), and the precipitate was filtered, washed with saturated sodium bicarbonate solution (15 ml) and dried to afford the desired compound as a white solid. (1.1 g, 59.7%). ^{1}H NMR(400MHz, DMSO-d_6) δ 1.21-1.26(m, 3H), 1.26-1.32(m, 2H), 1.67-1.69(m, 2H), 1.76-1.79(m, 2H), 2.05(m, 1H), 5.79(d, 1H J=11.4Hz), 6.28-6.32(d, 1H J=16.9Hz), 6.46-6.52(dd, 1H J=10.2Hz and 17Hz), 6.64(br s, 1H), 7.14(br s, 1H),7.22-7.27(m, 2H), 7.43(d, 1H J= 7.4Hz), 7.74(d, 1H J=7.8Hz), 8.01(s, 1H), 8.86(br s, 1H), 10.15(s, 1H). MS m/z: 415.2 (ES+, M+H).

Example 121

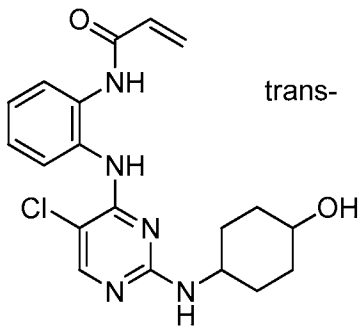


I-100

[00470] N-(2-((5-chloro-2-((trans-(4-methoxycyclohexyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-100** was prepared in a manner similar to Example 120,

substituting *trans*-4-methoxycyclohexanamine for cis-3-aminocyclohexanecarboxamide: MS m/z 402.2 (ES+, M+H)

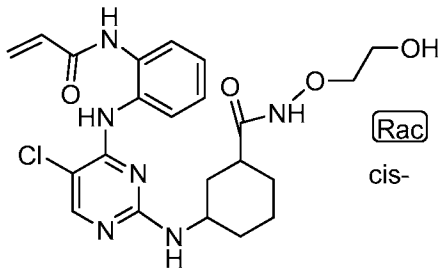
Example 122



I-101

[00471] N-(2-((5-chloro-2-((trans-(4-hydroxycyclohexyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-101** was prepared in a manner similar to Example 120, substituting trans-4-hydroxycyclohexanamine for cis-3-aminocyclohexanecarboxamide: MS m/z 388.2 (ES+, M+H) 1H NMR (DMSO-d6) δ 1.12-1.22 (m, 4H), 1.76-1.78 (m, 4H), 2.29 (br s, 1H), 4.46 (br s, 1H), 5.78-5.80 (dd, J= 1.6, 10.1 Hz, 1H), 6.30 (d, 1H, J=17.0 Hz), 6.45-6.52 (dd, J=10.1, 16.9 Hz, 1H), 7.15-7.24 (m, 2H), 7.35-7.37 (d, 1H, J = 7.7 Hz), 7.81 (s, 1H), 7.91 (s, 1H), 8.27 (s, 1H), 8.30 (s, 1H), 10.16 (s, 1H).

Example 123

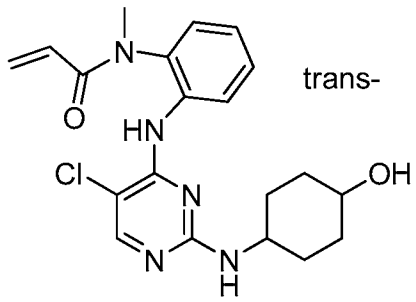


I-103

[00472] Rac-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)-*cis*-cyclohexanecarboxamide. Compound **I-103** was prepared in a manner similar to Example 120, substituting cis-3-amino-N-(2-hydroxyethoxy)cyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide: MS m/z 475.1 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 1.31-1.42 (m, 6H), 1.74 (d, J = 9.8 Hz, 2H), 1.85 (d, J = 12.0 Hz, 1H), 1.96 (d, J = 9.8 Hz, 1H), 3.57 (br s, 1H), 3.65-3.69 (m, 2H), 3.89-3.92 (m, 2H), 5.80-5.83 (dd, J = 2.3, 9.7 Hz, 1H), 6.37-

6.47 (m, 2H), 7.23-7.27 (dt, J = 1.5, 7.6 Hz, 1H), 7.30-7.34 (dt, J = 1.5, 7.4 Hz, 1H), 7.45 (d, J = 7.1 Hz, 1H), 7.79 (d, J = 6.9 Hz,1H), 7.85 (s, 1H).

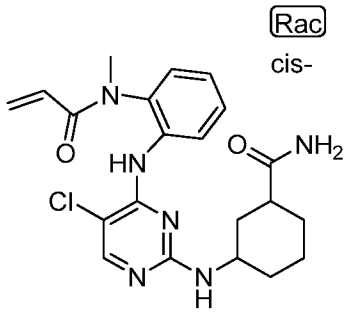
Example 124



I-104

[00473] N-(2-((5-chloro-2-(trans-(4-hydroxycyclohexyl)amino)pyrimidin-4-yl)amino)phenyl)-N-methylacrylamide. Compound **I-104** was prepared in a manner similar to Example 120, substituting trans-4-aminocyclohexanol for cis-3-aminocyclohexanecarboxamide, and substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide**:** MS m/z 402.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 1.27-1.35 (m, 4H), 1.94-1.99 (m,4H), 3.33 (br s, 2H), 3.55 (br s, 2H), 5.53-5.56 (dd, J =2.3 Hz, J=10.1 Hz, 1H), 6.18-6.23 (m, 1H), 6.23-6.28 (dd, J = 2.2 Hz, 16.7 Hz, 1H), 7.32 (br s, 2H), 7.47-7.49 (br s, 2H), 7.87 (br s, 1H), 8.05 (br s, 1H).

Example 125

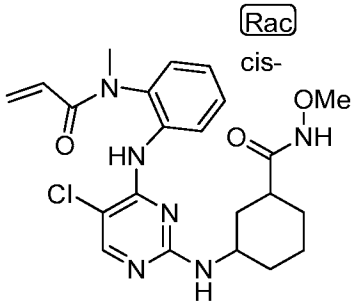


I-105

[00474] Rac-cis-3-((5-chloro-4-((2-(N-methylacrylamido)phenyl)amino)pyrimidin-2-yl)amino)cyclohexanecarboxamide. Compound **I-105** was prepared in a manner similar to Example 120, substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide**:** MS m/z 429.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 1.35-1.43 (m, 2H), 1.82-1.89 (m, 3H), 1.90-1.98 (m, 1H), 2.03-2.10 (m, 1H), 2.31(br s,1H), 3.33 (s, 3H), 3.62-3.74

(m, 1H), 3.75-3.76 (m, 1H), 5.54-5.57 (dd, J=2.9Hz, 9.4 Hz, 1H), 6.18 (br s, 1H), 6.23-6.27 (dd, J=2.2Hz, 16.8 Hz, 1H), 7.31 (s, 1H), 7.32 (d, J=1.8 Hz), 7.46-7.49 (m, 1H), 7.87 (s, 1H), 8.0 (br s, 1H).

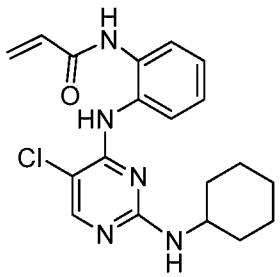
Example 126



I-106

[00475] Rac-cis-3-((5-chloro-4-((2-(N-methylacrylamido)phenyl)amino) pyrimidin-2-yl)amino)-N-methoxycyclohexanecarboxamide Compound **I-106** was prepared in a manner similar to Example 120, substituting cis-3-amino-N-methoxycyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide, and substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide**:** MS m/z 459.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 1.73-1.85 (m, 1H), 1.83-1.93 (m, 1H), 1.94 (m, 1H), 1.95-1.96 (m, 3H), 1.98-2.04 (m, 2H), 2.08-2.14 (m, 1H), 3.33 (s, 3H), 3.63-3.67 (m, 1H), 3.68 (s, 3H), 5.54-5.57 (dd, J=2.3Hz, 9.8Hz, 1H), 6.16-6.27 (m, 2H), 7.30-7.34 (m, 2H), 7.45-7.49 (m, 1H), 7.87 (s, 1H), 7.99 (br s, 1H).

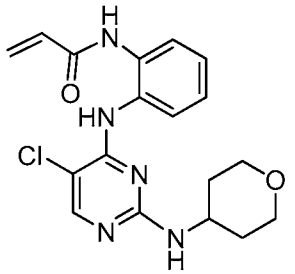
Example 127



I-107

[00476] N-(2-((5-chloro-2-(cyclohexylamino)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-107** was prepared in a manner similar to Example 120, substituting cyclohexanamine for cis-3-aminocyclohexanecarboxamide**:** MS m/z 372.2 (ES+, M+H).

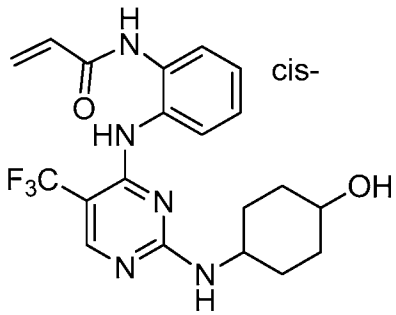
Example 128



I-108

[00477] N-(2-((5-chloro-2-((tetrahydro-2H-pyran-4-yl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-108** was prepared in a manner similar to Example 120, substituting tetrahydro-2H-pyran-4-amine for cis-3-aminocyclohexanecarboxamide**:** MS m/z 374.2 (ES+, M+H).

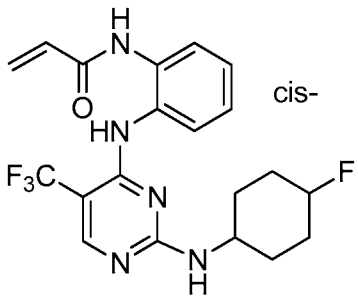
Example 129



I-109

[00478] N-(2-((2-(cis-(4-hydroxycyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl) amino)phenyl)acrylamide: Compound **I-109** was prepared in a manner similar to Example 120, substituting cis-4-aminocyclohexanol for cis-3-aminocyclohexanecarboxamide. MS m/z 422.1 (ES+, M+H).

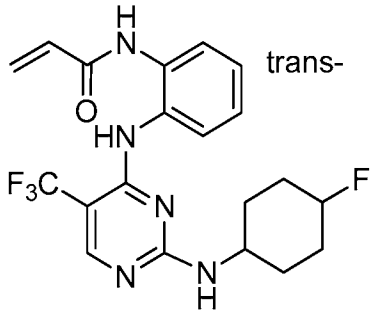
Example 130



I-110

[00479] N-(2-((2-(cis-(4-fluorocyclohexyl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-110** was prepared in a manner similar to Example 120, substituting cis-4-fluorocyclohexanamine for cis-3-aminocyclohexanecarboxamide. MS m/z 424.4 (ES+, M+H).

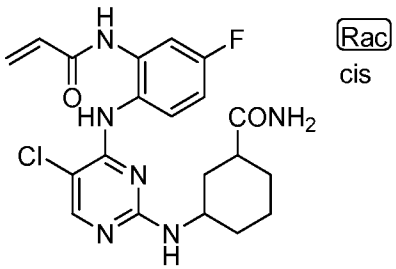
Example 131



I-111

[00480] N-(2-((2-(trans-(4-fluorocyclohexyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-111** was prepared in a manner similar to Example 120 substituting trans-4-fluorocyclohexanamine for cis-3-aminocyclohexanecarboxamide. MS: m/z 424.1 (ES+, M+H).

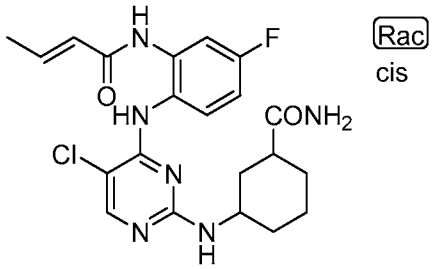
Example 132



I-112

[00481] Rac-cis-3-((4-((2-acrylamido-4-fluorophenyl)amino)-5-chloropyrimidin-2-yl)amino)cyclohexanecarboxamide: Compound **I-112** was prepared in a manner similar to Example 120, substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 433.2 (ES+, M+H).

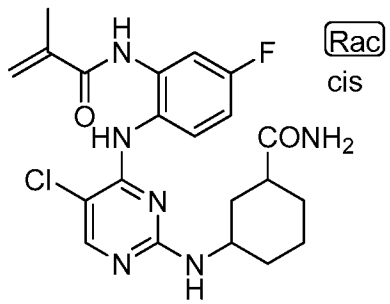
Example 133



I-113

[00482] Rac-cis-(E)-3-((4-((2-(but-2-enamido)-4-fluorophenyl)amino)-5-chloropyrimidin-2-yl)amino)cyclohexanecarboxamide. Compound **I-113** was prepared in a manner similar to Example 120, substituting (E)-N-(2-amino-5-fluorophenyl)but-2-enamide for N-(2-aminophenyl)acrylamide: MS m/z 447.5 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.1-1.27 (m, 4H), 1.6-1.82 (m, 4H), 1.84-1.86 (dd, J = 1.5, 6.9 Hz, 3H), 2.09 (br s, 1H), 3.6 (br s, 1H), 6.17-6.21 (dd, J = 1.6, 15.3 Hz, 1H), 6.61 (br s, 1H), 6.81-6.88 (m, 2H), 7-7.05 (m, 1H), 7.13 (br s, 1H), 7.42 (d, J = 10.4 Hz, 1H), 7.61 (br s, 1H), 7.89 (s, 1H), 8.24 (br s, 1H), 9.8 (br s, 1H).

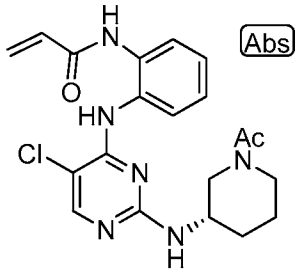
Example 134



I-114

[00483] Rac-cis-3-((5-chloro-4-((4-fluoro-2-methacrylamidophenyl)amino)pyrimidin-2-yl)amino)cyclohexanecarboxamide. Compound **I-114** was prepared in a manner similar to Example 120, substituting N-(2-amino-5-fluorophenyl)methacrylamide for N-(2-aminophenyl)acrylamide: MS m/z 447.5 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.14-1.36 (m, 4H), 1.66-1.78 (m, 4H), 1.9 (s, 3H), 2.1 (br s, 1H), 3.63 (br s, 1H), 5.53 (s, 1H), 5.82 (s, 1H), 6.62 (s, 1H), 6.8-6.9 (m, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.14 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.62-7.71 (m, 1H), 7.92 (br s, 1H), 8.16-8.23 (m, 1H), 9.5-9.7 (m, 1H).

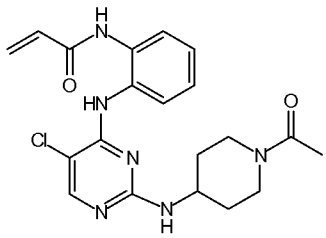
Example 135



I-115

[00484] (S)-N-(2-((2-((1-acetylpiperidin-3-yl)amino)-5-chloropyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-115** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then deprotecting with TFA followed by amide formation with acetic anhydride**:** MS m/z 415.1 (ES+, M+H); ^{1}HNMR(DMSO-d_6) δ 1.22-1.27(m, 2H), 1.32-1.6(m, 2H), 1.6-1.9(m, 3H), 1.99(s, 2H),2.6(m, 2H), 2.7-3.0(m, 1H), 3.6-3.63(d, 1H, J=13.4Hz), 3.94-3.98(d,1H,J=12.1Hz), 5.7-5.8(d, 1H, J=10Hz), 6.28-6.32(d, 1H, J=17Hz), 6.45-6.52(dd, 1H,J=10.2, 17Hz), 7.16-7.37(m, 2H), 7.4(d,1H J=8.8Hz), 7.72-7.74(d, 1H, J=7.2Hz), 7.95-7.97(d, 1H,J=9.7Hz), 8.30(br s, 1H),10.15(br s, 1H).

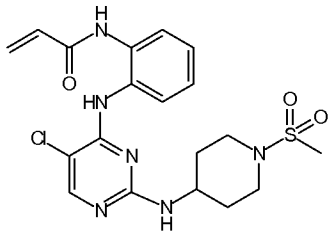
Example 136



I-116

[00485] N-(2-((2-((1-acetylpiperidin-4-yl)amino)-5-chloropyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-116** was prepared in a manner similar to Example 120, substituting tert-butyl 4-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, , then deprotecting with TFA followed by amide formation with acetic anhydride. MS m/z 415.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.12-1.38 (m, 3H), 1.70-1.84 (m, 2H), 1.96 (s, 3H), 2.99 (br s, 1H), 3.58 (br s, 1H), 3.75 (m, 1H), 4.24 (d, J = 13.2 Hz, 1H), 5.78-5.81 (dd, J = 1.6, 10.2 Hz, 1H), 6.3 (d, J = 17.1 Hz, 1H), 6.45-6.52 (dd, J = 10.2, 17.2 Hz, 1H), 6.95 (br s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.93 (s, 1H), 8.28 (br s, 1H), 10.1 (br s, 1H).

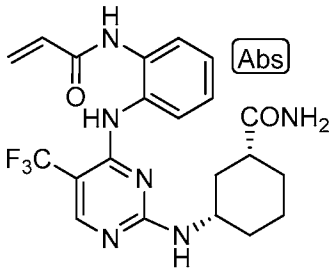
Example 137



I-117

[00486] N-(2-((5-chloro-2-((1-(methylsulfonyl)piperidin-4-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-117** was prepared in a manner similar to Example 120, substituting tert-butyl 4-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA followed by reaction with methylsulfonyl chloride. MS m/z 451.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.20-1.27 (m, 1H), 1.37-1.50 (m, 2H), 1.84-1.86 (d, J = 10.0 Hz, 2H), 2.72 (br s, 2H), 2.84 (s, 3H), 3.49 (d, J = 12.1 Hz, 2H), 5.78-5.81 (dd, J = 1.9, 10.0 Hz, 1H), 6.27-6.32 (dd, J = 1.8, 17.0 Hz, 1H), 6.45-6.52 (dd, J = 10.1, 17.0 Hz, 1H), 6.95 (br s, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 7.38-7.39 (d, J = 6.8 Hz, 1H), 7.75-7.77 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 8.3 (s, 1H), 10.14 (s, 1H).

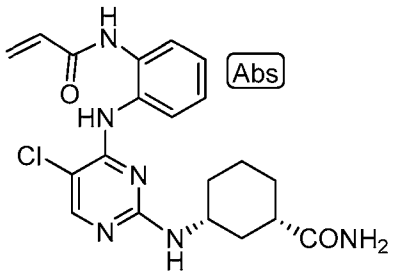
Example 138



I-118

[00487] (1R,3S)-3-((4-((2-acrylamidophenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)cyclohexanecarboxamide: Compound **I-118** was prepared in a manner similar to Example 1, substituting (1R,3S)-3-aminocyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide. MS m/z 449.2 (ES+, M+H).

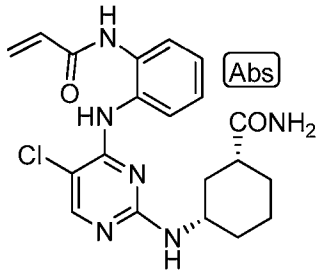
Example 139



I-119

[00488] (1S,3R)-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino) cyclohexanecarboxamide: Compound **I-119** was prepared in a manner similar to Example 120, substituting (1S,3R)-3-aminocyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide. MS m/z 415.1 (ES+, M+H).

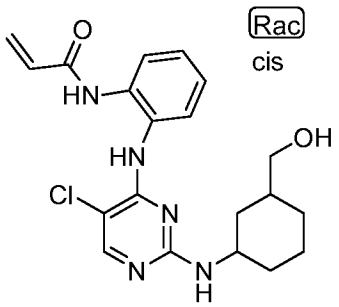
Example 140



I-120

[00489] (1R,3S)-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)cyclohexanecarboxamide: Compound **I-120** was prepared in a manner similar to Example 120, substituting (1R,3S)-3-aminocyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide. MS m/z 415.1 (ES+, M+H).

Example 141

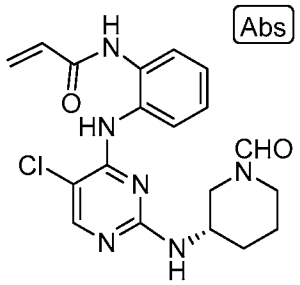


I-121

[00490] Rac-cis-N-(2-((5-chloro-2-((3-(hydroxymethyl)cyclohexyl)amino) pyrimidin-4-yl)amino)phenyl)acrylamide Compound **I-121** was prepared in a manner similar to Example

120, substituting cis-3-aminocyclohexylmethanol for cis-3-aminocyclohexanecarboxamide: MS m/z 402.5 (ES+, M+H); ^{1}HNMR(DMSO-d_6) δ 0.72-0.84 (m, 2H), 1.08-1.1 (m, 1H), 1.18-1.28 (m, 3H), 1.62-1.70 (m, 2H), 1.77-1.80 (d, 1H, J=11Hz), 1.86-1.89 (d, 1H, J=11.9Hz), 3.19-3.20 (br s, 2H),4.36 (s, 1H), 5.78-5.81 (d, 1H, J=10.22Hz), 6.28-6.32 (d, 1H, J=16.8Hz), 6.45-6.52 (dd, 1H, J=10, 17Hz), 7.14-7.18 (m, 1H), 7.22-7.26 (m, 1H), 7.33-7.35 (m, 1H), 7.83 (br s, 1H), 7.91 (s, 1H), 8.24 (br s, 1H), 10.18 (s, 1H).

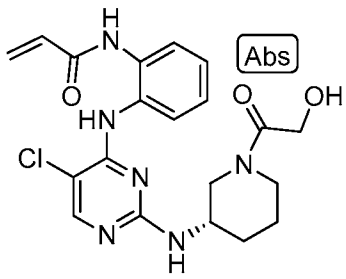
Example 142



I-122

[00491] (S)-N-(2-((5-chloro-2-((1-formylpiperidin-3-yl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-122** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA, followed by reaction with formic acid, HATU and DIPEA in DMA. MS m/z 401.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.18-1.22 (m, 2H), 1.27-1.3 (m, 1H), 1.47-1.5 (m, 1H), 1.6-1.80 (m, 1H), 1.86-1.89 (m, 1H), 1.90-1.95 (m, 1H), 3.49-3.51 (m, 1H), 3.62 (d, J = 13.3 Hz, 1H), 5.78-5.81 (dd, J = 1.7, 10.1 Hz, 1H), 6.3 (d, J = 16.9 Hz, 1H), 6.45-6.52 (dd, J = 10.2, 17.0 Hz, 1H), 7.0 (br s, 1H), 7.15-7.24 (m, 2H), 7.37-7.39 (m, 1H), 7.75-7.77 (m, 1H), 7.97 (d, J = 17.3 Hz, 1H), 8.33 (br s, 1H), 10.15 (br s, 1H).

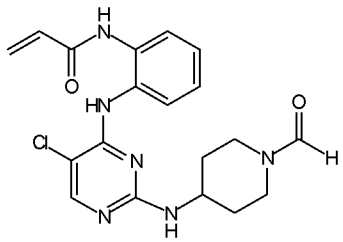
Example 143



I-123

[00492] (S)-N-(2-((5-chloro-2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-123** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA, followed by reaction with $ClCOCH_2OAc$ and hydrolysis with aqueous LiOH. MS m/z 461.1 (ES+, M+H); ^{1}H NMR (400MHz, CD_3OD) δ 1.49-1.63(m,2H), 1.77-1.80(m, 1H), 1.95-2.05(m, 2H), 2.94-3.15(m, 2H), 3.49-3.54(m, 1H), 3.65-3.72(m, 1H), 3.91-3.95(m, 1H), 4.24(s, 1H), 5.81-5.84(dd, 1H, J=2.2, 9.6Hz), 6.38-6.50(m, 2H),7.21-7.33(m, 2H), 7.37-7.44(dd, 1H, J=7.7, 22.1Hz), 7.74-7.76(m, 1H), 7.84-7.91(m, 1H).

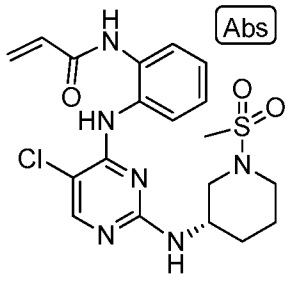
Example 144



I-124

[00493] N-(2-((5-chloro-2-((1-formylpiperidin-4-yl)amino)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-124** was prepared in a manner similar to Example 120, substituting tert-butyl 4-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA, followed by reaction with formic acid, HATU and DIPEA in DMA**.** MS m/z 401.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.16-1.32 (m, 3H), 1.80 (t, J = 12.3 Hz, 2H), 2.59 (br s, 1H), 2.98 (br s, 1H), 3.63 (d, J = 13.6 Hz, 1H), 4.06 (d, J = 13.2 Hz, 1H), 5.77-5.80 (dd, J = 1.6, 10.1 Hz, 1H), 6.27-6.32 (dd, J = 1.3, 16.9 Hz, 1H), 6.45-6.52 (dd, J = 10.1, 16.9 Hz, 1H), 6.9 (br s, 1H), 7.17 (t, J = 7.0 Hz, 1H), 7.25 (t, J = 7.0 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.94 (s, 2H), 8.3 (s, 1H), 10.1 (s, 1H).

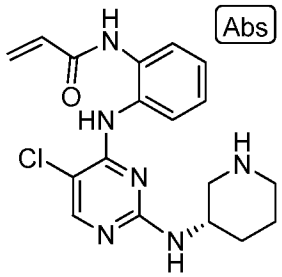
Example 145



I-125

(S)-N-(2-((5-chloro-2-((1-(methylsulfonyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-125** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA, followed by reaction with MsCl. MS m/z 451.1 (ES+, M+H)

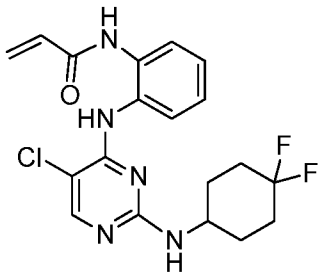
Example 146



I-126

[00494] (S)-N-(2-((5-chloro-2-(piperidin-3-ylamino)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-126** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA. MS m/z 373.1 (ES+, M+H)

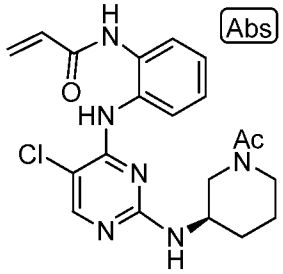
Example 147



I-127

[00495] N-(2-((5-chloro-2-((4,4-difluorocyclohexyl)amino)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-127** was prepared in a manner similar to Example 120, substituting 4,4-difluorocyclohexanamine for cis-3-aminocyclohexanecarboxamide: MS m/z 408.2 (ES+, M+H); ^{1}HNMR(CD_3OD) δ 1.31-1.39 (m, 1H), 1.52-1.55 (m, 2H), 1.60-1.75 (m, 2H), 1.93-1.96 (m, 2H), 2.01-2.04 (m, 2H), 5.80-5.83 (dd, 1H, J=2.2, 9.6Hz), 6.38-6.47 (m, 2H), 7.24-7.33 (m, 2H), 7.45-7.47 (m, 1H), 7.77-7.79 (m, 1H), 7.87 (s, 1H).

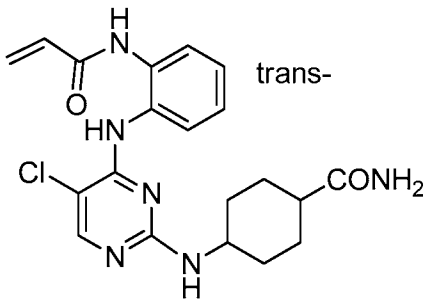
Example 148



I-128

[00496] (R)-N-(2-((2-((1-acetylpiperidin-3-yl)amino)-5-chloropyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-128** was prepared in a manner similar to Example 120, substituting (R)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, then Boc-deprotection with TFA, followed by reaction with acetic anhydride. MS m/z 415.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.10-1.18 (m, 1H)), 1.75-1.89 (m, 1H), 1.30-1.52 (m, 2H), 1.60-1.73 (m, 1H), 1.80-1.82 (m, 1H), 1.89-1.99 (m, 1H), 2.72-3.0 (m, 2H), 3.61 (br s 1H), 3.64 (br s 1H), 3.96 (d, J=11.7 Hz, 1H), 5.79 (d, J=10.0 Hz, 1H), 6.29 (d, J=17.0 Hz, 1H), 6.45-6.52(dd, J=10.1, 17.0Hz, 1H), 6.8-7.0 (m, 1H), 7.12-7.28 (m, 2H), 7.29-7.40 (m, 1H), 7.70-7.90 (m, 1H), 7.95 (d, J=10.6Hz, 1H), 8.32 (br s, 1H), 10.25 (br s, 1H).

Example 149

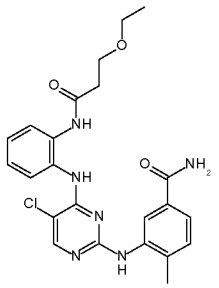


I-129

[00497] trans-4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-cyclohexanecarboxamide. Compound **I-129** was prepared in a manner similar to Example 120, substituting trans-4-aminocyclohexanecarboxamide for cis-3-aminocyclohexanecarboxamide. MS m/z 415.2 (ES+, M+H); ^{1}HNMR(DMSO-d_6) δ 1.14-1.22(m, 2H), 1.22-1.26(m, 2H), 1.26-1.34(m, 2H),1 .70-1.73(d, 2H, J=12.3Hz), 1.84-1.87(d, 2H, J=9.7Hz), 1.95-2.01(m, 1H), 5.78-5.81(d, 1H, J=10.2Hz), 6.28-6.32(d, 1H, J=16.4Hz), 6.45-6.52(dd, 1H, J=10.2, J=17Hz), 6.62(br

s, 1H), 7.15-7.24(m, 3H), 7.34-7.36(d, 1H, J=7.4Hz), 7.8(br s, 1H),7.9(br s, 1H), 8.25(br s, 1H), 10.2(br s,1H).

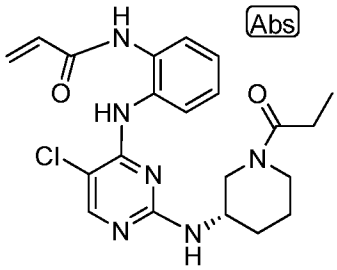
Example 150



I-130

[00498] Compound **I-130** was prepared in a manner similar to Example 162, substituting N-(2-aminophenyl)-3-ethoxypropanamide for N-(2-aminophenyl)acrylamide. MS: m/z 469.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.03 (t, J = 7.0 Hz, 3H), 2.15 (s, 3H), 2.56 (t, J = 6.3 Hz, 2H), 3.38-3.4 (dd, J = 7, 2.2.0 Hz, 2H), 3.62-3.65 (t, J = 6.2 Hz, 2H), 7.0-7.07 (m, 2H), 7.14-7.19 (m, 2H), 7.26 (br s, 1H), 7.51-7.54 (dd, J = 1.59, 7.7 Hz, 1H), 7.71-7.73 (d, J = 9.5 Hz, 1H), 7.86 (br s, 1H), 7.91 (d, J = 1.2 Hz, 1H), 8.05 (s, 1H), 8.34 (s, 1H), 8.61 (s, 1H), 9.9 (s, 1H).

Example 151

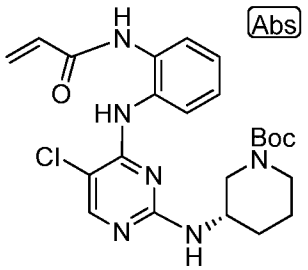


I-131

(S)-N-(2-((5-chloro-2-((1-propionylpiperidin-3-yl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide. Compound **I-131** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and reaction with $ClCOCH_2CH_3$: MS m/z 429.5 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 0.83-1.0 (m, 2H), 1.14 (t, J=7.5Hz, 1H), 1.38-1.42 (m, 2H), 1.45-1.68 (m, 2H), 1.7-1.84(m, 1H), 1.93-2.20 (m, 1H), 2.35 (q, J=2.5Hz, 1H), 2.90-3.03 (m, 1H), 3.62-3.80 (m, 2H), 4.0-4.21 (m, 1H), 5.81-5.84 (dd, J=2.1,

9.7Hz, 1H), 6.38-6.48 (m, 2H), 7.22-7.31 (m, 2H), 7.42-7.45 (dd, J=1.4, 7.7Hz, 1H), 7.76-7.78 (dd, J=1.2, 7.7Hz, 1H), 7.89 (d, J=15.8Hz, 1H). Mixture of Rotamers.

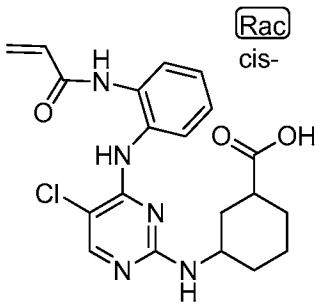
Example 152



I-132

[00499] (S)-tert-butyl 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino) piperidine-1-carboxylate. Compound **I-132** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide: MS m/z 507.5 (ES+, M+H)

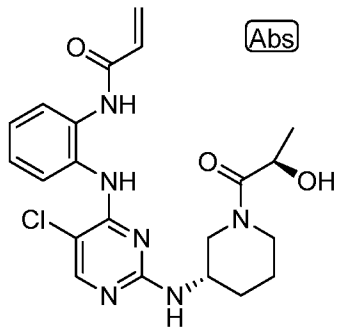
Example 153



I-133

[00500] Rac-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-cis-cyclohexanecarboxylic acid. Compound **I-133** was prepared in a manner similar to Example 120, substituting cis-t-butyl 3-aminocyclohexanecarboxylate for cis-3-aminocyclohexanecarboxamide, followed by deprotection with TFA. MS m/z 416.5 (ES+, M+H); ^{1}HNMR(DMSO-d_6) δ 1.1-1.16(m, 4H), 1.69-1.89(m, 4H), 2.02-2.05(d, 1H, J=11.6Hz), 2.99(br s, 1H), 5.78-5.80(d, 1H, J=20.2Hz), 6.28-6.32(d, 1H, J=16.5Hz), 6.46-6.53(dd, 1H, J=10.3, 17.1Hz), 6.7(br s, 1H), 7.14-7.18(m, 1H), 7.22-7.25(t, 1H, J=7.7Hz), 7.34-7.36(d, 1H, J=7.4Hz), 7.79-7.82(br s, 1H), 7.92(s, 1H), 8.2(br s, 1H), 10.2(br s, 1H), 12.0(br s, 1H).

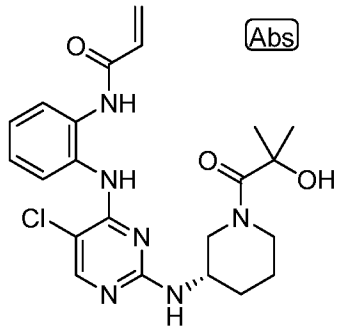
Example 154



I-134

[00501] N-(2-((5-chloro-2-(((S)-1-((R)-2-hydroxypropanoyl)piperidin-3-yl)amino) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-134** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and amide formation with (R)-2-hydroxypropanoic acid, HATU and DIPEA in DMA. MS m/z 445.2 (ES+, M+H).

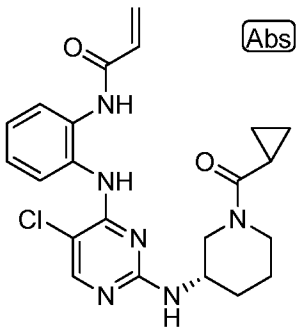
Example 155



I-135

[00502] (S)-N-(2-((5-chloro-2-((1-(2-hydroxy-2-methylpropanoyl)piperidin-3-yl)amino) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-135** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and amide formation with 2-hydroxy-2-methylpropanoic acid, HATU and DIPEA in DMA. MS m/z 459.2 (ES+, M+H).

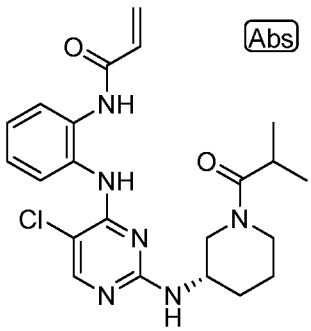
Example 156



I-136

[00503] (S)-N-(2-((5-chloro-2-((1-(cyclopropanecarbonyl)piperidin-3-yl)amino)pyrimidin -4-yl)amino)phenyl)acrylamide. Compound **I-136** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and amide formation with cyclopropanecarboxylic acid, HATU and DIPEA in DMA. MS m/z 441.2 (ES+, M+H).

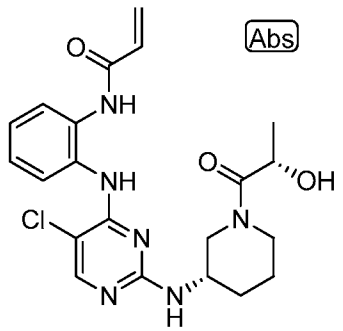
Example 157



I-137

[00504] (S)-N-(2-((5-chloro-2-((1-isobutyrylpiperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-137** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and amide formation with isobutyric acid, HATU and DIPEA in DMA. MS m/z 443.1 (ES+, M+H).

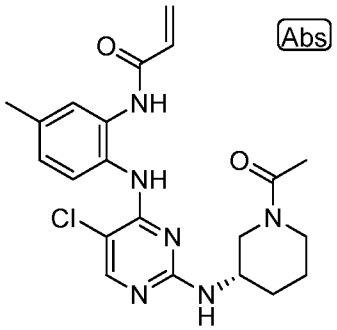
Example 158



I-138

[00505] N-(2-((5-chloro-2-(((S)-1-((S)-2-hydroxypropanoyl)piperidin-3-yl)amino) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-138** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, followed by Boc-deprotection with TFA and amide formation with (S)-2-hydroxypropanoic acid, HATU and DIPEA in DMA. MS m/z 445.1 (ES+, M+H).

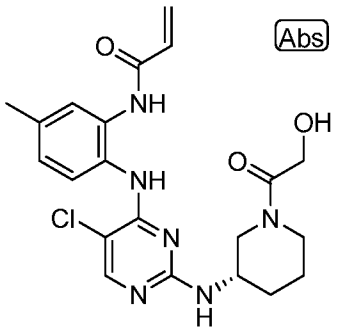
Example 159



I-139

[00506] (S)-N-(2-((2-((1-acetylpiperidin-3-yl)amino)-5-chloropyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-139** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, and by substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, followed by Boc-deprotection with TFA then amide formation with acetic anhydride. MS m/z 429.6 (ES+, M+H;) ^{1}HNMR (DMSO-d_6) δ 1.29 (m, 1H), 1.47-1.50 (m, 2H), 1.61-1.64 (m, 1H), 1.80 (br s, 1H), 1.99 (br s, 1H), 2.30 (s, 3H), 2.75 (br s, 1H), 2.84-2.89 (dd, J = 9.2, 13.2 Hz, 1H), 3.12 (br s, 1H), 3.49 (s, 3H), 5.76-5.79 (dd, J = 1.8, 10 Hz, 1H), 6.26-6.31 (dd, J = 1.8, 16.9 Hz, 1H), 6.44-6.51 (dd, J = 10.1, 17 Hz, 1H), 7.03-7.05 (d, J = 8.2 Hz, 1H), 7.27-7.37 (d, J = 19.3 Hz, 1H), 7.48-7.50 (d, J = 8.1 Hz, 1H), 7.82 (br s, 1H), 8.12 (s, 1H), 9.38 (br s, 1H), 10.04 (s, 1H).

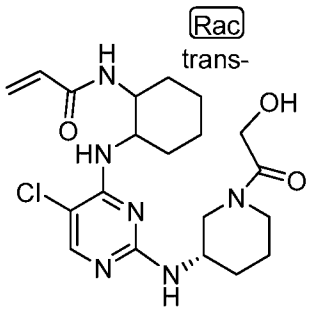
Example 160



I-140

[00507] (S)-N-(2-((5-chloro-2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-140** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, and by substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, followed by Boc-deprotection with TFA then amide formation with $ClCOCH_2OAc$ and final hydrolysis with aqueous LiOH. MS m/z 445.6 (ES+, M+H); ^1H NMR (DMSO-d_6) δ 1.22 (m, 2H), 1.67 (m, 1H), 1.82 (m, 1H), 1.97 (s, 1H), 2.28 (s, 3H), 2.83 (m, 2H), 3.50 (m, 2H), 3.99 (br s, 1H), 4.02-4.06 (m, 1H), 4.45 (br s, 1H), 5.76-5.79 (d, J = 10.0 Hz, 1H), 6.26-6.30 (d, J = 15.5 Hz, 1H), 6.44-6.50 (dd, J = 10.0, 16.8 Hz, 1H), 6.86 (br s, 1H), 7.03 (d, J = 7.9 Hz, 1H), 7.18 (s, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.21 (br s, 1H), 10.07 (s, 1H).

Example 161

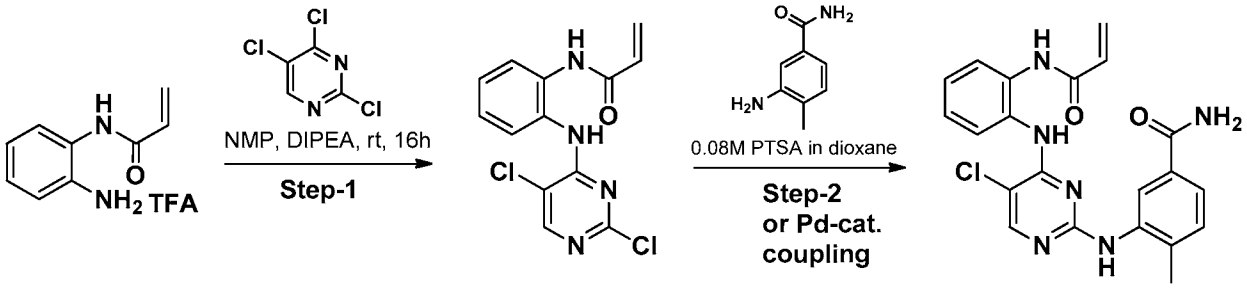


I-141

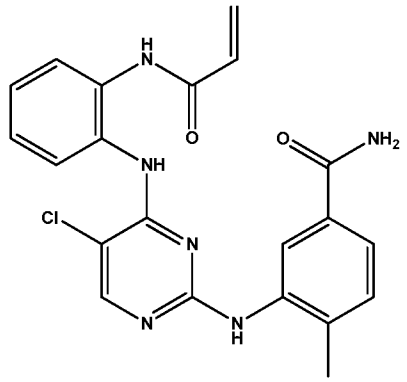
[00508] Rac-N-(2-((5-chloro-2-(((R)-1-(2-hydroxyacetyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)-trans-cyclohexyl)acrylamide. Compound **I-141** was prepared in a manner similar to Example 120, substituting (S)-tert-butyl 3-aminopiperidine-1-carboxylate for cis-3-aminocyclohexanecarboxamide, and by substituting N-trans-(2-aminocyclohexyl)acrylamide for

N-(2-aminophenyl)acrylamide, followed by Boc-deprotection with TFA then reaction with $ClCOCH_2OAc$ and final hydrolysis with aqueous LiOH. MS m/z 437.1 (ES+, M+H).

[00509] Similar to Method B and C, **Method E** was to introduce an acrylamide-containing or Boc-protected ring system first at the C-4 position of 2,4,5-trichloropyrimidine, followed by the introduction of a second aniline at the C-5 position. General practice of this method is described below.



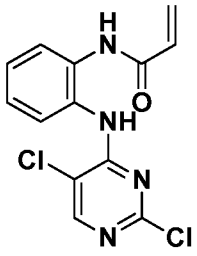
Example 162



I-319

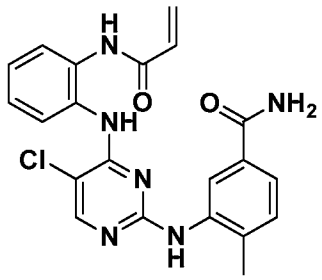
[00510] 3-(4-(2-acrylamidophenylamino)-5-chloropyrimidin-2-ylamino)-4-methylbenzamide: The title compound was prepared according to the steps and intermediates as described below.

Step 1: N-(2-(2, 5-dichloropyrimidin-4-ylamino) phenyl) acrylamide (Intermediate 1)



[00511] To a solution of N-(2-aminophenyl) acrylamide (TFA salt) (10 g, 38.6 mmol) in N-methyl pyrrolidinone (30 mL) was added DIPEA (12.6 g, 98.36 mmol), and 2, 4, 5-trichloropyrimidine (9.5 g, 49.18 mmol), and the mixture was stirred at rt for 16h. TLC showed completion of starting material (TLC system: 50% ethyl acetate/hexane, **(R_f):** 0.5). The reaction mixture was diluted with ethyl acetate (100 mL) and washed with water (3x 50 mL). The organic layer was separated, dried over sodium sulfate and concentrated to obtain the crude compound (11 g). MS m/z: 309.1 (ES+, M+1).

Step 2:Acid catalyzed coupling condition.

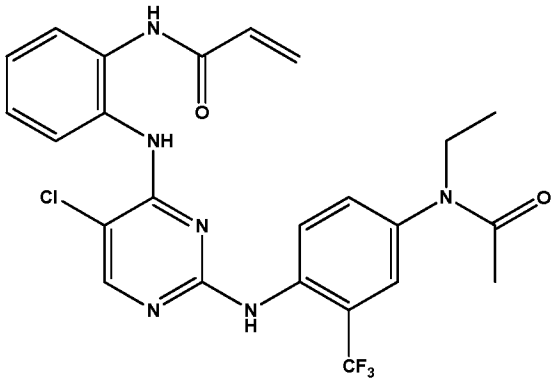


[00512] **3-(4-(2-acrylamidophenylamino)-5-chloropyrimidin-2-ylamino)-4-methylbenzamide.** A solution of **Intermediate 1** (1 g, 3.24 mmol) and 3-amino-4-methylbenzamide (584 mg, 3.89 mmol) in 0.08 M PTSA in 1,4-dioxane was heated to 90 °C for 48h. TLC showed the completion of starting material (TLC system: 10% methanol/DCM, **(R_f):** 0.5). The reaction mixture was concentrated, quenched with water, and the precipitated solid was filtered and dried under vacuum. The crude solid was purified by silica gel column chromatography by using 3% methanol/DCM as eluents. The purified solid was further triturated with ether, filtered and dried under vacuum to get the title compound as an off-white solid (430 mg, 31%). ^{1}HNMR(400MHz, D_6-DMSO) δ 2.17(s, 3H), 5.78-5.81(dd, 1H *J*=1.8, 10.1Hz), 6.28-6.32(dd, 1H *J*= 1.8, 17Hz), 6.43-6.50(dd, 1H *J*=10.1, 17Hz), 7.04-7.08(m, 2H), 7.18-7.24(m, 2H), 7.27(br s, 1H), 7.52-7.54(dd, 1H *J*=1.7, 7.9Hz), 7.73-7.76(m, 1H), 7.87(br s, 1H), 7.92(d, 1H), 8.03(s, 1H), 8.39(s, 1H), 8.62(s, 1H), 10.19(s, 1H). MS m/z: 423.5 (ES+, M+H).

Step-2 -- Palladium catalyzed coupling condition.

[00513] **3-(4-(2-acrylamidophenylamino)-5-chloropyrimidin-2-ylamino)-4-methylbenzamide.** Alternatively, compound **I-319** was also synthesized under a similar Pd-coupling condition substituting N-(2-(2, 5-dichloropyrimidin-4-ylamino) phenyl) acrylamide for N-(2-(2-Chloro-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide. MS m/z: 423.5 (ES+, M+H).

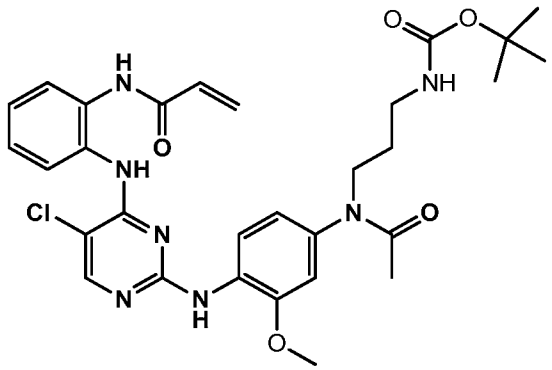
Example 163



I-320

[00514] N-(2-(5-chloro-2-(4-(N-ethylacetamido)-2-(trifluoromethyl)phenylamino) pyrimidin-4-ylamino)phenyl)acrylamide. To a stirred solution of **Intermediate 1** from **Example 162** (100 mg, 0.3246 mmol) in tetrahydrofuran (5 mL), N-(4-amino-3-(trifluoro methyl)phenyl)-N-ethylacetamide (80 mg, 0.3246 mmol) and cesium carbonate (316 mg, 0.9738 mmol) were added and degassed for 10min. To the reaction mixture palladium acetate (38 mg, 0.1623 mmol) and xanthphos (36.8 mg, 0.0973 mmol) were added and again degassed for another 5min. The mixture was irradiated by microwave at 80 °C for 20min. TLC showed completion of starting material (TLC system: 10% methanol/chloroform, (R_f): 0.5). The reaction was quenched with water (15 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was separated, dried over sodium sulfate and concentrated. The crude compound was purified by prep-HPLC to obtain the title compound as yellow solid. (30 mg, 17%). ^{1}HNMR(DMSO-d_6) δ 0.98(m, 3H), 1.70(m, 3H), 1.85(s, 1H), 3.63(m, 2H), 5.77-5.80(dd, 1H J= 1.8Hz and 10.2Hz), 6.26-6.31(dd, 1H J= 1.8, 17Hz), 6.44-6.51(dd, 1H J=10.2, 17Hz), 7.09-7.17(m, 2H), 7.32-7.35(dd, 1H J= 1.7, 7.5Hz), 7.48(d, 1H J= 7.1Hz), 7.55(s, 1H), 7.63(d, 1H J= 8.2Hz), 7.72(d, 1H J=8.2Hz), 8.08(s, 1H), 8.49(s, 1H), 10.12(s, 1H). MS m/z: 519.5 (ES+, M+H).

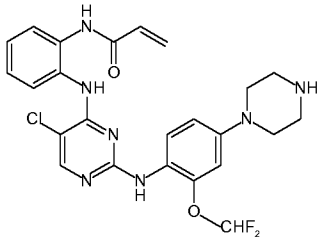
Example 164



I-173

[00515] tert-butyl (3-(N-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)acetamido)propyl)carbamate: To a stirred solution of tert-butyl-3-(N-(4-amino-3-methoxyphenyl) acetamido) propyl carbamate (109 mg, 0.324 mmol), **Intermediate 1** from **Example 162** (100 mg, 0.324 mmol), diphenylphosphino-N,N-dimethylamine (56 mg, 0.1428 mmol) in tert-amyl alcohol (5 mL), and sodium carbonate (245 mg, 1.948 mmol) was added, and the mixture was degassed for 20min. To this mixture, tris-dibenzylamino dipalladium (41 mg, 0.045 mmol) catalyst was added, and the mixture was degassed again for 10min. The temperature was raised to 90 °C, and the mixture was stirred for 2h. TLC showed completion of starting material (TLC system: 5% methanol/chloroform (R_f): 0.5). The reaction was quenched with water (15 mL) and extracted with ethyl acetate (3×10 mL). The organic layer was separated, dried over sodium sulfate and concentrated. The crude compound was purified by prep-HPLC to obtain the title compound as an off-white solid. (10 mg, 53%). ^{1}HNMR(400MHz, DMSO-d_6) δ 1.34(s, 9H), 1.45-1.51(m, 2H), 1.71(s, 3H), 2.90(q, 2H J=6.4Hz), 3.56(t, 2H J=7.3Hz), 3.82(s, 3H), 5.76-5.79(dd, 1H J=1.8, 10.2Hz), 6.27-6.31(dd, 1H J=1.8, 17Hz), 6.45-6.52(dd, 1H J=10.2, 17Hz), 6.61(d, 1H J=7.7Hz), 6.72(m, 1H), 6.91(s, 1H), 7.22-7.31(m, 2H), 7.44(d, 1H J=6.8Hz), 7.68(d, 1H J=6.8Hz), 7.79(s, 1H), 7.88(s, 1H), 8.11(s, 1H), 8.58(s, 1H), 10.13(s, 1H). MS m/z: 608.1 (ES-, M-H).

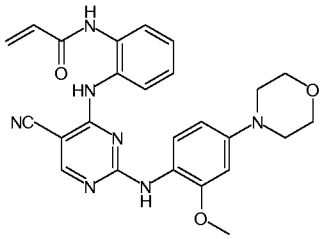
Example 165



I-142

[00516] N-(2-((5-chloro-2-((2-(difluoromethoxy)-4-(piperazin-1-yl)phenyl)amino) pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-142** was prepared in a manner similar to Example 162, substituting tert-butyl 4-(4-amino-3-(difluoromethoxy)phenyl)piperazine-1-carboxylate for 3-amino-4-methylbenzamide, followed by deprotecting with TFA. MS m/z: 516.2 (ES+, M+H).

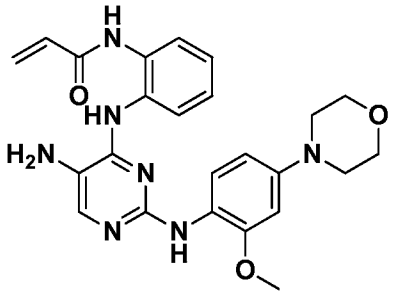
Example 166



I-143

[00517] N-(2-((5-cyano-2-((2-methoxy-4-morpholinophenyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-143** was prepared in a manner similar to Example 162, using 2,4-dichloro-5-cyanopyrimdine as the starting material, and substituting 2-methoxy-4-morpholinoaniline for 3-amino-4-methylbenzamide. MS m/z: 472.2 (ES+, M+H).

Example 167

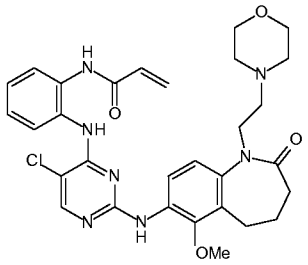


I-144

[00518] N-(2-((5-amino-2-((2-methoxy-4-morpholinophenyl)amino)pyrimidin-4-yl)amino)phenyl) acrylamide: Compound **I-144** was prepared in the similar way as described in Example 162, using 2,4-dichloro-5-aminopyrimidine as the starting material and substituting 2-methoxy-4-morpholinoaniline in for 3-amino-4-methylbenzamide. MS: m/z 462.3 (ES+, M+H); 1HNMR(DMSO-d_6) δ 3.00 (t, J = 4.6 Hz, 4H), 3.72 (t, J = 4.6 Hz, 4H), 3.78 (s, 3H), 4.1 (br s, 2H), 5.70-5.74 (dd, J = 1.7, 10.1 Hz, 1H), 6.19-6.24 (dd, J = 1.9, 17.0 Hz,1H), 6.27-6.30 (dd, J = 2.5, 8.8 Hz,1H), 6.43-6.49 (dd, J = 10.1, 16.9 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 6.91 (s,

1H), 7.12-7.14 (dt, J = 1.5, 7.6 Hz,1H), 7.19-7.24 (dt, J = 1.5, 7.6 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.74 (d, J = 6.9 Hz,1H), 7.88 (d, J = 8.7 Hz,1H), 7.95 (br s, 1H), 9.79 (s, 1H).

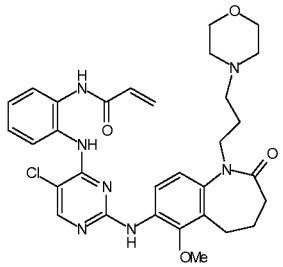
Example 168



I-145

[00519] N-(2-((5-chloro-2-((6-methoxy-1-(2-morpholinoethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-145** was prepared in a manner similar to Example 162, substituting 7-amino-6-methoxy-1-(2-morpholinoethyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one for 3-amino-4-methylbenzamide**:** MS m/z: 590.8 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 2.06(br s, 3H), 2.29(br s, 3H), 2.31(m, 3H), 2.87(br s, 2H), 3.34(m, 4H), 3,64(s, 3H), 4.27(br s, 1H), 5.76-5.79(dd, 1H J=1.8Hz and 10.2Hz), 6.26-6.31(dd, 1H J=1.8, 17Hz), 6.45-6.52(dd, 1H J=10.2, 17Hz), 6.94(d, 1H J= 8.9Hz), 7.20-7.30(m, 3H), 7.45(d, 1H J=7.6Hz), 7.72-7.79(m, 2H), 7.95(s, 1H), 8.11(s, 1H), 8.60(s, 1H), 10.18(s, 1H).

Example 169

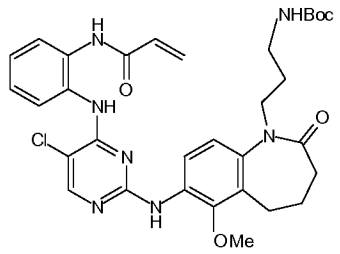


I-146

[00520] N-(2-((5-chloro-2-((6-methoxy-1-(3-morpholinopropyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-146** was prepared in a manner similar to Example 162, substituting 7-amino-6-methoxy-1-(3-morpholinopropyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one for 3-amino-4-methylbenzamide**:** MS m/z: 606.3 (ES+, M+H); 1H NMR (400MHz, DMSO-d_6) δ 1.54(br s, 2H), 2.09(br s, 1H),

2.15(br s, 2H), 2.17-2.21(t, 3H J=7Hz), 2.31(br s, 4H), 2.90(br s, 1H), 3.50(t, 4H J=4.6Hz), 3.64(s, 1H), 5.76-5.79(dd, 1H J=1.8, 10.2Hz), 6.27-6.31(dd, 1H J=1.9, 17Hz), 6.45-6.52(dd, 1H J=10.2, 17Hz), 6.91(d, 1H J=8.8Hz), 7.20-7.32(m, 3H), 7.42-7.44(dd, 1H J=1.6, 7.6Hz), 7.73(m, 2H), 8.0(s, 1H), 8.11(s, 1H), 8.58(s, 1H), 10.12(s, 1H).

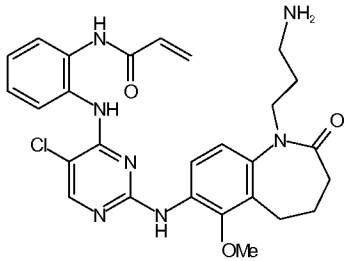
Example 170



I-147

[00521] tert-butyl (3-(7-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-6-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)propyl)carbamate: Compound **I-147** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(7-amino-6-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)propyl)carbamate for 3-amino-4-methylbenzamide**:** MS m/z: 636.3 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 0.84(t, 2H J=7.1Hz), 1.08(t, 1H), 1.21(br s, 2H), 1.22(m, 2H), 1.34(s, 9H), 1.5(m, 3H), 1.73(m, 2H), 2.09(br s, 3H), 2.76(s, 1H), 2.84-2.86(m, 2H), 3.65(s, 3H), 3.95(br s, 1H), 5.77-5.79(d, 1H J=10.2Hz), 6.27-6.31(d, 1H J=16.6Hz), 6.45-6.49(dd, 1H J=10.2, 16.7Hz), 6.74(m, 1H), 6.87(d, 1H J= 8.9Hz), 7.23-7.27(m, 2H), 7.43(d, 1H J=7.4Hz), 7.71-7.77(m, 3H), 7.98(s, 1H), 8.11(s, 1H), 8.58(s, 1H), 10.13(s, 1H).

Example 171

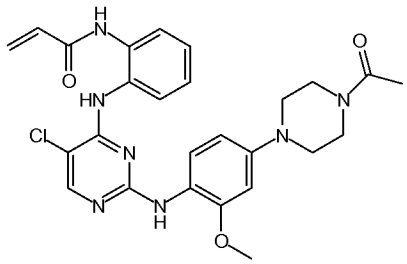


I-148

[00522] N-(2-((2-((1-(3-aminopropyl)-6-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-148** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(7-amino-6-

methoxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-1-yl)propyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA. MS m/z: 536.3 (ES+, M+H).

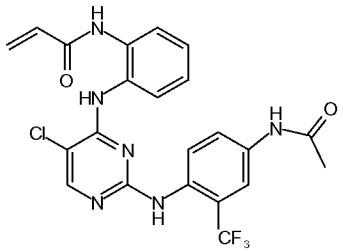
Example 172



I-149

[00523] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-149** was prepared in a manner similar to Example 162, substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide**:** MS m/z: 522.2 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.2(s, 1H), 2.03(s, 3H), 3.02-3.03(m, 2H), 3.07-3.09(m, 2H), 3.54-3.58(q, 4H J=4.6Hz), 3.76(s, 3H), 5.77-5.80(dd, 1H J=1.9, 10.2Hz), 6.27-6.33(m, 2H), 6.45-6.51(dd, 1H J=10.2, 17Hz), 6.60(d, 1H J=2.5Hz), 7.19-7.27(m, 2H), 7.37-7.39(dd, 1H J= 1.8, 7.7Hz), 7.55(d, 1H J= 8.7Hz), 7.65(s, 1H), 7.72-7.24(dd, 1H J= 1.6, 7.8Hz), 8.03(s, 1H), 8.44(s, 1H), 10.16(s, 1H).

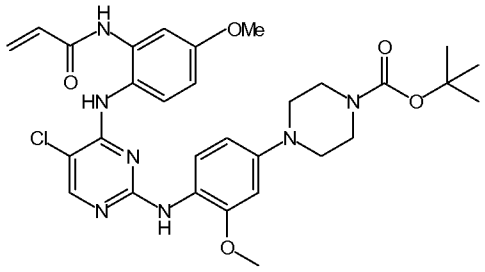
Example 173



I-150

[00524] N-(2-((2-((4-acetamido-2-(trifluoromethyl)phenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-150** was prepared in a manner similar to Example 162, substituting N-(4-amino-3-(trifluoromethyl)phenyl)acetamide for 3-amino-4-methylbenzamide. MS m/z: 491.2 (ES+, M+H).

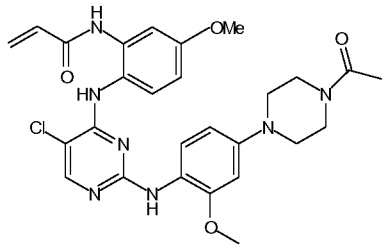
Example 174



I-151

[00525] tert-butyl 4-(4-((4-((2-acrylamido-4-methoxyphenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)piperazine-1-carboxylate: Compound **I-151** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate for 3-amino-4-methylbenzamide. MS: m/z 610.2 (ES+, M+H).

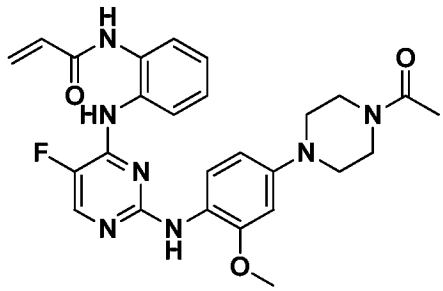
Example 175



I-152

[00526] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-152** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide. MS: m/z 552.2 (ES+, M+H).

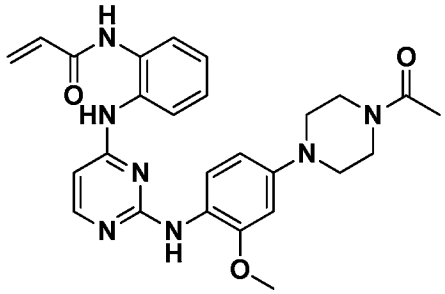
Example 176



I-153

[00527] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-fluoropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-153** was prepared in a manner similar to Example 162, using 2,4-dichloro-5-fluoropyrimidine as the starting material and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide. MS: m/z 506.2 (ES+, M+H).

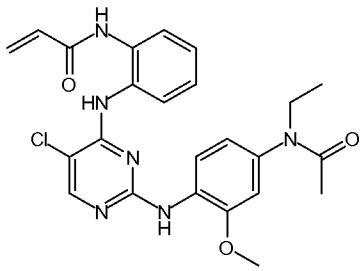
Example 177



I-154

[00528] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-154** was prepared in a manner similar to Example 162, using 2,4-dichloro-pyrimidine as the starting material, and substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide. MS: m/z 488.3 (ES+, M+H).

Example 178

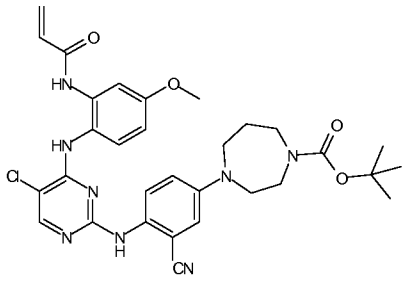


I-155

[00529] N-(2-((5-chloro-2-((4-(N-ethylacetamido)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-155** was prepared in a manner similar to Example 162, substituting N-(4-amino-3-methoxyphenyl)-N-ethylacetamide for 3-amino-4-methylbenzamide. MS m/z: 481.3 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 0.98(t, 3H J=7.1Hz), 1.71(s, 3H), 3.58(q, 2H J= 7.1Hz), 3.81(s, 3H), 5.76-5.79(dd, 1H J=1.9, 10.2Hz), 6.26-6.31(dd, 1H J=1.9, 17Hz), 6.45-6.51(dd, 1H J=10.2, 17Hz), 6.59-6.62(dd, 1H J=1.7, 8.4Hz),

6.89(d, 1H J=1.9Hz), 7.21-7.30(m, 2H), 7.43-7.45(dd, 1H J=1.6, 7.8Hz), 7.67-7.69(dd, 1H J=1.4, 7.8Hz), 7.80(s, 1H), 7.86(d, 1H), 8.11(s, 1H), 8.58(s, 1H), 10.13(s, 1H).

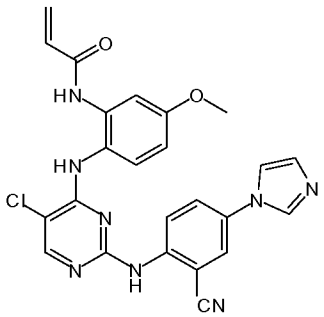
Example 179



I-156

[00530] tert-butyl 4-(4-((4-((2-acrylamido-4-methoxyphenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-cyanophenyl)-1,4-diazepane-1-carboxylate: Compound **I-155** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting tert-butyl 4-(4-amino-3-cyanophenyl)-1,4-diazepane-1-carboxylate for 3-amino-4-methylbenzamide. MS m/z: 619.2 (ES+, M+H).

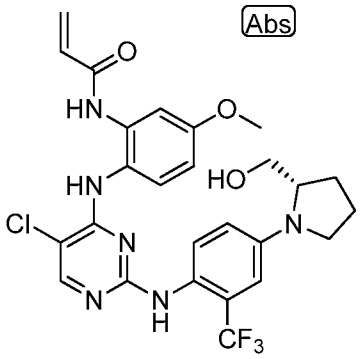
Example 180



I-157

[00531] N-(2-((5-chloro-2-((2-cyano-4-(1H-imidazol-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-157** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-amino-5-(1H-imidazol-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 487.1 (ES+, M+H).

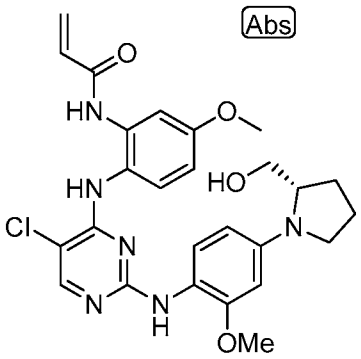
Example 181



I-158

[00532] (S)-N-(2-((5-chloro-2-((4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(trifluoromethyl) phenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-158** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting (S)-(1-(4-amino-3-(trifluoromethyl)phenyl)pyrrolidin-2-yl)methanol for 3-amino-4-methylbenzamide. MS m/z: 563.2 (ES+, M+H).

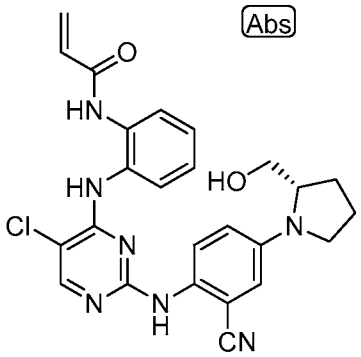
Example 182



I-159

[00533] (S)-N-(2-((5-chloro-2-((4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-methoxyphenyl) amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-159** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting (S)-(1-(4-amino-3-methoxyphenyl)pyrrolidin-2-yl)methanol for 3-amino-4-methylbenzamide. MS m/z: 525.2 (ES+, M+H).

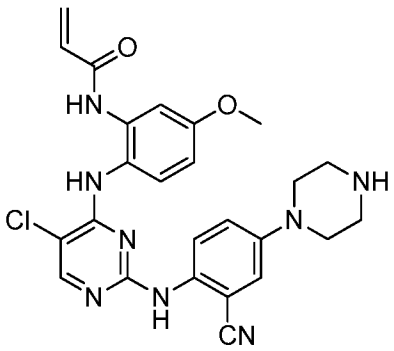
Example 183



I-160

[00534] (S)-N-(2-((5-chloro-2-((2-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)phenyl) amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-160** was prepared in a manner similar to Example 162, substituting (S)-2-amino-5-(2-(hydroxymethyl)pyrrolidin-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 491.1 (ES+, M+H).

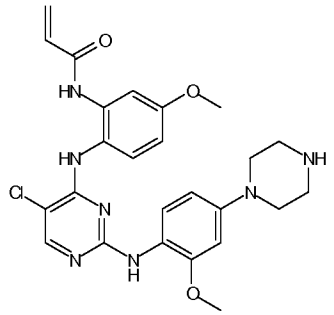
Example 184



I-161

[00535] N-(2-((5-chloro-2-((2-cyano-4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-161** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting tert-butyl 4-(4-amino-3-cyanophenyl)piperazine-1-carboxylate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA. MS m/z: 506.1 (ES+, M+H).

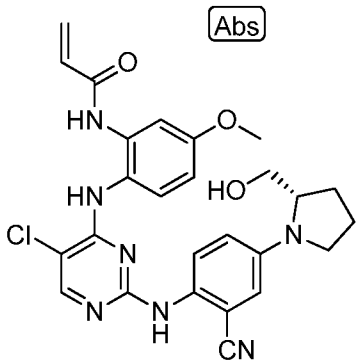
Example 185



I-162

[00536] N-(2-((5-chloro-2-((2-methoxy-4-(piperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-162** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA. MS m/z: 510.2 (ES+, M+H).

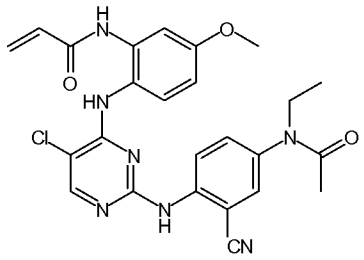
Example 186



I-163

[00537] (S)-N-(2-((5-chloro-2-((2-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)phenyl) amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-163** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting (S)-2-amino-5-(2-(hydroxymethyl)pyrrolidin-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 520.2 (ES+, M+H).

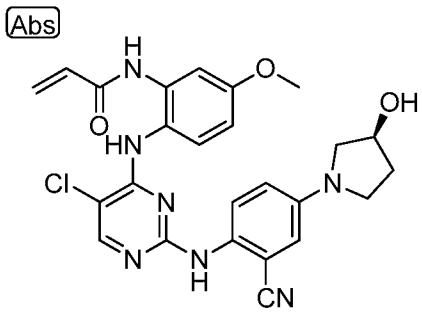
Example 187



I-164

[00538] N-(2-((5-chloro-2-((2-cyano-4-(N-ethylacetamido)phenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-164** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting N-(4-amino-3-cyanophenyl)-N-ethylacetamide for 3-amino-4-methylbenzamide. MS m/z: 506.1 (ES+, M+H).

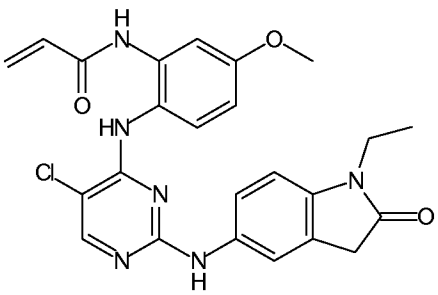
Example 188



I-165

[00539] (S)-N-(2-((5-chloro-2-((2-cyano-4-(3-hydroxypyrrolidin-1-yl)phenyl)amino) pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-165** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting (S)-2-amino-5-(3-hydroxypyrrolidin-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 506.1 (ES+, M+H).

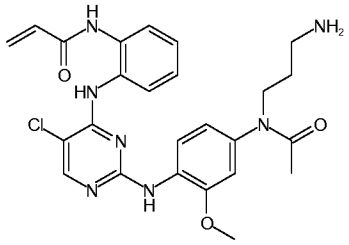
Example 189



I-166

[00540] N-(2-((5-chloro-2-((1-ethyl-2-oxoindolin-5-yl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-166** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-amino-1-ethylindolin-2-one for 3-amino-4-methylbenzamide. MS m/z: 479.1 (ES+, M+H).

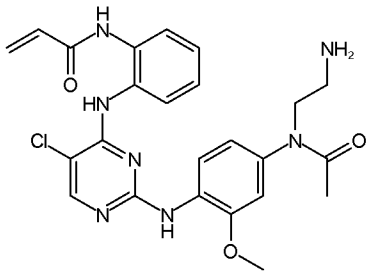
Example 190



I-167

[00541] N-(2-((2-((4-(N-(3-aminopropyl)acetamido)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-167** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(N-(4-amino-3-methoxyphenyl)acetamido)propyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA. MS m/z: 510.2 (ES+, M+H).

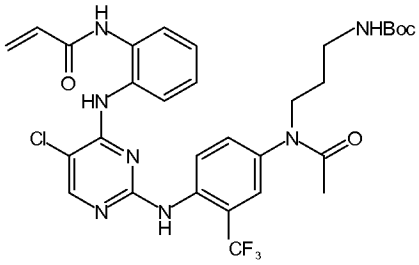
Example 191



I-168

[00542] N-(2-((2-((4-(N-(2-aminoethyl)acetamido)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-168** was prepared in a manner similar to Example 162, substituting tert-butyl (2-(N-(4-amino-3-methoxyphenyl)acetamido)ethyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc deprotection with TFA. MS m/z: 496.2 (ES+, M+H).

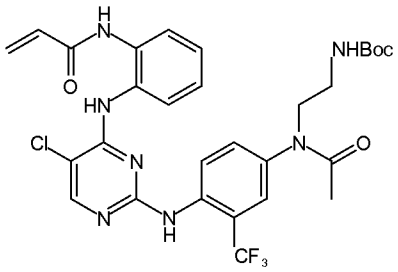
Example 192



I-169

[00543] tert-butyl (3-(N-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-(trifluoromethyl)phenyl)acetamido)propyl)carbamate: Compound **I-169** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(N-(4-amino-3-(trifluoromethyl)phenyl)acetamido)propyl)carbamate for 3-amino-4-methylbenzamide. MS m/z: 648.4 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.35(s, 9H), 1.47(m, 2H), 1.69(m, 3H), 2.88-2.93(q, 2H, J=6.3Hz), 3.59(t, 2H, J=7.1Hz), 5.77-5.78(dd, 1H, J=1.8, 10.2Hz), 6.27-6.31(dd, 1H, J=1.8, 17Hz), 6.44-6.51(dd, 1H, J=10.2, 17Hz), 6.75(br s, 1H), 7.107-7.18(m, 2H), 7.33(d, 1H, J=6.3Hz), 7.49(d, 1H, J=6.7Hz), 7.57(s, 1H), 7.63(d, 1H, J=7.1Hz), 7.74(d, 1H, J= 7.8Hz), 8.08(s, 1H), 8.43(s, 1H), 8.53(s, 1H), 10.13(s, 1H).

Example 193

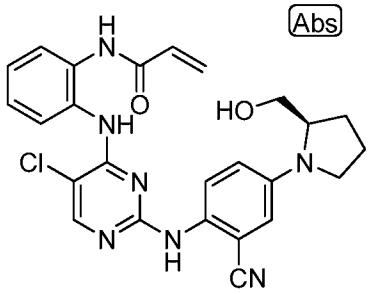


I-170

[00544] tert-butyl (2-(N-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-(trifluoromethyl)phenyl)acetamido)ethyl)carbamate: Compound **I-170** was prepared in a manner similar to Example 162, substituting tert-butyl (2-(N-(4-amino-3-(trifluoromethyl)phenyl)acetamido)ethyl)carbamate for 3-amino-4-methylbenzamide. MS m/z: 634.2 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.32(s, 9H), 1.67(br s, 3H), 302(m, 2H), 3.61(s, 2H), 5.79(dd, 1H, J=1.7, 10.1Hz), 6.27-6.31(dd, 1H, J=1.7, 16.9Hz), 6.44-6.51(dd, 1H,

J=10.1, 16.9Hz), 6.88(br s, 1H), 7.10-7.19(m, 2H), 7.33(d, 1H, J=7.2Hz), 7.54(d, 1H, J=7.8Hz), 7.65(d, 1H, J=7.9Hz), 7.74(d, 1H, J=7.6Hz), 8.08(s, 1H), 8.40(s, 1H), 8.53(s, 1H), 10.13(s, 1H).

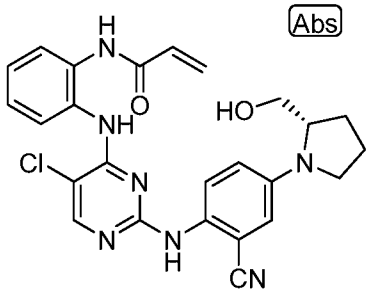
Example 194



I-171

[00545] (R)-N-(2-((5-chloro-2-((2-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)phenyl) amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-171** was prepared in a manner similar to Example 162, substituting (R)-2-amino-5-(2-(hydroxymethyl)pyrrolidin-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 490.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 1.88-2.03(m, 4H), 3.10-3.16(m, 1H), 3.25-3.30(m, 1H), 3.43-3.48(m, 2H), 3.85-3.86(m, 1H), 5.78-5.81(dd, 1H, J=1.6, 10.2Hz), 6.29- 6.34(dd, 1H, J=1.8, 17Hz), 6.49-6.56(dd, 1H, J= 10.2, 17Hz), 7.22(d, 1H, J=9.1Hz), 7.34-7.43(m, 4H), 7.61-7.64(dd, 1H, J= 1.5Hz and 7.7Hz), 7.72-7.74(dd, 1H, J=1.3, 7.9Hz), 9.33(s, 1H) for TFA salt.

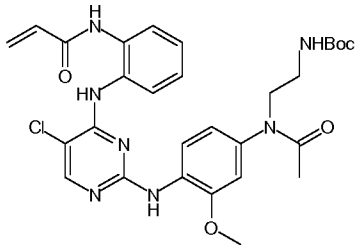
Example 195



I-172

[00546] (S)-N-(2-((5-chloro-2-((2-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)phenyl) amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-172** was prepared in a manner similar to Example 162, substituting (S)-2-amino-5-(2-(hydroxymethyl)pyrrolidin-1-yl)benzonitrile for 3-amino-4-methylbenzamide. MS m/z: 490.2 (ES+, M+H).

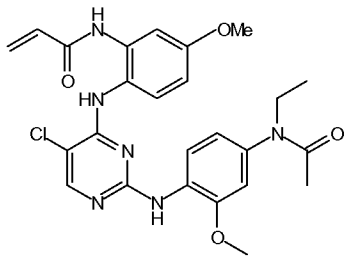
Example 196



I-174

[00547] tert-butyl (2-(N-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)acetamido)ethyl)carbamate: Compound **I-174** was prepared in a manner similar to Example 162, substituting tert-butyl (2-(N-(4-amino-3-methoxyphenyl)acetamido)ethyl)carbamate for 3-amino-4-methylbenzamide. MS m/z: 596.3 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.32(s, 9H), 1.71(s, 3H), 3.02(m, 2H), 3.58(t, 2H J=6.4Hz), 3.82(s, 3H), 5.76-5.79(dd, 1H, J=1.9, 10.2Hz), 6.27-6.32(dd, 1H, J= 1.9, 17Hz), 6.45-6.52(dd, 1H, J=10.2, 17Hz), 6.67(d, 1H J=8.5Hz), 6.80(m, 1H), 6.99(s, 1H), 7.22-7.32(m, 2H), 7.43(d, 1H, J=7.9Hz), 7.69(d, 1H, J=6.7Hz), 7.76(s, 1H), 7.87(d, 1H, J=8.3Hz), 8.11(s, 1H), 8.58(s, 1H), 10.16(s, 1H).

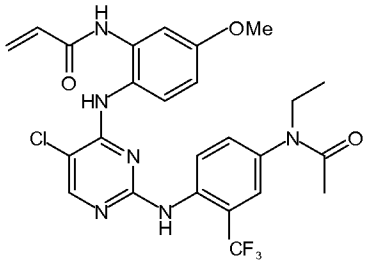
Example 197



I-175

[00548] N-(2-((5-chloro-2-((4-(N-ethylacetamido)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-175** was prepared in a manner similar to Example 162, substituting N-(4-amino-3-methoxyphenyl)-N-ethylacetamide for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 511.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 0.84(t, 2H), 0.98(t, 3H, J = 7.19Hz), 1.22-1.26(m, 3H), 1.70(s, 3H), 3.57(q, 2H, J=7.2Hz), 3.75(s, 3H), 3.81(s, 3H), 5.74-5.77(dd, 1H, J=1.8, 10.2Hz), 6.24-6.29(dd, 1H, J= 1.8, 17.0Hz), 6.44-6.51(dd, 1H, J=10.2, 17.0Hz), 6.57(d, 1H, J=8.7Hz), 6.85-6.87(m, 2H), 7.17(d, 1H, J=2.8Hz), 7.46(d, 1H, J=8.8Hz), 7.69(s, 1H), 7.85(d, 1H, J=8.3Hz), 8.05(s, 1H), 8.43(s, 1H), 9.95(s, 1H).

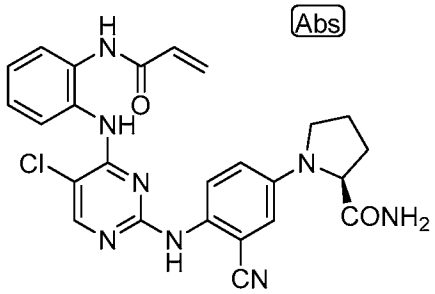
Example 198



I-176

[00549] N-(2-((5-chloro-2-((4-(N-ethylacetamido)-2-(trifluoromethyl)phenyl)amino) pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-176** was prepared in a manner similar to Example 162, substituting N-(4-amino-3-(trifluoromethyl)phenyl)-N-ethylacetamide for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 549.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 0.97(br s, 3H), 1.68(br s, 3H), 3.63(m, 2H), 3.71(s, 3H), 5.75-5.78(dd, 1H J=1.8, 10.2Hz), 6.24-6.29(dd, 1H J= 1.8, 17Hz), 6.44-6.50(dd, 1H J= 10.2, 17Hz), 6.74-6.77(dd, 1H J= 2.9, 9Hz), 7.04(d, 1 H, J = 2.7Hz), 7.42-7.46(m, 2H), 7.53(br s, 1H), 7.73(d, 1H, J=8Hz), 8.04(s, 1H), 8.29(s, 1H), 8.38(s, 1H), 9.95(s, 1H).

Example 199

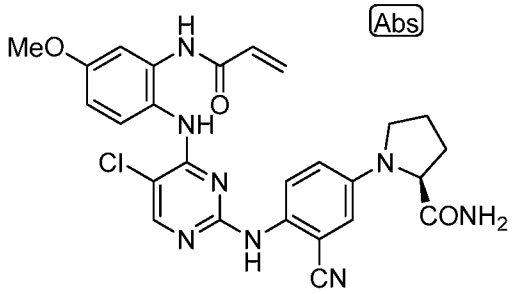


I-177

[00550] (S)-1-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-cyanophenyl)pyrrolidine-2-carboxamide: Compound **I-177** was prepared in a manner similar to Example 162, substituting (S)-1-(4-amino-3-cyanophenyl)pyrrolidine-2-carboxamide for 3-amino-4-methylbenzamide. MS m/z: 503.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 1.93-2.0(m, 3H), 2.19-2.24(m, 1H), 3.19-3.24(m, 1H), 3.51-3.55(m, 1H), 3.92-3.95(m, 1H), 5.77-5.80(dd, 1H, J=1.9, 10.1Hz), 6.28-6.32(dd, 1H, J=1.9, 17Hz), 6.45-6.52(dd, 1H, J= 10.2, 17.1Hz), 6.66-6.68(m, 2H), 7.09(br s, 1H), 7.14-7.17(m, 2H), 7.23(d, 1H, J= 9.4Hz), 7.31-

7.33(m, 1H), 7.43(br s, 1H), 7.72-7.75(m, 1H), 8.01(s, 1H), 8.40(s, 1H), 8.88(s, 1H), 10.16(s, 1H).

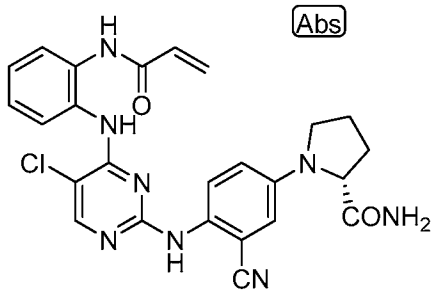
Example 200



I-178

[00551] (S)-1-(4-((4-((2-acrylamido-4-methoxyphenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-cyanophenyl)pyrrolidine-2-carboxamide: Compound **I-178** was prepared in a manner similar to Example 162, substituting (S)-1-(4-amino-3-cyanophenyl)pyrrolidine-2-carboxamide for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 533.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 1.96(q, 3H, J=5.75Hz), 2.18-2.20(m, 1H), 3.20(m, 1H), 3.52(m, 1H), 3.74(s, 3H), 3.93(d, 1H J=7.7Hz), 3.76-3.79(dd, 1H, J=1.7, 10.1Hz), 6.26-6.31(dd, 1H, J=1.8, 16.9Hz), 6.45-6.51(dd, 1H, J= 10.1, 16.9Hz), 6.65(m, 2H), 6.76-6.78(dd, 1H J=2.7, 8.9Hz), 7.03(br s, 1H), 7.19-7.23(m, 1H), 7.42(br s, 1H), 7.51(d, 1H J= 9.0Hz), 7.96(s, 1H), 8.26(s, 1H), 8.78(s, 1H), 10.01(s, 1H).

Example 201

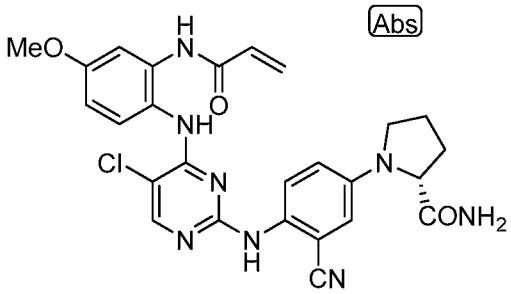


I-179

[00552] (R)-1-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-cyanophenyl)pyrrolidine-2-carboxamide: Compound **I-179** was prepared in a manner similar to Example 162, substituting (R)-1-(4-amino-3-cyanophenyl)pyrrolidine-2-carboxamide for 3-amino-4-methylbenzamide. MS m/z: 503.2 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.94-

2.0 (m, 3H), 2.19-2.24(m, 1H), 3.51-3.55(m, 1H), 3.92-3.95(m, 1H), 5.77-5.80(dd, 1H, J=1.9, 10.2Hz), 6.28-6.32(dd, 1H J=1.9, 17Hz), 6.45-6.52(dd, 1H, J=10.2, 17.1Hz), 6.66-6.68(m, 2H), 7.09(br s ,1H), 7.14-7.17(m, 2H), 7.23(d, 1H, J=9.4Hz), 7.31-7.33(m, 1H), 7.42(br s, 1H), 7.72-7.75(m, 1H), 8.01(s, 1H), 8.4(s, 1H), 8.88(s, 1H), 9.14(s, 1H), 10.16(s, 1H).

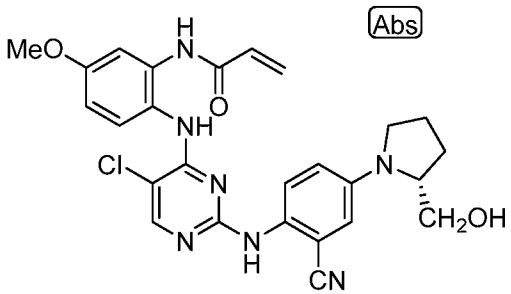
Example 202



I-180

[00553] (R)-1-(4-((4-((2-acrylamido-4-methoxyphenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-cyanophenyl)pyrrolidine-2-carboxamide: Compound **I-180** was prepared in a manner similar to Example 162, substituting (R)-1-(4-amino-3-cyanophenyl)pyrrolidine-2-carboxamide for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide**.** MS m/z: 520.2 (ES+, M+H); ^{1}H NMR(400MHz, DMSO-d_6) δ 1.89-2.02(m, 3H), 2.22(m, 1H), 3.29(q, 1H, J=7.5Hz), 3.60-3.64(m, 1H), 3.80(s, 3H), 4.12(d, 1H, J=8.4Hz), 5.78-.581(dd, 1H, J= 1.8, 10.1Hz), 6.28-6.33(dd, 1H, J=1.9, 17Hz), 6.49-6.56(dd, 1H J= 10.2, 17Hz), 6.90-6.94(m, 2H), 7.33-7.36(m, 2H), 7.41-7.46(m, 2H), 9.30(s, 1H), 9.9(s, 1H) for TFA salt.

Example 203

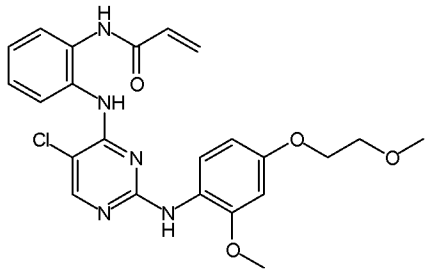


I-181

[00554] (R)-N-(2-((5-chloro-2-((2-cyano-4-(2-(hydroxymethyl)pyrrolidin-1-yl)phenyl) amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-181** was prepared in a manner similar to Example 162, substituting (R)-2-amino-5-(2-(hydroxymethyl)pyrrolidin-

1-yl)benzonitrile for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 520.2 (ES+, M+H); ^{1}HNMR(400MHz, DMSO-d_6) δ 1.83-1.98(m, 5H), 2.97-3.03(m, 1H), 3.15-3.21(m, 1H), 3.34-3.38(m, 1H), 3.41-3.46(m, 1H), 3.62-3.67(m, 1H), 3.73(s, 3H), 4.76(t, 1H, J= 6.1Hz), 5.76-5.79(dd, 1H, J=1.9, 10.2Hz), 6.26-6.30(dd, 1H, J=1.9, 17Hz), 6.44-6.51(dd, 1H, J=10.1, 17Hz), 6.73-6.83(m, 3H), 7.0(d, 1H, J=2.7Hz), 7.18(d, 1H, J=8.8Hz), 7.52(d, 1H, J=8.9Hz), 7.96(s, 1H), 8.25(s, 1H), 8.77(s, 1H), 10.01(s, 1H).

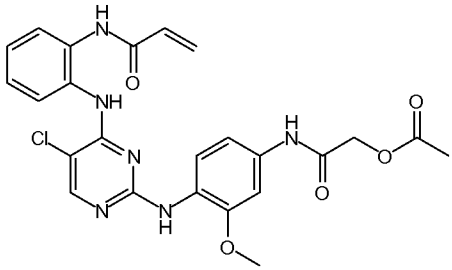
Example 204



I-182

[00555] N-(2-((5-chloro-2-((2-methoxy-4-(2-methoxyethoxy)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-182** was prepared in a manner similar to Example 162, substituting 2-methoxy-4-(2-methoxyethoxy)aniline for 3-amino-4-methylbenzamide. MS m/z: 470.2 (ES+, M+H).

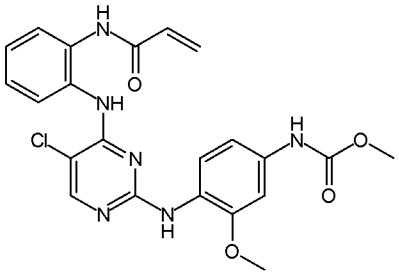
Example 205



I-183

[00556] 2-((4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)amino)-2-oxoethyl acetate: Compound **I-183** was prepared in a manner similar to Example 162, substituting tert-butyl (4-amino-3-methoxyphenyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and reaction with $ClCOCH_2OAc$. MS m/z: 511.1 (ES+, M+H).

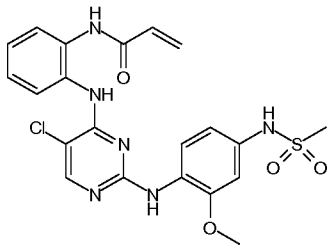
Example 206



I-184

[00557] methyl (4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)carbamate: Compound **I-184** was prepared in a manner similar to Example 162, substituting tert-butyl (4-amino-3-methoxyphenyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and reaction with methyl chloroformate. MS m/z: 469.0 (ES+, M+H).

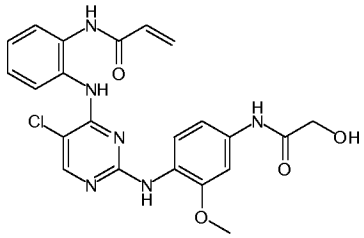
Example 207



I-185

[00558] N-(2-((5-chloro-2-((2-methoxy-4-(methylsulfonamido)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound I-185 was prepared in a manner similar to Example 162, substituting tert-butyl (4-amino-3-methoxyphenyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and reaction with MsCl. MS m/z: 489.1 (ES+, M+H).

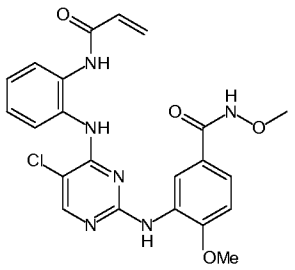
Example 208



I-186

[00559] N-(2-((5-chloro-2-((4-(2-hydroxyacetamido)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-186** was prepared in a manner similar to Example 162, substituting tert-butyl (4-amino-3-methoxyphenyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and reaction with $ClCOCH_2OAc$ and hydrolysis with aqueous LiOH. MS m/z: 469.0 (ES+, M+H).

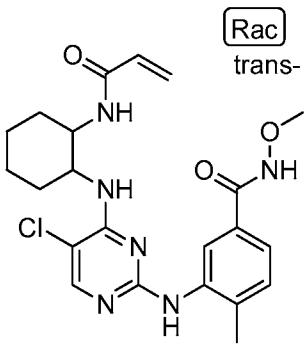
Example 209



I-187

[00560] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N,4-dimethoxybenzamide: Compound **I-187** was prepared in a manner similar to Example 162, substituting 3-amino-N,4-dimethoxybenzamide for 3-amino-4-methylbenzamide. MS m/z: 469.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.68 (s, 3H), 3.81 (s, 3H), 5.77-5.80 (dd, J = 1.8, 10.1 Hz, 1H), 6.27-6.32 (dd, J = 1.8, 17 Hz, 1H), 6.44-6.50 (dd, J = 10.1, 16.9 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 7.11-7.18 (m, 2H), 7.29 (d, J = 2.2 Hz, 1H), 7.40-7.42 (dd, J = 2.1, 8.5 Hz, 1H), 7.73-7.75 (dd, J = 2.2, 7.7 Hz, 1H), 7.96 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 8.52 (s, 1H), 10.18 (s, 1H), 11.47 (s, 1H).

Example 210

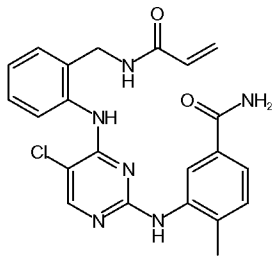


I-188

[00561] Rac-trans-3-((4-((2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-N-methoxy-4-methylbenzamide. Compound **I-188** was prepared in a manner similar

to Example 162, substituting 3-amino-N-methoxy-4-methylbenzamide for 3-amino-4-methylbenzamide and substituting trans-N-(2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 459.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.04-1.28 (m, 4H), 1.54-1.63 (m, 2H), 1.81 (m, 1H), 2.04 (m, 1H), 2.25 (s, 3H), 3.58-3.68 (m, 1H), 3.67 (s, 3H), 3.80-3.85 (m, 1H), 5.51-5.54 (dd, J = 2.6, 9.6 Hz, 1H), 6.01-6.14 (m, 2H), 6.64 (d, J = 6.8 Hz, 1H), 7.23 (d, J = 7.9 Hz, 2H), 7.35-7.38 (dd, J = 1.6, 7.8 Hz, 1H), 7.84 (s, 1H), 7.99 (d, J = 1.4 Hz, 1H), 8.0 (d, J = 8.1 Hz, 1H), 8.42 (s, 1H), 11.60 (s, 1H).

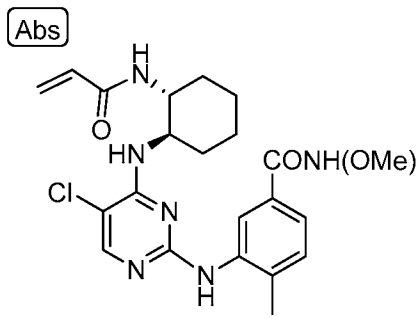
Example 211



I-189

[00562] 3-((4-((2-(acrylamidomethyl)phenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-189** was prepared in a manner similar to Example 162, substituting N-(2-aminobenzyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z: 437.1 (ES+, M+H).

Example 212

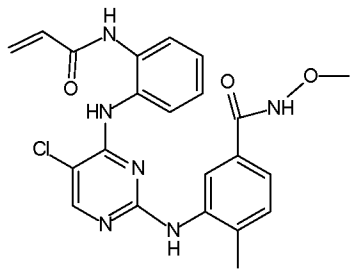


I-190

[00563] 3-((4-(((1R,2R)-2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-N-methoxy-4-methylbenzamide: Compound **I-190** was prepared in a manner similar to Example 162, substituting 3-amino-N-methoxy-4-methylbenzamide for 3-amino-4-methylbenzamide and substituting N-((1R,2R)-2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 459.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.04-1.1(m, 1H),

1.20-1.28(m, 6H), 1.54-1.63(m, 2H), 1.82(d, 1H J=9.2Hz), 2.24(s, 3H), 3.58-3.63(m, 1H), 3.67(s, 3H), 3.77-3.85(m, 1H), 5.51-5.54(dd, 1H J=2.6, 9.6Hz), 6.0-6.05(dd, 1H J=2.6, 17.1Hz), 6.08-6.14(dd, 1H J=10.7, 17.1Hz), 6.64(d, 1H J=7.8Hz), 7.23(d, 1H J=7.9Hz), 7.35-7.38(dd, 1.7, 7.8Hz), 7.84(s, 1H), 7.99(d, 1H J= 7.9Hz), 8.03(s, 1H), 8.42(s, 1H), 11.6(s, 1H).

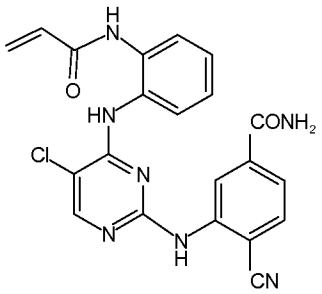
Example 213



I-191

[00564] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N-methoxy-4-methylbenzamide: Compound **I-191** was prepared in a manner similar to Example 162, substituting 3-amino-N-methoxy-4-methylbenzamide for 3-amino-4-methylbenzamide. MS m/z: 453.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.17 (s, 3H), 3.69 (s, 3H), 5.78-5.81 (dd, J = 1.8, 10.0 Hz, 1H), 6.27-6.32 (dd, J = 1.9, 17.0 Hz, 1H), 6.43-6.50 (dd, J = 10.1, 17.0 Hz, 1H), 7.01-7.10 (m, 2H), 7.20-7.25 (dt, J = 1.4, 7.8 Hz, 1H), 7.39-7.41 (dd, J = 1.6, 7.8 Hz, 1H), 7.70-7.72 (dd, J = 1.4, 7.8 Hz, 1H), 7.81 (d, J =1.5 Hz, 1H), 8.06 (s, 1H), 8.43 (s, 1H), 8.65 (s, 1H), 10.20 (s, 1H), 11.63 (s, 1H).

Example 214

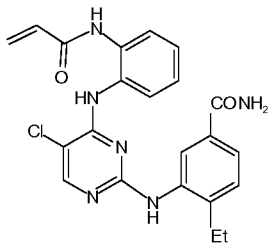


I-192

[00565] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-cyanobenzamide: Compound **I-192** was prepared in a manner similar to Example 162, substituting 3-amino-4-cyanobenzamide for 3-amino-4-methylbenzamide. MS m/z: 434.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 5.78-5.81(dd, 1H, J=1.9, 10.2Hz), 6.28-6.33(dd, 1H, J=1.9, 17Hz),

6.44-6.51(dd, 1H, J= 10.2, 17Hz), 7.10-7.13(m, 2H), 7.27-7.31(m, 1H), 7.63-7.66(m, 2H), 7.69-7.01(m, 1H), 7.79(d, 1H, J=8.1Hz), 8.0(d, 1H, J=1.4Hz), 8.11-8.13(m, 2H), 8.57(s, 1H), 10.2(s, 1H).

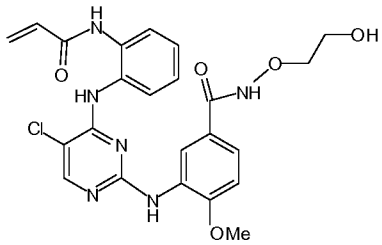
Example 215



I-193

[00566] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-ethylbenzamide: Compound **I-193** was prepared in a manner similar to Example 162, substituting 3-amino-4-ethylbenzamide for 3-amino-4-methylbenzamide. MS m/z: 437.1 (ES+, M+H).

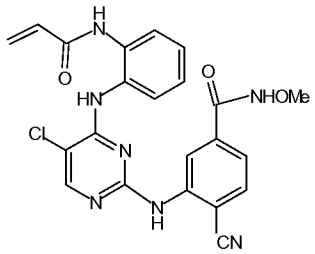
Example 216



I-194

[00567] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)-4-methoxybenzamide: Compound **I-194** was prepared in a manner similar to Example 162, substituting 3-amino-N-(2-hydroxyethoxy)-4-methoxybenzamide for 3-amino-4-methylbenzamide. MS m/z: 499.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.58 (q, J = 5.3 Hz, 2H), 3.89 (t, J = 5.1 Hz, 2H), 4.76 (t, J = 5.7 Hz, 1H), 5.77-5.80 (dd, J = 1.8, 10.0 Hz, 1H), 6.27-6.32 (dd, J = 1.8, 16.9 Hz, 1H), 6.44-6.50 (dd, J = 10.0, 16.9 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 7.13-7.17 (m, 2H), 7.29-7.31 (dd, J = 1.9, 6.7 Hz, 1H), 7.42-7.45 (dd, J = 2.2, 8.8 Hz, 1H), 7.72-7.75 (dd, J = 2.6, 7.7 Hz, 1H), 7.97 (s, 1H), 8.12 (s, 1H), 8.17 (d, J =1.7 Hz, 1H), 8.53 (s, 1H), 10.19 (s, 1H), 11.51 (s, 1H).

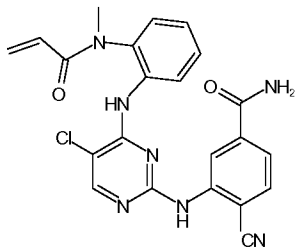
Example 217



I-195

[00568] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-cyano-N-methoxybenzamide: Compound **I-195** was prepared in a manner similar to Example 162, substituting 3-amino-4-cyano-N-methoxybenzamide for 3-amino-4-methylbenzamide**:** MS m/z: 464.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.70 (s, 3H), 5.78-5.81 (dd, 1H, J=1.8, 10Hz), 6.28-6.33 (dd, 1H, J=1.8, 16.97Hz), 6.45-6.51 (dd, 1H, J=10, J=17Hz), 7.08-7.15 (m, 2H), 7.30-7.32 (dd, 1H, J=1.9, J=7.7Hz), 7.50-7.52 (dd, 1H, J=1.3, 8Hz), 7.67-7.69 (dd, 1H, J=1.68, 7Hz), 7.80-7.82 (d, 1H, J=8Hz), 7.88 (s, 1H), 8.14(s, 1H), 8.60 (s, 1H), 9.48 (s, 1H), 10.21 (s, 1H), 11.91 (s, 1H).

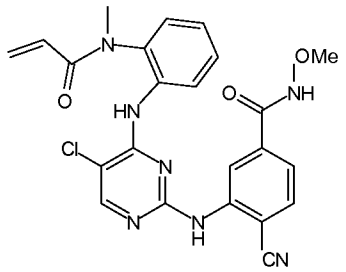
Example 218



I-196

[00569] 3-((5-chloro-4-((2-(N-methylacrylamido)phenyl)amino)pyrimidin-2-yl)amino)-4-cyanobenzamide: Compound **I-196** was prepared in a manner similar to Example 162, substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide**.** MS m/z: 448.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ.3.07 (s, 3H), 5.31-5.36 (dd, J = 2.4, 10.0 Hz, 1H), 5.80-5.87 (dd, J = 10.0, 16.7 Hz, 1H), 5.98-6.02 (dd, J = 2.4, 16.7 Hz, 1H), 7.20 (d, J = 1.4 Hz, 1H), 7.23-7.27 (m, 1H), 7.41-7.16 (m, 1H), 7.58-7.63 (m, 3H), 7.73 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 1.0 Hz, 1H), 8.07 (s, 1H), 8.10 (s, 1H), 8.51 (s, 1H), 9.34 (s, 1H).

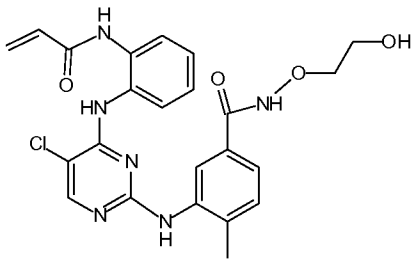
Example 219



I-197

[00570] 3-((5-chloro-4-((2-(N-methylacrylamido)phenyl)amino)pyrimidin-2-yl)amino)-4-cyano-N-methoxybenzamide: Compound **I-197** was prepared in a manner similar to Example 162, substituting 3-amino-4-cyano-N-methoxybenzamide for 3-amino-4-methylbenzamide, and substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 479.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ.3.21 (s, 3H), 3.83 (s, 3H), 5.42-5.45 (dd, J = 1.9, 10.3 Hz, 1H), 5.97-6.04 (dd, J = 10.2, 16.8 Hz, 1H), 6.15-6.20 (dd, J = 1.8, 16.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.41-7.16 (dd, J = 6.6, 13.4 Hz, 2H), 7.68-7.71 (dd, J = 2.5, 7.8 Hz, 2H), 8.09 (s, 1H), 8.13 (s, 1H).

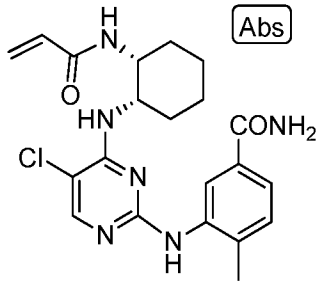
Example 220



I-198

[00571] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N-(2-hydroxyethoxy)-4-methylbenzamide: Compound **I-198** was prepared in a manner similar to Example 162, substituting 3-amino-N-(2-hydroxyethoxy)-4-methylbenzamide for 3-amino-4-methylbenzamide. MS m/z: 483.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.31 (s, 3H), 3.58 (t, J = 5.0 Hz, 2H), 3.90 (t, J = 5.0 Hz, 2H), 4.80 (br s, 1H), 5.78-5.81 (dd, J = 1.8, 10.0 Hz, 1H), 6.27-6.32 (dd, J = 1.8, 16.9 Hz, 1H), 6.43-6.50 (dd, J = 10.0, 17.0 Hz, 1H), 7.00-7.09 (m, 2H), 7.20-7.25 (m, 2H), 7.41-7.43 (dd, J = 1.5, 7.8 Hz, 1H), 7.70-7.72 (dd, J = 1.4, 7.8 Hz, 1H), 7.82 (d, J =1.4 Hz, 1H), 8.05 (s, 1H), 8.43 (s, 1H), 8.66 (s, 1H), 10.22 (s, 1H).

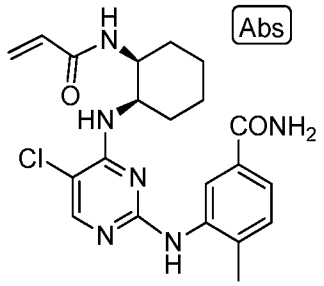
Example 221



I-199

[00572] 3-((4-(((1S,2R)-2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-199** was prepared in a manner similar to Example 162, substituting N-((1R,2S)-2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 429.2 (ES+, M+H).

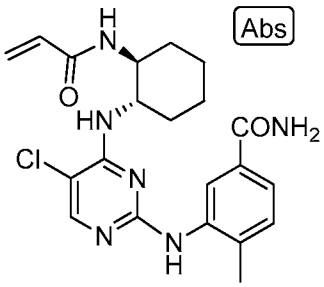
Example 222



I-200

[00573] 3-((4-(((1R,2S)-2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-200** was prepared in a manner similar to Example 162, substituting N-((1S,2R)-2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 429.2 (ES+, M+H).

Example 223

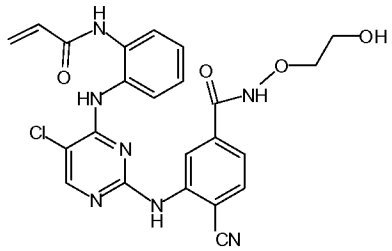


I-201

[00574] 3-((4-(((1S,2S)-2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-201** was prepared in a manner similar to Example 162,

substituting N-((1S,2S)-2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 429.2 (ES+, M+H).

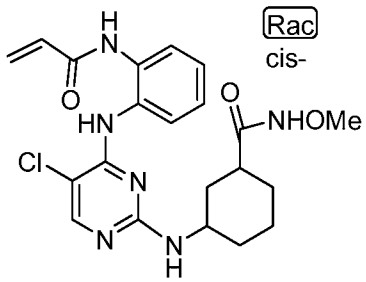
Example 224



I-202

[00575] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-cyano-N-(2-hydroxyethoxy)benzamide: Compound **I-202** was prepared in a manner similar to Example 162, substituting 3-amino-4-cyano-N-(2-hydroxyethoxy)benzamide for 3-amino-4-methylbenzamide. MS m/z: 492.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.6 (m, 2H), 3.91-3.92 (m, 2H), 4.72 (br s, 1H), 5.78-5.81 (dd, J = 1.7, 10.2 Hz, 1H), 6.28-6.33 (dd, J = 1.8, 16.9 Hz, 1H), 6.45-6.51 (dd, J = 10.2, 17.0 Hz, 1H), 7.08-7.15 (m, 2H), 7.30-7.32 (dd, J = 1.9, 7.3 Hz, 1H), 7.52-7.54 (dd, J = 1.4, 8.1 Hz, 1H), 7.67-7.70 (dd, J = 1.8, 7.3 Hz, 1H), 7.80 (d, J = 8.0Hz, 1H), 8.14 (s, 1H), 8.59 (s, 1H), 9.47 (s, 1H), 10.20 (s, 1H), 10.94 (s, 1H).

Example 225

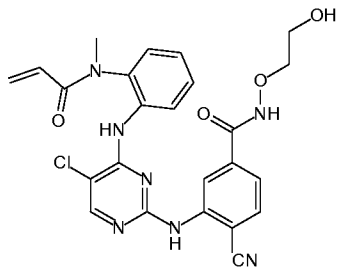


I-203

[00576] Rac-cis-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-N-methoxy-cyclohexanecarboxamide. Compound **I-203** was prepared in a manner similar to Example 120, substituting racemic cis-3-amino-N-methoxycyclohexanecarboxamide for 3 cis-3-aminocyclohexanecarboxamide. MS m/z: 445.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 0.8-1.11 (m, 2H), 1.19-1.27 (m, 2H), 1.27-1.31 (m, 1H), 1.57 (m, 1H), 1.71-1.89 (m, 3H), 1.95 (br s, 1H), 3.52 (s, 3H), 5.79 (d, J = 10.6 Hz, 1H), 6.30 (d, J = 16.3 Hz, 1H), 6.45-6.51 (dd, J = 10.1, 16.5

Hz, 1H), 7.17 (t, J = 6.4 Hz, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 7.7 Hz, 1H), 7.79 (br s, 1H), 7.91 (s, 1H), 8.25 (br s, 1H), 10.16 (s, 1H), 10.91 (s, 1H).

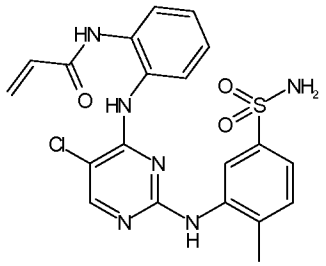
Example 226



I-204

[00577] 3-((5-chloro-4-((2-(N-methylacrylamido)phenyl)amino)pyrimidin-2-yl)amino)-4-cyano-N-(2-hydroxyethoxy)benzamide: Compound **I-204** was prepared in a manner similar to Example 162, substituting 3-amino-4-cyano-N-(2-hydroxyethoxy)benzamide for 3-amino-4-methylbenzamide, and substituting N-(2-aminophenyl)-N-methylacrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 506.2 (ES+, M+H), ^{1}HNMR (DMSO-d_6) δ 3.03 (s, 3H), 3.58-3.60 (m, 2H), 3.89-3.91 (t, J=4.25Hz, 2H), 4.71-4.74 (t, J=5.58Hz, 1H), 5.32-5.35 (dd, J=2.7Hz, 10.2Hz, 1H), 5.81-5.87 (dd, J=10.2Hz, 1H), 5.98-6.02 (dd, J=2.3Hz, 10.3Hz, 1H), 7.19-7.23 (m, 2H), 7.30-7.34 (m,1H), 7.48-7.50 (m, 1H), 7.59-7.61 (d, J=7.6Hz, 1H), 7.73-7.75 (d, J=8Hz, 1H), 7.83 (s, 1H), 8.10 (s, 1H), 8.57 (s, 1H), 9.37 (s, 1H), 11.89 (s, 1H).

Example 227

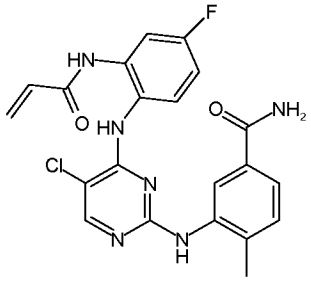


I-205

[00578] N-(2-((5-chloro-2-((2-methyl-5-sulfamoylphenyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-202** was prepared in a manner similar to Example 162, substituting 3-amino-4-methylbenzenesulfonamide for 3-amino-4-methylbenzamide. MS m/z: 459.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.18 (s, 3H), 5.78-7.81 (dd, 1H, J=1.8, 10Hz), 6.27-6.31 (dd, 1H, J=1.9, 17 Hz), 6.44-6.51 (dd, 1H, J=10, 17 Hz), 7.09-7.14 (m, 1H), 7.16-7.18 (m,

1H), 7.20 (s, 2H), 7.24-34 (m, 2H), 7.46-7.48 (dd, 1H, J=1.9. 7.9Hz), 7.70 (d, 1H, J=1.3Hz), 7.72 (d, 1H, J=1.3Hz), 7.79 (d, 1H, J=1.8Hz), 8.04 (s, 1H), 8.44 (s, 1H), 8.70 (s, 1H), 10.18 (s, 1H).

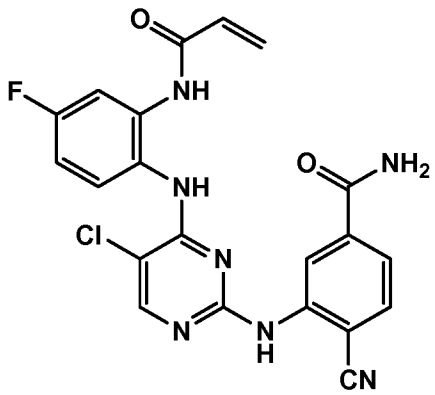
Example 228



I-206

[00579] 3-((4-((2-acrylamido-4-fluorophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-206** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide**.** MS m/z: 441.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.15 (s, 3H), 5.78-5.81 (dd, 1H, J=1.6, 10Hz), 6.26-6.31 (dd, 1H, J=1.7, 17Hz), 6.44-6.50 (dd, 1H, J=10, 17 Hz), 6.82-6.87 (m, 1H), 7.14-7.19 (d, 1H, J=7.9Hz), 7.27-7.29 (d, 2H, J=7.3Hz), 7.50-7.52 (d, 1H, J=7.8Hz), 7.62-7.64 (m, 1H), 7.87-7.89 (d, 2H, J=7Hz), 8.03 (s, 1H), 8.32 (s, 1H), 8.58 (s, 1H), 10.08 (s, 1H).

Example 229

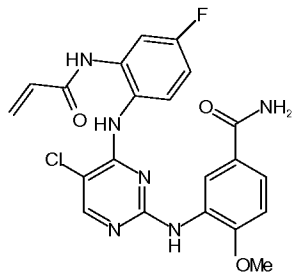


I-207

[00580] 3-(4-(2-acrylamido-4-fluorophenylamino)-5-chloropyrimidin-2-ylamino)-4-cyanobenzamide: Compound **I-207** was prepared according to the step described below. To a stirred solution of N-(2-((2,5-dichloropyrimidin-4-yl)amino)-5-fluorophenyl)acrylamide (200 mg, 0.613 mmol), which was prepared using N-(2-amino-5-fluorophenyl)acrylamide and 2,4,5-trichloropyrimidine in a method similar to **step 1** of **Example 162,** in tert-amyl alcohol (5 mL)

was added aqueous sodium carbonate (96 mg, 0.905 mmol), 3-amino-4-cyanobenzamide (100 mg, 0.324 mmol) and diphenylphosphino-N,N-dimethylamine (125 mg, 0.919 mmol). The mixture was degassed for 20min. To this mixture, $Pd_2(dba)_3$ (625 mg, 0.733 mmol) and Davephos (96 mg, 0.244 mmol) were added and again degassed for 10min. The reaction mixture was heated to 90 °C for 2h. TLC showed completion of starting material. The crude mixture was purified by silica gel column chromatography followed by preparative HPLC to yield 30 mg of the title compound. MS m/z: 452.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 5.77-5.80(dd, 1H J=2.0Hz and 10.2Hz), 6.26-6.31(dd, 1H J=1.9Hz and 17Hz), 6.46-6.52(dd, 1H J=10.2, 17Hz), 6.90-6.95(dt, 3.0, 8.4Hz), 7.38-7.41(dd, 1H J=3.0, 10.4Hz), 7.56-7.64(m, 3H), 7.78(d, 1H J=8.1Hz), 7.96(d, 1H J=1.2Hz), 8.10-8.12(m, 2H), 8.5(s, 1H), 9.4(s, 1H), 10.02(s, 1H). MS m/z: 452.1(ES+, M+H).

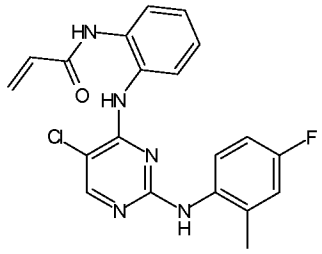
Example 230



I-208

[00581] 3-((4-((2-acrylamido-4-fluorophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methoxybenzamide: Compound **I-208** was prepared in a manner similar to Example 162, substituting 3-amino-4-methoxybenzamide for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 457.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.8 (s, 3H), 5.77-5.80 (dd, 1H, J=1.9, J=10Hz), 6.26-6.31 (dd, 1H, J=2, 18Hz), 6.44-6.51 (dd, 1H, J=10, 17Hz), 6.93-7.02 (m, 2H), 7.18 (s, 1H), 7.32-7.36 (dd, 1H, J=2, 10Hz), 7.53-7.56 (dd, 1H, J=2.2, 18Hz), 7.63-7.67 (m, 1H), 7.84 (s, 1H), 7.89 (s, 1H), 8.20 (d, 1H, J=1.8Hz), 8.42 (s, 1H), 10.07 (s, 1H).

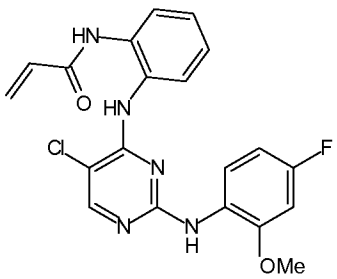
Example 231



I-209

[00582] N-(2-((5-chloro-2-((4-fluoro-2-methylphenyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-209** was prepared in a manner similar to Example 162, substituting 4-fluoro-2-methylaniline for 3-amino-4-methylbenzamide. MS m/z: 398.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.13 (s, 3H), 5.77-5.80 (dd, 1H, J=1.8, 10.1Hz), 6.27-6.33 (dd, 1H, J=1.8, 14Hz), 6.44-6.51 (dd, 1H, J=10, 16.9Hz), 6.86-6.91 (dt, 1H, J=10, 16.9Hz), 6.96-7.00 (dd, 1H, J=2.9, 9.7Hz), 7.12-7.18 (m, 2H), 7.31-7.36 (m, 2H), 7.67-7.69 (m, 1H), 8.01 (s, 1H), 8.38 (s, 1H), 8.45 (s, 1H), 10.15 (s, 1H).

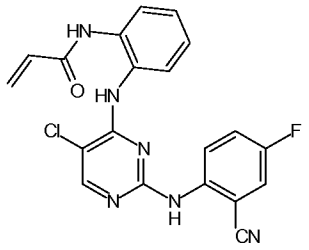
Example 232



I-210

[00583] N-(2-((5-chloro-2-((4-fluoro-2-methoxyphenyl)amino)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-210** was prepared in a manner similar to Example 162, substituting 4-fluoro-2-methoxyaniline for 3-amino-4-methylbenzamide. MS m/z: 414.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.78 (s, 3H), 5.76-5.79 (dd, 1H, J=1.9, 10 Hz), 6.27-6.31 (dd, 1H, J=1.8, 17Hz), 6.44-6.56 (m, 2H), 6.88-6.91 (dd, 1H, J=2.7, 10.8Hz), 7.20-7.28 (m, 2H), 7.40-7.42 (dd, 1H, J=1.6, 7.3Hz), 7.66-7.68 (dd, 1H, J=1.8, 7.6Hz), 7.78 (s, 1H), 8.07 (s, 1H), 8.52 (s, 1H), 10.15 (s, 1H).

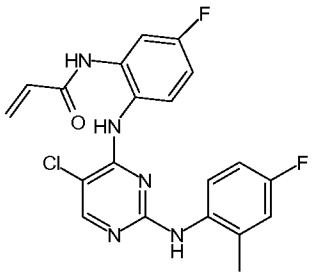
Example 233



I-211

[00584] N-(2-((5-chloro-2-((2-cyano-4-fluorophenyl)amino)pyrimidin-4-yl)amino)phenyl) acrylamide: Compound **I-211** was prepared in a manner similar to Example 162, substituting 2-amino-5-fluorobenzonitrile for 3-amino-4-methylbenzamide. MS m/z: 409.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 5.77-5.80 (dd, 1H, J=1.8, 10.1 Hz)), 6.28-6.32 (dd, 1H, J=1.8, 17Hz), 6.45-6.52 (dd, 1H, J=10, 17Hz), 7.15-7.23 (m, 2H), 7.36-7.48 (dd, 1H, J=1.2, 7Hz), 7.42-7.47 (m, 1H), 7.52-7.55 (m, 1H), 7.65-7.71 (m, 1H), 8.09 (s, 1H), 8.55 (s, 1H), 9.24 (s, 1H), 10.15 (s, 1H).

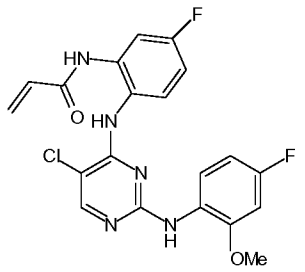
Example 234



I-212

[00585] N-(2-((5-chloro-2-((4-fluoro-2-methylphenyl)amino)pyrimidin-4-yl)amino)-5-fluorophenyl)acrylamide: Compound **I-212** was prepared in a manner similar to Example 162, substituting 3-amino-4-methoxybenzamide for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 416.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.11 (s, 3H), 5.77-5.80 (dd, 1H, J=1.4, 10.2 Hz), 6.26-6.30 (dd, 1H, J=1.8, 17 Hz), 6.47-6.53 (dd, 1H, J=10, 17 Hz), 6.83-6.88 (m, 1H), 6.94-7.02 (m, 2H), 7.28-7.32 (m, 1H), 7.43-7.47 (dd, 1H, J=2.9, 10.5Hz), 7.52-7.56 (m, 1H), 8.0 (s, 1H), 8.33 (s, 1H), 8.39 (s, 1H), 9.97 (s, 1H).

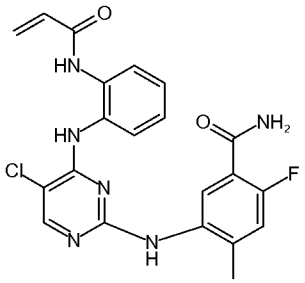
Example 235



I-213

[00586] N-(2-((5-chloro-2-((4-fluoro-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)-5-fluorophenyl)acrylamide: Compound **I-213** was prepared in a manner similar to Example 162, substituting 4-fluoro-2-methoxyaniline for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 432.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.78 (s, 3H), 5.75-5.78 (dd, 1H, J=1.9, 10.2Hz), 6.24-6.29 (dd, 1H, J=1.9, 17 Hz), 6.47-6.54 (m, 2H), 6.87-6.90 (dd, 1H, J=2.8, 10.8Hz), 7.05-7.09 (m, 1H), 7.53-7.58 (m, 2H), 7.64-7.69 (m, 2H), 8.05 (s, 1H), 8.49 (s, 1H), 9.96 (s, 1H).

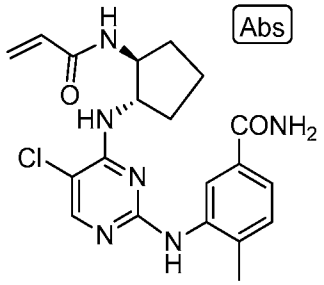
Example 236



I-214

[00587] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-fluoro-4-methylbenzamide: Compound **I-214** was prepared in a manner similar to Example 162, substituting 5-amino-2-fluoro-4-methylbenzamide for 3-amino-4-methylbenzamide. MS m/z: 441.0 (ES+, M+H).

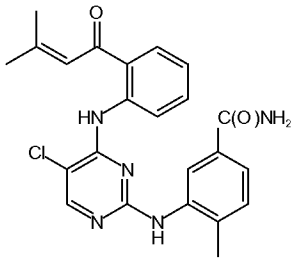
Example 237



I-215

[00588] 3-((4-(((1S,2S)-2-acrylamidocyclopentyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-215** was prepared in a manner similar to Example 162, substituting N-((1S,2S)-2-aminocyclopentyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 415.1 (ES+, M+H).

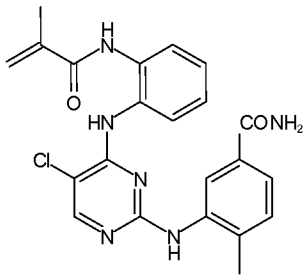
Example 238



I-216

[00589] 3-((5-chloro-4-((2-(3-methylbut-2-enoyl)phenyl)amino)pyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-216** was prepared in a manner similar to Example 162, substituting 1-(2-aminophenyl)-3-methylbut-2-en-1-one for N-(2-aminophenyl)acrylamide. MS m/z: 436.1 (ES+, M+H).

Example 239

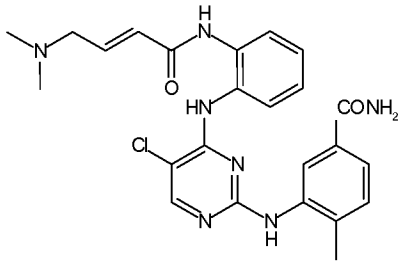


I-217

[00590] 3-((5-chloro-4-((2-methacrylamidophenyl)amino)pyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-217** was prepared in a manner similar to Example 162,

substituting N-(2-aminophenyl)methacrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 437.1 (ES+, M+H).

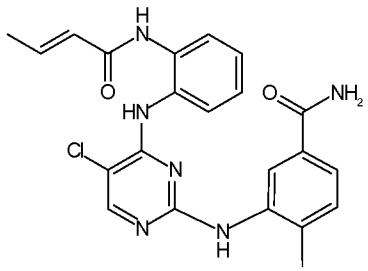
Example 240



I-218

[00591] (E)-3-((5-chloro-4-((2-(4-(dimethylamino)but-2-enamido)phenyl)amino) pyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-218** was prepared in a manner similar to Example 162, substituting (E)-N-(2-aminophenyl)-4-(dimethylamino)but-2-enamide for N-(2-aminophenyl)acrylamide. MS m/z: 480.2 (ES+, M+H).

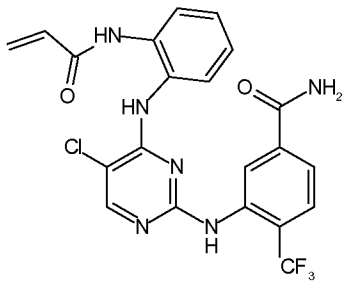
Example 241



I-219

[00592] (E)-3-((4-((2-(but-2-enamido)phenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-219** was prepared in a manner similar to Example 162, substituting (E)-N-(2-aminophenyl)but-2-enamide for N-(2-aminophenyl)acrylamide. MS m/z: 437.1 (ES+, M+H).

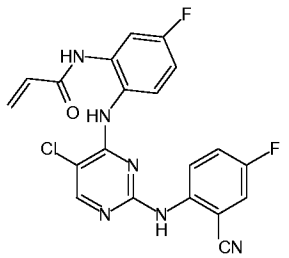
Example 242



I-220

[00593] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-(trifluoromethyl)benzamide: Compound **I-220** was prepared in a manner similar to Example 162, substituting 3-amino-4-(trifluoromethyl)benzamide for 3-amino-4-methylbenzamide. MS m/z: 477.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 5.78-5.81 (dd, J = 1.9, 10.1 Hz, 1H), 6.27-6.32 (dd, J = 1.9, 17.0 Hz, 1H), 6.43-6.50 (dd, J = 10.1, 17.0 Hz, 1H), 6. 79-7.01 (dd, J = 1.4, 8.0 Hz, 1H), 7.04-7.08 (dt, J = 1.4, 7.5 Hz, 1H), 7.23-7.25 (dd, J = 1.2, 7.8 Hz, 1H), 7.64 (t, J = 7.9 Hz, 2H), 7.71-7.73 (d, J = 8.3 Hz, 1H), 7.81-7.83 (d, J = 8.4 Hz, 1H), 8.08 (s, 1H), 8.13 (s, 1H), 8.16 (s, 1H), 8.47 (s, 1H), 8.67 (s, 1H), 10.19 (s, 1H).

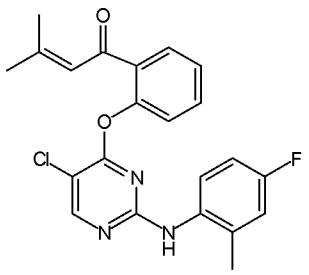
Example 243



I-221

[00594] N-(2-((5-chloro-2-((2-cyano-4-fluorophenyl)amino)pyrimidin-4-yl)amino)-5-fluorophenyl)acrylamide: Compound **I-221** was prepared in a manner similar to Example 162, substituting 2-amino-5-fluorobenzonitrile for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 427.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 5.78-5.84(dd, 1H J=2.2, 9.6Hz), 6.35-6.45(m, 2H), 6.98-7.03(dt, 1H J=3.0, 7.9Hz), 7.22-7.27(dt, 1H J=3.0, 8.1Hz), 7.39-7.42(dd, 1H J=3.0, 8.0Hz), 7.46-7.50(dd, 1H J=2.9, 10.1Hz), 7.52-7.56(dd, 1H J= 5.9, 9.0Hz), 7.66-7.70(dd, 1H J=4.9, 9.2Hz), 8.03(s, 1H).

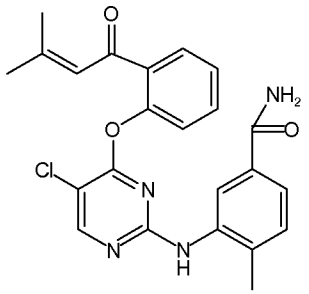
Example 244



I-222

[00595] 1-(2-((5-chloro-2-((4-fluoro-2-methylphenyl)amino)pyrimidin-4-yl)oxy)phenyl)-3-methylbut-2-en-1-one: Compound **I-222** was prepared in a manner similar to Example 162, substituting 4-fluoro-2-methylaniline for 3-amino-4-methylbenzamide, and substituting 1-(2-hydroxyphenyl)-3-methylbut-2-en-1-one for N-(2-aminophenyl)acrylamide. MS m/z: 412.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.81 (s, 3H), 1.89 (s, 3H), 2.04 (s, 3H), 6.37 (s, 1H),6.77 (br t, 1H), 6.92-6.95 (dd, 1H, J=2.7, 9.7Hz), 7.06-7.09 (m, 1H), 7.30-7.32 (d, 1H, J=8Hz), 7.36-7.39 (m, 1H), 7.57-7.59 (m, 1H), 7.61-7.66 (m, 1H), 8.29 (s, 1H), 8.84 (s, 1H).

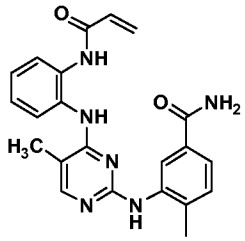
Example 245



I-223

[00596] 3-((5-chloro-4-(2-(3-methylbut-2-enoyl)phenoxy)pyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-223** was prepared in a manner similar to Example 162, substituting 1-(2-hydroxyphenyl)-3-methylbut-2-en-1-one for N-(2-aminophenyl)acrylamide. MS m/z: 437.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.81(s, 3H), 1.92(s, 3H), 2.08(s, 3H), 6.35(br s, 1H), 7.15-7.17(d, 1H, J=8.0Hz), 7.22(br s, 1H), 7.31-7.35(m, 2H), 7.51-7.60(m, 3H), 7.65(d, 1H, J=1.5Hz), 7.76(br s, 1H), 8.30(s, 1H), 8.98(s, 1H).

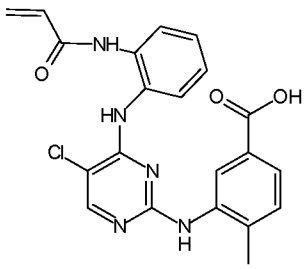
Example 246



I-224

[00597] 3-(4-(2-acrylamidophenylamino)-5-methylpyrimidin-2-ylamino)-4-methyl benzamide: Compound **I-224** was prepared in the similar way as described in **Method E** of **Example 162** using 2,4-dichloro-5-methylpyrimidine as the starting material. m/z 403.5 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H, Me), 2.17(s, 3H), 5.78-5.81(dd, 1H *J*=1.8, 10.1Hz), 6.28-6.32(dd, 1H *J*= 1.8, 17Hz), 6.43-6.50(dd, 1H *J*=10.1, 17Hz), 7.04-7.08(m, 2H), 7.16 (d, 1H, J = 8.0 Hz), 7.27(br s, 1H), 7.29 (m, 1H), 7.48 (dd, 1H *J*=1.7, 7.9Hz), 7.80 (m, 2H),7.83 (br s, 1H), 7.92(s, 1H), 7.97(s, 1H), 8.62(s, 1H), 10.11(s, 1H), 10.94 (s, 1H).

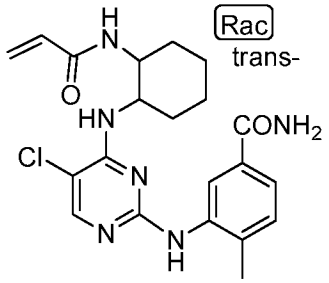
Example 247



I-225

[00598] 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzoic acid: Compound **I-225** was prepared in a manner similar to Example 162, substituting tert-butyl 3-amino-4-methylbenzoat efor 3-amino-4-methylbenzamide, and final t-butyl ester cleavage by TFA.. MS m/z: 424.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.2 (s, 3H), 5.77-5.8 (dd, J = 1.9, 10 Hz, 1H), 6.27-6.32 (dd, J = 1.9, 17 Hz, 1H), 6.44-6.5 (dd, J = 10.1, 17 Hz, 1H), 7.01-7.11 (m, 2H), 7.25 (t, J = 7.6 Hz, 2H), 7.56-7.58 (dd, J = 1.7, 7.9 Hz, 1H), 7.69-7.71 (dd, J = 1.2, 8 Hz, 1H), 7.93 (d, J = 1.5 Hz, 1H), 8.05 (s, 1H), 8.42 (s, 1H), 8.64 (s, 1H), 10.2 (s, 1H), 12.8 (s, 1H).

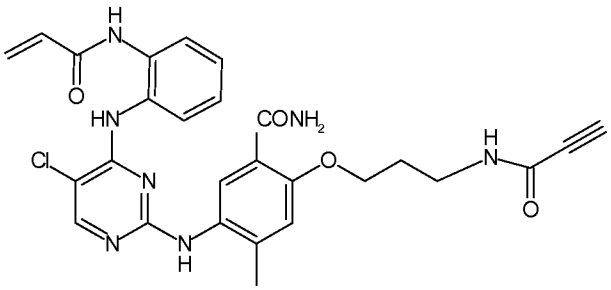
Example 248



I-226

[00599] Rac-trans-3-((4-((2-acrylamidocyclohexyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide. Compound **I-226** was prepared in a manner similar to Example 162, substituting trans-N-(2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 429.2 (ES+, M+H).

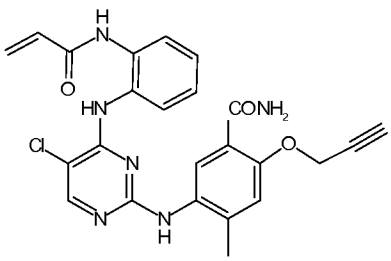
Example 249



I-227

[00600] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methyl-2-(3-propiolamidopropoxy)benzamide: Compound **I-227** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(4-amino-2-carbamoyl-5-methylphenoxy)propyl)carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and amide formation with propiolic acid, HATU, DIPEA in DMA. MS m/z: 548.2 (ES+, M+H).

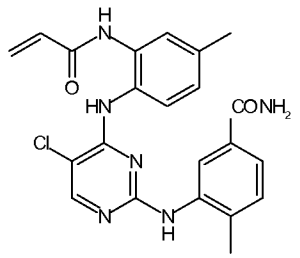
Example 250



I-228

[00601] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methyl-2-(prop-2-yn-1-yloxy)benzamide: Compound **I-228** was prepared in a manner similar to Example 162, substituting 5-amino-4-methyl-2-(prop-2-yn-1-yloxy)benzamide for 3-amino-4-methylbenzamide. MS m/z: 477.1 (ES+, M+H).

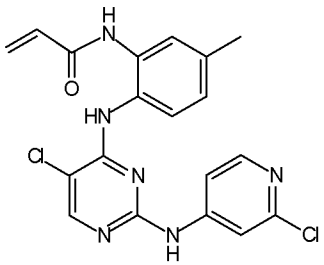
Example 251



I-229

[00602] 3-((4-((2-acrylamido-4-methylphenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-229** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 437.1 (ES+, M+H).

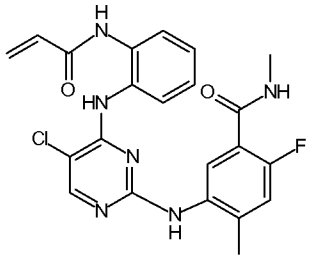
Example 252



I-230

[00603] N-(2-((5-chloro-2-((2-chloropyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-230** was prepared in a manner similar to Example 162, substituting 2-chloropyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 415.1 (ES+, M+H).

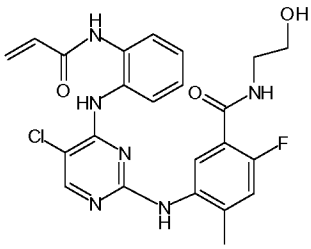
Example 253



I-231

[00604] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-fluoro-N,4-dimethylbenzamide: Compound **I-231** was prepared in a manner similar to Example 162, substituting tert-butyl 5-amino-2-fluoro-4-methylbenzoate for 3-amino-4-methylbenzamide, followed by t-Bu ester deprotection with TFA, then coupling with methylamine in the presence of HATU and DIPEA. MS m/z: 455.1 (ES+, M+H).

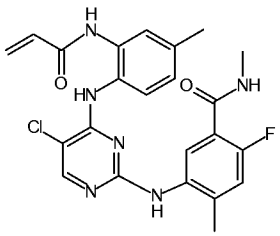
Example 254



I-232

[00605] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-fluoro-N-(2-hydroxyethyl)-4-methylbenzamide: Compound **I-232** was prepared in a manner similar to Example 162, substituting tert-butyl 5-amino-2-fluoro-4-methylbenzoate for 3-amino-4-methylbenzamide, followed by t-Bu ester deprotection with TFA, then coupling with 2-aminoethanol in the presence of HATU and DIPEA. MS m/z: 485.1 (ES+, M+H).

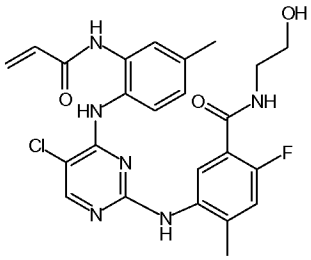
Example 255



I-233

[00606] 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-fluoro-N,4-dimethylbenzamide: Compound **I-233** was prepared in a manner similar to Example 162, substituting tert-butyl 5-amino-2-fluoro-4-methylbenzoate for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, followed by t-Bu ester deprotection with TFA, then coupling with methylamine in the presence of HATU and DIPEA. MS m/z: 469.1 (ES+, M+H).

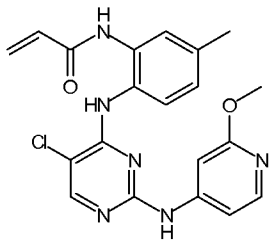
Example 256



I-234

[00607] 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-fluoro-N-(2-hydroxyethyl)-4-methylbenzamide: Compound **I-234** was prepared in a manner similar to Example 162, substituting tert-butyl 5-amino-2-fluoro-4-methylbenzoate for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, followed by t-Bu ester deprotection with TFA, then coupling with 2-aminoethanol in the presence of HATU and DIPEA. MS m/z: 499.1 (ES+, M+H).

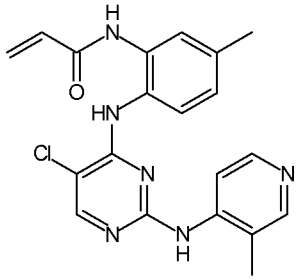
Example 257



I-235

[00608] N-(2-((5-chloro-2-((2-methoxypyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-235** was prepared in a manner similar to Example 162, substituting 2-methoxypyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 411.0 (ES+, M+H).

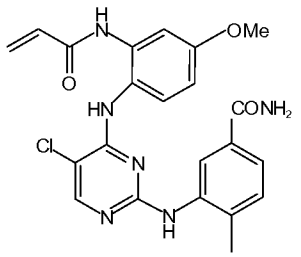
Example 258



I-236

[00609] N-(2-((5-chloro-2-((3-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-236** was prepared in a manner similar to Example 162, substituting 3-methylpyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 395.1 (ES+, M+H).

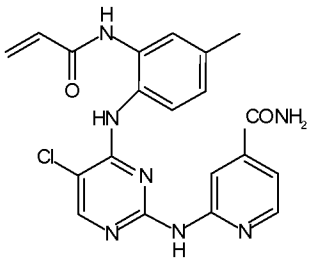
Example 259



I-237

[00610] 3-((4-((2-acrylamido-4-methoxyphenyl)amino)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide: Compound **I-237** was prepared in a manner similar to Example 162, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 444.4 (ES+, M+H).

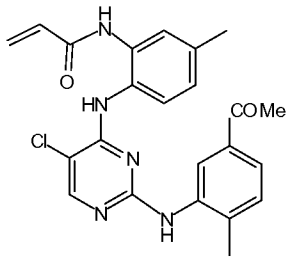
Example 260



I-238

[00611] 2-((4-((2-acrylamido-4-methylphenyl)amino)-5-chloropyrimidin-2-yl)amino)isonicotinamide: Compound **I-238** was prepared in a manner similar to Example 162, substituting 2-aminoisonicotinamide for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 424.1 (ES+, M+H).

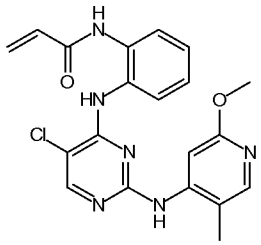
Example 261



I-239

[00612] N-(2-((2-((5-acetyl-2-methylphenyl)amino)-5-chloropyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-239** was prepared in a manner similar to Example 162, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 436.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.22 (s, 6H), 2.38 (m, 3H), 5.76-5.79 (dd, J = 1.7, 10.1 Hz, 1H), 6.25-6.30 (dd, J = 1.7, 17 Hz, 1H), 6.42-6.48 (dd, J = 10.2, 17.0 Hz, 1H), 7.12 (t, J = 8.1 Hz, 2H), 7.45 (d, J = 8.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.56-7.59 (dd, J = 1.7, 7.9 Hz, 1H), 7.92 (d, J = 1.4 Hz, 1H), 8.04 (s, 1H), 8.38 (s, 1H), 8.61 (s, 1H), 10.11 (s, 1H).

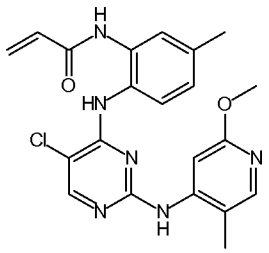
Example 262



I-240

[00613] N-(2-((5-chloro-2-((2-methoxy-5-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-240** was prepared in a manner similar to Example 162, 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z: 411.0 (ES+, M+H).

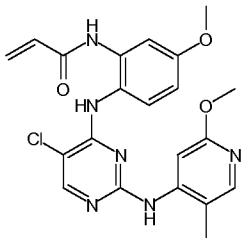
Example 263



I-241

[00614] N-(2-((5-chloro-2-((2-methoxy-5-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-241** was prepared in a manner similar to Example 162, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 425.1 (ES+, M+H).

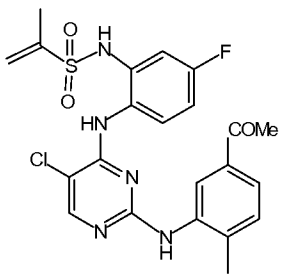
Example 264



I-242

[00615] N-(2-((5-chloro-2-((2-methoxy-5-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-242** was prepared in a manner similar to Example 162, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 441.0 (ES+, M+H).

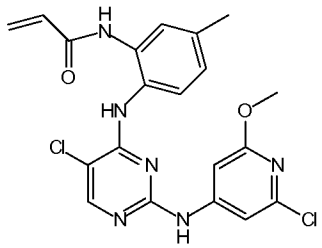
Example 265



I-243

[00616] N-(2-((2-((5-acetyl-2-methylphenyl)amino)-5-chloropyrimidin-4-yl)amino)-5-fluorophenyl)prop-1-ene-2-sulfonamide: Compound **I-243** was prepared in a manner similar to Example 162, substituting 1-(3-amino-4-methylphenyl)ethanone for 3-amino-4-cyanobenzamide, and substituting N-(2-amino-5-fluorophenyl)prop-1-ene-2-sulfonamide for N-(2-aminophenyl)acrylamide. MS m/z: 490.1 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.96 (s, 3H), 2.20 (s, 3H), 2.38 (m, 3H), 5.65 (s, 1H), 5.68 (s, 1H), 6.80 (t, J = 2.9 Hz, 1H), 6.94-6.97 (dd, J = 3.6, 9.8 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.59-7.61 (m, 2H), 7.83 (d, J = 1.6 Hz, 1H), 8.10 (s, 1H), 8.30 (s, 1H), 8.71 (s, 1H), 9.68 (s, 1H).

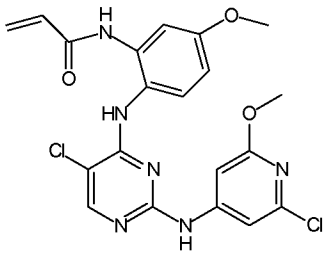
Example 266



I-244

[00617] N-(2-((5-chloro-2-((2-chloro-6-methoxypyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide: Compound **I-244** was prepared in a manner similar to Example 162, substituting 2-chloro-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 446.1 (ES+, M+H).

Example 267

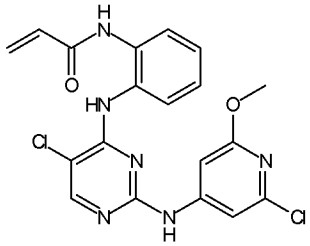


I-245

[00618] N-(2-((5-chloro-2-((2-chloro-6-methoxypyridin-4-yl)amino)pyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide: Compound **I-245** was prepared in a manner similar to Example 162, substituting 2-chloro-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide

and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 462.1 (ES+, M+H).

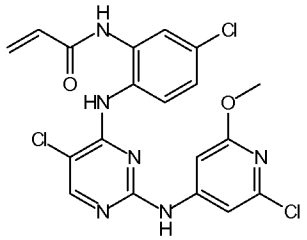
Example 268



I-246

[00619] N-(2-((5-chloro-2-((2-chloro-6-methoxypyridin-4-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-246** was prepared in a manner similar to Example 162, substituting 2-chloro-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z: 431.0 (ES+, M+H).

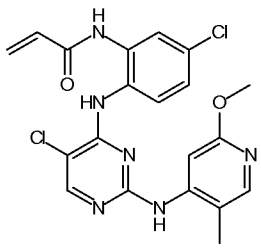
Example 269



I-247

[00620] N-(5-chloro-2-((5-chloro-2-((2-chloro-6-methoxypyridin-4-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-247** was prepared in a manner similar to Example 162, substituting 2-chloro-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-chlorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 465.0 (ES+, M+H).

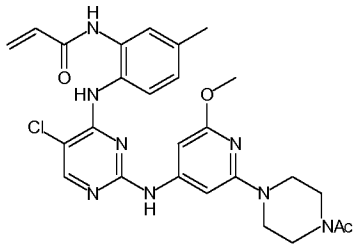
Example 270



I-248

[00621] N-(5-chloro-2-((5-chloro-2-((2-methoxy-5-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide: Compound **I-248** was prepared in a manner similar to Example 162, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide and substituting N-(2-amino-5-chlorophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 445.1 (ES+, M+H).

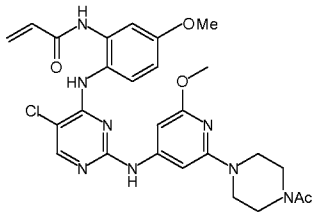
Example 271



I-296

[00622] N-(2-((2-((2-(4-acetylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-chloropyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-296** was prepared in a manner similar to Example 162, substituting 1-(4-(4-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z = 537.2 (ES+, M+H).

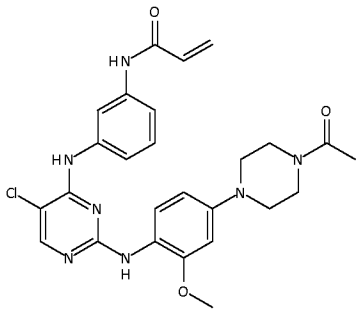
Example 272



I-297

[00623] N-(2-((2-((2-(4-acetylpiperazin-1-yl)-6-methoxypyridin-4-yl)amino)-5-chloropyrimidin-4-yl)amino)-5-methoxyphenyl)acrylamide. Compound **I-297** was prepared in a manner similar to Example 162, substituting 1-(4-(4-amino-6-methoxypyridin-2-yl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z = 553.8 (ES+, M+H).

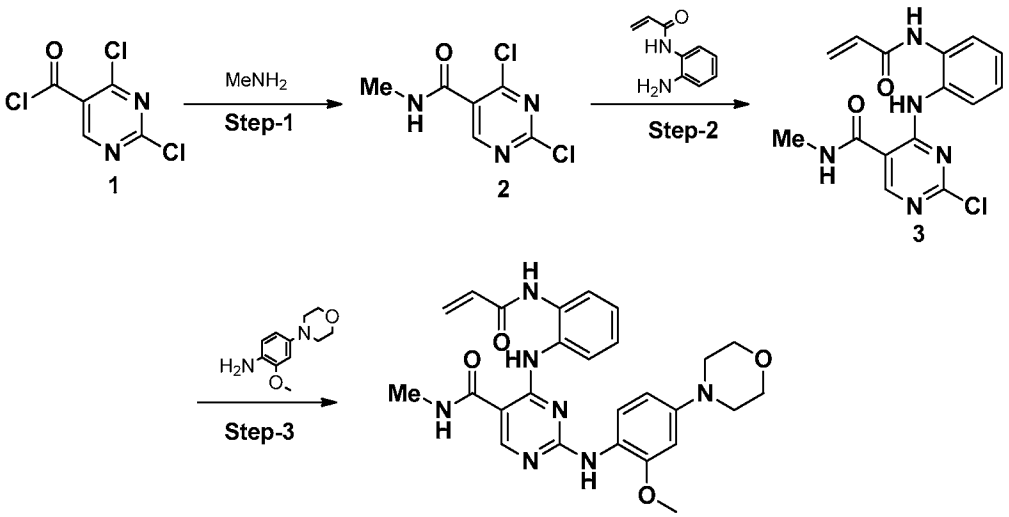
Example 273



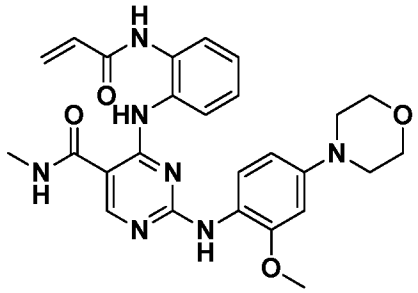
I-298

[00624] N-(3-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-298** was prepared in a manner similar to Example 162, substituting 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone for 3-amino-4-methylbenzamide, and substituting N-(3-aminophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z = 523.2 (ES+, M+H).

[00625] **Method F** starts with 2,4-dichloropyrimidine-5-carbonyl chloride reacting with various amines to construct the C5-substitution, then follows the chemistry in **Method E** to finish all the final targets.



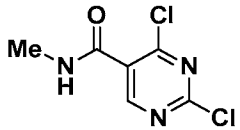
Example 274



I-250

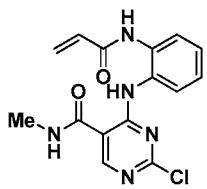
[00626] 4-((2-acrylamidophenyl)amino)-2-((2-methoxy-4-morpholinophenyl)amino) pyrimidine-5-carboxamide: The title compound was prepared according to the steps and intermediates described below.

Step-1. Preparation of 2,4-dichloro-N-methylpyrimidine-5-carboxamide (2):



[00627] To a solution of methyl amine (2M) in THF (2.4mL, 4.70mmol) in DCM (50ml), TEA (963mg, 9.50mmol) and 2,4-dichloropyrimidine-5-carbonyl chloride (1g, 4.70mmol) were added slowly at-78°C for 1h. TLC showed completion of starting material (TLC system: 10% ethyl acetate in hexane **(R_f):** 0.3). The reaction mixture was diluted with DCM (50ml), washed with water (2x30ml) and a saturated solution of $NaHCO_3$. The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200 mesh) with 5% ethyl acetate in hexane to obtain 2, 4-dichloro-N-methylpyrimidine-5-carboxamide as white solid. Yield: (400mg, 33%). ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 6.50 (br s, 1H), 3.07 (d, 3H, J = 4.8 Hz).

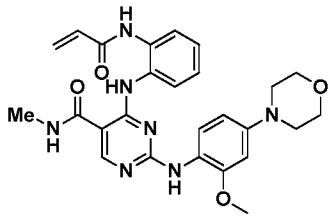
Step-2. Preparation of 4-(2-acrylamidophenylamino)-2-chloro-N-methylpyrimidine-5-carboxamide



[00628] To a solution of 2,4-dichloro-N-methylpyrimidine-5-carboxamide (400mg, 1.95mmol) in NMP (1ml), N-(2-aminophenyl)acrylamide (316mg, 1.951mmol) and DIPEA (503mg, 3.902mmol) were added and heated at 120 °C for 1h. TLC showed completion of

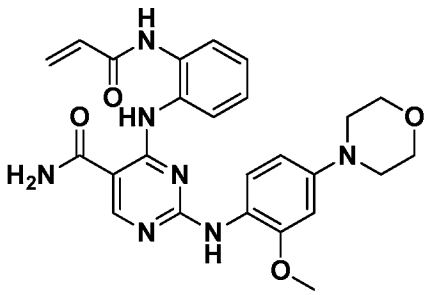
starting material (TLC system: 5% methanol in DCM **(R_f):** 0.3). The reaction mixture was diluted with water (30ml) and extracted with ethyl acetate (3x15ml). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200mesh) with 2% methanol in DCM to obtain 4-(2-acrylamidophenylamino)-2-chloro-N-methylpyrimidine-5-carboxamide as an off white solid. Yield: (180mg, 28%). MS: m/z 332.1 (ES+, M+H).

Step 3. Preparation of 4-(2-acrylamidophenylamino)-2-(2-methoxy-4-morpholino phenylamino)-N-methylpyrimidine-5-carboxamide:



[00629] To a solution of 4-(2-acrylamidophenylamino)-2-chloro-N-methylpyrimidine-5-carboxamide (40mg, 0.12mmol) in 0.08M p-TSA/1,4-dioxane (5mL), 2-methoxy-4-morpholinoaniline (25.13mg, 0.12mmol) was added and heated at 100° C for 1h. TLC showed completion of starting material (TLC system: 5% methanol in DCM **(R_f):** 0.3). 1, 4 dioxane was evaporated, and the residue was diluted with ethyl acetate (15mL) and washed with water (2x5mL). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200 mesh) with 2% methanol in DCM to obtain 4-(2-acrylamidophenylamino)-2-(2-methoxy-4-morpholino phenylamino)-N-methylpyrimidine-5-carboxamide as off white solid. Yield: (8mg, 13%). MS: m/z 504.3 (ES+, M+H).

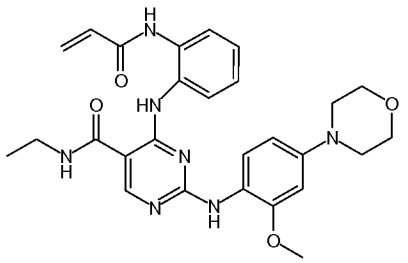
Example 275



I-249

[00630] 4-((2-acrylamidophenyl)amino)-2-((2-methoxy-4-morpholinophenyl)amino) pyrimidine-5-carboxamide. Compound **I-249** was made in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine in step-1. MS: m/z 490.4 (ES+).

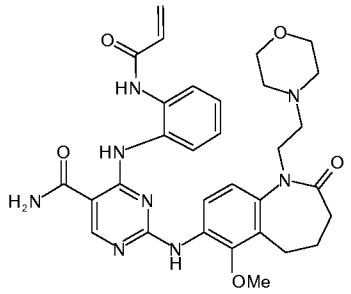
Example 276



I-251

[00631] 4-((2-acrylamidophenyl)amino)-N-ethyl-2-((2-methoxy-4-morpholinophenyl) amino)pyrimidine-5-carboxamide: Compound **I-251** was prepared in a manner similar to Example 274, substituting ethyl amine for methyl amine in step-1**:** MS m/z 518.3 (ES+, M+H).

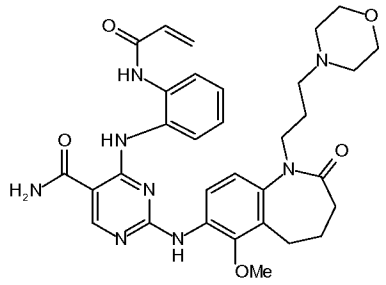
Example 277



I-252

[00632] 4-((2-acrylamidophenyl)amino)-2-((6-methoxy-1-(2-morpholinoethyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidine-5-carboxamide: Compound **I-252** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, and substituting 7-amino-6-methoxy-1-(2-morpholinoethyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one for 2-methoxy-4-morpholinoaniline**.** MS m/z 601.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.46 (m, 1H), 1.68 (m, 1H), 1.89 (m, 1H), 2.03 (s, 3H), 2.88-2.90 (m, 2H), 3.30 (m, 1H), 3.64 (m, 1H), 3.64-3.76 (m, 2H), 4.06-4.09 (m, 2H), 4.46 (s, 1H), 5.65 (s, 1H), 5.69 (s, 1H), 6.94-7.12 (m, 2H), 7.61 (d, J = 7.1 Hz, 1H), 7.90-8.29 (br s, 1H), 8.21-8.29 (m, 2H), 9.6 (s, 1H).

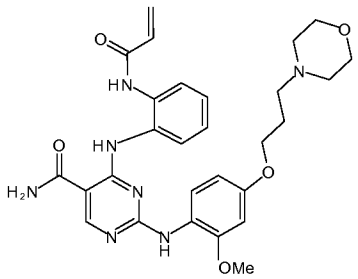
Example 278



I-253

[00633] 4-((2-acrylamidophenyl)amino)-2-((6-methoxy-1-(3-morpholinopropyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidine-5-carboxamide: Compound **I-253** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, and substituting 7-amino-6-methoxy-1-(3-morpholinopropyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one for 2-methoxy-4-morpholinoaniline. MS m/z 615.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.22-1.26 (m, 3H), 1.59 (br s, 3H), 2.2 (m, 10H), 3.49 (br s, 4H), 3.67 (s, 3H), 5.68-5.71 (dd, J = 2.0, 10.0 Hz, 1H), 6.16-6.21 (dd, J = 2.0, 17.1 Hz, 1H), 6.39-6.46 (dd, J = 10.3, 17.1 Hz, 1H), 7.03 (t, J = 6.2 Hz, 1H), 7.07 (m, 2H), 7.30 (d, J = 7.6 Hz, 1H), 7.41 (br s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.93 (br s, 1H), 8.17 (d, J = 8.0 Hz, 1H), 8.65 (d, J= 5.0 Hz, 1H), 8.68 (s, 1H), 9.68 (s, 1H), 11.44 (s, 1H).

Example 279

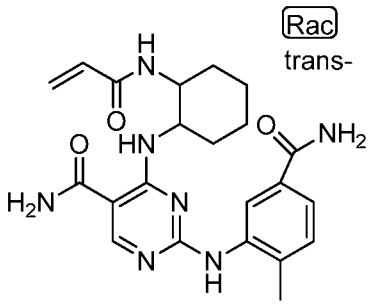


I-254

[00634] 4-((2-acrylamidophenyl)amino)-2-((2-methoxy-4-(3-morpholinopropoxy)phenyl) amino)pyrimidine-5-carboxamide: Compound **I-254** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, and substituting 2-methoxy-4-(3-morpholinopropoxy)aniline for 2-methoxy-4-morpholinoaniline. MS m/z 546.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6)) δ 1.88 (m, 2H), 2.37 (br s, 4H), 2.44 (d, J = 7.2 Hz, 2H), 3.57 (t, J = 4.5 Hz,4H), 3.74 (s, 3H), 4.03 (t, 6.2 Hz, 2H), 5.68-5.71 (dd, J = 1.6, 10.3 Hz, 1H), 6.16-6.21 (dd, J = 1.9, 17.0 Hz,1H), 6.39-6.47 (m, 2H), 6.62 (d, J = 2.6 Hz, 1H), 6.97-7.04 (m, 2H), 7.25 (d, J =

7.69 Hz,1H), 7.45 (d, J = 8.3 Hz,1H), 7.80 (br s, 1H), 8.19 (br s, 1H), 8.35 (s, 1H), 8.59 (s, 1H), 9.67 (s, 1H), 11.45 (s, 1H).

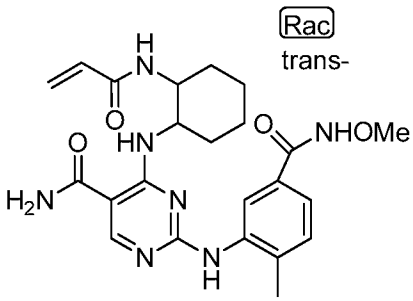
Example 280



I-255

[00635] Rac-trans-4-((2-acrylamidocyclohexyl)amino)-2-((5-carbamoyl-2-methylphenyl) amino)pyrimidine-5-carboxamide. Compound **I-255** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, substituting 3-amino-4-methylbenzamide for 2-methoxy-4-morpholinoaniline, and substituting trans-N-(2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 438.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.23 (m, 4H), 1.16 (m, 2H),1.58 (d, J = 10.2 Hz, 2H), 1.80 (d, J = 12.3 Hz, 1H), 2.01 (d, J = 9.8 Hz, 1H), 2.28 (s, 3H), 5.43-5.46 (dd, J = 3.3, 8.9 Hz, 1H), 5.94 (m, 2H), 6.90 (br s, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.33 (s, 1H), 7.53-7.56 (dd, J = 1.7, 7.8 Hz, 1H), 7.87 (t, J = 8.3 Hz, 2H), 8.18 (s, 1H), 8.43 (s, 1H), 8.72 (s, 1H), 9.02 (d, J = 7.5 Hz, 1H).

Example 281

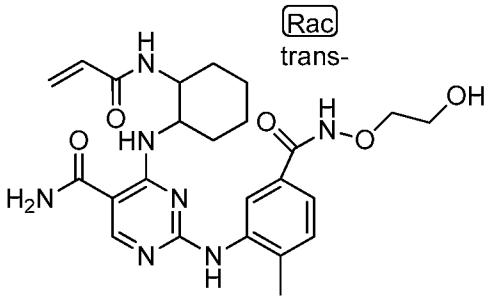


I-256

[00636] Rac-trans-4-((2-acrylamidocyclohexyl)amino)-2-((5-(methoxycarbamoyl)-2-methylphenyl)amino)pyrimidine-5-carboxamide. Compound **I-256** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, substituting 3-amino-N-methoxy-4-methylbenzamide for 2-methoxy-4-morpholinoaniline, and substituting

trans-N-(2-aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 468.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.08-1.14 (m, 4H), 1.22 (m, 2H), 1.57 (d, J = 10.0 Hz, 2H), 1.81 (d, J = 11.5 Hz, 1H), 2.04 (d, J = 10.0 Hz, 1H), 2.28 (s, 3H), 3.64 (s, 3H), 5.44-5.47 (dd, J = 3.6, 8.6 Hz, 1H), 5.94 (m, 2H), 6.90 (br s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.39-7.42 (dd, J = 1.4, 7.8 Hz, 1H), 7.68 (br s, 1H), 7.81 (d, J = 7.7 Hz, 1H), 8.05 (s, 1H), 8.43 (s, 1H), 8.76 (s, 1H), 9.02-9.04 (d, J = 6.7 Hz, 1H), 11.63 (s, 1H).

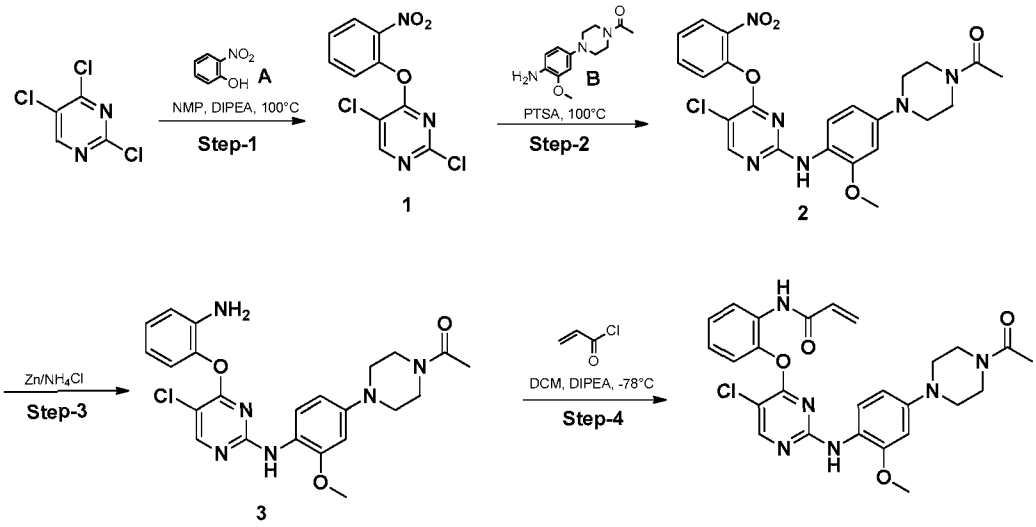
Example 282



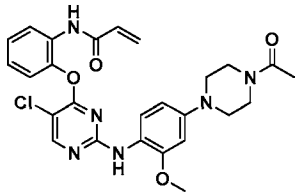
I-257

[00637] Rac-trans-4-((2-acrylamidocyclohexyl)amino)-2-((5-((2-hydroxyethoxy) carbamoyl)-2-methylphenyl)amino)pyrimidine-5-carboxamide. Compound **I-257** was prepared in a manner similar to Example 274, substituting ammonia hydroxide for methyl amine, substituting 3-amino-N-(2-hydroxyethoxy)-4-methoxybenzamide for 2-methoxy-4-morpholinoaniline, and substituting trans-N-2-(aminocyclohexyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z 498.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.08-1.25 (m, 4H), 1.57 (d, J = 8.8 Hz, 2H), 1.80 (br s, 1H), 1.86 (br s, 2H), 2.05 (d, J = 12.0 Hz, 2H), 2.31 (s, 3H), 3.57 (t, J = 5.0 Hz, 2H), 3.59 (m, 3H), 3.88 (t, J = 5.0 Hz, 2H), 5.44-5.47 (dd, J = 3.5, 8.9 Hz, 1H), 5.95 (m, 2H), 6.90 (br s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.42-7.44 (dd, J = 1.6, 7.7 Hz, 1H), 7.68 (br s, 1H), 7.82 (d, J = 7.5 Hz, 1H), 8.04 (s, 1H), 8.43 (s, 1H), 8.76 (s, 1H), 9.02 (d, J = 6.9 Hz, 1H).

[00638] **Method G** describes the synthesis of final targets with an ether linkage between the aromatic ring substituted with a warhead group and the pyrimidine core. The chemistry sequence and conditions are demonstrated below.



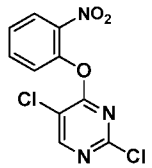
Example 283



I-259

[00639] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)oxy)phenyl)acrylamide. The title compound was prepared according to the steps and intermediates described below.

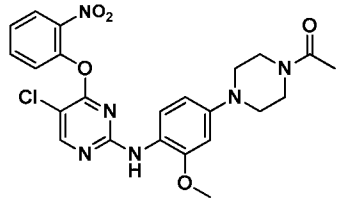
Step-1. Preparation of 2,5-dichloro-4-(2-nitrophenoxy)pyrimidine:



[00640] To a stirred solution of 2, 4, 5-trichloropyrimidine (1.3g, 7.19mmol) in NMP (3mL), DIPEA (1.85g, 14.3mmol) and 2-nitrophenol (1g, 7.19mmol) were added and heated to 100°C for 1h. TLC showed completion of starting material (TLC system: 20% ethyl acetate in hexane (R_f): 0.3). The reaction mixture was poured into crushed ice (50mL). The obtained solid was filtered, washed with water (50mL) and dried to obtain 2,5-dichloro-4-(2-

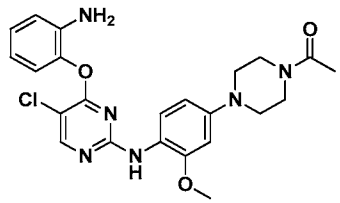
nitrophenoxy)pyrimidine as an off-white solid. (Yield: 1.7g, 85%). ^{1}H NMR(400MHz, D_6-DMSO) δ 8.98 (s, 1H), 8.25 (d, 1H), 7.92 (t, 1H), 7.70 (m, 2H).

Step-2. Preparation of 1-(4-(4-(5-chloro-4-(2-nitrophenoxy)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazin-1-yl)ethanone



[00641] To a stirred solution of 2,5-dichloro-4-(2-nitrophenoxy)pyrimidine (300mg, 1.052mmol) in 0.08M p-PTSA/1,4-dioxane (10mL) was added 1-(4-(4-amino-3-methoxy phenyl)piperazin-1-yl)ethanone (262mg, 1.052mmol), and the mixture was heated to 100°C for 16h. TLC showed completion of starting material (TLC system: 5% methanol in chloroform **(R_f):** 0.4). 1, 4-dioxane was evaporated under reduced pressure, and the remainder was diluted with ethyl acetate (35mL) and the remainder was washed with water (10mL) followed by saturated $NaHCO_3$ solution (10mL). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200 mesh) with 3% methanol in chloroform to obtain 1-(4-(4-(5-chloro-4-(2-nitrophenoxy)pyrimidin-2-ylamino)-3-methoxyphenyl) piperazin-1-yl)ethanone as a grey solid. (Yield: 140mg, 26.6%). MS: m/z 308.4 (ES+, M+H).

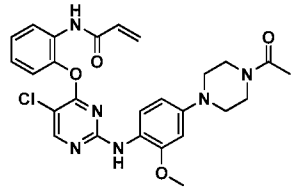
Step-3. Preparation of 1-(4-(4-(4-(2-aminophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxy phenyl)piperazin-1-yl)ethanone:



[00642] To a stirred solution of 1-(4-(4-(5-chloro-4-(2-nitrophenoxy)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazin-1-yl)ethanone (140mg, 0.28mmol) in 1,4-dioxane:water (10mL:4mL), Zinc dust (81mg, 1.4mmol) and ammonium chloride (74mg, 1.4mmol) were added, and the mixture was stirred at rt for 30min. TLC showed completion of starting material (TLC system:5% methanol in chloroform **(R_f):** 0.3). The reaction mixture was filtered, concentrated, diluted with water (20mL) and extracted with ethyl acetate (3x10mL). The organic layer was

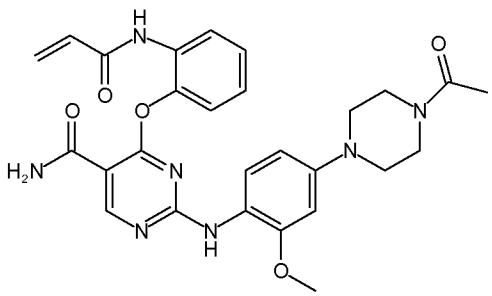
separated, dried over sodium sulphate, and concentrated. Crude compound was washed with n-pentane to obtain 1-(4-(4-(4-(2-aminophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxy phenyl)piperazin-1-yl)ethanone as a pale yellow solid. (Yield: 90mg, 68.7%). ^{1}HNMR (DMSO-d_6) δ 8.30 (s, 1H), 7.90 (s, 1H), 7.35 (d, 1H), 7.00 (m, 2H), 6.80 (d, 1H), 6.58 (m, 2H), 6.20 (br s, 1H), 4.90 (br s, 2H), 3.75 (s, 3H), 3.55 (m, 4H), 3.05 (m, 2H), 2.95 (m, 2H), 2.02 (s, 3H).

Step-4. Preparation of N-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloro pyrimidin-4-yloxy)phenyl)acrylamide:



[00643] To a stirred solution of 1-(4-(4-(4-(2-aminophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxy phenyl)piperazin-1-yl)ethanone (75mg, 0.16mmol) in DCM (5mL), DIPEA (42mg, 0.33mmol) and acryloyl chloride (15mg, 0.165mmol) were added at -78°C, and the mixture was stirred for 15min. TLC showed completion of starting material (TLC system: 10% methanol in chloroform (R_f): 0.2). The reaction mixture was quenched with water (15mL) and extracted with DCM (2x 10mL). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by prep-HPLC to obtain N-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-yloxy)phenyl) acrylamide as a yellow solid. (Yield: 28mg, 33.7%). MS: m/z 523.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 9.54 (s, 1H), 8.33 (s, 1H), 8.01 (s, 1H), 7.99 (br s, 1H), 7.25 (m, 4H), 6.56 (s, 1H), 6.50 (d, 1H, J = 10.4 Hz), 6.22 (br s, 1H), 6.127 (s, 1H), 5.70 (dd, 1H, J = 2.0, 10.4 Hz), 3.73 (s, 3H), 3.57 (m, 4H), 3.06 (br t, 2), 3.00 (br t, 2H), 2.03 (s, 3H).

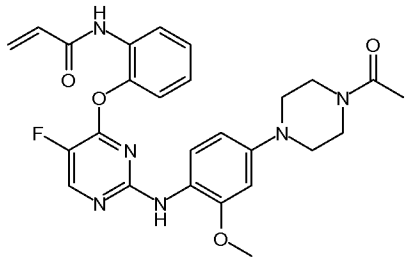
Example 284



I-258

[00644] 2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-4-(2-acrylamidophenoxy) pyrimidine-5-carboxamide: Compound **I-258** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine**:** MS m/z 532.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.05 (s, 3H), 3.12 (t, J = 4.9 Hz, 2H), 3.18 (t, J = 4.9 Hz, 2H), 3.60 (d, J = 4.9 Hz, 4H), 3.75 (s, 3H), 6.14 (dd, J = 1.4, 10.2 Hz, 1H), 6.41-6.48 (dd, J = 10.2, 17.3 Hz, 1H), 6.50-6.58 (m, 2H), 6.68 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 5.8 Hz, 1H), 7.15 (d, J = 9.3 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.93 (br s, 1H), 8.52 (br s, 1H), 8.60 (s, 1H), 11.75 (s, 1H).

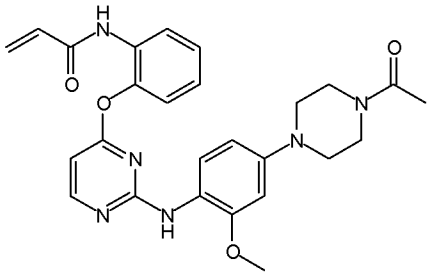
Example 285



I-260

[00645] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-fluoropyrimidin -4-yl)oxy)phenyl)acrylamide: Compound **I-260** was prepared in a manner similar to Example 283, using 2,4-dichloro-5-fluoropyrimidine as the pyrimidine**:** MS m/z 507.3 (ES+, M+H).

Example 286

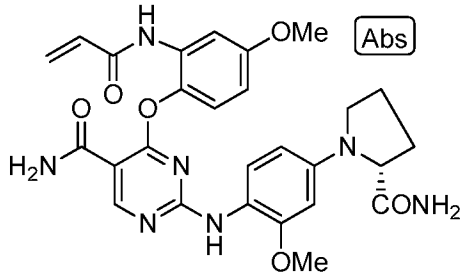


I-261

[00646] N-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide: Compound **I-261** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine as the pyrimidine**.** MS m/z 489.3 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.02 (s, 3H), 3.00 (t, J = 4.8 Hz, 2H), 3.06 (t, J = 4.8 Hz, 2H), 3.55 (d, J = 4.8 Hz, 4H), 3.76 (s, 3H), 5.65-5.68 (dd, J = 1.8, 10.2 Hz, 1H), 6.15-6.20 (dd, J = 1.9, 17.0 Hz, 1H), 6.26-6.31 (m, 2H), 6.50-6.56 (dd, J = 10.1, 17.0 Hz, 1H), 6.59 (d, J = 2.4 Hz, 1H), 7.19-7.22 (m, 2H), 7.25

(m, 1H), 7.44 (d, J = 8.6 Hz, 1H), 7.81 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 8.24 (d, J = 5.5 Hz,1H), 9.60 (s, 1H).

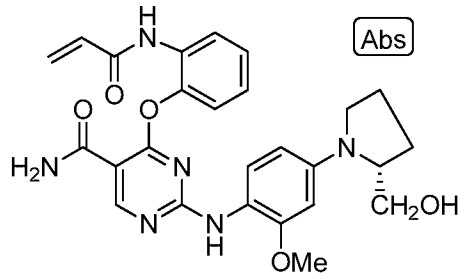
Example 287



I-262

[00647] (R)-4-(2-acrylamido-4-methoxyphenoxy)-2-((4-(2-carbamoylpyrrolidin-1-yl)-2-methoxyphenyl)amino)pyrimidine-5-carboxamide: Compound **I-262** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting 4-methoxy-2-nitrophenol for 2-nitrophenol, and substituting (R)-1-(4-amino-3-methoxyphenyl)pyrrolidine-2-carboxamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone. MS m/z 548.2 (ES+, M+H).

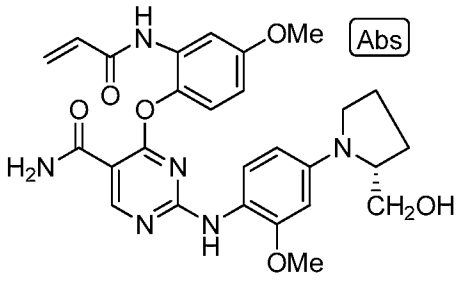
Example 288



I-263

[00648] (R)-4-(2-acrylamidophenoxy)-2-((4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-methoxyphenyl)amino)pyrimidine-5-carboxamide: Compound **I-263** was prepared in a manner similar to Example 283, substituting (R)-(1-(4-amino-3-methoxyphenyl)pyrrolidin-2-yl)methanol for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone. MS m/z 505.2 (ES+, M+H).

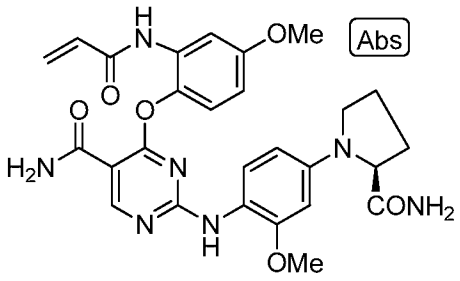
Example 289



I-264

[00649] (R)-4-(2-acrylamido-4-methoxyphenoxy)-2-((4-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-methoxyphenyl)amino)pyrimidine-5-carboxamide: Compound **I-264** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting 4-methoxy-2-nitrophenol for 2-nitrophenol, and substituting (R)-(1-(4-amino-3-methoxyphenyl)pyrrolidin-2-yl)methanol for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone. MS m/z 535.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.85-2.05 (m, 3H), 3.05 (q, J=8.2 Hz, 1H), 3.15-3.21 (m, 1H), 3.15-3.21 (m, 1H), 3.39 (t, J=8.0 Hz, 1H), 3.51-3.58 (m, 1H), 3.65-3.69 (m, 1H), 3.73 (s, 3H), 4.75 (t, J=5.3 Hz, 1H), 6.11- 6.16 (m, 2H), 6.24 (d, J=2.3 Hz, 1H), 6.39-6.46 (dd, J=10.2, 17.3 Hz, 1H), 6.52-6.56 (m, 2H), 7.05 (d, J=8.8 Hz, 1H), 7.24 (d, J=8.6 Hz, 1H), 7.33 (br s, 1H), 7.88 (br s, 1H), 8.03 (br s, 1H), 8.39 (s, 1H), 8.58 (s, 1H), 11.8 (s, 1H).

Example 290

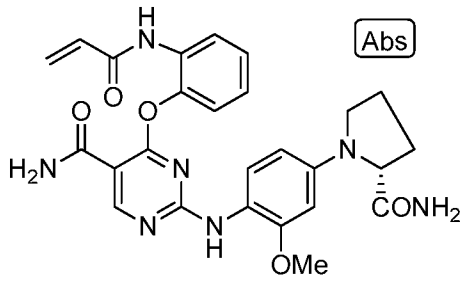


I-265

[00650] (S)-4-(2-acrylamido-4-methoxyphenoxy)-2-((4-(2-carbamoylpyrrolidin-1-yl)-2-methoxyphenyl)amino)pyrimidine-5-carboxamide: Compound **I-265** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting 4-methoxy-2-nitrophenol for 2-nitrophenol, and substituting (S)-1-(4-amino-3-methoxyphenyl)pyrrolidine-2-carboxamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone: MS m/z 548.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.01-2.03 (m, 1H), 2.18-2.23

(m, 1H), 3.21-3.24 (m, 1H), 3.50-3.53 (m, 1H), 3.56-3.60 (m, 2H), 3.72 (s, 3H), 3.89-3.91 (m, 1H), 6.02-6.05 (dd, J = 2.4, 8.6 Hz, 1H), 6.11-6.14 (dd, J = 1.5, 10.1 Hz, 1H), 6.17 (d, J = 2.4 Hz, 1H), 6.39-6.46 (dd, J = 10.1, 17.3 Hz, 1H), 6.51-6.56 (m, 2H), 7.03-7.06 (m, 2H), 7.28 (d, J = 8.6 Hz, 1H), 7.32 (br s, 2H), 7.88 (br s, 1H), 8.06 (br s, 1H), 8.39 (s, 1H), 8.57 (br s, 1H), 11.79 (s, 1H).

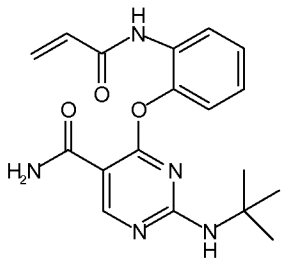
Example 291



I-266

[00651] (R)-4-(2-acrylamidophenoxy)-2-((4-(2-carbamoylpyrrolidin-1-yl)-2-methoxyphenyl)amino)pyrimidine-5-carboxamide: Compound **I-266** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, and substituting (R)-1-(4-amino-3-methoxyphenyl)pyrrolidine-2-carboxamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone. MS m/z 518.2 (ES+, M+H); ^{1}HNMR ($CDCl_3$) δ 2.03-2.08 (m, 2H), 2.27-2.33 (m, 2H), 3.22-3.29 (m, 1H), 3.63-3.68 (m, 1H), 3.84 (s, 3H), 4.00 (m, 1H), 5.39 (br s, 1H), 5.60 (br s, 2H), 6.01-6.03 (dd, J = 1.0, 10.4 Hz, 1H), 6.19 (d, J = 2.4 Hz, 1H), 6.22-6.25 (dd, J = 2.4, 8.8 Hz, 1H), 6.39-6.48 (m, 2H), 6.63-6.68 (m, 2H), 7.12 (d, J = 8.8 Hz, 1H), 7.38 (br s, 1H), 8.05 (br s, 2H), 8.07 (br s, 1H), 8.34 (s, 1H), 11.14 (br s, 1H).

Example 292

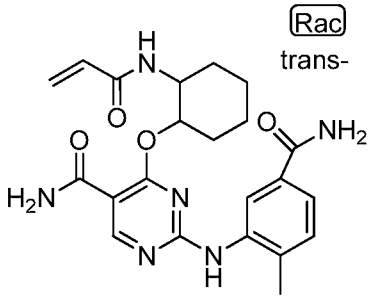


I-267

[00652] 4-(2-acrylamidophenoxy)-2-(tert-butylamino)pyrimidine-5-carboxamide: Compound **I-267** was prepared in a manner similar to Example 283, using 2,4-

dichloropyrimidine-5-carboxamide as the pyrimidine, and substituting t-Butyl amine for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone. MS m/z 356.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.38 (s, 9H), 6.13-6.16 (dd, J= 1.1, 10.3 Hz, 1H), 6.40-6.58 (m, 2H), 7.05 (br s, 2H), 7.17-7.25 (m, 2H), 7.81 (br s, 1H), 8.56 (br s, 1H), 11.68 (s, 1H).

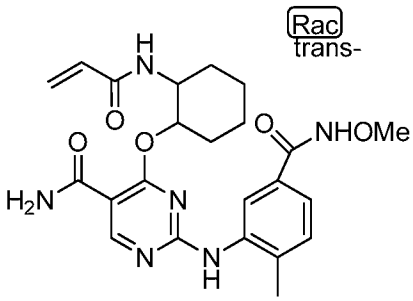
Example 293



I-268

[00653] Rac-trans-4-((2-acrylamidocyclohexyl)oxy)-2-((5-carbamoyl-2-methylphenyl) amino)pyrimidine-5-carboxamide. Compound **I-267** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting tert-butyl trans-2-(hydroxycyclohexyl)carbamate for 2-nitrophenol, and substituting 3-amino-4-methylbenzamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone**:** MS m/z 439.3 (ES+, M+H).

Example 294

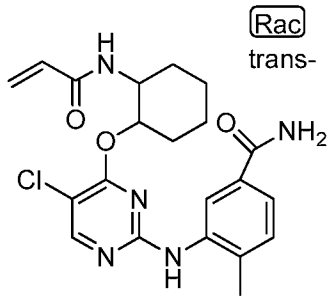


I-269

[00654] Rac-trans-4-((2-acrylamidocyclohexyl)oxy)-2-((5-(methoxycarbamoyl)-2-methylphenyl)amino)pyrimidine-5-carboxamide. Compound **I-269** was prepared in a manner similar to Example 283, using 2,4-d(ichloropyrimidine-5-carboxamide as the pyrimidine, substituting tert-butyl trans-2-hydroxycyclohexyl)carbamate for 2-nitrophenol, and substituting 3-amino-N-methoxy-4-methylbenzamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone, followed by Boc-deprotection using TFA and amide formation with acryloyl

chloride. MS m/z 469.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.04-1.28 (m, 4H), 1.60 (d, J = 8.6 Hz, 2H), 1.81 (br s, 1H), 1.86 (br s, 2H), 2.10-2.20 (br s, 1H), 2.26 (s, 3H), 3.68 (s, 3H), 4.01-4.07 (m, 1H), 4.70 (br s, 1H), 5.52-5.55 (dd, J = 3.2, 9.1 Hz, 1H), 6.01-6.14 (m, 2H), 7.08 (s, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.47-7.50 (dd, J = 1.6, 7.8 Hz, 1H), 7.90 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.63 (s, 1H), 9.38 (s, 1H), 11.64 (s, 1H).

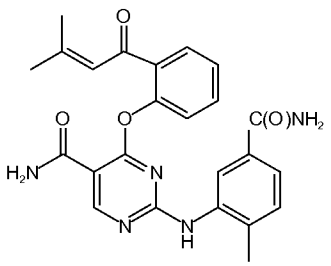
Example 295



I-270

[00655] Rac-trans-3-((4-((2-acrylamidocyclohexyl)oxy)-5-chloropyrimidin-2-yl)amino)-4-methylbenzamide. Compound **I-270** was prepared in a manner similar to Example 283, substituting tert-butyl trans-2-(hydroxycyclohexyl)carbamate for 2-nitrophenol, and substituting 3-amino-4-methylbenzamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone, followed by Boc-deprotection using TFA and amide formation with acryloyl chloride. MS m/z 430.1 (ES+, M+H).

Example 296

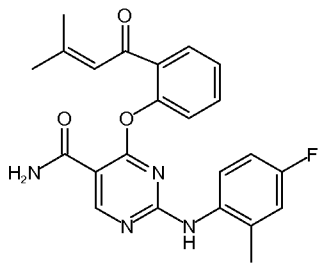


I-271

[00656] 2-((5-carbamoyl-2-methylphenyl)amino)-4-(2-(3-methylbut-2-enoyl)phenoxy) pyrimidine-5-carboxamide: Compound **I-271** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting 2-hydroxy-N-methoxy-N-methylbenzamide for 2-nitrophenol, and substituting 3-amino-4-methylbenzamide for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone, followed by reaction with (2-

methylprop-1-en-1-yl)magnesium chloride. MS m/z 446.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.78 (s, 3H), 1.88 (s, 3H), 2.06 (s, 3H), 6.4 (br s, 1H), 7.16 (d, J = 7.5 Hz, 1H), 7.2 (s, 1H), 7.3-7.32 (m, 1H), 7.36 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 8.5 Hz, 3H), 7.59 (d, J = 8.4 Hz, 1H), 7.62 (s, 1H), 7.77 (s, 1H), 8.68 (s, 1H), 9.28 (s, 1H).

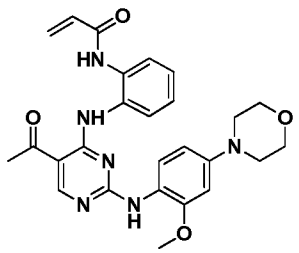
Example 297



I-272

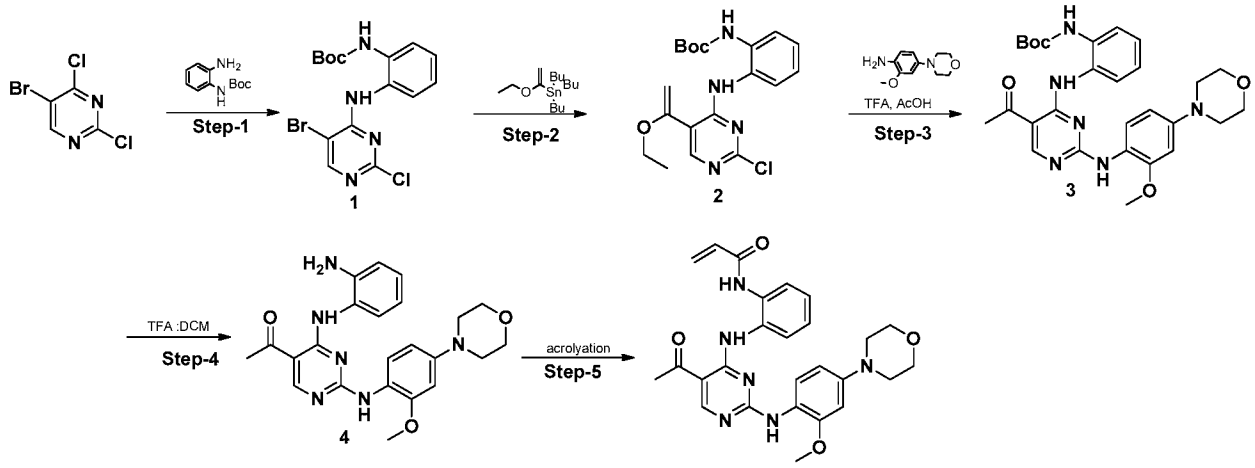
[00657] 2-((4-fluoro-2-methylphenyl)amino)-4-(2-(3-methylbut-2-enoyl)phenoxy) pyrimidine-5-carboxamide: Compound **I-272** was prepared in a manner similar to Example 283, using 2,4-dichloropyrimidine-5-carboxamide as the pyrimidine, substituting 2-hydroxy-N-methoxy-N-methylbenzamide for 2-nitrophenol, and substituting 4-fluoro-2-methylaniline for 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone, followed by reaction with (2-methylprop-1-en-1-yl)magnesium chloride. MS m/z 421.4 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 1.78 (s, 3H), 1.85 (s, 3H), 2.05 (s, 3H), 6.44 (s, 1H), 6.75 (br s, 1H), 6.93 (d, J=7.6 Hz, 1H), 7.05-7.09 (m, 1H), 7.36-7.38 (m, 3H), 7.55-7.60 (m, 2H), 7.65-7.67 (dd, J=1.5 Hz, 7.6 Hz, 1H), 8.69 (s, 1H), 9.14 (s, 1H).

Example 298

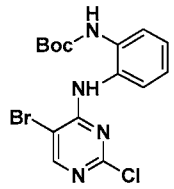


I-273

[00658] N-(2-(5-acetyl-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-yl amino)phenyl) acrylamide: The title compound was prepared according to the steps and intermediates described below.

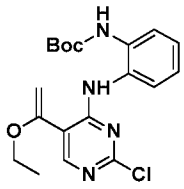


Step-1. Preparation of tert-butyl 2-(5-bromo-2-chloropyrimidin-4-ylamino) phenylcarbamate :



[00659] To a solution of tert-butyl 2-aminophenylcarbamate (2g, 9.6mol) in NMP (15mL), DIPEA (3.1g, 24mmol) and 5-bromo-2,4-dichloropyrimidine (2.78g, 14.4mmol) were added and heated to 120°C for 1h. TLC showed completion of starting material (TLC system: 5% methanol in DCM **(R_f):** 0.6). The reaction mixture was diluted with water (50mL). The obtained solid was filtered, washed with water (35mL) and dried to obtain tert-butyl 2-(5-bromo-2-chloropyrimidin-4-ylamino) phenylcarbamate as a pale yellow solid. Yield: (2.2g, 62%). MS: m/z 399.1 (ES+, M+H).

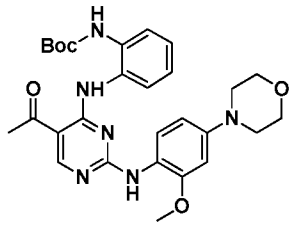
Step-2. Preparation of tert-butyl 2-(2-chloro-5-(1-ethoxyvinyl)pyrimidin-4-ylamino)phenyl carbamate :



[00660] To a solution of tert-butyl 2-(5-bromo-2-chloropyrimidin-4-ylamino) phenylcarbamate (1.4g, 3.5mmol) in dry DMF (15mL), tributyl(1-ethoxyvinyl)stannane (2.5g, 7mmol) was added and degassed for 20min. To the reaction mixture $PdCl_2$ $(PPh_3)_2$ (122mg,

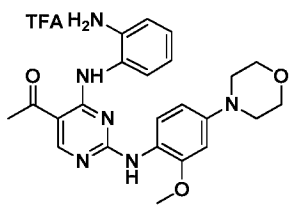
0.1mmol) was added and again degassed for another 5min. The temperature was raised to 100° C, and the mixture was stirred for 4h. TLC showed completion of starting material (TLC system: 30% ethyl acetate in hexane **(R_f):** 0.4). The reaction mixture was quenched with water (60mL) and extracted with ethyl acetate (3x35mL). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200mesh) with 10% ethyl acetate in hexane to obtain tert-butyl 2-(2-chloro-5-(1-ethoxyvinyl)pyrimidin-4-ylamino)phenyl carbamate as a pale yellow solid. Yield: (500mg, 38%). MS: m/z 391.1 (ES+, M+H).

Sep-3. Preparation of tert-butyl 2-(5-acetyl-2-(2-methoxy-4-morpholinophenylamino) pyrimidin-4-ylamino)phenylcarbamate:



[00661] To a solution of tert-butyl 2-(2-chloro-5-(1-ethoxyvinyl)pyrimidin-4-ylamino) phenyl carbamate (350mg, 0.897mmol) in 1, 4 dioxane (10mL), acetic acid (54mg, 0.897mmol) and TFA (9mg, 0.0897mmol) were added and heated to 80°C for 1h. The reaction mixture was cooled; 2-methoxy-4-morpholinoaniline (186mg, 0.897mmol) was added and stirred at 100°C for 4h. TLC showed completion of starting material (TLC system: 30% ethyl acetate in hexane **(R_f):** 0.3). The reaction mixture was evaporated under reduced pressure. Crude compound was purified by column chromatography using silica gel (100-200mesh) with 20% ethyl acetate in hexane to obtain tert-butyl 2-(5-acetyl-2-(2-methoxy-4-morpholino phenylamino)pyrimidin-4-ylamino)phenyl carbamate as a yellow solid. Yield: (250mg, 52%). MS: m/z 535.3 (ES+, M+H).

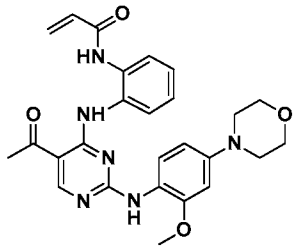
Step-4. Preparation of 1-(4-(2-aminophenylamino)-2-(2-methoxy-4-morpholinophenylamino) pyrimidin-5-yl) ethanone (4):



[00662] To a solution of tert-butyl 2-(5-acetyl-2-(2-methoxy-4-morpholinophenyl amino)pyrimidin-4-ylamino)phenylcarbamate (100mg) in DCM (5ml), TFA (1ml) was added at

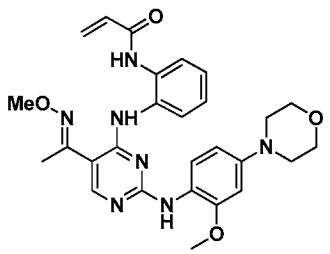
0°C, and the mixture was stirred for 1h at rt. TLC showed completion of starting material (TLC system: 5% methanol in DCM **(R_f):** 0.5). After removal of TFA under reduced pressure, the residue was triturated with diethyl ether to give the desired compound as a yellow solid 85mg (Yield: 98%). MS: m/z 435.2 (ES+).

Step-5. Preparation of N-(2-(5-acetyl-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-yl amino)phenyl)acrylamide:



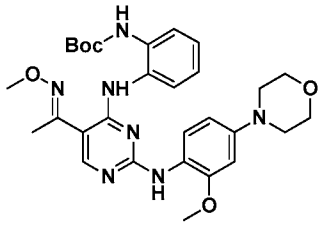
[00663] To a solution of 1-(4-(2-aminophenylamino)-2-(2-methoxy-4-morpholinophenylamino) pyrimidin-5-yl)ethanone (100mg, 0.23mmol) in DCM (10ml), DIPEA (55mg, 0.46mmol) and acrolyl chloride (20.7mg, 0.23mmol) were added at -20°C, and and the mixture was stirred for 30 min. TLC showed completion of starting material (TLC system: 5% methanol in DCM. **(R_f):** 0.5). The reaction mixture was diluted with DCM (20mL) and washed with water (2x10mL). The organic layer was separated, dried over sodium sulphate, and concentrated. Crude compound was purified by column chromatography using silica gel (100-200mesh) with 3% methanol in DCM to obtain N-(2-(5-acetyl-2-(2-methoxy-4-morpholinophenylamino) pyrimidin-4-yl amino) phenyl) acrylamide as a pale yellow solid. Yield: (30mg, 26%). MS: m/z 489.2 (ES+); ^{1}HNMR (DMSO-d_6) δ 11.25 (s, 1H), 9.76 (s, 1H), 8.77 (s, 1H), 8.73 (s, 1H), 8.10 (br s, 1H), 7.35 (d, 1H, J = 8.4 Hz), 7.25 (br s, 1H), .06 (br t, 2H), 6.65 (s, 1H), 6.45 (m, 2H), 6.20 (dd, 1H, J = 2.0, 17.2 Hz), 5.74 (dd, 1H, J = 8.0 Hz), 3.72 (m, 7H), 3.12 (m, 4 H, 3.24 (br s, 3H).

Example 299

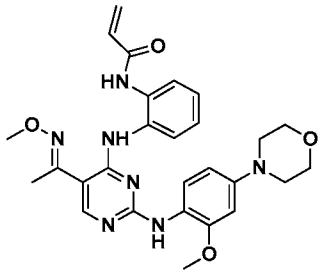


I-274

[00664] (E)-N-(2-((2-((2-methoxy-4-morpholinophenyl)amino)-5-(1-(methoxyimino)ethyl) pyrimidin -4-yl)amino)phenyl)acrylamide. This compound was synthesized through the following intermediates:

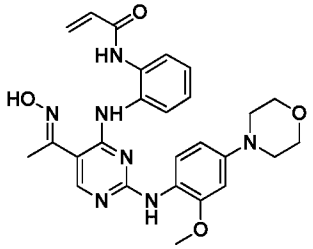


[00665] (E)-tert-butyl 2-(2-(2-methoxy-4-morpholinophenylamino)-5-(1-(methoxy imino)ethyl) pyrimidin-4-ylamino)phenylcarbamate. To a solution of tert-butyl 2-(5-acetyl-2-(2-methoxy-4-morpholino phenylamino)pyrimidin-4-ylamino)phenylcarbamate **(Intermediate 3 in Example 298**) (100mg, 0.18mmol) in ethanol (5mL), methoxylamine hydrochloride (55mg, 0.79mmol), DIPEA (46mg, 0.36mmol) and pyridine (0.5mL) were added and heated to 100° C for 16h. TLC showed completion of starting material (TLC system: 5% methanol in DCM **(R_f):** 0.3). The ethanol was evaporated under reduced pressure, and the remainder was diluted with water (10mL), filtered and dried to obtain (E)-tert-butyl 2-(2-(2-methoxy-4-morpholinophenylamino)-5-(1-(methoxyimino)ethyl)pyrimidin -4-ylamino) phenyl carbamate as white solid. Yield: (70mg, 66%). MS: m/z 564.3 (ES+, M+H).



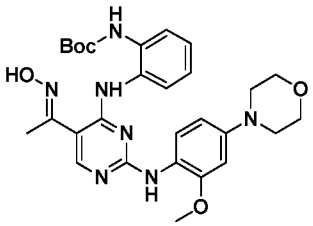
[00666] (E)-N-(2-(2-(2-methoxy-4-morpholinophenylamino)-5-(1-(methoxyimino) ethyl) pyrimidin-4-ylamino) phenyl) acrylamide: The title compound was prepared in the same manner as described in Step 4 of **Example 283** with Boc-deprotection using TFA followed by reaction with acryloyl chloride. MS: m/z 518.4 (ES+, M+H).

Example 300

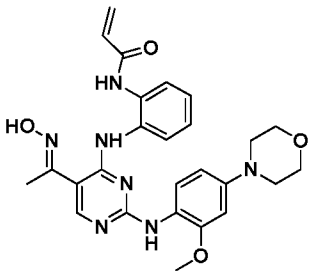


I-275

[00667] (E)-N-(2-((5-(1-(hydroxyimino)ethyl)-2-((2-methoxy-4-morpholinophenyl) amino)pyrimidin-4-yl)amino)phenyl)acrylamide. This compound was synthesized through the following intermediates:

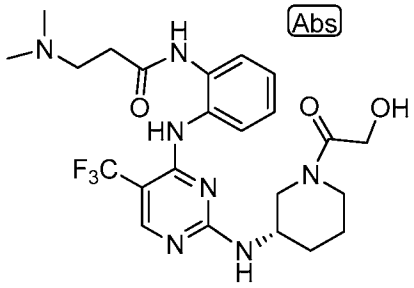


[00668] (E)-tert-butyl 2-(5-(1-(hydroxyimino)ethyl)-2-(2-methoxy-4-morpholino phenylamino)pyrimidin-4-ylamino)phenylcarbamate. This intermediate was prepared in the same way as for Intermediate 3 in Example 298 in **Example 299**, using hydroxylamine hydrochloride instead of methoxylamine hydrochloride. MS: m/z 550.4 (ES+).



[00669] (E)-N-(2-((5-(1-(hydroxyimino)ethyl)-2-((2-methoxy-4-morpholinophenyl) amino)pyrimidin-4-yl)amino)phenyl)acrylamide. The title compound was prepared in same manner as described in Step 4 of **Example 283** with Boc-deprotection using TFA followed by reaction with acryloyl chloride. MS: m/z 504.3 (ES+, M+H).

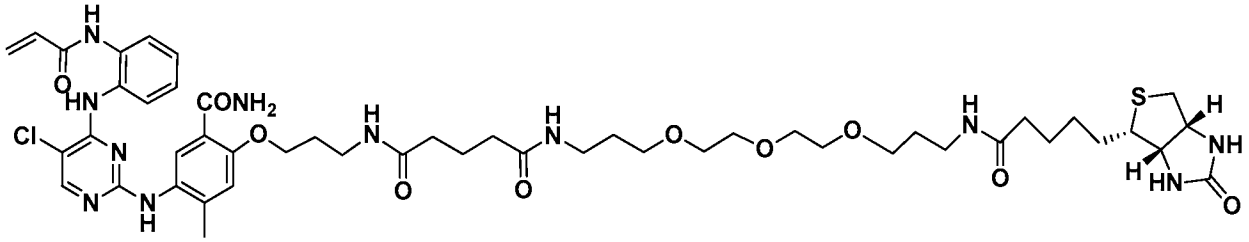
Example 301



I-276

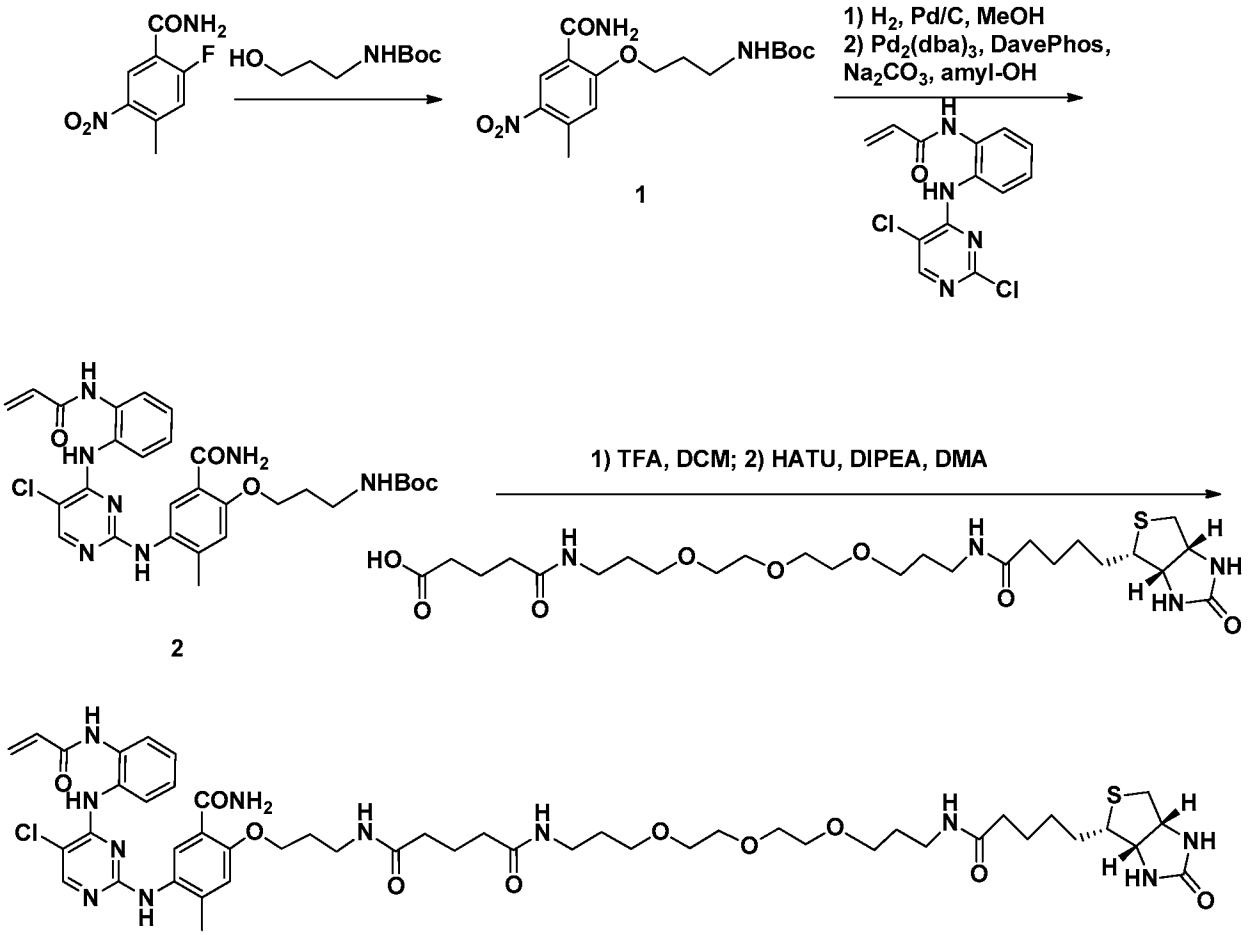
[00670] (S)-3-(dimethylamino)-N-(2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)propanamide: Compound **I-276** was prepared in a manner similar to Example 1, substituting N-(2-aminophenyl)-3-(dimethylamino)propanamide for N-(2-aminophenyl)acrylamide. MS: m/z 510.2 (ES+, M+H); ^{1}HNMR (CD_3OD) δ 1.47 (br s, 1H), 1.62-2.0 (m, 4H), 2.96 (s, 6H), 3.04 (br s, 2H), 3.14 (br s, 1H), 3.51 (t, J=7.0Hz, 4H), 3.65-3.80 (m, 2H), 3.90 (br s, 1H), 7.27-7.43 (m, 2H), 7.50-7.65 (m, 2H), 8.38 (s, 1H).

Example 302-Covalent Probes

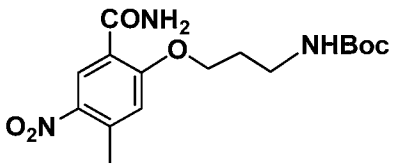


I-299

[00671] N^1-(3-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-carbamoyl-5-methylphenoxy)propyl)-N^5-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide. The title compound was prepared according to the steps and intermediates as described below.



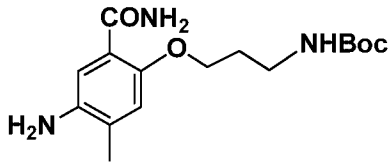
Step-1: tert-butyl (3-(2-carbamoyl-5-methyl-4-nitrophenoxy)propyl)carbamate.



[00672] To a suspension of sodium hydride (200 mg, 60% in mineral oil, 5 mmol) in 4 mL of anhydrous THF, was added tert-butyl (3-hydroxypropyl)carbamate (100 mg, 0.57 mmol) in 1 mL of anhydrous THF. After stirring at rt for 5 min, 2-fluoro-4-methyl-5-nitrobenzamide (100 mg, 0.50 mmol) was added in one portion. The resulting mixture was stirred for an additional 30 min; and LC-MS showed completion of the reaction. The reaction was quenched with ice-water, and the final product was extracted with EtOAc, washed with aqueous NH_4Cl, and dried over anhydrous sodium sulfate. After concentration, 133 mg of white solid was obtained as the desired product in 75% yield. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 6.83 (s, 1H), 4.25 (t,

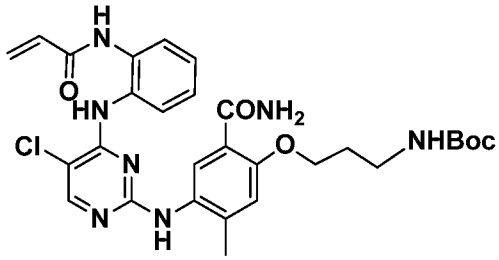
2H, *J* = 6.8 Hz), 3.33 (br t, 2H), 2.65 (s, 3H, Me), 2.05 (m, 2H), 1.39 (s, 9H). MS: m/z 254.1 (ES+, M+H-Boc).

tert-butyl (3-(4-amino-2-carbamoyl-5-methylphenoxy)propyl)carbamate



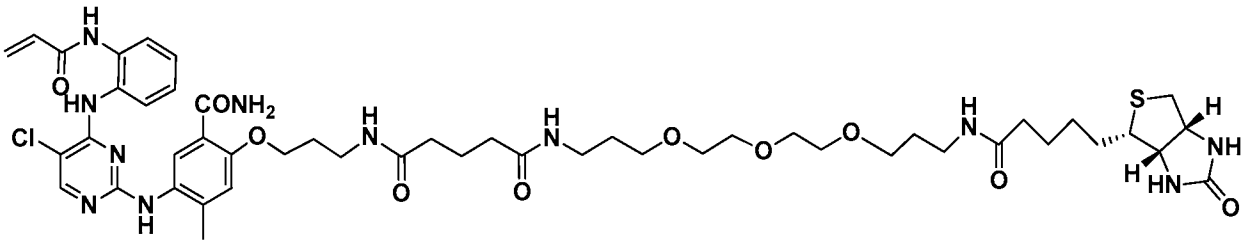
[00673] The nitro-intermediate obtained above was dissolved in MeOH, and stirred with 30 mg of 10% Pd/C under hydrogen at rt for 1 hr. After filtration, the desired aniline was obtained in quantitative yield as a red solid. MS: m/z 224.1 (ES+, M+H-Boc).

Step 2. tert-butyl (3-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-carbamoyl-5-methylphenoxy)propyl)carbamate



[00674] To a mixture of N-(2-((2,5-dichloropyrimidin-4-yl)amino)phenyl)acrylamide (15 mg, 49 umol), tert-butyl (3-(4-amino-2-carbamoyl-5-methylphenoxy)propyl)carbamate (22 mg, 68 umol), and sodium carbonate (25 mg, 23 umol) in 1 mL of amyl alcohol under Ar, was added $Pd_2(dba)_3$ (9.6 mg) and DavePhos (15 mg). The resulting mixture was heated at 100°C for 2 hr. After filtration, the product was purified by prep-HPLC, giving 18 mg of white powder (62%). MS: m/z 596.2 (ES+, M+H).

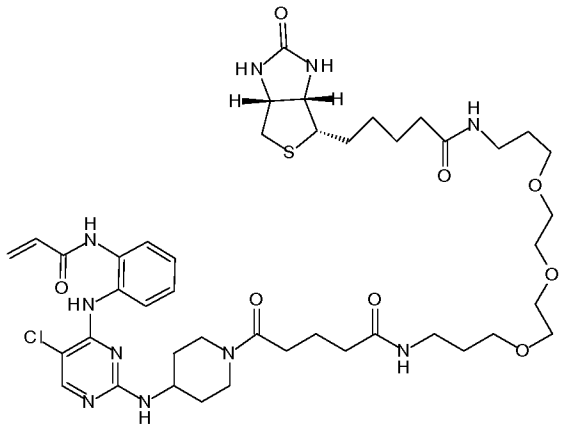
Step 3. N^1-(3-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-carbamoyl-5-methylphenoxy)propyl)-N^5-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide.



[00675] To the NBoc intermediate (18 mg) obtained from the previous step in 1 mL of dichloromethane, was added 1 mL of trifluoroacetic acid. After stirring for 15 min, the solvent was removed completely under reduced pressure, giving de-Boc intermediate. MS: m/z 496.3 (M+H).

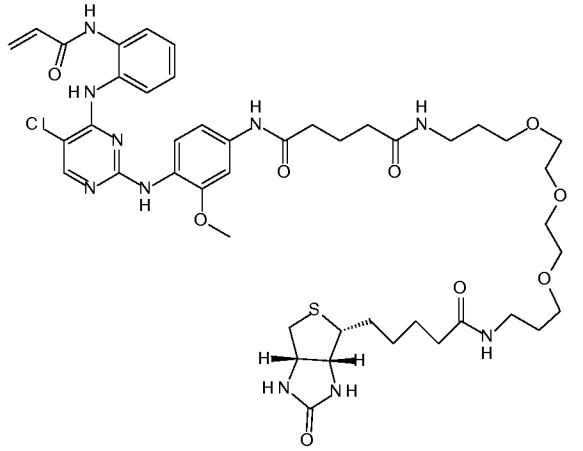
[00676] The de-Boc intermediate was re-dissolved in 1 mL of acetonitrile and 1 mL of DMA, followed by addition of 100 uL of N,N-diisopropyl ethylamine, 30 mg of 20-atom biotin acid, and 40 mg of HATU. After 10 min stirring at rt, LC-MS showed completion of the reaction. The reaction mixture was subject to prep-HPLC purification, giving desired biotin-linked compound 17.4 mg as white powder. MS: m/z 1038.3 (ES+, M+H).

Compound I-300



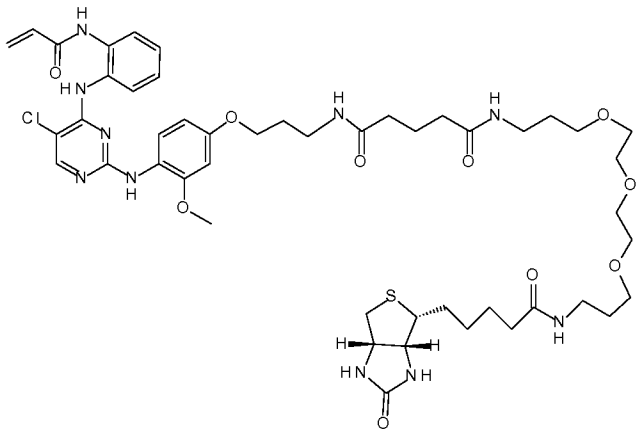
[00677] **5-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)piperidin-1-yl)-5-oxo-N-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)pentanamide.** Compound **I-300** was prepared in a manner similar to Compound **I-299,** using **I-116** for the starting material, then coupled to the acid to provide the titled compound. MS m/z 915.3 (ES+, M+H).

Compound I-301



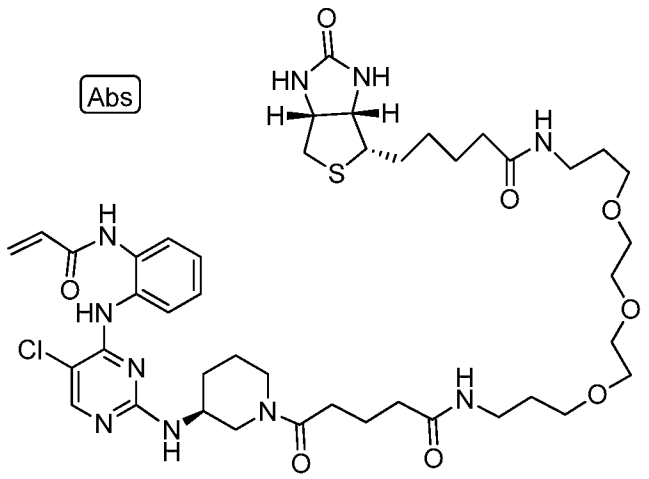
[00678] N^1-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenyl)-N^5-(15-oxo-19-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide. Compound **I-301** was prepared in a manner similar to Compound **I-299,** using **I-183** intermediate as the starting material, followed by coupling with the acid to provide the title compound. MS m/z 953.3 (ES+, M+H).

Compound I-302



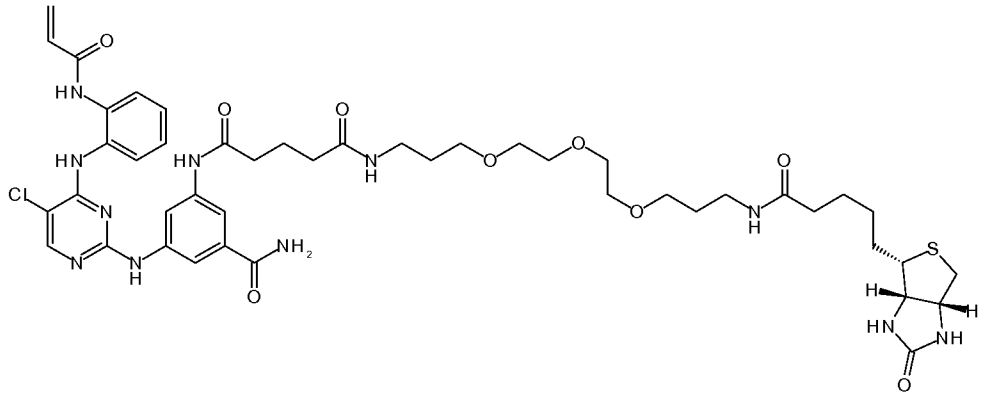
[00679] N^1-(3-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-methoxyphenoxy)propyl)-N^5-(15-oxo-19-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide. Compound **I-302** was prepared in a manner similar to Compound **I-299,** substituting 4-fluoro-2-methoxy-1-nitrobenzene for 2-fluoro-4-methyl-5-nitrobenzamide. MS m/z 1011.3 (ES+, M+H).

Compound I-303



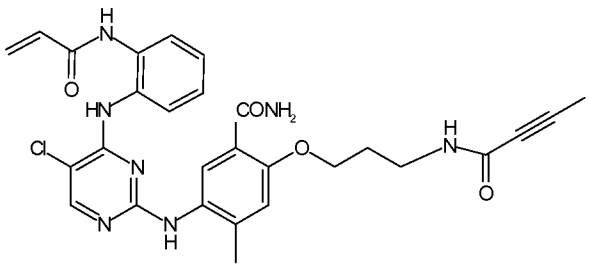
[00680] 5-((S)-3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)piperidin-1-yl)-5-oxo-N-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)pentanamide. Compound **I-303** was prepared similar to Compound **I-299** via amide formation between **I-126** and commercially available 20-atom biotin acid in the presence of HATU, DIPEA in DMA. MS m/z 915.3 (ES+, M+H).

Compound I-304



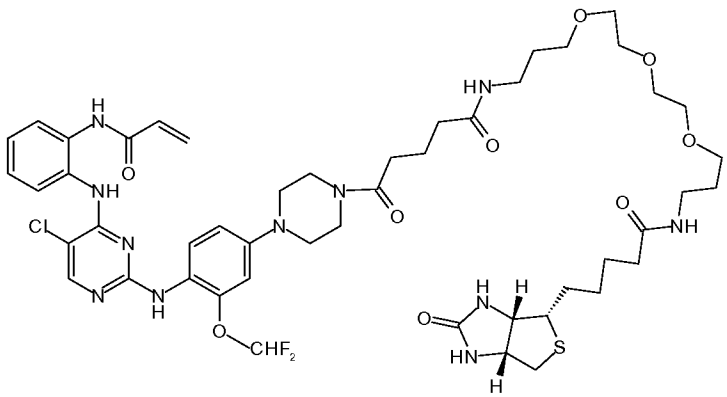
[00681] N^1-(3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-5-carbamoylphenyl)-N^5-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)glutaramide. Compound **I-304** was prepared in a manner similar to Compound **I-299** via amide formation between 3-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-5-aminobenzamide and commercially available 20-atom biotin acid in the presence of HATU, DIPEA in DMA. MS m/z 967.1 (ES+, M+H).

Compound I-305



[00682] 5-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-2-(3-(but-2-ynamido)propoxy)-4-methylbenzamide. Compound **I-305** was prepared in a manner similar to Example 162, substituting tert-butyl (3-(4-amino-2-carbamoyl-5-methylphenoxy)propyl) carbamate for 3-amino-4-methylbenzamide, followed by Boc-deprotection with TFA and amide formation with but-2-ynoic acid, HATU, DIPEA in DMA. MS m/z 562.2 (ES+, M+H).

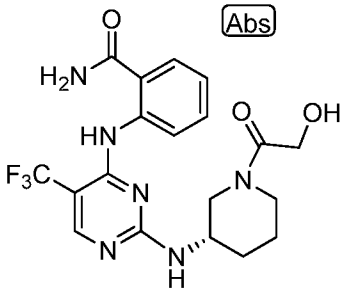
Compound I-306



[00683] 5-(4-(4-((4-((2-acrylamidophenyl)amino)-5-chloropyrimidin-2-yl)amino)-3-(difluoromethoxy)phenyl)piperazin-1-yl)-5-oxo-N-(15-oxo-19-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10-trioxa-14-azanonadecyl)pentanamide. Compound **I-306** was prepared in a manner similar to Compound **I-299,** using **I-142** for the starting material, then coupled with commercially available 20-atom biotin acid in the presence of HATU, DIPEA in DMA.. MS m/z 1170.3 (ES+, M+H).

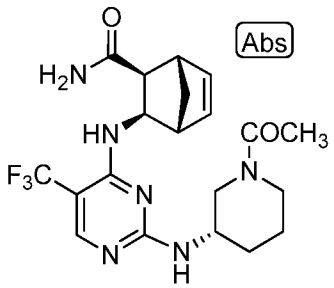
Example 303

Compound I-307



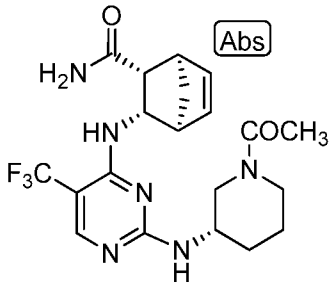
[00684] (S)-2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)benzamide: The title compound was prepared in a manner similar to Compound **I-15**, using 2-amino aniline as the starting material. MS: m/z 439.2 (ES+, M+H); (CD_3OD) δ 1.42 (m, 1H), 1.50-170 (m, 2H), 1.84-1.88 (m, 1H), 2.0-2.09 (m, 1H), 2.98-3.13 (m, 2H), 3.59-3.69 (m, 1H), 3.88-4.09 (m, 1H), 4.11-4.12 (m, 1H), 4.27 (s, 2H), 7.13 (t, J =7.8 Hz, 1H), 7.51 (t, J =7.4 Hz, 1H), 7.73-7.75 (m, 1H), 8.26 (br s, 1H), 8.69 (m, 1H).

Compound I-308



[00685] (1S,2S,3R,4R)-3-((2-(((S)-1-acetylpiperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxamide: The title compound was prepared as described in Example 1, by substituting (1S,2S,3R,4R)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide for N-(2-aminophenyl)acrylamide. MS m/z: 439.1 (ES+, M+H).

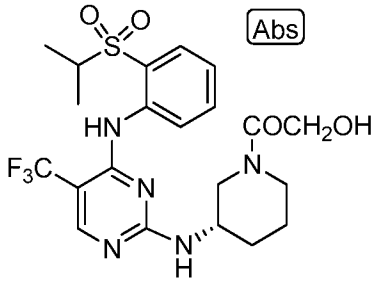
Compound I-309



[00686] (1R,2R,3S,4S)-3-((2-(((S)-1-acetylpiperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)bicyclo[2.2.1]hept-5-ene-2-carboxamide: The title compound was

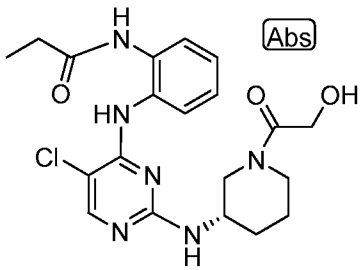
prepared as described in Example 1, by substituting (1R,2R,3S,4S)-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxamide for N-(2-aminophenyl)acrylamide. MS m/z: 439.1 (ES+, M+H).

Compound I-310



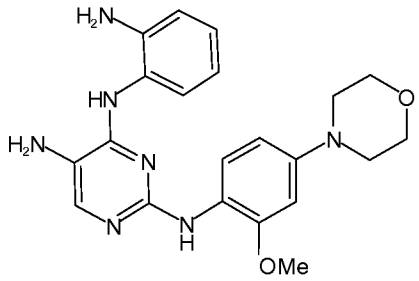
[00687] (S)-2-hydroxy-1-(3-((4-((2-(isopropylsulfonyl)phenyl)amino)-5-(trifluoromethyl) pyrimidin-2-yl)amino)piperidin-1-yl)ethanone: The title compound was prepared as described in Example 1, by substituting 2-(isopropylsulfonyl)aniline for N-(2-aminophenyl)acrylamide. MS m/z: 502.1 (ES+, M+H).

Compound I-311



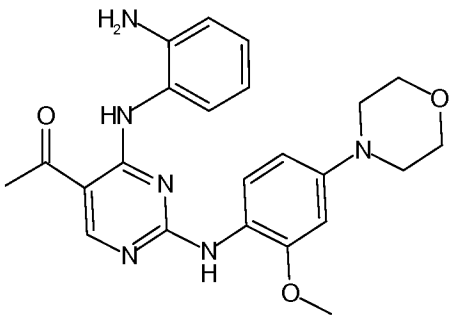
[00688] (S)-N-(2-((5-chloro-2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)pyrimidin-4-yl)amino)phenyl)propionamide. The title compound was made by the palladium mediated hydrogenation over **I-123**. MS m/z: 433.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 2.16 (s, 3H), 5.77-5.80 (dd, 1H, J=1.9Hz and J=10Hz), 6.26-6.31 (dd, 1H, J=1.9, 17Hz), 6.40-6.47 (dd, 1H, J=10, 17Hz), 7.08 (br s, 1H), 7.10-7.1615 (t, 1H, J=7, 16 Hz), 7.24-7.26 (d, 1H, J=7.9Hz), 7.60-7.62 (dd, 2H, J=1.5, 7.8Hz), 7.86 (s, 1H), 8.21 (s, 1H), 8.28 (s, 1H), 9.13(s, 1H), 10.28 (s, 1H), 12.81 (s, 1H)

Compound I-312



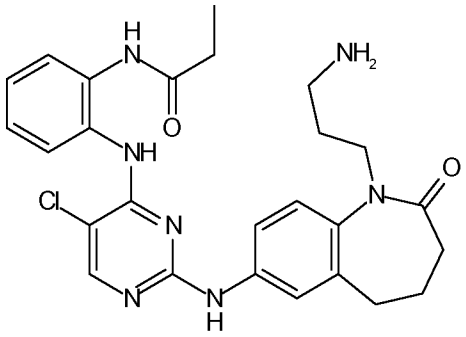
[00689] **N^4-(2-aminophenyl)-N^2-(2-methoxy-4-morpholinophenyl)pyrimidine-2,4,5-triamine**: The title compound was prepared in a manner similar to Example 162, using tert-butyl (2-aminophenyl)carbamate as the starting material, and substituting 2-methoxy-4-morpholinoaniline for 3-amino-4-methylbenzamide, and finally Boc deprotection with TFA. MS m/z: 408.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 3.01 (t, J = 4.5 Hz, 4H), 3.72 (t, J = 4.5 Hz, 4H), 3.77 (s, 3H), 4.50 (br s, 2H), 4.92 (br s, 2H), 6.24-6.27 (dd, J = 2.3, 8.8 Hz, 1H), 6.57-6.60 (m, 2H), 6.62 (d, J = 1.2 Hz,1H), 6.78 (dd, J = 1.1, 7.9 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.8 Hz,1H), 7.39 (s, 1H), 7.70 (s, 1H), 8.15 (s, 1H).

Compound I-313



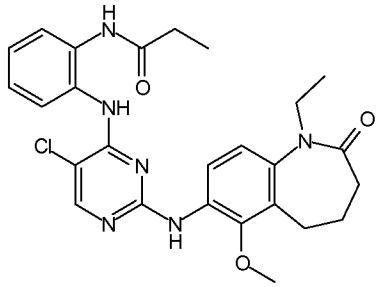
[00690] **1-(4-((2-aminophenyl)amino)-2-((2-methoxy-4-morpholinophenyl)amino) pyrimidin-5-yl)ethanone**: Compound **I-313** was prepared in a manner similar to **I-273,** substituting tert-butyl (2-aminophenyl)carbamate for the starting material, and finally Boc deprotection with TFA. MS m/z: 435.3 (ES+, M+H); ^{1}HNMR ($CDCl_3$) δ 2.54 (s, 3H), 3.08 (t, J = 4.5 Hz, 4H), 3.85 (br s, 2H), 3.86-3.87 (m, 7H), 6.19 (br s, 1H), 6.45 (d, J = 2.0 Hz, 1H), 6.82 (d, J = 1.2 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.4 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.78 (br s, 1H), 8.01 (br s, 1H), 8.67 (s, 1H), 10.77 (s, 1H).

Compound I-314



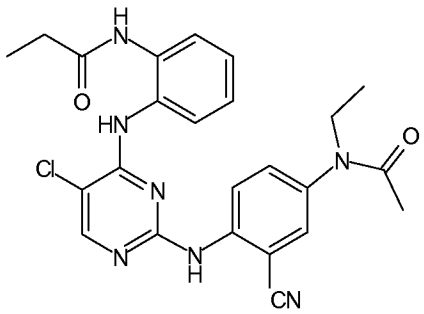
[00691] N-(2-((2-((1-(3-aminopropyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)propionamide: Compound **I-148** (20 mg) was hydrogenated in 4 mL of methanol with 5 mg of 10% palladium on charcoal under hydrogen. After stirring 30 min at rt, the catalyst was filtered out, and the desiredproduct was obtained after solvent removal. MS m/z: 508.2 (ES+, M+H).

Compound I-315



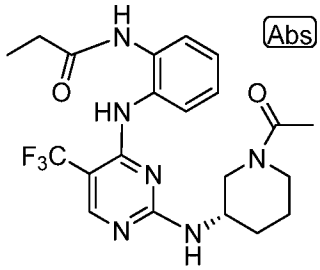
[00692] N-(2-((5-chloro-2-((1-ethyl-6-methoxy-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b]azepin-7-yl)amino)pyrimidin-4-yl)amino)phenyl)propionamide: Compound **I-315** was prepared in a manner similar to Example 162, substituting 7-amino-6-methoxy-1-(ethyl)-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one for 3-amino-4-methylbenzamide, which was then hydrogenated in 4 mL of methanol with 5 mg of 10% palladium on charcoal under hydrogen. After stirring 30 min at rt, the catalyst was filtered out, and the desired product was obtained after solvent removal. MS m/z: 509.1 (ES+, M+H).

Compound I-316



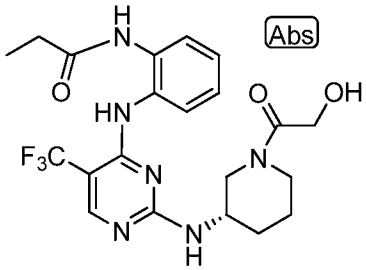
[00693] N-(2-((5-chloro-2-((2-cyano-4-(N-ethylacetamido)phenyl)amino)pyrimidin-4-yl)amino)phenyl)propionamide: Compound **I-316** was prepared in a manner similar to Example 162, substituting N-(4-amino-3-cyanophenyl)-N-ethylacetamide for 3-amino-4-methylbenzamide, which was hydrogenated in 4 mL of methanol with 5 mg of 10% palladium on charcoal under hydrogen. After stirring 30 min at rt, the catalyst was filtered out, and the desired product was obtained after solvent removal. MS m/z: 478.3 (ES+, M+H).

Compound I-317



[00694] (S)-N-(2-((2-((1-acetylpiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)propionamide: Compound **I-317** was prepared by Pd-catalyzed hydrogenation of compound **I-10**. MS m/z: 451.1 (ES+, M+H).

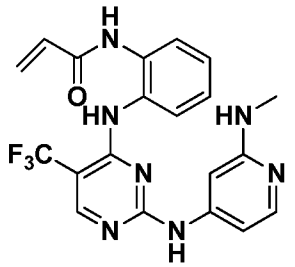
Compound I-318



I-318

[00695] (S)-N-(2-((2-((1-(2-hydroxyacetyl)piperidin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)propionamide. Compound **I-318** was prepared by Pd-catalyzed hydrogenation of compound **I-15.** MS: m/z 467.1 (ES+, M+H).

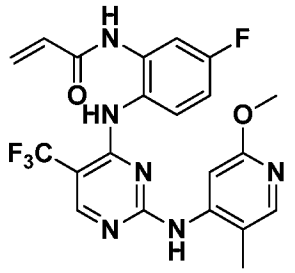
Example 304



I-321

[00696] N-(2-((2-((2-(methylamino)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-321** was prepared in a manner similar to Example 68, substituting N^2-methylpyridine-2,4-diamine for 3-amino-4-methylbenzamide. MS m/z 430.1 (ES+, M+H).

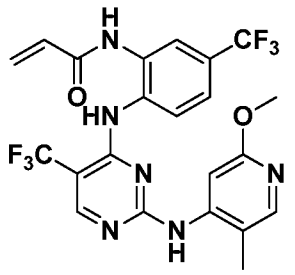
Example 305



I-322

[00697] N-(5-fluoro-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-322** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-fluorophenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 463.5 (ES+, M+H).

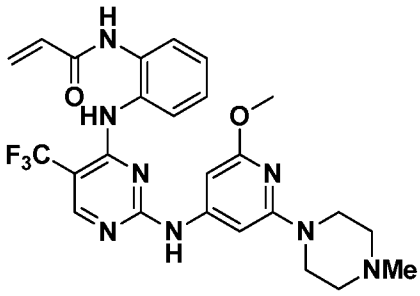
Example 306



I-323

[00698] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(trifluoromethyl)phenyl)acrylamide. Compound **I-323** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-(trifluoromethyl)phenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 513.2 (ES+, M+H).

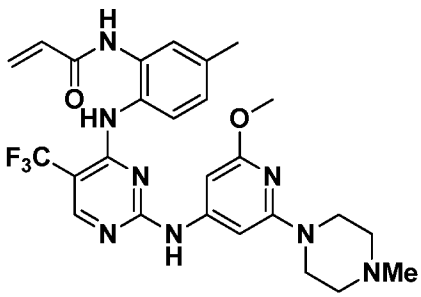
Example 307



I-324

[00699] N-(2-((2-((2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-324** was prepared in a manner similar to Example 68, substituting 2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 529.6 (ES+, M+H).

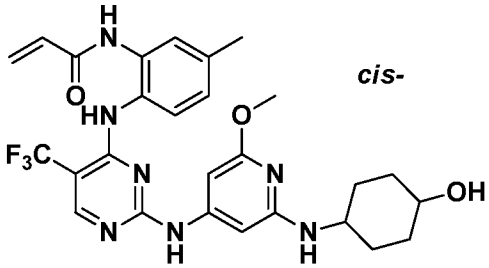
Example 308



I-325

[00700] N-(2-((2-((2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-325** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 543.2 (ES+, M+H).

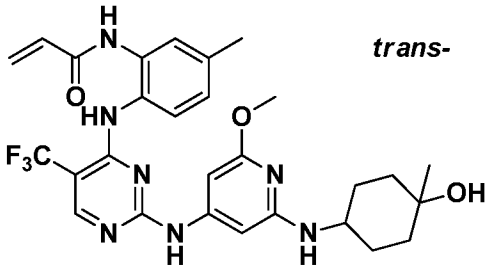
Example 309



I-326

[00701] N-(2-((2-((2-((cis-4-hydroxycyclohexyl)amino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-326** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting *cis*-4-((4-amino-6-methoxypyridin-2-yl)amino)cyclohexanol for 3-amino-4-methylbenzamide. MS m/z 558.2 (ES+, M+H).

Example 310

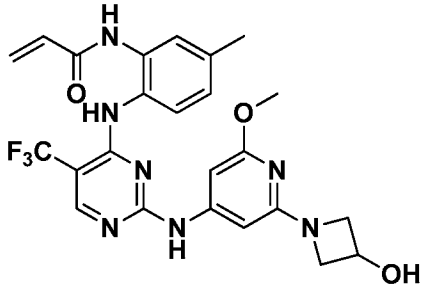


I-327

[00702] N-(2-((2-((2-((*trans*-4-hydroxy-4-methylcyclohexyl)amino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide.
Compound **I-327** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting *trans*- 4-((4-

amino-6-methoxypyridin-2-yl)amino)-1-methylcyclohexanol for 3-amino-4-methylbenzamide. MS m/z 572.3 (ES+, M+H).

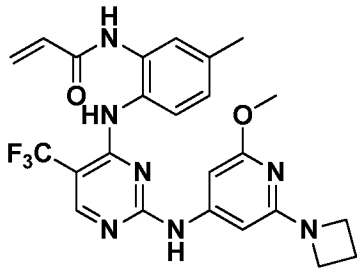
Example 311



I-328

[00703] N-(2-((2-((2-(3-hydroxyazetidin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-328** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 1-(4-amino-6-methoxypyridin-2-yl)azetidin-3-ol for 3-amino-4-methylbenzamide. MS m/z 516.2 (ES+, M+H).

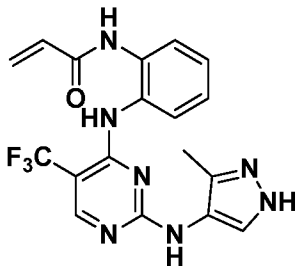
Example 312



I-329

[00704] N-(2-((2-((2-(azetidin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-329** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-(azetidin-1-yl)-6-methoxypyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 500.1 (ES+, M+H).

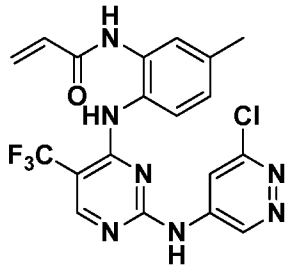
Example 313



I-330

[00705] N-(2-((2-((3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-330** was prepared in a manner similar to Example 68, substituting 3-methyl-1H-pyrazol-4-amine for 3-amino-4-methylbenzamide. MS m/z 404.1 (ES+, M+H).

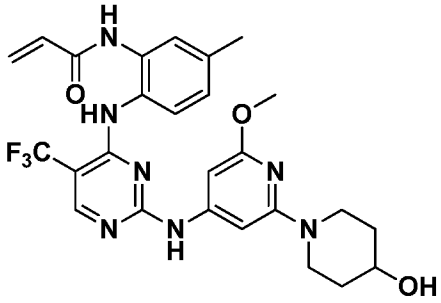
Example 314



I-331

[00706] N-(2-((2-((6-chloropyridazin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-331** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 6-chloropyridazin-4-amine for 3-amino-4-methylbenzamide. MS m/z 450.1 (ES+, M+H).

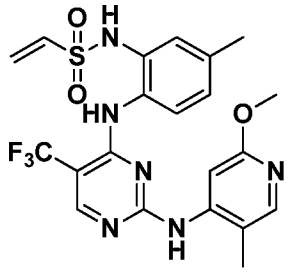
Example 315



I-332

[00707] N-(2-((2-((2-(4-hydroxypiperidin-1-yl)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-332** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 1-(4-amino-6-methoxypyridin-2-yl)piperidin-4-ol for 3-amino-4-methylbenzamide. MS m/z 544.3 (ES+, M+H).

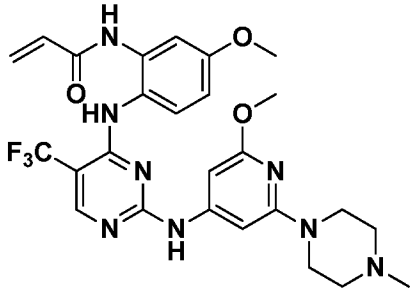
Example 316



I-333

[00708] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)ethenesulfonamide. Compound **I-333** was prepared in a manner similar to Example 116, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting tert-butyl (2-aminophenyl)carbamate for N-(2-aminophenyl)acrylamide, followed by deprotection with TFA and reaction with 2-chloroethylsulfonyl chloride. MS m/z 495.5 (ES+, M+H).

Example 317

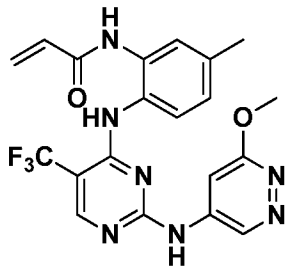


I-334

[00709] N-(5-methoxy-2-((2-((2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-334** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methoxyphenyl)acrylamide for N-

(2-aminophenyl)acrylamide, and substituting 2-methoxy-6-(4-methylpiperazin-1-yl)pyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 557.4 (ES+, M+H).

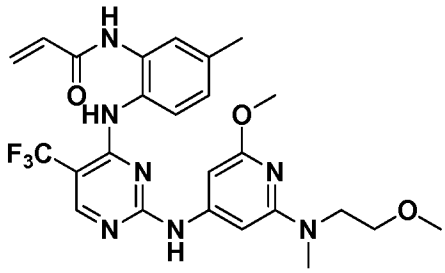
Example 318



I-335

[00710] N-(2-((2-((6-methoxypyridazin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-335** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 6-methoxypyridazin-4-amine for 3-amino-4-methylbenzamide. MS m/z 446.1 (ES+, M+H).

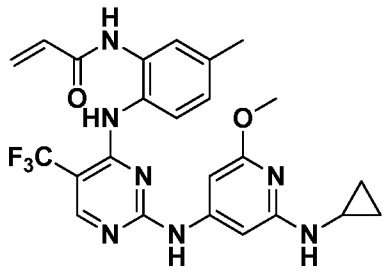
Example 319



I-336

[00711] N-(2-((2-((2-methoxy-6-((2-methoxyethyl)(methyl)amino)pyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-336** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 6-methoxy-N^2-(2-methoxyethyl)-N^2-methylpyridine-2,4-diamine for 3-amino-4-methylbenzamide. MS m/z 532.3 (ES+, M+H).

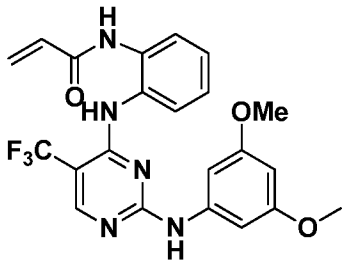
Example 320



I-337

[00712] N-(2-((2-((2-(cyclopropylamino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-337** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting N^2-cyclopropyl-6-methoxypyridine-2,4-diamine for 3-amino-4-methylbenzamide. MS m/z 500.2 (ES+, M+H).

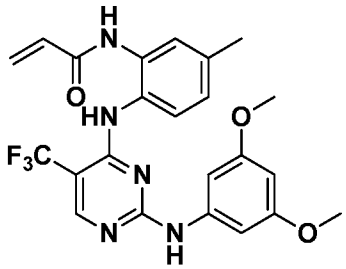
Example 321



I-338

[00713] N-(2-((2-((3,5-dimethoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-338** was prepared in a manner similar to Example 68, substituting 3,5-dimethoxyaniline for 3-amino-4-methylbenzamide. MS m/z 460.5 (ES+, M+H).

Example 322

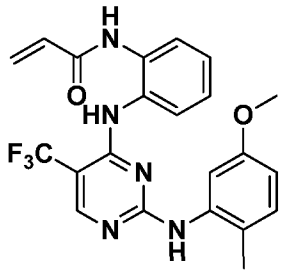


I-339

[00714] N-(2-((2-((3,5-dimethoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-339** was prepared in a manner similar to

Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 3,5-dimethoxyaniline for 3-amino-4-methylbenzamide. MS m/z 474.2 (ES+, M+H).

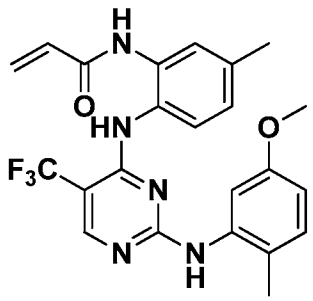
Example 323



I-340

[00715] N-(2-((2-((5-methoxy-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-338** was prepared in a manner similar to Example 68, substituting 5-methoxy-2-methylaniline for 3-amino-4-methylbenzamide. MS m/z 444.2 (ES+, M+H).

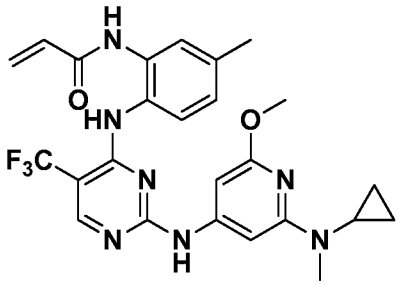
Example 324



I-341

[00716] N-(2-((2-((5-methoxy-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-341** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-methoxy-2-methylaniline for 3-amino-4-methylbenzamide. MS m/z 458.2 (ES+, M+H).

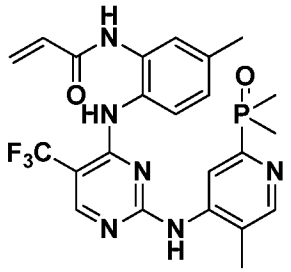
Example 325



I-342

[00717] N-(2-((2-((2-(cyclopropyl(methyl)amino)-6-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-342** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting N^2-cyclopropyl-6-methoxy-N^2-methylpyridine-2,4-diamine for 3-amino-4-methylbenzamide. MS m/z 514.3 (ES+, M+H).

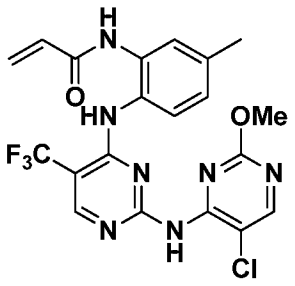
Example 326



I-343

[00718] N-(2-((2-((2-(dimethylphosphoryl)-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-343** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting (4-amino-5-methylpyridin-2-yl)dimethylphosphine oxide for 3-amino-4-methylbenzamide. MS m/z 505.3 (ES+, M+H).

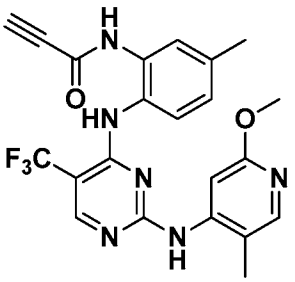
Example 327



I-344

[00719] N-(2-((2-((5-chloro-2-methoxypyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-344** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-chloro-2-methoxypyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 480.2 (ES+, M+H).

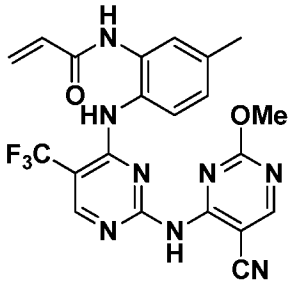
Example 328



I-345

[00720] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)propiolamide. Compound **I-345** was prepared in a manner similar to Example 116, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting tert-butyl (2-aminophenyl)carbamate for N-(2-aminophenyl)acrylamide, followed by deprotection with TFA and amide coupling with propiolic acid in the presence of HATU and DIPEA. MS m/z 457.2 (ES+, M+H).

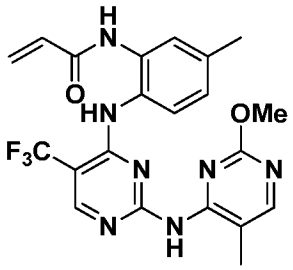
Example 329



I-346

[00721] N-(2-((2-((5-cyano-2-methoxypyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-346** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 4-amino-2-methoxypyrimidine-5-carbonitrile for 3-amino-4-methylbenzamide. MS m/z 471.2 (ES+, M+H).

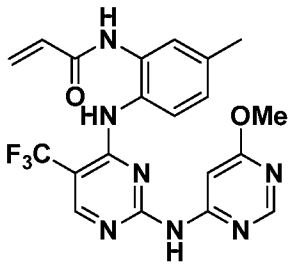
Example 330



I-347

[00722] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-347** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-methylpyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 460.3 (ES+, M+H).

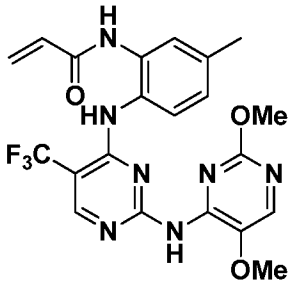
Example 331



I-348

[00723] N-(2-((2-((6-methoxypyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-348** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 6-methoxypyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 446.1 (ES+, M+H).

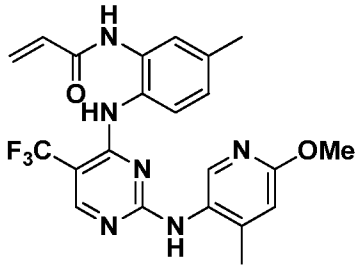
Example 332



I-349

[00724] N-(2-((2-((2,5-dimethoxypyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-349** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2,5-dimethoxypyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 476.1 (ES+, M+H).

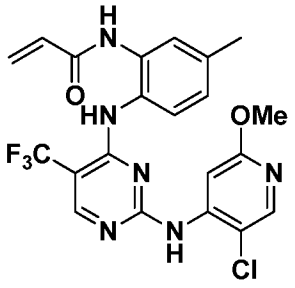
Example 333



I-350

[00725] N-(2-((2-((6-methoxy-4-methylpyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-350** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 6-methoxy-4-methylpyridin-3-amine for 3-amino-4-methylbenzamide. MS m/z 459.2 (ES+, M+H).

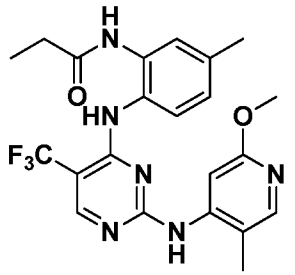
Example 334



I-351

[00726] N-(2-((2-((5-chloro-2-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide**.** Compound **I-351** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-chloro-2-methoxypyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 479.1 (ES+, M+H).

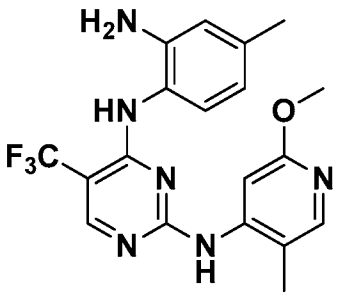
Example 335



I-352

[00727] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)propionamide. Compound **I-352** was prepared by Pd-catalyzed hydrogenation of compound **I-90.** MS: m/z 469.1 (ES+, M+H).

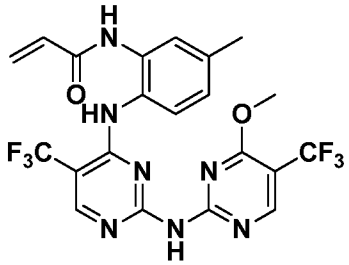
Example 336



I-353

[00728] N^4-(2-amino-4-methylphenyl)-N^2-(2-methoxy-5-methylpyridin-4-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine: The title compound was prepared in a manner similar to Example 116, substituting tert-butyl (2-amino-5-methylphenyl)carbamate for tert-butyl (2-amino-5-methylphenyl)carbamate, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and followed by Boc deprotection with TFA. MS m/z: 405.2 (ES+, M+H); ^{1}HNMR (DMSO-d_6) δ 8.45 (s, 1H), 8.32 (br s, 2H), 7.74 (s, 1H), 7.12 (s, 1H), 6.86 (d, 1H, J = 8.0 Hz), 6.39 (d, 1H, J = 8.0 Hz), 4.60 (s, 2H), 3.70 (s, 3H), 2.70 (s, 3H), 2.59 (s, 3H).

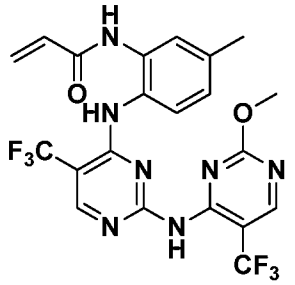
Example 337



I-354

[00729] N-(2-((2-((4-methoxy-5-(trifluoromethyl)pyrimidin-2-yl)amino)-5-(trifluoro methyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-354** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 4-methoxy-5-(trifluoromethyl)pyrimidin-2-amine for 3-amino-4-methylbenzamide. MS m/z 514.1 (ES+, M+H).

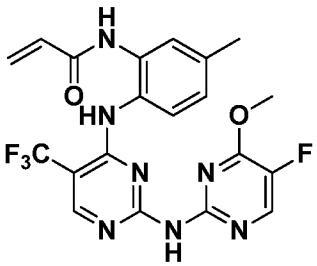
Example 338



I-355

[00730] N-(2-((2-((2-methoxy-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-355** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-(trifluoromethyl)pyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 514.1 (ES+, M+H).

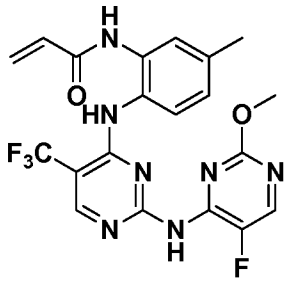
Example 339



I-356

[00731] N-(2-((2-((5-fluoro-4-methoxypyrimidin-2-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-356** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-fluoro-4-methoxypyrimidin-2-amine for 3-amino-4-methylbenzamide. MS m/z 464.1 (ES+, M+H).

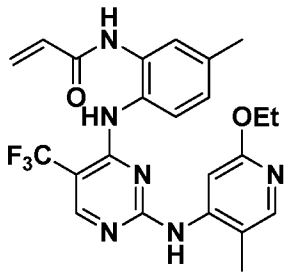
Example 340



I-357

[00732] N-(2-((2-((5-fluoro-2-methoxypyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-357** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-fluoro-2-methoxypyrimidin-4-amine for 3-amino-4-methylbenzamide. MS m/z 464.1 (ES+, M+H).

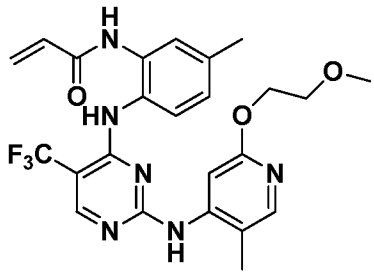
Example 341



I-358

[00733] N-(2-((2-((2-ethoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-358** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-ethoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 473.5 (ES+, M+H).

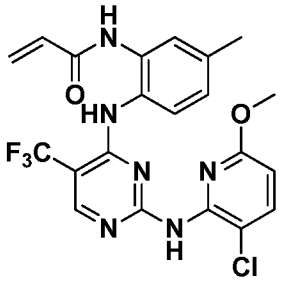
Example 342



I-359

[00734] N-(2-((2-((2-(2-methoxyethoxy)-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-359** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-(2-methoxyethoxy)-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 503.2 (ES+, M+H).

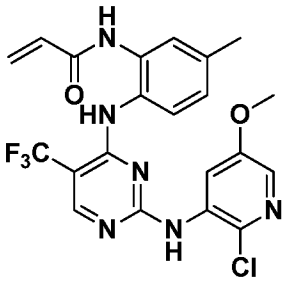
Example 343



I-360

[00735] N-(2-((2-((3-chloro-6-methoxypyridin-2-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-360** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 3-chloro-6-methoxypyridin-2-amine for 3-amino-4-methylbenzamide. MS m/z 479.2 (ES+, M+H).

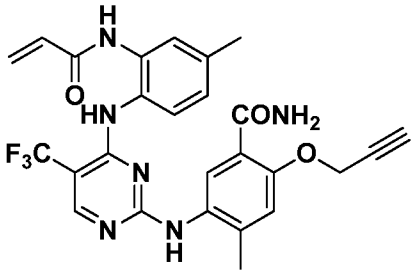
Example 344



I-361

[00736] N-(2-((2-((2-chloro-5-methoxypyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-361** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-chloro-5-methoxypyridin-3-amine for 3-amino-4-methylbenzamide. MS m/z 479.1 (ES+, M+H).

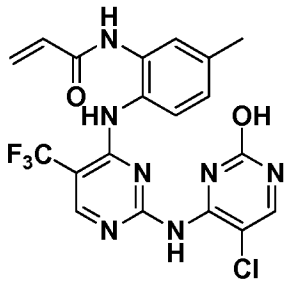
Example 345



I-362

[00737] 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-4-methyl-2-(prop-2-yn-1-yloxy)benzamide. Compound **I-362** was prepared in a manner similar to Example 68, substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 5-amino-4-methyl-2-(prop-2-yn-1-yloxy)benzamide for 3-amino-4-methylbenzamide. MS m/z 491.1 (ES+, M+H).

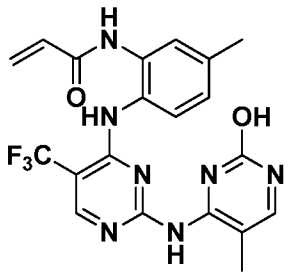
Example 346



I-363

[00738] N-(2-((2-((5-chloro-2-hydroxypyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. 50 mg of **I-344** was treated with 1M solution of BBr_3 in dichloromethane (4 equiv.) at 40 °C for 16 hr. After evaporation of solvent, the residue was treated with DBU (10 equiv.) in dichlorometane for 3 hr. The reaction mixture was subject to a aqueous work up and the extracted product was purified by prep-HPLC, giving 10 mg of white powder as **I-363**. MS m/z 466.1 (ES+, M+H).

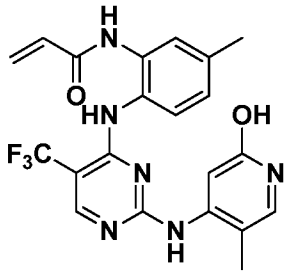
Example 347



I-364

[00739] N-(2-((2-((2-hydroxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-364** was prepared in a manner similar to Example 346, substituting starting material **I-347** for **I-344**. MS m/z 446.1 (ES+, M+H).

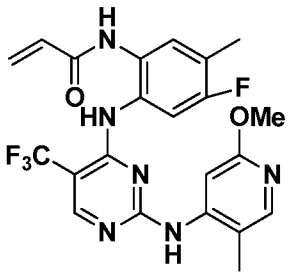
Example 348



I-365

[00740] N-(2-((2-((2-hydroxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-365** was prepared in a manner similar to Example 346, substituting starting material **I-90** for **I-344**. MS m/z 445.2 (ES+, M+H).

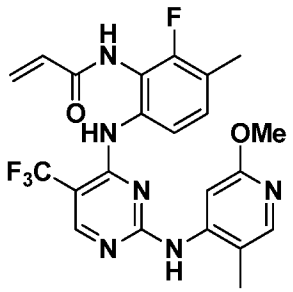
Example 349



I-366

[00741] N-(4-fluoro-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-366** was prepared in a manner similar to Example 68, substituting N-(2-amino-4-fluoro-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 477.2 (ES+, M+H).

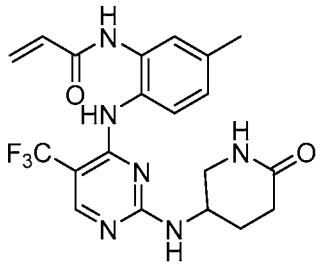
Example 350



I-367

[00742] N-(2-fluoro-6-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-3-methylphenyl)acrylamide. Compound **I-367** was prepared in a manner similar to Example 68, substituting N-(6-amino-2-fluoro-3-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide, and substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide. MS m/z 477.1 (ES+, M+H).

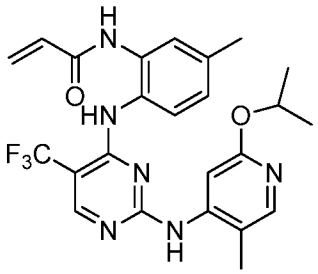
Example 351



I-368

[00743] Rac-N-(5-methyl-2-((2-((6-oxopiperidin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino) phenyl)acrylamide: Compound **I-368** was prepared in a manner similar to Example 1, substituting rac-5-aminopiperidin-2-one for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS m/z: 435.2 (ES+, M+H).

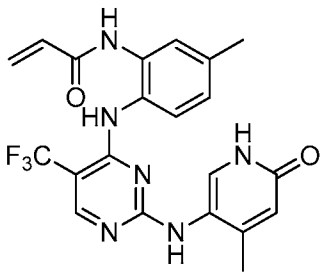
Example 352



I-369

[00744] N-(2-((2-((2-isopropoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-369** was prepared in a manner similar to Example 68, substituting 2-isopropoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and substituting N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 487.1 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.27 (d, J = 6.1 Hz, 6H), 2.27 (s, 3H), 5.15 (br s, 1H), 6.54 (br s, 1H), 6.84 (br s, 3H), 7.11 (br s, 2H), 7.74 (br s, 2H), 8.19 (br s, 2H), 8.30 (br s, 1H), 9.58 (s, 1H).

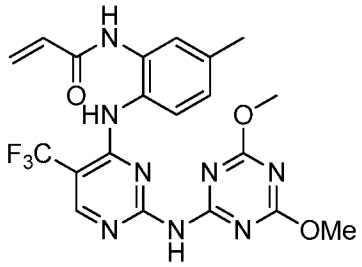
Example 353



I-370

[00745] N-(5-methyl-2-((2-((4-methyl-6-oxo-1,6-dihydropyridin-3-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-370** was prepared in a manner similar to Example 68, substituting 5-amino-4-methylpyridin-2(1H)-one for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 445.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.92 (s, 3H), 2.26 (s, 3H), 5.78 (d, J = 9.9 Hz, 1H), 6.14 (s, 1H), 6.28 (d, J = 17.2 Hz, 1H), 6.39-6.46 (dd, J = 10.1, 16.6 Hz, 1H), 6.96-7.08 (m, 2H), 7.19 (s, 1H), 7.45-7.54 (m, 1H), 8.11 (s, 1H), 8.20 (s, 1H), 8.69-8.71 (m, 1H), 10.21 (s, 1H), 11.29 (s, 1H).

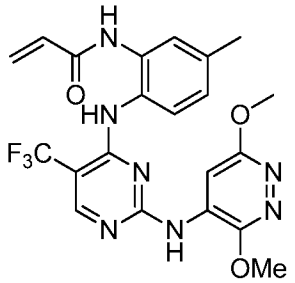
Example 354



I-371

[00746] N-(2-((2-((4,6-dimethoxy-1,3,5-triazin-2-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-371** was prepared in a manner similar to Example 68, substituting 4,6-dimethoxy-1,3,5-triazin-2-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 477.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.29 (s, 3H), 3.84 (s, 6H), 5.78 (d, J = 10.2 Hz, 1H), 6.28 (d, J = 16.0 Hz, 1H), 6.39-6.46 (dd, J = 9.7, 16.5 Hz, 1H), 7.04 (s, 2H), 7.94 (d, J = 8.6 Hz, 1H), 8.48 (s, 1H), 8.55 (s, 1H), 10.24 (s, 1H), 10.65 (s, 1H).

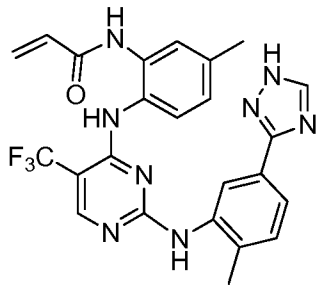
Example 355



I-372

[00747] N-(2-((2-((3,6-dimethoxypyridazin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-372** was prepared in a manner similar to Example 68, **substituting** 3,6-dimethoxypyridazin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 476.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.38 (s, 3H), 3.86 (s, 3H), 3.97 (s, 3H), 5.76-5.79 (dd, J = 1.8, 10.0 Hz, 1H), 6.25-6.30 (dd, J = 1.9, 17.0 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 17.0 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 7.19 (s, 1H), 7.32 (s, 1H), 7.46 (d, J = 8.1 Hz, 1H), 8.33 (s, 1H), 8.45 (s, 1H), 8.55 (s, 1H), 10.22 (s, 1H).

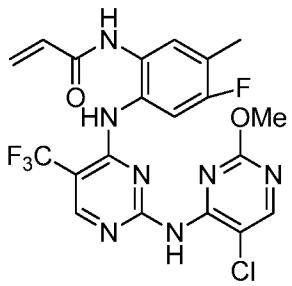
Example 356



I-373

[00748] N-(5-methyl-2-((2-((2-methyl-5-(1H-1,2,4-triazol-3-yl)phenyl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-373** was prepared in a manner similar to Example 68, substituting 2-methyl-5-(1H-1,2,4-triazol-3-yl)aniline for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)**acrylamide**. MS: m/z 495.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.09 (s, 3H), 2.16 (s, 3H), 5.76-5.79 (dd, J = 1.8, 10.0 Hz, 1H), 6.24-6.29 (dd, J = 1.9, 17.0 Hz, 1H), 6.38-6.45 (dd, J = 10.0, 16.9 Hz, 1H), 6.91 (s, 1H), 7.23-7.25 (m, 1H), 7.47 (br s, 1H), 7.68 (br s, 1H), 7.95 (br s, 1H), 8.03 (br s, 1H), 8.12 (br s, 1H), 8.26 (s, 1H), 8.61 (br s, 1H), 9.07-9.13 (m, 1H), 10.19 (s, 1H), 14.05 (s, 0.50H), 14.25 (s, 0.35H).

Example 357

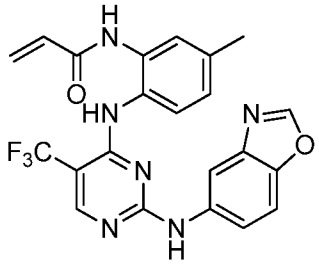


I-374

[00749] N-(2-((2-((5-chloro-2-methoxypyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-4-fluoro-5-methylphenyl)acrylamide. Compound **I-374** was prepared in a manner similar to Example 68, substituting 5-chloro-2-methoxypyrimidin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-4-fluoro-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 498.1 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.19 (s, 3H), 3.81 (s, 3H), 5.80 (d, J = 10.3 Hz, 1H), 6.29 (d, J = 17.0 Hz, 1H), 6.38-6.45 (dd, J = 10.0,

17.0 Hz, 1H), 7.11 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 11.4 Hz, 1H), 8.47 (s, 1H), 8.49 (s, 2H), 10.24 (d, J = 4.0 Hz, 2H).

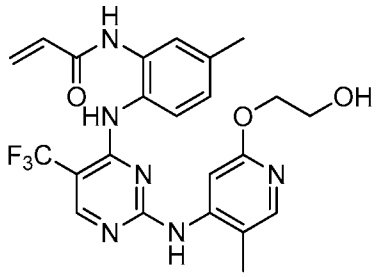
Example 358



I-375

[00750] N-(2-((2-(benzo[d]oxazol-5-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-375** was prepared in a manner similar to Example 68, substituting benzo[d]oxazol-5-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 455.1 (ES+, M+H).

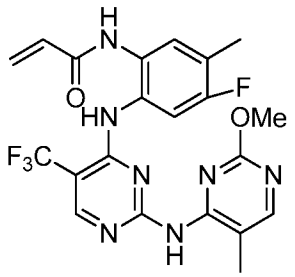
Example 359



I-376

[00751] N-(2-((2-((2-(2-hydroxyethoxy)-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-376** was prepared in a manner similar to Example 68, substituting 2-((4-amino-5-methylpyridin-2-yl)oxy)ethanol for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 489.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 3H), 2.31 (s, 3H), 3.71 (t, J = 5.2 Hz, 2H), 4.17 (t, J = 5.3 Hz, 2H), 4.80 (br s, 1H), 5.77-5.80 (dd, J = 1.8, 10.0 Hz, 1H), 6.26-6.31 (dd, J = 1.8, 16.9 Hz, 1H), 6.40-6.47 (dd, J = 10.1, 17.0 Hz, 1H), 7.06 (s, 1H), 7.18 (d, J = 10.3 Hz, 2H), 7.56 (d, J = 8.2 Hz, 1H), 7.78 (s, 1H), 8.37 (s, 2H), 8.70 (s, 1H), 10.26 (s, 1H). 9.07-9.13 (m, 1H), 10.19 (s, 1H), 14.05 (s, 0.50H), 14.25 (s, 0.35H).

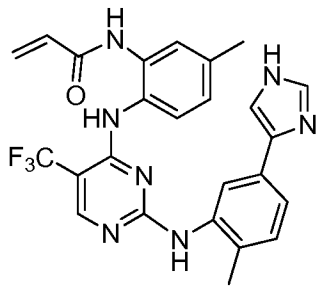
Example 360



I-377

[00752] N-(4-fluoro-2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-377** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyrimidin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-4-fluoro-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 478.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.00 (s, 3H), 2.18 (s, 3H), 3.78 (s, 3H), 5.79 (d, J = 10.0 Hz, 1H), 6.28 (dd, J = 1.8, 17.2 Hz, 1H), 6.41 (dd, J = 10.1, 17.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 11.3 Hz, 1H), 8.22 (s, 1H), 8.38 (s, 1H), 8.43 (s, 1H), 9.88 (s, 1H), 10.21 (s, 1H).

Example 361

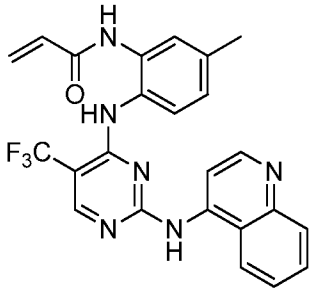


I-378

[00753] N-(2-((2-((5-(1H-imidazol-4-yl)-2-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-378** was prepared in a manner similar to Example 68, substituting 5-(1H-imidazol-4-yl)-2-methylaniline for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 494.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 6H), 5.75-5.78 (dd, J = 1.9, 12.0 Hz, 1H), 6.24-6.29 (dd, J = 1.7, 16.9 Hz, 1H), 6.38-6.45 (dd, J = 10.0, 17.0 Hz, 1H), 6.90 (br s, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.13-7.15 (m, 0.27H), 7.29-7.33 (m,

0.46H), 7.47 (d, J = 7.8 Hz, 1H), 7.54-7.55 (m, 2H), 7.70 (d, J = 9.5 Hz, 2H), 8.08 (s, 1H), 8.23 (s, 1H), 8.97 (br s, 1H), 10.19 (s, 1H), 12.10 (s, 0.62H), 12.42 (s, 0.17H).

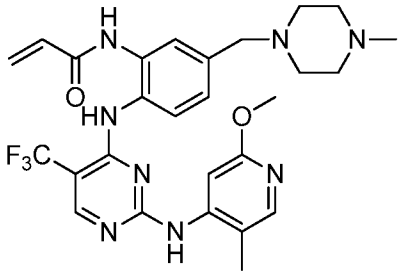
Example 362



I-379

[00754] N-(5-methyl-2-((2-(quinolin-4-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-379** was prepared in a manner similar to Example 68, substituting quinolin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 465.1 (ES+, M+H).

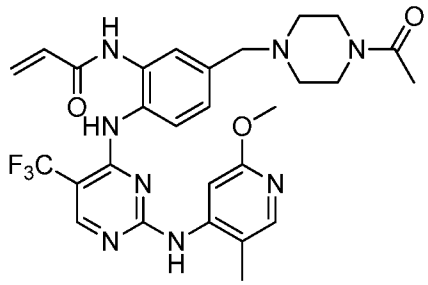
Example 363



I-380

[00755] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-methylpiperazin-**1-yl)methyl)phenyl)acrylamide.** Compound **I-380** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-((4-methylpiperazin-1-yl)methyl)phenyl) acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 555.3 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 2.08 (s, 3H), 2.16 (s, 3H), 2.37 (m, 8H), 3.44 (s, 2H), 3.76 (s, 3H), 5.79 (d, J = 8.5 Hz, 1H), 6.29 (d, J = 15.5 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H), 7.07-7.19 (m, 3H), 7.61 (d, J = 6.9 Hz, 1H), 7.79 (br s, 1H), 8.37 (s, 1H), 8.41 (s, 1H), 8.79 (br s, 1H), 10.32 (br s, 1H).

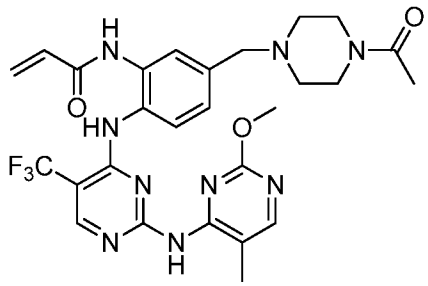
Example 364



I-381

[00756] N-(5-((4-acetylpiperazin-**1-yl)methyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide.** Compound **I-381** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and tert-butyl 4-(3-acrylamido-4-aminobenzyl)piperazine-1-carboxylate for N-(2-aminophenyl)acrylamide. After Boc-deprotection with TFA, the resulting amine was acylated with acetyl chloride to yield desired compound **I-381**. MS: m/z 585.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 2.09 (s, 3H), 2.31 (m, 2H), 2.37 (m, 2H), 3.41 (m, 4H), 3.49 (m, 2H), 3.77 (s, 3H), 5.79 (d, J = 10.4 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.42 (dd, J = 10.0, 17.7 Hz, 1H), 7.10 (s, 1H), 7.19 (d, J = 8.8 Hz, 1H), 7.22 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.79 (s, 1H), 8.37 (s, 1H), 8.42 (s, 1H), 8.81 (s, 1H), 10.33 (s, 1H).

Example 365

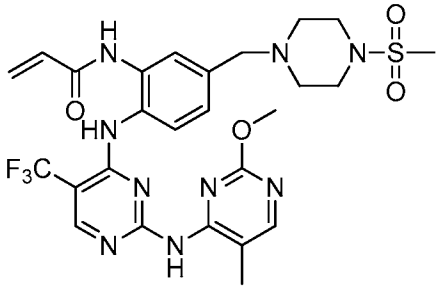


I-382

[00757] N-(5-((4-acetylpiperazin-1-yl)methyl)-2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)**pyrimidin-4-yl)amino)phenyl)acrylamide.** Compound **I-382** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyrimidin-4-amine for 3-amino-4-methylbenzamide, and tert-butyl 4-(3-acrylamido-4-aminobenzyl)piperazine-1-carboxylate for N-(2-aminophenyl)acrylamide. After Boc-deprotection with TFA, the resulting amine was acylated with acetyl chloride to yield desired compound **I-382**. MS: m/z 586.3 (ES+,

M+H). ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 1.98 (s, 3H), 2.27 (m, 2H), 2.35 (m, 2H), 3.40-3.44 (m, 6H), 3.83 (s, 3H), 5.80 (d, J = 11.4 Hz, 1H), 6.27-6.31 (dd, J = 1.7, 17.0 Hz, 1H), 6.40-6.46 (dd, J = 10.2, 17.0 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.81 (s, 1H), 10.32 (s, 1H).

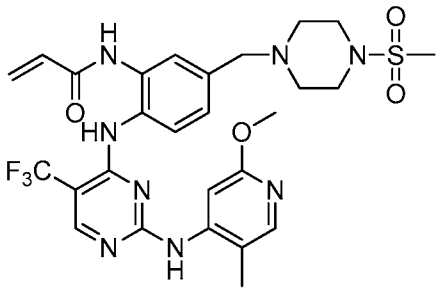
Example 366



I-383

[00758] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-383** was prepared in a manner similar to Example 365, substituting methanesulfonyl chloride for acetyl chloride in the final step. MS: m/z 622.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.98 (s, 3H), 2.49 (m, 4H), 2.87 (s, 3H), 3.10 (m, 4H), 3.48 (s, 2H), 3.83 (s, 3H), 5.78-5.81 (dd, J = 1.6, 10.0 Hz, 1H), 6.27-6.31 (dd, J = 1.8, 17.0 Hz, 1H), 6.40-6.47 (dd, J = 10.2, 17.2 Hz, 1H), 7.03-7.05 (dd, J = 1.4, 8.2 Hz, 1H), 7.15 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.81 (s, 1H), 10.35 (s, 1H).

Example 367

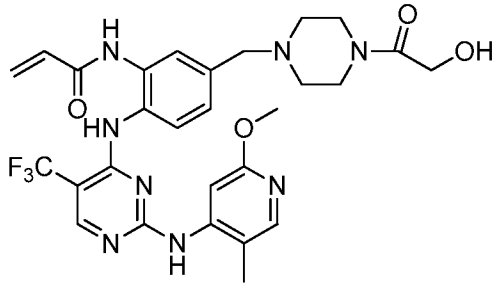


I-384

[00759] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-(methylsulfonyl)piperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-384** was prepared in a manner similar to Example 364, substituting methanesulfonyl chloride for acetyl chloride in the final step. MS: m/z 621.3 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.09 (s,

3H), 2.49 (m, 4H), 2.86 (s, 3H), 3.10 (m, 4H), 3.52 (s, 2H), 3.77 (s, 3H), 5.79 (d, J = 9.7 Hz, 1H), 6.27-6.31 (dd, J = 1.6, 16.9 Hz, 1H), 6.40-6.47 (dd, J = 10.0, 17.2 Hz, 1H), 7.10 (s, 1H), 7.19-7.22 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 8.37 (s, 1H), 8.41 (s, 1H), 8.80 (s, 1H), 10.32 (s, 1H).

Example 368

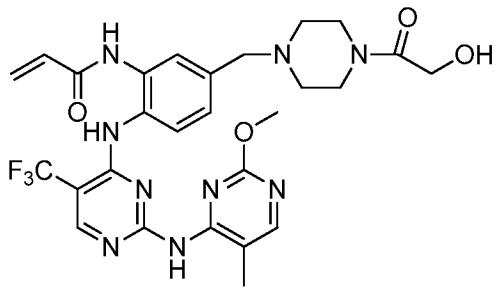


I-385

[00760] N-(5-((4-(2-hydroxyacetyl)piperazin-1-yl)methyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide.

Compound **I-385** was prepared in a manner similar to Example 364, substituting 2-chloro-2-oxoethyl acetate for acetyl chloride followed by basic hydrolysis with aqueous LiOH in the final step. MS: m/z 601.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.09 (s, 3H), 2.34-2.36 (m, 4H), 3.34 (m, 2H), 3.48 (m, 4H), 3.77 (s, 3H), 4.06 (d, J = 5.4 Hz, 2H), 4.52 (t, J = 5.5 Hz, 1H), 5.79 (d, J = 9.8 Hz, 1H), 6.31 (d, J = 16.9 Hz, 1H), 6.41 (d, J = 9.6 Hz, 1H), 7.11 (s, 1H), 7.20 (m, 2H), 7.62 (br s, 1H), 7.79 (s, 1H), 8.36 (br s, 1H), 8.42 (br s, 1H), 8.81 (br s, 1H), 10.33 (s, 1H).

Example 369



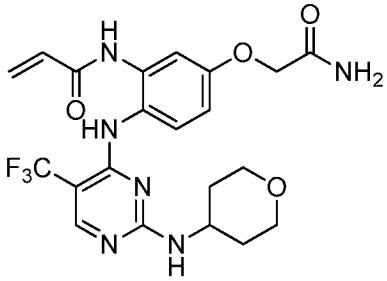
I-386

[00761] N-(5-((4-(2-hydroxyacetyl)piperazin-1-yl)methyl)-2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl**)pyrimidin-4-yl)amino)phenyl)acrylamide.**

Compound **I-386** was prepared in a manner similar to Example 365, substituting 2-chloro-2-oxoethyl acetate for acetyl chloride followed by basic hydrolysis with aqueous LiOH in the final

step. MS: m/z 602.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.98 (s, 3H), 2.31-2.34 (m, 4H), 3.45 (m, 6H), 3.83 (s, 3H), 4.06 (d, J = 5.3 Hz, 2H), 4.51 (t, J = 5.5 Hz, 1H), 5.80 (d, J = 10.7 Hz, 1H), 6.29 (d, J = 16.7 Hz, 1H), 6.39-6.46 (dd, J = 9.9, 16.8 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 7.14 (s, 1H), 7.76 (d, J = 8.3 Hz, 1H), 8.19 (s, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 9.81 (s, 1H), 10.32 (s, 1H).

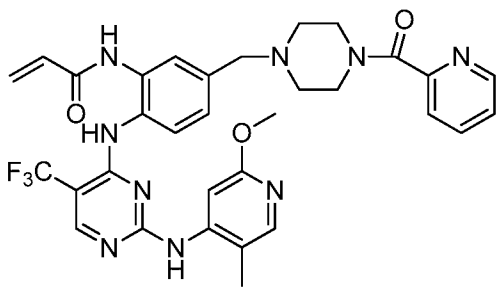
Example 370



I-387

[00762] N-(5-(2-amino-2-oxoethoxy)-2-((2-((tetrahydro-2H-pyran-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-387** was prepared in a manner similar to Example 1, substituting tetrahydro-2H-pyran-4-amine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-(2-amino-2-oxoethoxy)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 481.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.32-1.47 (m, 2H), 1.65-1.67 (m, 2H), 3.15-3.20 (m, 2H), 3.27 (m, 1H), 3.80 (d, J = 10.6 Hz, 2H), 4.43 (s, 2H), 5.79 (d, J = 9.6 Hz, 1H), 6.26-6.31 (dd, J = 10.2, 16.9 Hz, 1H), 6.41-6.48 (dd, J = 9.9, 16.9 Hz, 1H), 6.85-6.88 (dd, J = 2.7, 8.9 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 7.38 (s, 1H), 7.46-7.57 (m, 2H), 7.63 (m, 1H), 8.15-8.25 (m, 2H), 10.17-10.24 (m, 1H).

Example 371

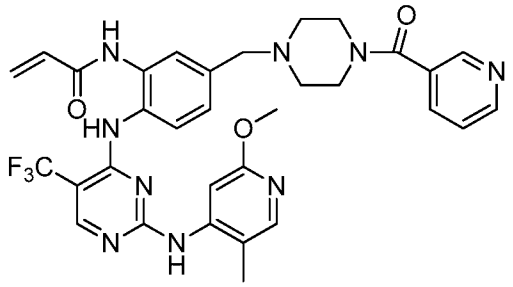


I-388

[00763] N-(2-((2-((2-methoxy**-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-picolinoylpiperazin-1-yl)methyl)phenyl)acrylamide.** Compound **I-388** was prepared in a manner similar to Example 364, substituting picolinic acid /HATU/DIPEA for

acetyl chloride in the final step. MS: m/z 646.5 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 2.27 (s, 3H), 3.32-3.33 (m, 8H), 3.82 (s, 3H), 4.43 (s, 2H), 5.81-5.84 (dd, J = 2.6, 9.2 Hz, 1H), 6.36-6.41 (dd, J = 2.6, 17.0 Hz, 1H), 6.41-6.48 (dd, J = 9.2, 17.0 Hz, 1H), 7.48-7.50 (dd, J = 2.0, 8.3 Hz, 1H), 7.55-7.57 (m, 1H), 7.67 (d, J = 1.9 Hz, 1H), 7.74-7.78 (m, 2H), 7.89 (s, 1H), 7.91 (br s, 1H), 7.99-8.03 (dt, J = 1.6, 7.8 Hz, 1H), 8.53 (s, 1H), 8.64 (d, J = 4.6 Hz, 1H).

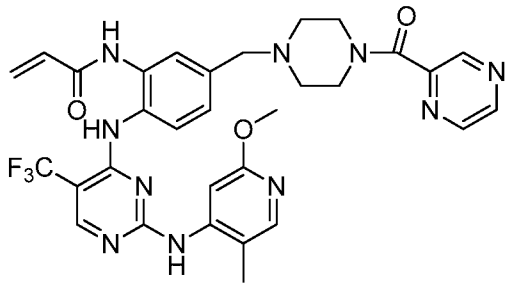
Example 372



I-389

[00764] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-nicotinoylpiperazin-**1-yl)methyl)phenyl)acrylamide.** Compound **I-389** was prepared in a manner similar to Example 364, substituting nicotinic acid /HATU/DIPEA for acetyl chloride in the final step. MS: m/z 646.4 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 2.08 (s, 3H), 2.44 (m, 4H), 3.49 (m, 2H), 3.51 (s, 2H), 3.64-3.65 (m, 2H), 3.75 (s, 3H), 5.78-5.81 (dd, J = 1.7, 10.0 Hz, 1H), 6.27-6.31 (dd, J = 1.8, 16.9 Hz, 1H), 6.40-6.46 (dd, J = 9.9, 17.0 Hz, 1H), 7.09 (s, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.22 (s, 1H), 7.45-7.48 (dd, J = 4.9, 7.8 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.76 (s, 1H), 7.80-7.83 (m, 1H), 8.37 (s, 1H), 8.42 (s, 1H), 8.59 (d, J = 2.0 Hz, 1H), 8.63-8.64 (dd, J = 1.5, 4.8 Hz, 1H), 8.82 (s, 1H), 10.34 (s, 1H).

Example 373

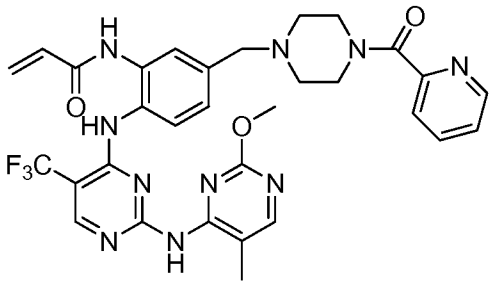


I-390

[00765] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-(pyrazine-**2-carbonyl)piperazin-1-yl)methyl)phenyl)acrylamide.**

Compound **I-390** was prepared in a manner similar to Example 364, substituting pyrazine-2-carboxylic acid/HATU/DIPEA for acetyl chloride in the final step. MS: m/z 649.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.08 (s, 3H), 2.42 (br s, 2H), 2.49 (s, 2H), 3.42 (br s, 2H), 3.52 (s, 2H), 3.67 (br s, 2H), 3.76 (s, 3H), 5.80 (d, J = 10.0 Hz, 1H), 6.30 (d, J = 17.0 Hz, 1H), 6.40-6.47 (dd, J = 10.1, 16.9 Hz, 1H), 7.10 (s, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.23 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.77 (s, 1H), 8.37 (s, 1H), 8.42 (s, 1H), 8.66 (br s, 1H), 8.73 (d, J = 2.4 Hz, 1H), 8.81 (s, 1H), 8.83 (s, 1H), 10.34 (s, 1H).

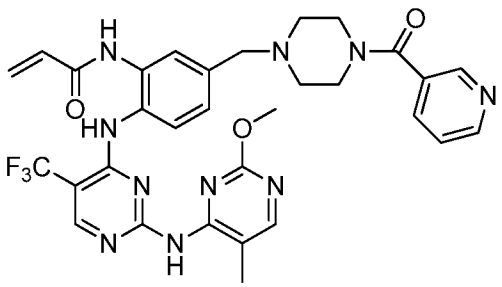
Example 374



I-391

[00766] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-picolinoylpiperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-391** was prepared in a manner similar to Example 365, substituting picolinic acid /HATU/DIPEA for acetyl chloride in the final step. MS: m/z 647.2 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 2.34 (m, 2H), 2.42 (m, 2H), 3.39 (m, 2H), 3.46 (s, 2H), 3.65 (m, 2H), 3.81 (s, 3H), 5.77-5.80 (dd, J = 1.6, 10.0 Hz, 1H), 6.26-6.30 (dd, J = 1.8, 17.0 Hz, 1H), 6.38-6.45 (dd, J = 10.0, 16.9 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 7.20 (br s, 1H), 7.44-7.47 (m, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.88-7.93 (m, 1H), 8.16 (s, 1H), 8.37 (s, 1H), 8.57 (d, J = 4.4 Hz, 1H), 10.32 (br s, 1H).

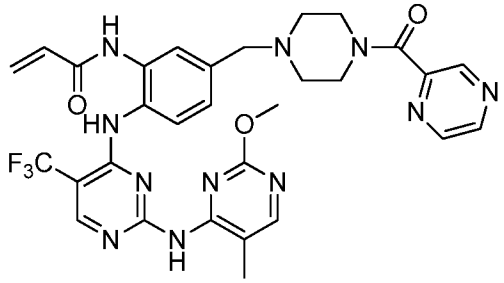
Example 375



I-392

[00767] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-nicotinoylpiperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-392** was prepared in a manner similar to Example 365, substituting nicotinic acid /HATU/DIPEA for acetyl chloride in the final step. MS: m/z 649.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 2.36-2.41 (m, 4H), 3.30 (m, **2H**), 3.47 (s, 2H), 3.64 (br s, 2H), 3.81 (s, 3H), 5.78-5.80 (d, J = 9.5 Hz, 1H), 6.27-6.31 (d, J = 17.2 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 17.0 Hz, 1H), 7.04 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 7.45-7.48 (dd, J = 4.8, 7.6 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 8.16 (s, 1H), 8.41 (s, 1H), 8.48 (s, 1H), 8.59 (s, 1H), 8.64 (d, J = 3.7 Hz, 1H), 9.81 (s, 1H), 10.32 (s, 1H).

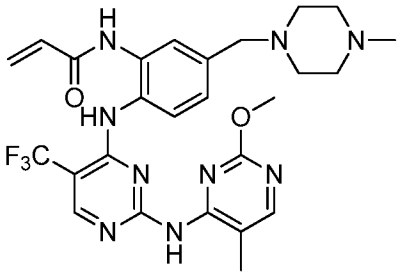
Example 376



I-393

[00768] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-(pyrazine-2-carbonyl)piperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-393** was prepared in a manner similar to Example 365, substituting pyrazine-2-carboxylic acid /HATU/DIPEA for acetyl chloride in the final step. MS: m/z 648.5 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 2.00 (s, 3H), 3.18 (m, 4H), 3.34-3.39 (m, 2H), 3.84 (s, 3H), 4.33 (s, 2H), 5.83 (d, J = 9.1 Hz, 1H), 6.31 (d, J = 16.5 Hz, 1H), 6.44-6.48 (dd, J = 10.2, 16.4 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.40 (s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.20 (s, 1H), 8.47 (s, 1H), 8.53 (s, 1H), 8.69 (s, 1H), 8.78 (s, 1H), 8.89 (s, 1H), 9.90 (br s, 1H), 10.42 (s, 1H).

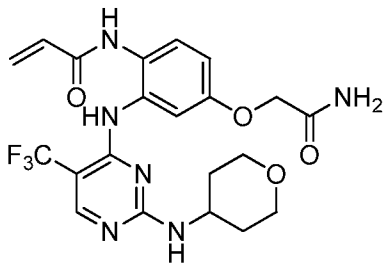
Example 377



I-394

[00769] N-(2-((2-((2-methoxy-5-methylpyrimidin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide. Compound **I-394** was prepared in a manner **similar** to Example 68, substituting 2-methoxy-5-methylpyrimidin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-((4-methylpiperazin-1-yl)methyl)phenyl) acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 558.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.97 (s, 3H), 2.16 (s, 3H), 2.35 (m, 8H), 3.40 (s, 2H), 3.83 (s, 3H), 5.79 (d, J = 9.2 Hz, 1H), 6.29 (d, J = 16.6 Hz, 1H), 6.40-6.46 (m, 1H), 7.02 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 8.18 (s, 1H), 8.40 (s, 1H), 8.48 (s, 1H), 9.80 (s, 1H), 10.33 (s, 1H).

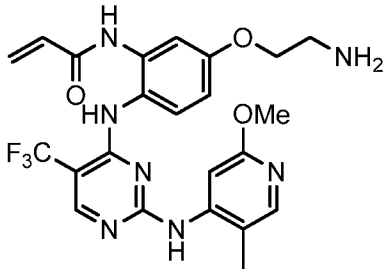
Example 378



I-395

[00770] N-(4-(2-amino-2-oxoethoxy)-2-((2-((tetrahydro-2H-pyran-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-395** was prepared in a manner similar to Example 1, **substituting** tetrahydro-2H-pyran-4-amine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-4-(2-amino-2-oxoethoxy)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 481.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.38-1.50 (m, 2H), 1.69-1.72 (m, 2H), 3.17 (t, J = 11.4 Hz, 2H), 3.61-3.83 (m, 3H), 3.75-3.83 (m, 2H), 4.43 (d, J = 16.0 Hz, 2H), 5.77 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 16.9 Hz, 1H), 6.38-6.45 (dd, J = 10.1, 16.9 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 7.38 (s, 1H), 7.41 (s, 1H), 7.49 (br s, 1H), 7.57 (d, J = 7.0 Hz, 1H), 8.15 (s, 1H), 8.21 (s, 1H), 10.18 (s, 1H).

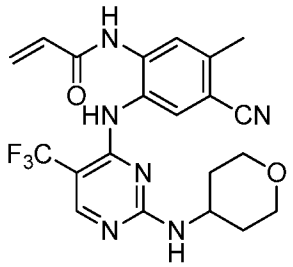
Example 379



I-396

[00771] N-(5-(2-aminoethoxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-396** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, tert-butyl (2-(3-acrylamido-4-aminophenoxy)ethyl)carbamate for N-(2-aminophenyl)acrylamide, and final Boc-deprotection with TFA in the last step. MS: m/z 504.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 3H), 3.21 (t, J = 5.1 Hz, 2H), 3.75 (s, 3H), 4.12 (t, J = 4.9 Hz, 2H), 5.77-5.80 (dd, J = 1.8, 10.0 Hz, 1H), 6.25-6.30 (dd, J = 1.9, 17.0 Hz, 1H), 6.40-6.47 (dd, J = 10.0, 16.9 Hz, 1H), 6.85-6.88 (dd, J = 2.8, 8.8 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 7.11 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 8.28 (br s, 1H), 8.36 (s, 1H), 8.71 (s, 1H), 10.15 (s, 1H).

Example 380

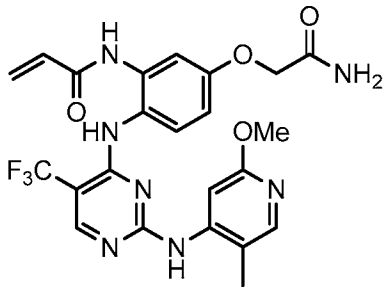


I-397

[00772] N-(4-cyano-5-methyl-2-((2-((tetrahydro-2H-pyran-4-yl)amino)-5-(trifluoromethyl) pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-397** was prepared in a manner similar to Example 1, substituting tetrahydro-2H-pyran-4-amine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-4-cyano-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 447.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6, with D_2O exchange) δ 1.38-1.43 (m, 2H), 1.62-.165 (m, 2H), 2.43 (s, 3H), 3.17-3.23 (m, 2H), 3.49 (m,

1H), 3.77-3.82 (m, 2H), 5.84 (d, J = 9.6 Hz, 1H), 6.29 (d, J = 17.0 Hz, 1H), 6.38-6.45 (dd, J = 10.1, 17.1 Hz, 1H), 7.38 (s, 1H), 8.09 (s, 1H), 8.12 (s, 1H). (Based on D_2O values updated)

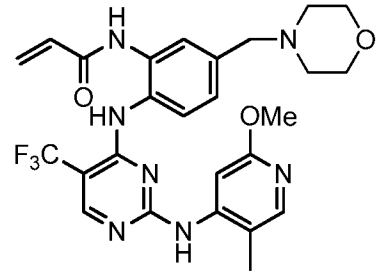
Example 381



I-398

[00773] N-(5-(2-amino-2-oxoethoxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-398** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(2-amino-2-oxoethoxy)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 518.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 3H), 3.74 (s, 3H), 4.42 (s, 2H), 5.78 (d, J = 10.3 Hz, 1H), 6.28 (d, J = 17.5 Hz, 1H), 6.44 (dd, J = 10.0, 16.9 Hz, 1H), 6.85 (d, J = 7.1 Hz, 1H), 6.92 (br s, 1H), 7.09 (s, 1H), 7.41 (br s, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.54 (br s, 1H), 7.78 (s, 1H), 8.26 (s, 1H), 8.35 (s, 1H), 8.69 (s, 1H), 10.26 (s, 1H).

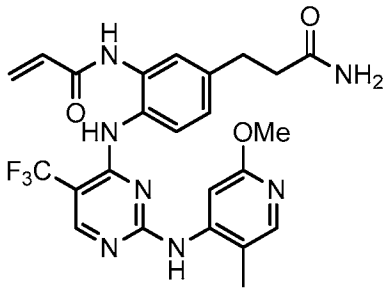
Example 382



I-399

[00774] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(morpholinomethyl)phenyl)acrylamide. Compound **I-399** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(morpholinomethyl)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 544.2 (ES+, M+H).

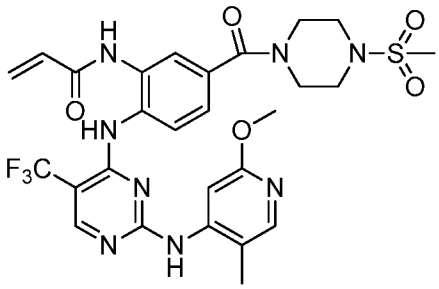
Example 383



I-400

[00775] N-(5-(3-amino-3-oxopropyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-400** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(3-amino-3-oxopropyl)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 516.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.10 (s, 3H), 2.36 (t, J = 7.8 Hz, 2H), 2.81 (t, J = 7.5 Hz, 2H), 3.76 (s, 3H), 5.79 (d, J = 10.0 Hz, 1H), 6.29 (d, J = 17.0 Hz, 1H), 6.40-6.47 (dd, J = 10.3, 16.8 Hz, 1H), 6.76 (br s, 1H), 7.11 (m, 3H), 7.30 (br s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.80 (s, 1H), 8.36 (s, 2H), 8.74 (s, 1H), 10.31 (s, 1H).

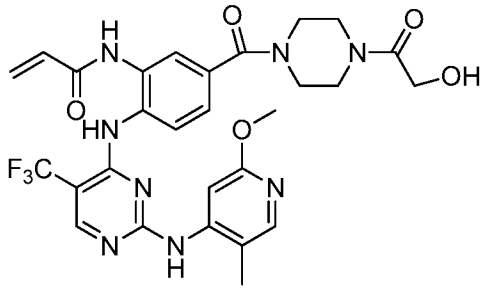
Example 384



I-401

[00776] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl)acrylamide. Compound **I-401** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(4-(methylsulfonyl)piperazine-1-carbonyl)phenyl) acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 635.1 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.09 (s, 3H), 2.91 (s, 3H), 3.17 (m, 4H), 3.58 (m, 4H), 3.72 (s, 3H), 5.82 (dd, J = 1.9, 11.9 Hz, 1H), 6.31 (dd, J = 1.8, 17.0 Hz, 1H), 6.45 (dd, J = 10.2, 17.0 Hz, 1H), 7.09 (s, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.39 (d, J = 1.7 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.81 (s, 1H), 8.41 (s, 1H), 8.50 (s, 1H), 8.90 (s, 1H), 10.37 (s, 1H).

Example 385

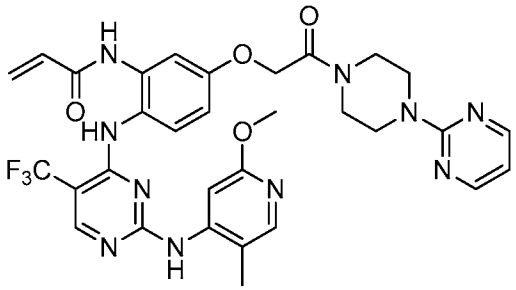


I-402

[00777] N-(5-(4-(2-hydroxyacetyl)piperazine-1-carbonyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide.

Compound **I-402** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(4-(2-hydroxyacetyl)piperazine-1-carbonyl)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 615.3 (ES+, M+H).

Example 386

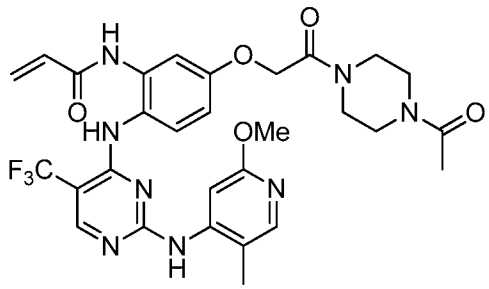


I-403

[00778] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethoxy)phenyl)acrylamide.

Compound **I-**403 was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(2-oxo-2-(4-(pyrimidin-2-yl)piperazin-1-yl)ethoxy)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 664.8 (ES+, M+H).

Example 387

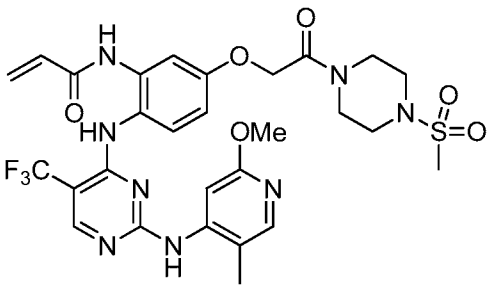


I-404

[00779] N-(5-(2-(4-acetylpiperazin-1-yl)-2-oxoethoxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide.

Compound **I-404** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(5-(2-(4-acetylpiperazin-1-yl)-2-oxoethoxy)-2-aminophenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 628.7 (ES+, M+H).

Example 388

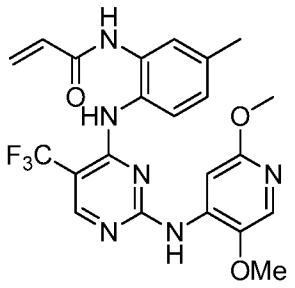


I-405

[00780] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(2-(4-(methylsulfonyl)piperazin-1-yl)-2-oxoethoxy)phenyl)acrylamide.

Compound **I-405** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(2-(4-(methylsulfonyl)piperazin-1-yl)-2-oxoethoxy)phenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 664.5 (ES+, M+H).

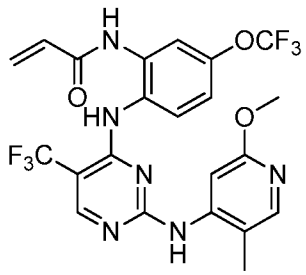
Example 389



I-406

[00781] N-(2-((2-((2,5-dimethoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-406** was prepared in a manner similar to Example 68, substituting 2,5-dimethoxy pyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl) acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 475.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.36 (s, 3H), 3.72 (s, 3H), 3.83 (s, 3H), 5.76-5.79 (dd, J = 1.9, 10.0 Hz, 1H), 6.26-6.31 (dd, J = 2.0, 17.0 Hz, 1H), 6.40-6.47 (dd, J = 10.1, 17.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.29 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.70 (s, 1H), 8.02 (s, 1H), 8.40 (s, 1H), 8.47 (s, 1H), 10.25 (s, 1H).

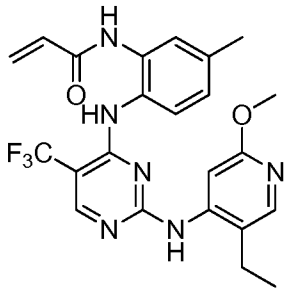
Example 390



I-407

[00782] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-(trifluoromethoxy**)phenyl)acrylamide.** Compound **I-407** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(trifluoromethoxy)phenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 528.7 (ES+, M+H).

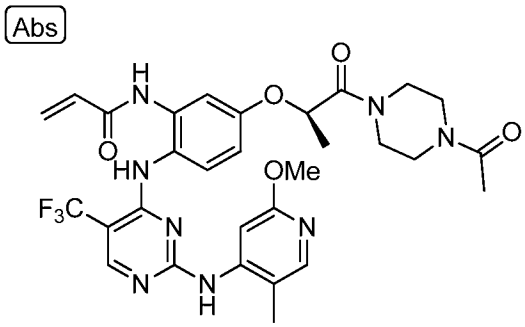
Example 391



I-408

[00783] N-(2-((2-((5-ethyl-2-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide**.** Compound **I-408** was prepared in a manner similar to Example 68, substituting 5-ethyl-2-methoxypyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl) acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 473.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.04 (t, J = 7.5 Hz, 3H), 2.32 (s, 3H), 2.57-2.69 (m, 2H), 3.76 (s, 3H), 5.76-5.79 (dd, J = 1.9, 10.0 Hz, 1H), 6.26-6.30 (dd, J = 1.8, 17.0 Hz, 1H), 6.39-6.46 (dd, J = 10.2, 17.1 Hz, 1H), 7.07-7.08 (m, 3H), 7.51 (d, J = 8.6 Hz, 1H), 7.80 (s, 1H), 8.35 (s, 2H), 8.75 (s, 1H), 10.24 (br s, 1H).

Example 392

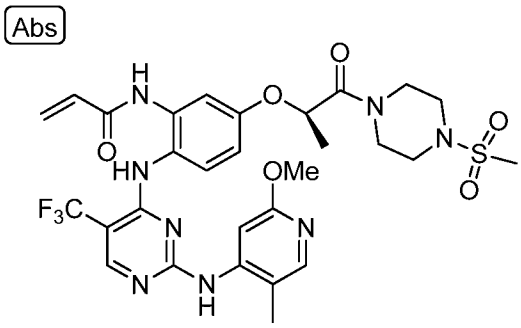


I-409

[00784] (R)-N-(5-((1-(4-acetylpiperazin-1-yl)-1-oxopropan-2-yl)oxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-409** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (R)-tert-butyl 4-(2-(3-acryl amido-4-aminophenoxy)propanoyl)piperazine-1-carboxylate for N-(2-aminophenyl)acrylamide. After Boc-deprotection with TFA, the resulting amine was acylated with acetyl chloride to yield desired compound **I-409**. MS: m/z 643.3 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.45 (d, J = 6.4

Hz, 3H), 1.99 (s, 3H), 2.08 (s, 3H), 3.45-3.59 (m, 8H), 3.75 (s, 3H), 5.18-5.21 (m, 1H), 5.76-5.79 (dd, J = 1.5, 10.1 Hz, 1H), 6.24-6.28 (dd, J = 1.6, 16.9 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 17.0 Hz, 1H), 6.78-6.79 (m, 1H), 6.89 (s, 1H), 7.10 (s, 1H), 7.48 (d, J = 9.0 Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.72 (s, 1H), 10.13 (br s, 1H).

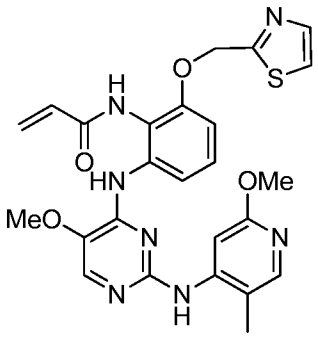
Example 393



I-410

[00785] (R)-N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((1-(4-(methylsulfonyl)piperazin-1-yl)-1-oxopropan-2-yl)oxy)phenyl) acrylamide. Compound **I-410** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (R)-tert-butyl 4-(2-(3-acryl amido-4-aminophenoxy)propanoyl)piperazine-1-carboxylate for N-(2-aminophenyl) acrylamide. After Boc-deprotection with TFA, the resulting amine reacted with methanesulfonyl chloride to yield desired compound **I-410**. MS: m/z 679.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.46 (d, J = 6.5 Hz, 3H), 2.08 (s, 3H), 2.85 (s, 3H), 3.08 (m, 4H), 3.54-3.64 (m, 4H), 3.75 (s, 3H), 5.17-5.22 (m, 1H), 5.75-5.78 (dd, J = 1.9, 10.0 Hz, 1H), 6.26 (d, J = 15.4 Hz, 1H), 6.40-6.46 (dd, J = 9.9, 16.9 Hz, 1H), 6.77-6.80 (dd, J = 2.2, 8.9 Hz, 1H), 6.90 (s, 1H), 7.09 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.73 (s, 1H), 10.13 (s, 1H).

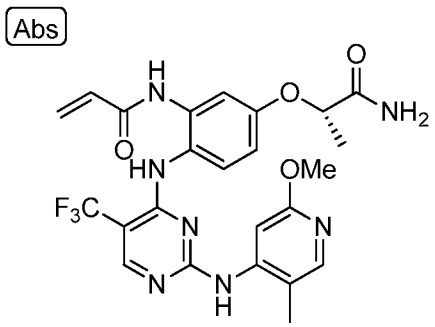
Example 394



I-411

[00786] N-(2-((5-methoxy-2-((2-methoxy-5-methylpyridin-4-yl)amino)pyrimidin-4-yl)amino)-6-(thiazol-2-ylmethoxy)phenyl)acrylamide. Compound **I-411** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methyl benzamide, and N-(2-amino-6-(thiazol-2-ylmethoxy)phenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 520.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.14 (s, 3H), 3.79 (s, 3H), 3.88 (s, 3H), 5.42 (s, 2H), 5.79 (d, J = 10.8 Hz, 1H), 6.29 (d, J = 17.1 Hz, 1H), 6.52-6.56 (dd, J = 10.1, 17.2 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 7.16 (t, J = 8.3 Hz, 1H), 7.54 (br s, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.71 (s, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.81-7.82 (m, 1H), 7.86 (br s, 1H), 7.90 (s, 1H), 7.92 (s, 1H), 9.61 (s, 1H).

Example 395

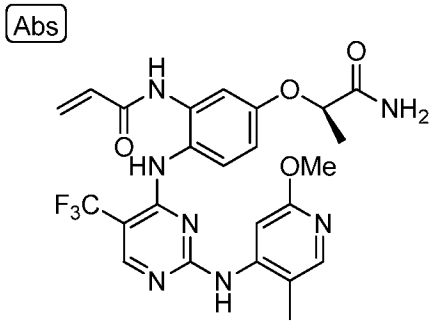


I-412

[00787] (S)-N-(5-((1-amino-1-oxopropan-2-yl)oxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-**4-yl)amino)phenyl)acrylamide.** Compound **I-412** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (S)-N-(2-amino-5-((1-amino-1-oxopropan-2-yl)oxy)phenyl) acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 532.2 (ES+, M+H).

^{1}HNMR (DMSO-d_6) δ 1.46 (d, J = 6.6 Hz, 3H), 2.09 (s, 3H), 3.76 (s, 3H), 4.54-4.59 (m, 1H), 5.76-5.79 (dd, J = 1.9, 10.1 Hz, 1H), 6.25-6.30 (dd, J = 1.9, 17.0 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 16.9 Hz, 1H), 6.80-6.83 (dd, J = 2.9, 8.9 Hz, 1H), 6.86 (d, J = 2.8 Hz, 1H), 7.11 (s, 1H), 7.26 (br s, 1H), 7.48 (br s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.71 (s, 1H), 10.23 (s, 1H).

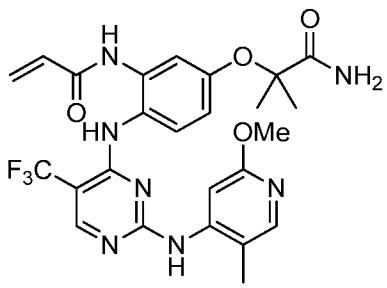
Example 396



I-413

[00788] (R)-N-(5-((1-amino-1-oxopropan-2-yl)oxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-413** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (R)-N-(2-amino-5-((1-amino-1-oxopropan-2-yl)oxy)phenyl) acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 530.2 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 1.46 (d, J = 6.7 Hz, 3H), 2.09 (s, 3H), 3.76 (s, 3H), 4.54-4.59 (m, 1H), 5.76-5.79 (dd, J = 1.8, 10.2 Hz, 1H), 6.25-6.30 (dd, J = 1.9, 16.9 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 17.0 Hz, 1H), 6.80-6.83 (dd, J = 2.8, 8.9 Hz, 1H), 6.86 (d, J = 2.9 Hz, 1H), 7.11 (s, 1H), 7.26 (br s, 1H), 7.48 (br s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.70 (s, 1H), 10.22 (s, 1H).

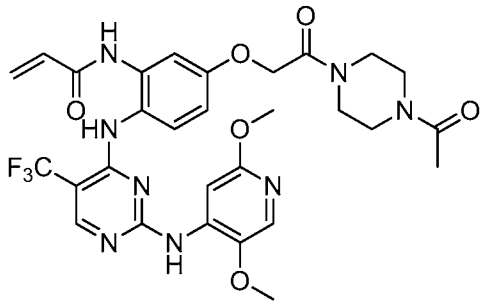
Example 397



I-414

[00789] N-(5-((1-amino-2-methyl-1-oxopropan-2-yl)oxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-414** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-((1-amino-2-methyl-1-oxopropan-2-yl)oxy)phenyl) acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 546.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.43 (s, 6H), 2.09 (s, 3H), 3.77 (s, 3H), 5.77-5.80 (dd, J = 1.3, 11.8 Hz, 1H), 6.26-6.30 (dd, J = 1.9, 16.9 Hz, 1H), 6.38-6.45 (dd, J = 9.9, 17.2 Hz, 1H), 6.80-6.83 (m, 2H), 7.12 (s, 1H), 7.25 (s, 1H), 7.47 (s, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.80 (s, 1H), 8.28 (s, 1H), 8.35 (s, 1H), 8.75 (s, 1H), 10.25 (s, 1H).

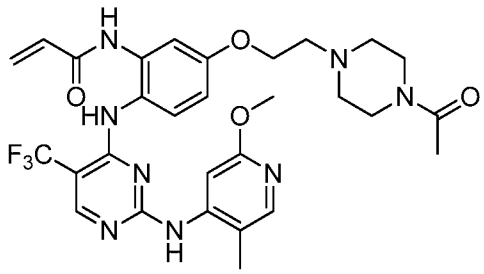
Example 398



I-415

[00790] N-(5-(2-(4-acetylpiperazin-1-yl)-2-oxoethoxy)-2-((2-((2,5-dimethoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-415** was prepared in a manner similar to Example 68, substituting 2,5-dimethoxypyridin-4-amine for 3-amino-4-methylbenzamide, and N-(5-(2-(4-acetylpiperazin-1-yl)-2-oxoethoxy)-2-aminophenyl) acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 644.6 (ES+, M+H).

Example 399

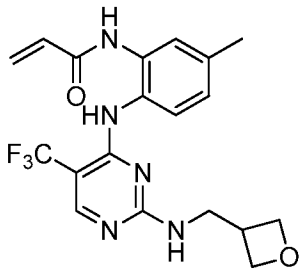


I-416

[00791] N-(5-(2-(4-acetylpiperazin-1-yl)ethoxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-416**

was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(5-(2-(4-acetylpiperazin-1-yl)ethoxy)-2-aminophenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 614.8 (ES+, M+H).

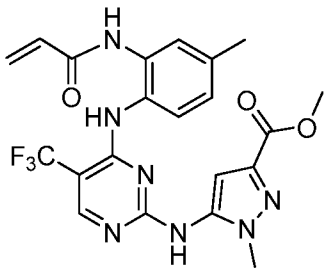
Example 400



I-417

[00792] N-(5-methyl-2-((2-((oxetan-3-ylmethyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino) phenyl)acrylamide**.** Compound **I-417** was prepared in a manner similar to Example 1, substituting oxetan-3-ylmethanamine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. MS: m/z 407.8 (ES+, M+H).

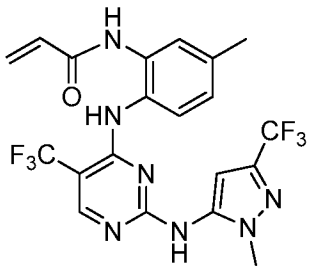
Example 401



I-418

[00793] Methyl 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1-methyl-1H-pyrazole**-3-carboxylate.** Compound **I-418** was prepared in a manner similar to Example 68, substituting methyl 5-amino-1-methyl-1H-pyrazole-3-carboxylate for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 475.7 (ES+, M+H).

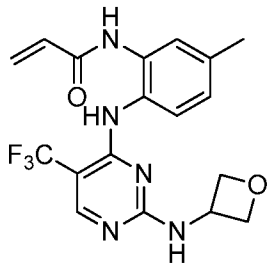
Example 402



I-419

[00794] N-(5-methyl-2-((2-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-**4-yl)amino)phenyl)acrylamide.** Compound **I-419** was prepared in a manner similar to Example 68, substituting methyl 1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 485.8 (ES+, M+H).

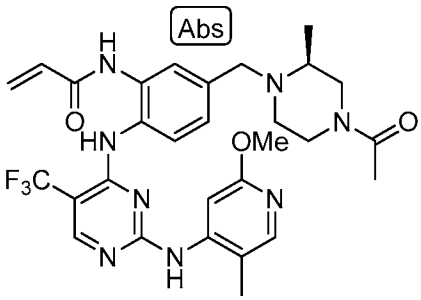
Example 403



I-420

[00795] N-(5-methyl-2-((2-(oxetan-3-ylamino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl) acrylamide. Compound **I-420** was prepared in a manner similar to Example 1, substituting oxetan-3-amine for (S)-tert-butyl 3-aminopiperidine-1-carboxylate, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl)acrylamide. . MS: m/z 394.2 (ES+, M+H).

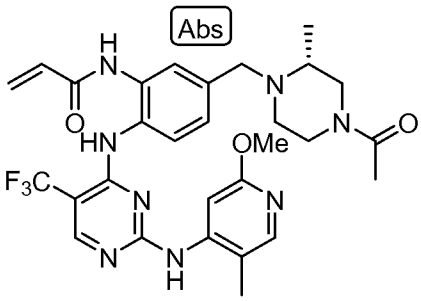
Example 404



I-421

[00796] (S)-N-(5-((4-acetyl-2-methylpiperazin-1-yl)methyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-421** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (S)-N-(5-((4-acetyl-2-methylpiperazin-1-yl)methyl)-2-aminophenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 598.7 (ES+, M+H).

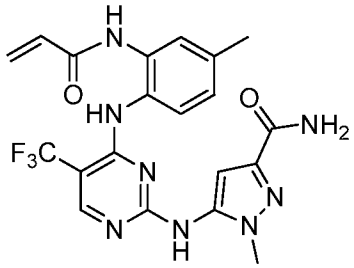
Example 405



I-422

[00797] (R)-N-(5-((4-acetyl-2-methylpiperazin**-1-yl)methyl)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide.** Compound **I-422** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (R)-N-(5-((4-acetyl-2-methylpiperazin-1-yl)methyl) -2-aminophenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 598.7 (ES+, M+H).

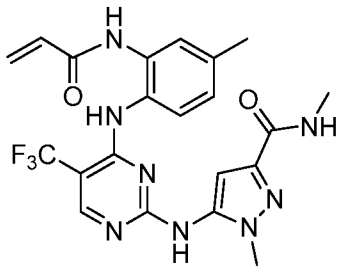
Example 406



I-423

[00798] 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-1-methyl-1H-pyrazole-3-carboxamide. Compound **I-423** was prepared in a manner similar to Example 68, substituting 5-amino-1-methyl-1H-pyrazole-3-carboxamide for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 461.7 (ES+, M+H).

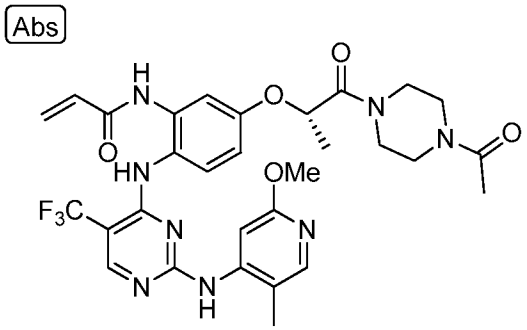
Example 407



I-424

[00799] 5-((4-((2-acrylamido-4-methylphenyl)amino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)-N,1-dimethyl-1H-pyrazole-3-carboxamide. Compound **I-424** was prepared in a manner similar to Example 68, substituting 5-amino-N,1-dimethyl-1H-pyrazole-3-carboxamide for 3-amino-4-methylbenzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 461.7 (ES+, M+H).

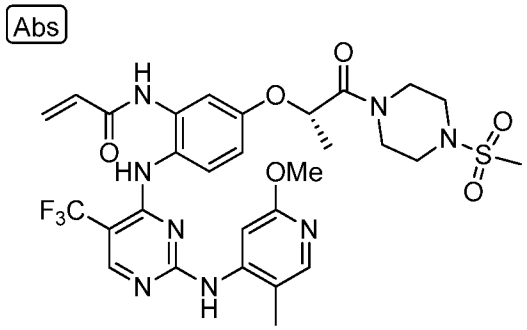
Example 408



I-425

[00800] (S)-N-(5-((1-(4-acetylpiperazin-1-yl)-1-oxopropan-2-yl)oxy)-2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)acrylamide. Compound **I-425** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (S)-tert-butyl 4-(2-(3-acryl amido-4-aminophenoxy)propanoyl)piperazine-1-carboxylate for N-(2-aminophenyl)acrylamide. After Boc-deprotection with TFA, the resulting amine was acylated with acetyl chloride to yield desired compound **I-425**. MS: m/z 643.4 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 1.45 (d, J = 6.5 Hz, 3H), 1.99 (s, 3H), 2.08 (s, 3H), 3.41 (m, 8H), 3.75 (s, 3H), 5.19 (m, 1H), 5.76-5.79 (dd, J = 1.5, 10.0 Hz, 1H), 6.24-6.28 (dd, J = 1.5, 16.9 Hz, 1H), 6.39-6.46 (dd, J = 10.0, 16.8 Hz, 1H), 6.79 (m, 1H), 6.89 (s, 1H), 7.10 (s, 1H), 7.46-7.48 (m, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.72 (s, 1H), 10.12 (br s, 1H).

Example 409

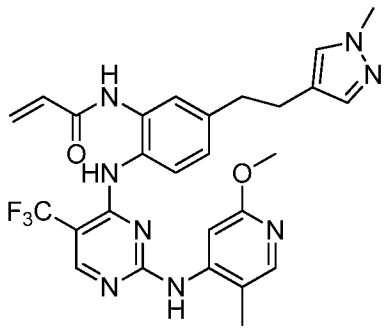


I-426

[00801] (S)-N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-((1-(4-(methylsulfonyl)piperazin-1-yl)-1-oxopropan-2-yl)oxy)phenyl) acrylamide. Compound **I-426** was prepared in a manner similar to

Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and (S)-tert-butyl 4-(2-(3-acryl amido-4-aminophenoxy)propanoyl)piperazine-1-carboxylate for N-(2-aminophenyl) acrylamide. After Boc-deprotection with TFA, the resulting amine reacted with methanesulfonyl chloride to yield desired compound **I-426**. MS: m/z 677.2 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 1.46 (d, J = 6.4 Hz, 3H), 2.08 (s, 3H), 2.85 (s, 3H), 3.07 (m, 4H), 3.59-3.64 (m, 4H), 3.75 (s, 3H), 5.20 (m, 1H), 5.75-5.78 (dd, J = 1.7, 10.0 Hz, 1H), 6.24-6.28 (dd, J = 1.6, 16.9 Hz, 1H), 6.39-6.46 (dd, J = 10.1, 17.0 Hz, 1H), 6.77-6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.90 (d, J = 2.6 Hz, 1H), 7.09 (s, 1H), 7.48 (d, J = 8.9 Hz, 1H), 7.79 (s, 1H), 8.24 (s, 1H), 8.35 (s, 1H), 8.73 (s, 1H), 10.11 (s, 1H).

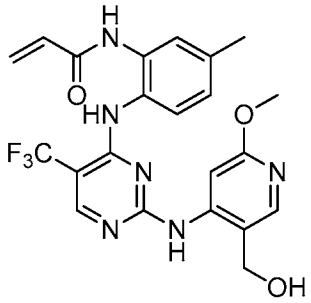
Example 410



I-427

[00802] N-(2-((2-((2-methoxy-5-methylpyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl) amino)-5-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)phenyl)acrylamide. Compound **I-427** was prepared in a manner similar to Example 68, substituting 2-methoxy-5-methylpyridin-4-amine for 3-amino-4-methylbenzamide, and N-(2-amino-5-(2-(1-methyl-1H-pyrazol-4-yl)ethyl)phenyl) acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 553.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.12 (s, 3H), 2.71 (d, J = 7.7 Hz, 2H), 2.81 (d, J = 7.2 Hz, 2H), 3.71 (s, 3H), 3.73 (s, 3H), 5.78 (d, J = 9.4 Hz, 1H), 6.28 (d, J = 16.4 Hz, 1H), 6.40-6.46 (m, 1H), 7.12 -7.23 (m, 4H), 7.43 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.82 (s, 1H), 8.39 (s, 1H), 8.43 (s, 1H), 8.85 (s, 1H), 10.29 (s, 1H).

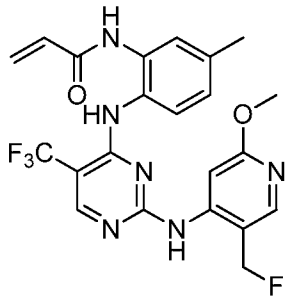
Example 411



I-428

[00803] N-(2-((2-((5-(hydroxymethyl)-2-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-428** was prepared in a manner similar to Example 68, substituting (4-amino-6-methoxypyridin-3-yl)methanol for 3-amino-4-methyl benzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 473.1 (ES-, M-H). ^{1}HNMR (DMSO-d_6) δ 2.35 (s, 3H), 3.76 (s, 3H), 4.51 (d, J = 4.8 Hz, 2H), 5.70 (t, J = 4.9 Hz, 1H), 5.77-5.80 (dd, J = 9.9, 1.7 Hz, 1H), 6.27-6.31 (dd, J = 1.7, 16.9 Hz, 1H), 6.40-6.47 (dd, J = 9.9, 16.8 Hz, 1H), 7.13-7.14 (m, 2H), 7.29 (s, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.82 (s, 1H), 8.38 (s, 1H), 8.44 (s, 1H), 9.06 (s, 1H), 10.27 (s, 1H).

Example 412

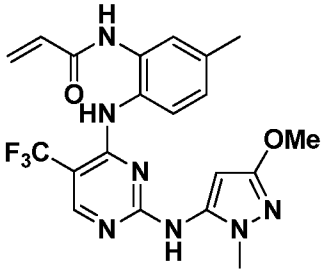


I-429

[00804] N-(2-((2-((5-(fluoromethyl)-2-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-429** was prepared by fluorination of **I-428** with DAST in dichloromethane. MS: m/z 477.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.34 (s, 3H), 3.80 (s, 3H), 5.45 (s, 1H), 5.57 (s, 1H), 5.76-5.79 (dd, J = 1.7, 10.1 Hz, 1H), 6.26-6.31 (dd, J = 1.9, 16.9 Hz, 1H), 6.40-6.46 (dd, J = 10.0, 16.9 Hz, 1H),

7.09 (s, 1H), 7.12 (s, 1H), 7.24 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 3.3 Hz, 1H), 8.40 (s, 1H), 8.43 (s, 1H), 8.84 (s, 1H), 10.25 (s, 1H).

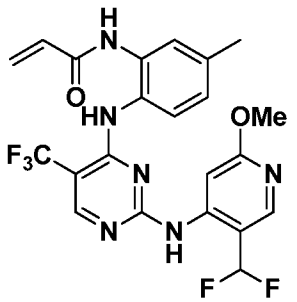
Example 413



I-430

[00805] N-(2-((2-((3-methoxy-1-methyl-1H-pyrazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-430** was prepared in a manner similar to Example 68, substituting 3-methoxy-1-methyl-1H-pyrazol-5-amine for 3-amino-4-methyl benzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 448.2 (ES+, M+H). ^{1}HNMR (DMSO-d_6) δ 2.30 (s, 3H), 3.42 (s, 3H), 3.64 (s, 3H), 4.51 (d, J = 4.8 Hz, 2H), 5.41 (s, 1H),, 5.77-5.80 (dd, J = 10, 2.0 Hz, 1H), 6.27-6.31 (dd, J = 2.0, 16.8 Hz, 1H), 6.40-6.47 (dd, J = 10, 16.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 7.11 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 8.25 (s, 1H), 8.30 (s, 1H), 9.5 (br s, 1H), 10.2 (br s, 1H).

Example 414



I-431

[00806] N-(2-((2-((5-(difluoromethyl)-2-methoxypyridin-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)-5-methylphenyl)acrylamide. Compound **I-431** was prepared in a manner similar to Example 68, substituting 5-(difluoromethyl)-2-methoxypyridin-4-amine for 3-amino-4-methyl benzamide, and N-(2-amino-5-methylphenyl)acrylamide for N-(2-aminophenyl) acrylamide. MS: m/z 494.8 (ES+, M+H).

EXAMPLE 415

[00807] Described below are in vitro assays used to measure the biological activity of provided compounds as selective inhibitors of one or both of ERK 1 and ERK 2.

Protien Mass Modification Assay

[00808] Intact protein: Erk1 from Millipore (Cat. No. 14-439) was incubated for 60 min. at room temperature with a 10-fold excess of test compound to protein. 4 μL aliquots of the resulting mixture were diluted with 15 μL of 0.2% 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, v/v). The centroid mass of the target protein in the control sample was compared with the centroid mass of the target protein incubated with compound. A shift in the centroid mass of the treated protein compared to the untreated protein was divided by the molecular weight of the compound. This number corresponds to the percentage of modified protein after one hour incubation. Results from this assay are reported in Table A under the column "**ERK1 Mass Mod (%).**"

Omnia Assay Protocol for Potency Assessment against MEK1 activated ERK1:

[00809] The protocol below describes continuous-read kinase assays to measure potency of compounds against activated ERK1 enzyme. The mechanics of the assay platform are best described by the vendor (Invitrogen, Carlsbad, CA) on their website at the following URL: invitrogen.com/site/us/en/home.html.

[00810] Briefly, a 1.25X stock of ERK1 enzyme (14-439-K) from Millipore (Billerica, MA), 5X ATP (AS001A) and ST17-Sox conjugated peptide substrate (KNZ1171C) 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. 10 μL of ATP/ST17-sox peptide substrate mix was combined with 0.5 μL volume of 100% DMSO and serially diluted compounds were prepared in 100% DMSO in a Corning (#3574) 384-well, white, non-binding surface microtiter plate (Corning, NY). Kinase reactions were started with the addition of 40 μL of ERK1 solution and monitored every 71 seconds for 30-240 minutes at $\lambda_{ex}360/\lambda_{em}485$ in a Synergy 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 or seconds) and then plotted against inhibitor concentration to estimate $^{App}IC_{50}$ from log[Inhibitor] vs Response, Variable Slope model in GraphPad Prism from GraphPad Software (San Diego, CA).

[Reagent] used in optimized protocol:

[ERK1] = 4 nM, [ATP] = 50 μM, [ST17-Sox] = 10 μM (ATP $^{app}K_M$ 48 μM)

[00811] The results of this assay show the degree of inhibition of ERK activity, which is a direct measurement of inhibition of ERK activity. Results from this assay are reported in Table A under the column "**ERK1 Omnia WT ATP KM IC_{50} (nM).**"

pRSK MSD Assay

[00812] The protocol below describes an assay to measure the kinase activity of ERK1/2 to phosphorylate a substrate, p90RSK, in the presence or absence of a test compound. This experiment was conducted using a Mesoscale Discovery plate. The day before the assay, HT29 cells were split and plated at 50,000 cells/well in complete growth media. After allowing cells to adhere, the media was removed and replaced with media containing 0.1% FBS and incubated overnight. Blank MSD plates (Mesoscale Discovery, Cat # L15XA3) were coated with 25 μl/well RSK capture antibody (BD Biosciences, Cat. # 610226) and incubated at 4 °C overnight, then blocked with 150 μl of 3% BSA solution. The next day, the media from the cell culture plate was removed and replaced with 100 μl of media containing a test compound and incubated for 120 minutes at 37 °C. The media was removed and replaced with 55 μl per well of lysis buffer with protease inhibitors (Roche Biosciences, Cat. # 11836170001) and phosphatase inhibitors (Sigma-Aldrich, Cat. # P-0044 and P-5726), followed by incubation at 4°C for 30 minutes. 50 μl of lysate was transferred to a blocked MSD plate, followed by incubation at room temperature for 2 hours under constant shaking. The plate was washed 3 times with MSD wash buffer (Mesoscale Discovery, Cat. # R617TX), and 25 μl/well phospho-RSK (pRSK) detection antibody (Cell Signaling Technology, Cat. # 9335) was added with Sulfo-tagged detection antibody (Mesoscale Discovery, Cat. # R32AB-1) diluted in 1% BSA in MSD wash buffer. This mixture was incubated for 1 hour at room temperature under constant shaking. The plate was washed 3 times, and 150μl 1X MSD read buffer was added, followed by signal detection in an MSD plate reader. Curve fitting analysis was done with variable slope in GraphPad software to generate EC_{50} based on DMSO control (untreated) being 100% pRSK signal and maximum

inhibition with a reference compound provided by the manufacturer as a positive control. Results from this assay, showing EC_{50} (i.e., the concentration at which a test compound inhibits phosphorylation of RSK by 50%) are reported in Table A under the column "**ERK1/ERK2 PRSK MSD HT29 EC_{50} (nM).**"

Measurment of Erk Occupancy with Biotinylated Covalent Probe

[00813] This experiment measured occupancy of the ERK1/ERK2 target by compounds according to the invention. This experiment was conducted using the Mesoscale Discovery test kit (Cat. # N45107B). One day before the assay, cells were split and added at 50,000 cells per well to a flat-bottom 96 well plate in 200 μl of growth medium. The next day, the medium was discarded, 100 μl medium containing test compound was added, and the plate was incubated at 37 °C for 120 minutes. The plate was rinsed once with PBS, and 50 μl lysis buffer with test compound was added. The plate was incubated at 4 °C for 30 min, and 30 μl of lysate was transferred to a plate to capture total and phosphor-Erk. Biotinylated probe **I-299** was diluted in lysis buffer and added to each well to a final concentration of 0.2 μM. The plate was incubated for 2 hr under constant shaking at room temperature. The plate was washed 3 times with MSD wash buffer. To detect the biotinylated probe bonding, tagged streptavidin was added (Mesoscale Discovery, Cat. # R32AD-1) at 1 μg/ml, 25 μl /well, followed by a 60 min incubation under shaking. The plate was washed 3 times, 150 μl MSD Read Buffer (Mesoscale Discovery, Cat. R61TX) was added and the plate was read in a plate reader manufactured by MSD. Percent occupancy by test compound at Erk was calculated by comparing the chemiluminescence readings from treated cells as compared to the chemiluminescence readings in untreated controls (which are defined as 100% probe bonding or 0% test compound occupancy). The amount of covalent probe signal divided by the amount of ERK signal for samples with no test compound treatment represents the maximum probe signal (MPS). In samples treated with test compound prior to covalent probe, the ratio of probe signal to ERK signal (the test probe signal, TPS) was reduced by the degree of target occupancy by the test compound which blocks covalent probe binding. The difference between the MPS and the TPS, divided by the MPS gave the target occupancy by the test compound. This ratio was then expressed as a percent occupancy. Results from this assay are provided in Table A below under the column "**Occupancy EC_{50} (nM) HT-29.**"

Measurment of Duration of Action of Test Compounds

[00814] This example shows the extended activity of compounds according to the invention. One day before the assay, the cells were split and added at 50,000 cells per well in flat-bottom 96 well plate in 200μl of growth media. The next day, the medium was discarded, 100μl medium containing test compounds was added, and the plate was incubated at 37°C for 120 minutes. The medium was discarded, and the cells were rinsed 3 times with PBS followed by addition of 200μl of fresh grow medium. The plate was returned to a 37°C incubator, and separate cell lysates were made using MSD lysis buffer after 0.25, 0.5, 1, 2, 4, 6, 8 and 18 or 24 hours. Thereafter, pRSK was measured as described above in the section entitled **pRSK MSD Assay.** The data is presented in Table A under the column titled **"p-RSK inhibition at 6 hr (%)."**

Measurement of Inhibition of Cancer Cell Proliferation (HT-29 / Colorectal Adenocarcinoma)

[00815] The following protocol used an HT-29 cell line, which cell line is a model for colorectal adenocarcinoma. HT-29 cells were split and 3000 cells in 100 μl of growth medium were added per well of a flat-bottom 96-well plate. A two–fold test compound solution in serum-free RPM1640 was made, starting at 5,000 nM. Then, 3-fold serial dilutions were made across the plate from well 1 to well 11. Well 12, the last well in a row on the plate, was left as untreated control. 100 μl compound solutions were then transferred to the wells, so the total volume of media was 200 μl per well. Plates were returned to a 37 °C incubator, and the cells were cultured for 72 hours. To measure cell proliferation after 72 hours, media was discarded from the plates, 50 μl/well of fresh medium was added, and 50 μl CellTiterGlo solution was added (Promega Cat#G7573) . The plate was covered with a dark lid and incubated for 10 min. A white sealing tape was applied to the bottom of the plate, and the plate was read in a luminescence plate reader. In order to calculate GI_{50} (the proliferation of HT29 was inhibited by 50%) a standard curve was established to measure luminescence readings at certain cell densities by the following method. A 2-fold serial dilution was used to generate 8 cell densities from 50,000-390 cells per well in 50 μl media. 50 μl CellTiterGlo was added per well, and the plate was read in a luminescence plate reader after 10min. The reading was plotted vs. cell number to generate a standard curve and the equation of the curve fit. The compound-treated sample luminescence readings were converted to cell numbers using the curve-fit equation. The percent of inhibition, using untreated control as 100% growth, was then calculated. GI_{50} was then calculated by GraphPad Prism. Accordingly,

this assay provides the dose at which 50% inhibition of cell growth was achieved and this data is shown in Table A, in the column entitled "**HT-29 GI_{50} (nM)**."

Measurement of Inhibition of Cancer Cell Proliferation (HCT116 / Colorectal Carcinoma)

[00816] The following protocol used a HCT116 cell line, which cell line is a model for colorectal carcinoma. HCT116 cells were split and 3000 cells in 100 μl of growth medium were added per well of a flat-bottom 96-well plate. A two–fold test compound solution in serum-free RPM1640 was made, starting at 5,000 nM. Then, 3-fold serial dilutions were made across the plate from well 1 to well 11. Well 12, the last well in a row on the plate, was left as untreated control. 100 μl compound solutions were then transferred to the wells, so the total volume of media was 200 μl per well. Plates were returned to a 37 °C incubator, and the cells were cultured for 72 hours. To measure cell proliferation after 72 hours, media was discarded from the plates, 50 μl/well of fresh medium was added, and 50 μl CellTiterGlo solution was added (Promega Cat#G7573) . The plate was covered with a dark lid and incubated for 10 min. A white sealing tape was applied to the bottom of the plate, and the plate was read in a luminescence plate reader. In order to calculate GI_{50} (the concentration at which 50% of growth is inhibited) a standard curve was established to measure luminescence readings at specific cell densities by the following method: a 2-fold serial dilution was used to generate 8 cell densities from 50,000-390 cells per well in 50 μl media. 50 μl CellTiterGlo was added per well, and the plate was read in a luminescence plate reader after 10min. The reading was plotted vs. cell number to generate a standard curve and the equation of the curve fit. The compound-treated sample luminescence readings were converted to cell numbers using the curve-fit equation. The percent of inhibition, using untreated control as 100% growth, was then calculated. GI_{50} was then calculated by GraphPad Prism. Accordingly, this assay provides the dose at which 50% inhibition of cell growth was achieved and this data is shown in Table A, in the column entitled "**HCT116 GI_{50} (nM)**."

Measurement of Inhibition of Cancer Cell Proliferation (A375 / Malignant Melanoma)

[00817] The following protocol used an A375 cell line, which cell line is a model for malignant melanoma. A375 cells were split and 3000 cells in 100 μl of growth medium were added per well of a flat-bottom 96-well plate. A two–fold test compound solution in serum-free DMEM was made, starting at 5,000 nM. Then, 3-fold serial dilutions were made across the plate from well 1 to well 11. Well 12, the last well in a row on the plate, was left as untreated control.

100 µl compound solutions were then transferred to the wells, so the total volume of media was 200 µl per well. Plates were returned to a 37 °C incubator, and the cells were cultured for 72 hours. To measure cell proliferation after 72 hours, media was discarded from the plates, 50 µl/well of fresh medium was added, and 50 µl CellTiterGlo solution was added (Promega Cat#G7573) . The plate was covered with a dark lid and incubated for 10 min. A white sealing tape was applied to the bottom of the plate, and the plate was read in a luminescence plate reader. In order to calculate GI_{50} (the concentration at which 50% of growth is inhibited) a standard curve was established to measure luminescence readings at specific cell densities by the following method: a 2-fold serial dilution was used to generate 8 cell densities from 50,000-390 cells per well in 50 µl media. 50 µl CellTiterGlo was added per well, and the plate was read in a luminescence plate reader after 10min. The reading was plotted vs. cell number to generate a standard curve and the equation of the curve fit. The compound-treated sample luminescence readings were converted to cell numbers using the curve-fit equation. The percent of inhibition, using untreated control as 100% growth, was then calculated. GI_{50} was then calculated by GraphPad Prism. Accordingly, this assay provides the dose at which 50% inhibition of cell growth was achieved and this data is shown in Table A, in the column entitled "**A375 GI_{50} (nM)**."

EXAMPLE 416

Detection of total and phosphor-RSK by MSD ELISA (A375)

[00818] The protocol below describes an assay to measure the kinase activity of ERK1/2 to phosphorylate a substrate, p90RSK, in the presence or absence of a test compound.

Cell Treatment

[00819] A375 cells were grown in DMEM/10%FBS. Twenty four hours prior to the assay, 50,000 cells per well were plated in a 96 well flat bottom plate. Once cells attached to the plate, the medium was replaced with 100 ul of DMEM/0.1% FBS. Cells were cultured overnight in an incubator at 37 °C.

Compound dilution

[00820] Compound stock solutions of 10 mM in DMSO were prepared. 1000x dilutions were then prepared in DMSO. 1 uL of DMSO solution was then transfered to 1 ml DMEM/0.1%FBS

in a deep well plate. Cell plate media was discarded, followed by addition of 100 uL of the compound-containing media. The preparation was incubated at 37 °C for 2 hrs.

[00821] Cell lysates were prepared as described below.

pRSK or total RSK MSD Assay

DAY 1

[00822] MSD plates: Blank MSD plates were coated with 30 uL capture antibody (BD 610226) at a final concentration of 1 ug/mL in PBS. Both pRSK and total RSK MSD assays used the same capture antibody at the same concentration. Antibody stock concentration was 250 ug/mL. Once antibody solution was added to the MSD plate, the sides were tapped to be certain it was coated completely (visual inspection). It was then covered and placed at 4 °C overnight on a level surface.

DAY 2

[00823] Block MSD Plate: The coating antibody was removed and the plate was washed on a plate washer in MSD wash buffer. The last bit of wash solution was tapped out and 150 uL/well of 3% BSA in MSD wash buffer was added in. The preparation was placed on a shaker at room temperature for at least an hour.

[00824] Add samples: Media was removed from compound-treated cells and replaced with 55 uL/well MSD cell lysis buffer containing protease and phosphotase I & II inhibitors. The preparation was incubated on a shaker in a cold room for 30-45 min. The blocked MSD plate was washed a on plate washer, tapping out the last bit of wash solution, followed by addition of 50 uL (of the 55 ul) cell lysate in a well-well transfer. The preparation was covered and incubated on a shaker at room temp for 2 hours. The lysate was removed, washed on a plate washer 3 times, and the last bit of wash buffer was tapped out and replace with 25 uL/well detection antibody (described below).

Detection antibody:

[00825] For pRSK detection, a pRSK antibody stock of 21 ug/mL was prepared as follows: 1 ug/mL pRSK Ser380 antibody (Cell Signaling Technology, Cat. # 9335) + 1:750 anti-rabbit SulfoTag (Mesoscale Discovery, Cat. # R32AB-1) in 1% BSA in MSD wash buffer.

[00826] For total RSK detection, a total RSK antibody stock of 200 ug/mL was prepared as follows: 1 ug/mL total RSK (Santa Cruz sc-231G) antibody + 1:750 anti-goat SulfoTag (from MSD, R32AG-1) in 1% BSA in MSD wash buffer.

[00827] The plate was incubated for 1 hr at room temperature on a shaker, followed by three washings. The last bit of wash buffer was tapped out. 150 uL/well 1X MSD Read buffer was added and the plate was then analyzed. Curve fitting analysis was done with variable slope in Graph Pad software to generate EC_{50} based on DMSO control (untreated) being 100% pRSK signal and maximum inhibition with a reference compound provided by the manufacturer as a positive control. Results from this assay, showing EC_{50} (i.e., the concentration at which a test compound inhibits phosphorylation of RSK by 50%) are reported in Table A under the column "**ERK1/ERK2 PRSK MSD A375 EC_{50} (nM).**"

EXAMPLE 417

Detection of total and phospho-RSK by MSD ELISA (HCT116)

[00828] The protocol below describes an assay to measure the kinase activity of ERK1/2 to phosphorylate a substrate, p90RSK, in the presence or absence of a test compound.

Cell Treatment

[00829] HCT116 cells were grown in RPMI/10%FBS. Prior to the assay, 50,000 cells per well were plated in a 96 well flat bottom plate. Cells were cultured overnight in an incubator at 37 °C.

Compound dilution

[00830] Compound stocks were 10 mM in DMSO. A 1000x dilution was made in DMSO. 1 uL of the DMSO solution was transfered to 1 ml RPMI/10%FBS in a deep well plate. Media in the cell plate was discarded, and 100 uL of the compound-containing media was added. The preparation was ncubated at 37 °C for 2 hrs.

Preparation of cell lysates are described below.

pRSK or total RSK MSD Assay

DAY 1

[00831] MSD plates: Blank MSD plates were coated with 30 uL capture antibody (BD 610226) at a final concentration of 1 ug/mL in PBS. Both pRSK and total RSK MSD assays used the same capture antibody at the same concentration. Antibody stock concentration was 250 ug/mL. Once antibody solution was added to MSD plate, the sides were tapped to be certain it was coated completely (visual inspection). It was then covered and placed at 4 °C overnight on a level surface.

DAY 2

[00832] Block MSD Plate: The coating antibody was removed and the plate was washed on a plate washer in MSD wash buffer. The last bit of wash solution was tapped out and 150 uL/well 3% BSA (MSD Blocker A) in MSD wash buffer was added. The preparation was placed on a shaker at room temperature for at least an hour.

[00833] Add samples: Media was removed from compound-treated cells and replaced with 55 uL/well MSD cell lysis buffer containing protease and phosphotase I & II inhibitors. The preparations was incubate on a shaker in a cold room for 30-45 min. The blocked MSD plate was washed on a plate washer, and the last bit of wash solution was tapped out. Next was added 50 uL (of the 55 uL) cell lysate in a well-well transfer. The preparation was covered and incubated on shaker at room temp for 2 hours. The lysate was then removed and washed on plate washer 3 times. The last bit of wash buffer was then tapped out and replaced with 25 uL/well detection antibody (described below).

Detection antibody:

[00834] For pRSK detection, a pRSK antibody stock of 21 ug/mL was prepared as follows: 1 ug/mL pRSK Ser380 antibody (Cell Signaling Technology, Cat. # 9335) + 1:750 anti-rabbit SulfoTag (from MSD, R32AB-1) in 1% BSA in MSD wash buffer.

[00835] For total RSK detection, a total RSK antibody stock of 200 ug/mL was prepared as follows: 1 ug/mL total RSK (Santa Cruz sc-231G) antibody + 1:750 anti-goat SulfoTag (from MSD, R32AG-1) in 1% BSA in MSD wash buffer.

[00836] The plate was incubated for 1 hr at room temperature on a shaker, followed by three washes. The last bit of wash buffer was tapped out. Next, 150 uL/well 1X MSD Read buffer was added and the plate was analyzed by the MSD reader. Curve fitting analysis was done with variable slope in Graph Pad software to generate EC_{50} based on DMSO control (untreated) being 100% pRSK signal and maximum inhibition with a reference compound provided by the manufacturer as a positive control. Results from this assay, showing EC_{50} (i.e., the concentration at which a test compound inhibits phosphorylation of RSK by 50%) are reported in Table A under the column "**ERK1/ERK2 PRSK MSD HCT116 EC_{50} (nM).**"

EXAMPLE 418

[00837] Table A shows data for selected compounds in various assays. Compound numbers in Table A correspond to Compound numbers in Table 3, above. Compounds having an activity designated as "A" provided an $EC_{50}/IC_{50}/GI_{50}$ $\leq$100 nM; compounds having an activity designated as "B" provided an $EC_{50}/IC_{50}/GI_{50}$ of 101-500 nM; compounds having an activity designated as "C" provided an $EC_{50}/IC_{50}/GI_{50}$ of 501-999 nM; compounds having an activity designated as "D" provided an $EC_{50}/IC_{50}/GI_{50}$ of $\geq$1000 nM.

[00838] Compounds having an activity designated as "E" provided a mass modification of $\geq$70%; compounds having an activity designated as "F" provided a mass modification of 31 – 69%; compounds having an activity designated as "G" proived a mass modification $\leq$30 %.

[00839] With regard to p-RSK inhibition at 6 hours, compounds having an activity designated as "E" provided a p-RSK inhibition percent of $\geq$70%; compounds having an activity designated as "F" provided a p-RSK inhibition percent of 31 – 69%; compounds having an activity designated as "G" proived a p-RSK inhibition percent of $\leq$30 %.

Table A.

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-1	B	B	G							
I-2	A	A	E	B	A					
I-3	B		E							
I-4	B		F							
I-5	A	B	E	B						
I-6	D	D	E							
I-7	A	C	E	C						
I-8	B	A	E	C						
I-9	A	A	E	B						
I-10	A	A	E	A					A	A
I-11	B	B	E	B						
I-12	B	B	E	B						
I-13	A	B	E	B						
I-14	B	D	E							
I-15	A	A	E	A		E	A		A	A

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-16	B	C	E							
I-17	A	B	F							
I-18	A	B	E	B					B	
I-19	A	A	E	A					A	A
I-20	A	A	E	A					A	A
I-21	B	D	G							
I-22	B	D	G	C					B	
I-23	A	B	E	A					B	
I-24	D	D	G							
I-25	D	D	G							
I-26	D		G							
I-27		C	F							
I-28										
I-29	D	D	G							
I-30	B	D	G							
I-31	C	D	G							
I-32	B	D	F							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-33	D	D	F							
I-34	B	D	F							
I-35	B	D	G							
I-36	A	C	E							
I-37	A	A	E	A					A	
I-38	A	D	E	C					B	
I-39	B	C	E							
I-40	A	D	F							
I-41	A	B	E	A					A	
I-42	A	B	E	D					D	
I-43	A	B	E	A					A	
I-44	D	D	E							
I-45	D	D	G							
I-46	A	C	G	C					C	
I-47	A	B	G	B					A	
I-48	A	D	G	D					D	
I-49	C		E							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-50	B		E							
I-51	B		E							
I-52	B		E	B					B	D
I-53	A	D	G							
I-54	A	D	G							
I-55	A	B	E	A					A	B
I-56	B	B	F	B					B	B
I-57	B	B	F	B					B	B
I-58	B	B	E	B					B	B
I-59	C	D	E	B					B	C
I-60	C	D	E	B					D	C
I-61	D	D	E							
I-62	D	D	F							
I-63	B	D	E							
I-64	A	A	E	A			B		A	A
I-65			E							
I-66	C		E							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-67	B	C	E							
I-68	A	A	E	A	A	E	B		A	A
I-69	A	B	E	A						
I-70	A	A	E	A					A	
I-71	A	A	E	B						
I-72	B		E	D						
I-73	B	B	E	B						
I-74	B	C	E	B						
I-75	B	D	E							
I-76	A	C	E	A	A				B	
I-77	A	B	E	A	A				B	B
I-78	C		E							
I-79	B	A	E	A		E			A	
I-80	B	B	E	A					B	
I-81	B	B	E	A					A	
I-82	C	D	E							
I-83	B	B	E							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-84	B	A	E	B					B	C
I-85	A	A	E	A		E	A	A	A	B
I-86	A	A	E	A		E			A	A
I-87	B	D	G							
I-88	A	B	E	A			B		A	A
I-89	B	B	F	A			B		A	A
I-90	A	A	E	B			A	B	B	C
I-91	A	B	E	A			A	A	A	A
I-92	A	A	E	A			A	A	A	A
I-93	B	A	E	A			A	A	A	A
I-94	B	A	F	A			B		A	A
I-95	A	A	E	A			A		A	A
I-96	B	A	E	A			B		B	A
I-97	C		G							
I-98	B	D	G							
I-99	C	D	G							
I-100	B	C	F	D						

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-101	B	B	E							
I-102	A	A	E	B	A					
I-103	A	B	E	A						
I-104	C	C	E	C						
I-105	C	D	F	C						
I-106	D	D	F							
I-107	B	B	E							
I-108	A	A	E	A					B	
I-109	C	D	E							
I-110	B	B	E							
I-111	B	B	E							
I-112	A	A	E	B						
I-113	D	D	F							
I-114	D	D	F							
I-115	A	A	E	A					A	B
I-116	B	B	E	B						
I-117	B	B	E	B						

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-118	A	A	E	B					B	
I-119	A	C	E	B						
I-120	A	A	E	A					B	
I-121	A	A	E	A						
I-122	A	A	E	B						
I-123	A	A	E	A					A	A
I-124	A	A	E	B						
I-125	A	B	E	B						
I-126	B	C	E	C						
I-127	B	B	E	B						
I-128	B		E							
I-129	B		E							
I-130	D		G	D						
I-131	A	A	E	A					A	
I-132	D		E							
I-133	B	D	E							
I-134	A	B	E	A					A	

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-135	B	D	E							
I-136	A	C	E							
I-137	A	C	E							
I-138	C	D	E							
I-139	A	A	E	A					A	A
I-140	A	A	E	A		F	A		A	A
I-141	B	C	E							
I-142	B		E							
I-143			F							
I-144			F							
I-145			E							
I-146			E							
I-147			E							
I-148			E							
I-149	B		E							
I-150	D		E							
I-151	D		F							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-152	C		E							
I-153	D		F							
I-154	D		G							
I-155	B	D	E	D						
I-156	B	C	E	D						
I-157	D		F							
I-158	D		F							
I-159	D		F							
I-160	D		G							
I-161	D		G							
I-162	D		E							
I-163	C		E							
I-164	B	D	E	D						
I-165	D		F							
I-166	B	B	E	B						
I-167	B	D	E	D						
I-168	B	D	E	D						

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-169	C		E							
I-170	D		E							
I-171	D		E							
I-172	D		F							
I-173	C		E							
I-174	C		E							
I-175	B		E							
I-176	C		E							
I-177	B		E							
I-178	B		E							
I-179	B	C	E	D						
I-180	C	C	E	D						
I-181	C		E							
I-182	D		E							
I-183	B	C	E	D						
I-184	D		E							
I-185	B	B	E	C						

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-186	B	C	E	D						
I-187	B	B								
I-188	D	D	F							
I-189	D		G							
I-190	D		F	D						
I-191	A	B	E	A					A	
I-192	A	A	E	A						
I-193	A	B	E	B						
I-194	B	C	E							
I-195	B	D	E							
I-196	C	D	E							
I-197	D	D	E							
I-198	B	B	E							
I-199	D		G							
I-200	D		G							
I-201	D		G							
I-202	B		F							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-203	B		E							
I-204	D		F							
I-205	A	A	E	A	A					
I-206	A	B	E	A	A					
I-207	B	D	E							
I-208	A	A	E	B						
I-209	B	B	F	C						
I-210	B	B	F							
I-211	A	A	F	B	A					
I-212	A	A	F	B	A					
I-213	B	B	E							
I-214	A	A	F	A	A					
I-215	D		G							
I-216	D		G							
I-217	D	D	G							
I-218	D	D	G							
I-219	D	D	G							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-220	B	C	E							
I-221	A	A	E	C						
I-222	D	D	G							
I-223	D	D	E							
I-224	B	B	E	B						
I-225	B	D	F							
I-226	C	C	E							
I-227	B	D	E							
I-228	B	B	E							
I-229	A	B	E	A		E			A	
I-230	C	B	E							
I-231	B	B	E	A					A	
I-232	B	B	E	A					B	
I-233	B	B	E	B					B	
I-234	B	B	F	B					B	
I-235	B	A	E	A					A	
I-236	B	B	E	B					A	

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-237	A	B	E	A					A	C
I-238	B	A	E	B					B	D
I-239	B		E	B					B	C
I-240	A	A	E	A		E			A	B
I-241	A	A	E	A		E			B	B
I-242	A	A	E	A		E	A	D	A	B
I-243	D	D	G							
I-244	D	B	E							
I-245	B	A	F	B					B	B
I-246	B	A	E	A					A	B
I-247	D	B	F							
I-248	A	B	E	C					C	D
I-249			F							
I-250			G							
I-251			G							
I-252			F							
I-253			F							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-254			E							
I-255	D		F	D						
I-256	D		G	D						
I-257	D		G							
I-258	A		E	D						
I-259	D		F							
I-260	D		G							
I-261	D		G							
I-262	D		F							
I-263	B	D	E	D						
I-264	D		F							
I-265	D		F							
I-266	B		E	D						
I-267	B	D	E	D						
I-268	D		G							
I-269	D		G							
I-270	D		G							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-271	D	D	G							
I-272	D	D	G							
I-273			G							
I-274			G							
I-275			G							
I-276	D	D	G	B					D	
I-277	D	D	E				D	D		
I-278	D	D	F				D	D		
I-279	C	D	E				D	D		
I-280	D	D	E				D	D		
I-281	A	A	E	A			A	A	A	A
I-282	B	B	E	A			A	A	A	A
I-283	A	A	E	A			A	A	A	A
I-284	A	A	E	C			A	A	A	B
I-285	C	B	E				D	D		
I-286	A	A	E	A			A	A	A	A
I-287	B	A	E				A	B		

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-288	C	B	E				B	B		
I-289	A	A	E				A	B		
I-290	D	D	E				D	C		
I-291	A	A	E	A			A	A	A	A
I-292	A	A	E	A			A	A	A	A
I-293	B	B	E	A			C	A	A	B
I-294	B	A	E	A			A	A	A	A
I-295	B	A	E				A	A		
I-296	A	A	E	A			A	A	A	A
I-297	A	A	E				D	A		
I-298	D		G							
I-299	B	D	E	D						
I-300	B	D	E	D						
I-301	C	D	E	D						
I-302	D	D	E	D						
I-303	D	D	G	D						
I-304	B	D	G							

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-305	B	D	E							
I-306	B		E							
I-307	A	D		B					A	
I-308	B	D	G	B					B	
I-309	D	D	G							
I-310	A	C	G	A					A	
I-311	A	C		C					D	D
I-312	D		G							
I-313			G							
I-314	A		G							
I-315	D		G							
I-316	D	D								
I-317	A	D	G	A					A	
I-318	A	C	G	B					A	
I-319	A	A	E	B	A					
I-320	C		F							
I-321	D	D	E				D	D		

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-322	A	A	E	B			A	B	A	B
I-323	B	A	E	B			A	B	B	C
I-324	A	B	E	A			B	A	A	A
I-325	B	B	E	A			B	A	A	A
I-326	B	A	E	A			A	A	A	A
I-327	B	A	E	A			A	A	A	A
I-328	A	A	E	A			A	A	A	A
I-329	D	B	E				D	B		
I-330	D	D	E				B	D		
I-331	D	B	E				C	D		
I-332	D	A	E				B	B		
I-333	B	B	E	D			B	D	D	D
I-334	A	A	E	A			A	A	A	A
I-335	D	C	E				C	C		
I-336	C	A	E	A			B	B	A	B
I-337	C	A	E	A			A	A	A	A
I-338	B	A	E	A			A	A	A	A

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-339	D	B	E	A			C	B	A	A
I-340	B	A	E	B			A	B	B	C
I-341	C	B	E				D	D		
I-342	C	B	E	A			B	B	B	B
I-343	B	B	F				B	B		
I-344	A	A	E	B			B	B	B	C
I-345	B	D	E				D	D		
I-346	C	B	E	B			B	B	B	C
I-347	A	A	E	B			B	B	A	C
I-348	D	B	G				C	C		
I-349	B	B	E	B			B	B	B	D
I-350	C	D	F				D	D		
I-351	B	B	F				B	C		
I-352	D	D	G				D	D		
I-353	D	D	G				D	D		
I-354	B	B	E	B			B	B	C	C
I-355	B	B	E	C			B	B	B	D

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-356	C	B	E	C			B	C	C	D
I-357	B	B	E	A			B	B	B	C
I-358	B	B	E				B	C		
I-359	B	B	E	C			B	C	B	D
I-360	D	B	E	D			B	C	B	D
I-361	A	A	E	B			B	B	B	C
I-362	D	C	E				C	D		
I-363	D	D	E				D	D		
I-364	A	A	E	B			A	B	A	B
I-365	D	D	E				D	D		
I-366	D	D	E				D	D		
I-367	B	B	E				B	C		
I-368	B	C	E				D	B		
I-369	D	D	F				D	D		
I-370	B	C	E				D	C		
I-371	B	B	F				B	D		
I-372	C	A	F				B	B		

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-373	D	B	F				C	C		
I-374	A	A	E	B			A	A	A	B
I-375	D	D	E				B	D		
I-376	B	A	E	B			A	A	B	C
I-377	A	A	E	A			A	A	B	D
I-378	C	B	E				C	D		
I-379	B	A	E	B			A	C	B	B
I-380	D	C	E				D			
I-381	A	A	E	B			A	A	B	B
I-382	B	B	E				D	C		
I-383	B	A	E				D	B		
I-384	A	A	E	A			A	A	A	B
I-385	A	A	E				A	A		
I-386	C	C	E				D	C		
I-387	B	B	E				B	B		
I-388	B	A	E				A	A		
I-389	A	A	E	A			A	A	A	B

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-390	A	A	E	A			A	A	A	B
I-391	B	B	E				D	B		
I-392	B	C	E				D	D		
I-393	C	C	E				D	C		
I-394	B	C	E				D	C		
I-395	D	D	E				D	D		
I-396	A	B	E				B	B		
I-397	D	C	F				C	D		
I-398	A	A	E	A			A	A	A	B
I-399	B	C	E				C	B		
I-400	A	A	E	B			A	A	B	C
I-401	B	B	E				B	B		
I-402		C	E				C	B		
I-403		A	E				B	B		
I-404		B					B	B		
I-405		A					B	A		
I-406		B					B	B		

Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-407	B	A					B	B		
I-408	B	B					B	C		
I-409	A	C					D	C		
I-410	A	B					B	B		
I-411	D	D					D	D		
I-412	A	D					A	B		
I-413	A	A					A	A		
I-414	A	A					A			
I-415	A	C					C	B		
I-416	A	B					B	B		
I-417	D	D					D	D		
I-418	B	C					C	B		
I-419	D	D					D	D		
I-420	D	D					D	D		
I-421	A	B					B	B		
I-422	A	B					B	A		
I-423	D	D					D	D		

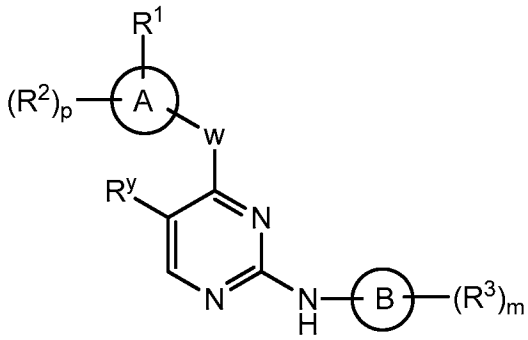
Cmpd #	ERK1 Omnia WT ATP KM IC_{50} (nM)	ERK1/ ERK2 PRSK MSD HT29 EC_{50} (nM)	ERK1 Mass Mod (%)	HT-29 GI_{50} (nM)	HT-29 Occupancy EC_{50} (nM)	p-RSK inhibition at 6 hr (%)	ERK1/ ERK2 PRSK A375 EC_{50} (nM)	ERK1/ ERK2 PRSK HCT116 EC_{50} (nM)	A375 GI_{50} (nM)	HCT116 GI_{50} (nM)
I-424	D	B					C	B		
I-425	B	B					C	C		
I-426	C	A					B	B		
I-427	B	B					B	C		
I-428	D						B	B		
I-429	D						B	C		
I-430	C						C	C		
I-431	C	B	E				B	C		

[00840] While we have described a number of embodiments of this invention, it is apparent that our basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. A compound of formula **I**:

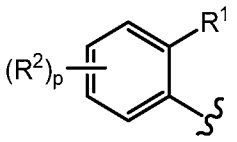
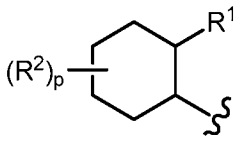
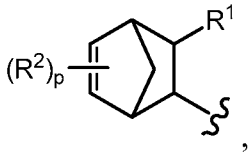
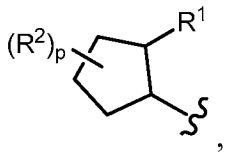
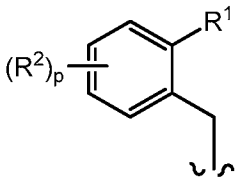


I

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted group selected from phenyl, a 3-8 membered saturated or partially unsaturated monocyclic carbocyclic ring, a 4-7 membered monocyclic heterocylic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or

Ring A is selected from

 ,  ,  ,  , and  ;

R^1 is a warhead group, wherein R^1 is attached to an atom adjacent to where W is attached;

each R^2 is independently hydrogen, an optionally substituted C_{1-6} aliphatic, halogen, or –OR;

Ring B (a) is an optionally substituted group selected from phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic 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 7-12 membered bicyclic saturated, partially

unsaturated or aryl ring, a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an 8-12 membered bicyclic heteroaryl ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur; or

(b) is absent and $(R^3)_m$ is attached to –NH-;

each R^3 is independently selected from -R, -Cy, halogen, –OR, –SR, –CN, –NO_2, -SO_2NR, -SO_2R, -SOR, -C(O)R, -C(O)OR, -OC(O)R, -OC(O)N$(R)_2$, -C(O)N$(R)_2$, -C(O)N(R)-OR -C(O)C(O)R, -P(O)$(R)_2$,-NRC(O)OR, -NRC(O)R, -NRC(O)N$(R)_2$, -NRSO_2R, or –N$(R)_2$; or two R^3 groups on the same carbon atom together form –C(O)-, -C(S)-, or -C(N-R)-;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-8 membered saturated or partially unsaturated carbocyclic ring, 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; or

two R groups on the same nitrogen are taken together with the nitrogen atom to which they are attached to form a 4-7 membered heterocylic ring having 0-2 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur, or a 4-7 membered heteroaryl ring having 0-4 additional heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Cy is an optionally substituted 5-6 membered monocyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur, or an optionally substituted 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

R^y is hydrogen, optionally substituted C_{1-6} aliphatic, halogen, haloalkyl, -CN, -C(O)R', -C(O)N$(R')_2$, -C(=N-R")R' or -N$(R')_2$;

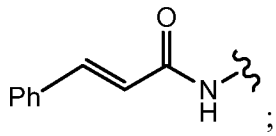
each R' is independently hydrogen or an optionally substituted C_{1-6} aliphatic;

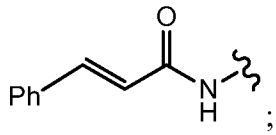
R" is hydrogen or –OR;

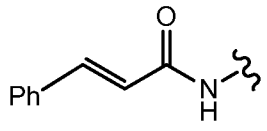
W is –O-, -NH-, -S-, -CH_2-, or -C(O)-; and

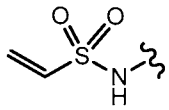
m and p are each independently 0-4;

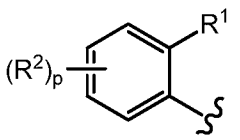
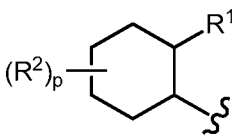
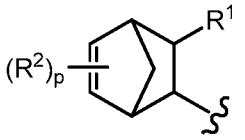
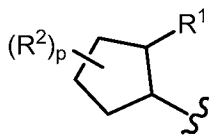
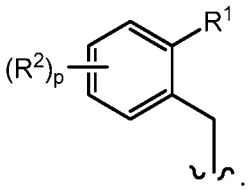
wherein:

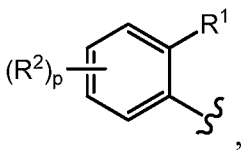
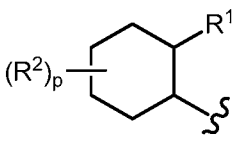
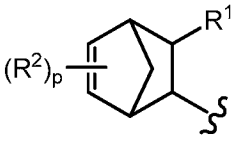
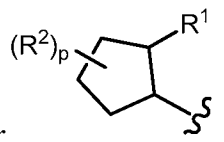
(a) when R^y is Cl and Ring B is phenyl para-substituted with morpholine, then R^1 is not  ;

(b) when R^y is Cl and Ring B is phenyl di-substituted with methoxy, then R^1 is not  ;

(c) when R^y is Cl and Ring B is a 7-12 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-5 heteroatoms independently selected from nitrogen, oxygen, or sulfur,, then R^1 is not  ; or

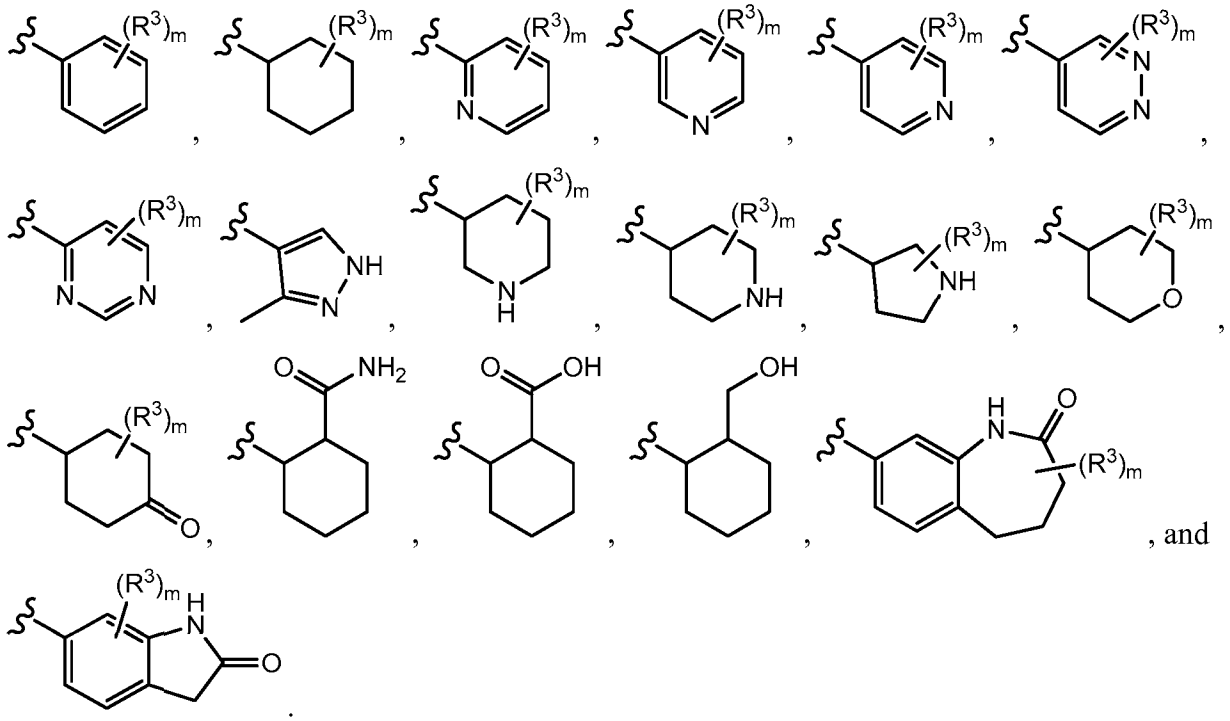
(d) when R^y is F and Ring B is phenyl tri-substituted with methoxy, then R^1 is not  .

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

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

4. The compound of claim 1, wherein each R^2 is independently hydrogen, F, Cl, Me, CF_3, or OMe.

5. The compound of claim 1, wherein Ring B is selected from:



6. The compound of claim 5, wherein each R^3 is independently an optionally substituted C_{1-6} aliphatic.

7. The compound of claim 5, wherein one R^3 is -Cy.

8. The compound of claim 5, wherein each R^3 is independently halogen, –OR, –SR, –CN, –NO_2, -SO_2R, -SOR, -C(O)R, -CO_2R, -C(O)N$(R)_2$, -NRC(O)R, -NRC(O)N$(R)_2$, -$NRSO_2R$, or –N$(R)_2$.

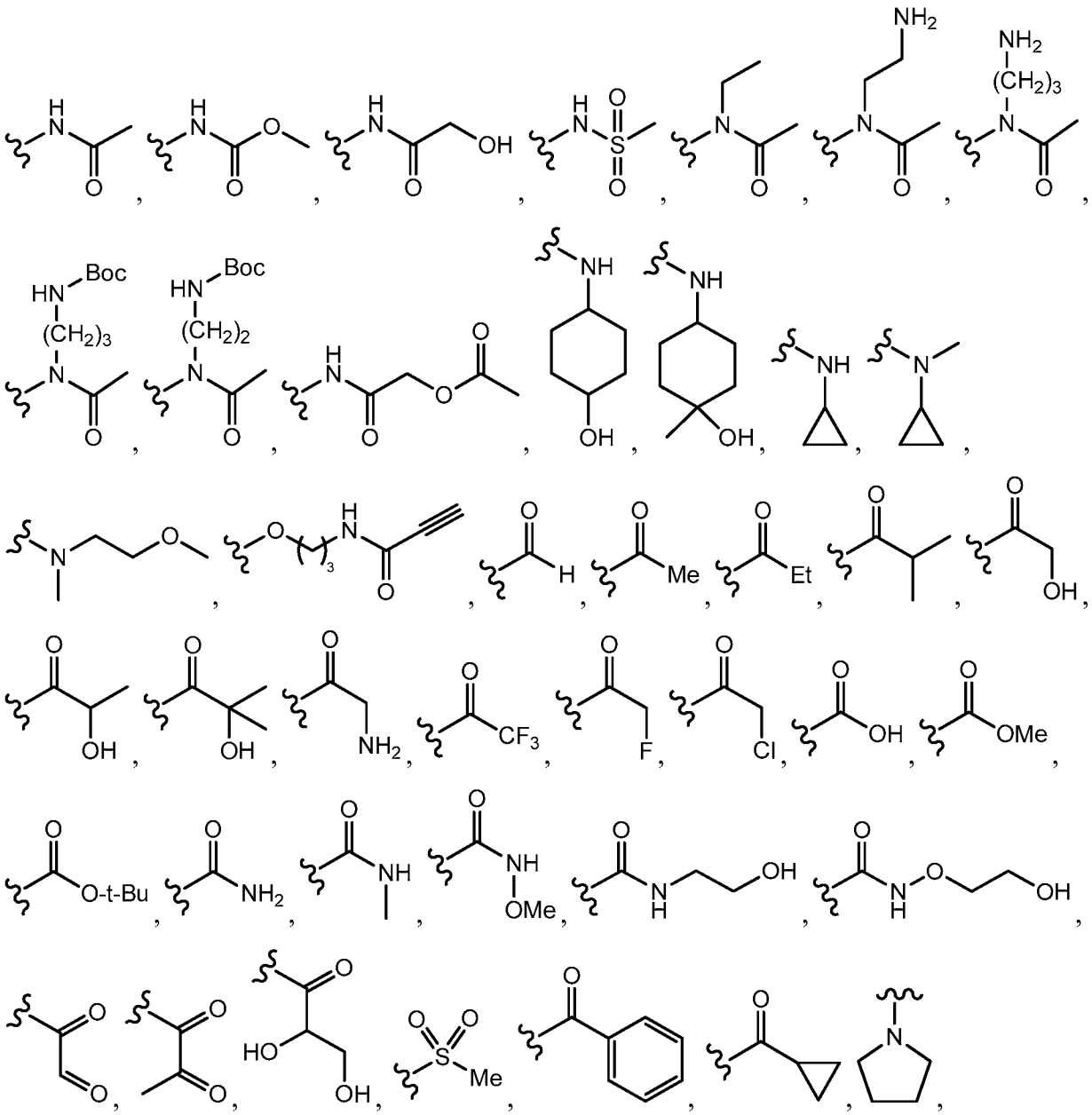
9. The compound of claim 5, wherein each R^3 is independently -Me, -Et, -t-Bu, -CH_2OH, , -CF_3, -$(CH_2)_3NHBoc$, -$(CH_2)_3NH_2$, -CN, –F, -Cl, -Br, –OH, -OMe, -OEt, -OCH_2CH_2OMe, -$NHCH_2CH_2OMe$, -OCH_2F, -$OCHF_2$, -OCF_3, -OCH_2CCH, -NH(Me), or -P(O)$(Me)_2$.

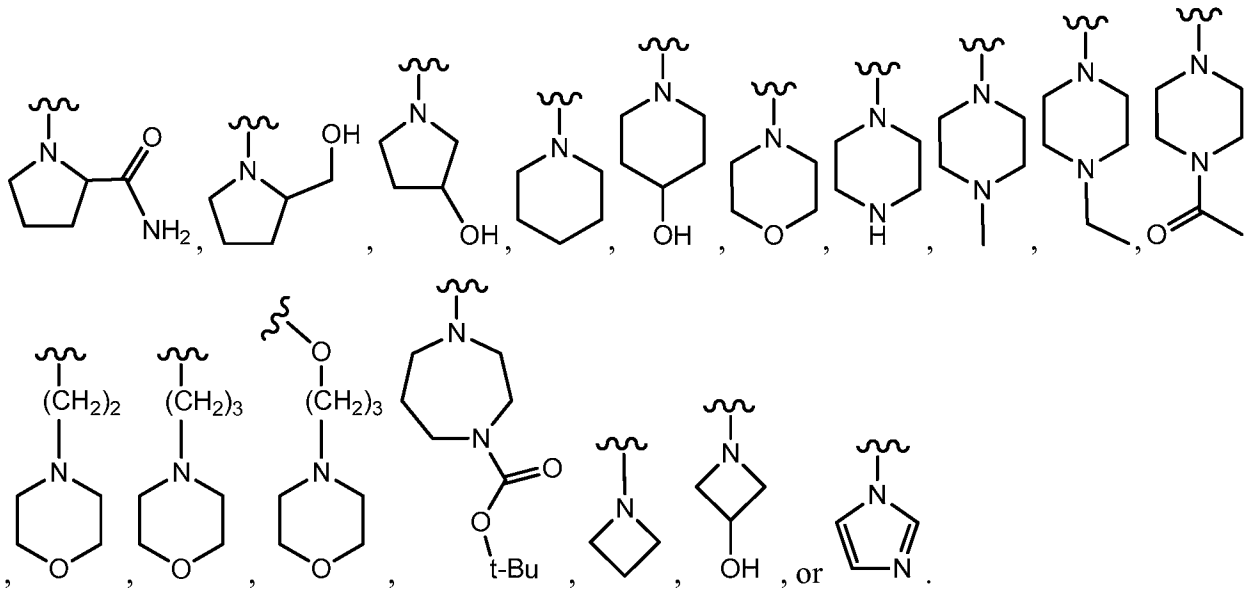
10. The compound of claim 5, wherein R^3 is an optionally substituted ring selected from piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl,

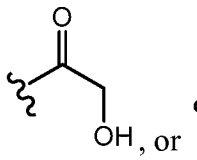
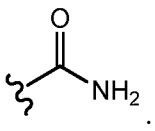
pyridazinyl, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, morpholinyl, or thiomorpholinyl, or azetidinyl.

11. The compound of claim 10, wherein the ring is substituted with Me, Et, OH, $C(O)NH_2$, or C(O)Me.

12. The compound of claim 5, wherein each R^3 is independently



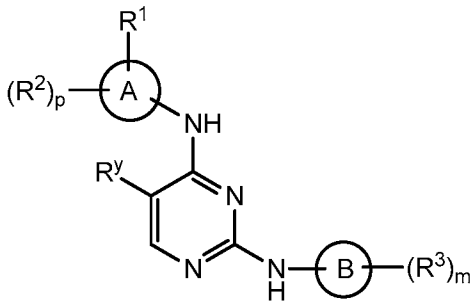


13. The compound of claim 5, wherein each R^3 is independently -Me, -OMe, -$NHCH_2CH_2OMe$,  , or  .

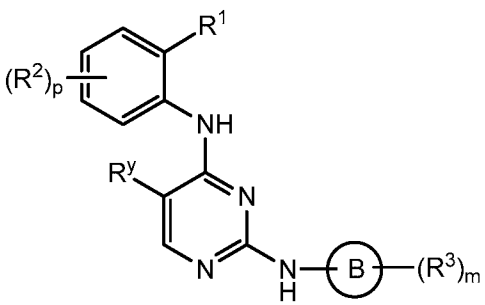
14. The compound of claim 1, wherein W is NH.

15. The compound of claim 1, wherein W is O.

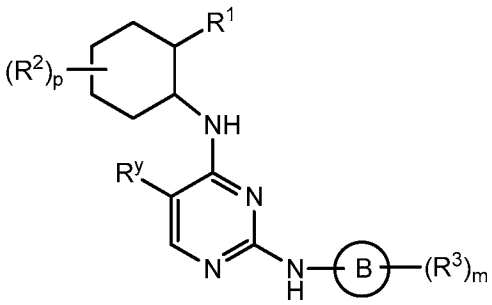
16. The compound according to claim 1, wherein said compound is of formula **I-a**, **I-b**, **I-c**, **I-d**, **I-e**, **I-f**, **I-g**, **I-h**, **I-j**, or **I-k**:



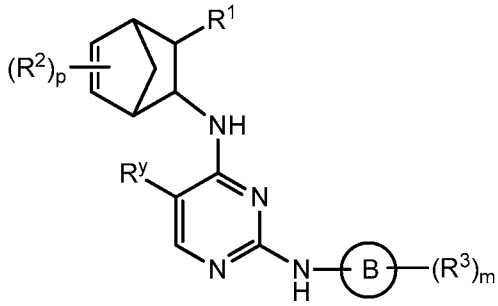
I-a



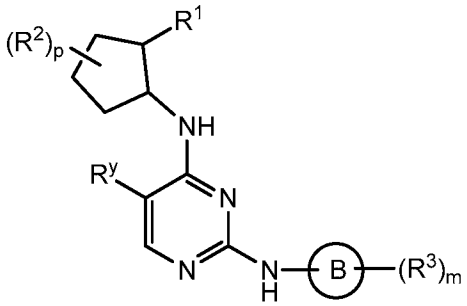
I-b



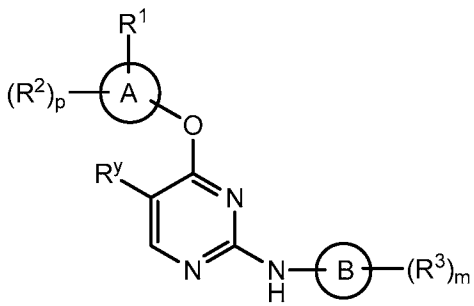
I-c



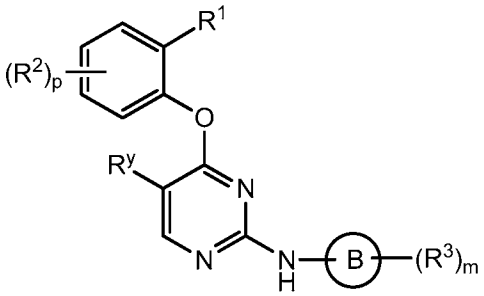
I-d



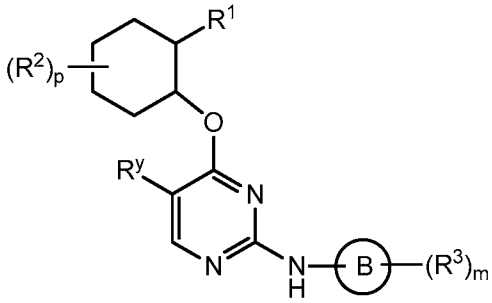
I-e



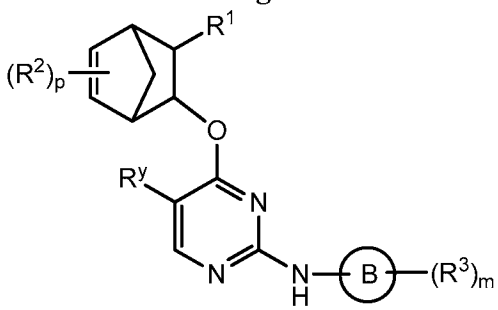
I-f



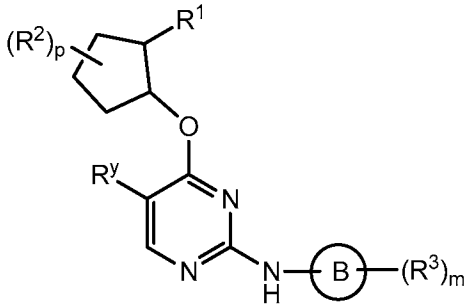
I-g



I-h



I-j



I-k

or a pharmaceutically acceptable salt thereof.

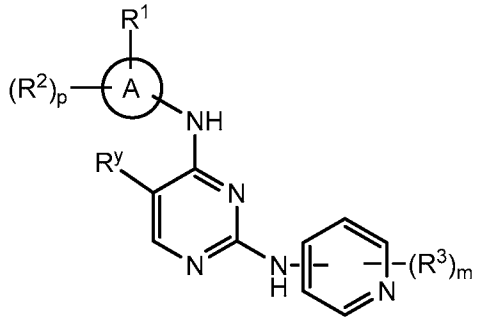
17. The compound according to any of claims 1-16, wherein R^y is haloaliphatic.

18. The compound according to claim 17, wherein R^y is $-CF_3$.

19. The compound according to any of claims 1-16, wherein R^y is halogen.

20. The compound according to claim 19, wherein R^y is –Cl.

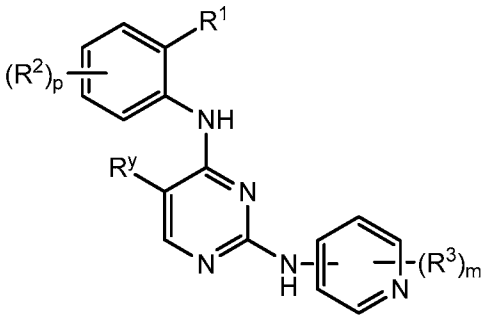
21. The compound according to claim 1, wherein said compound is of formula **VIII**:



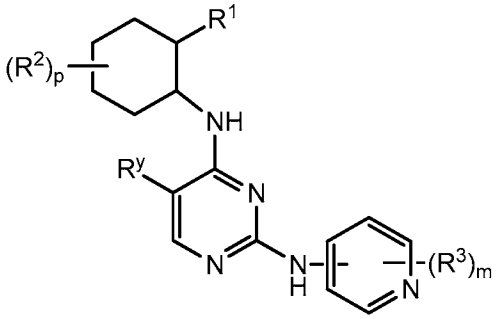
VIII

or a pharmaceutically acceptable salt thereof.

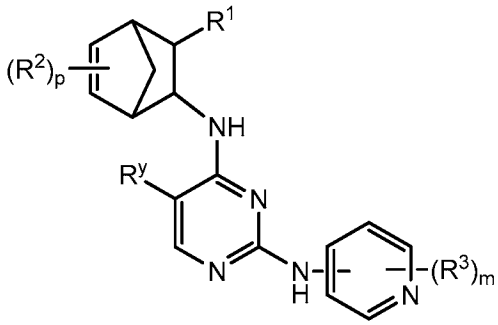
22. The compound according to claim 21, wherein said compound is any of formula **VIII-a**, **VIII-b**, **VIII-c**, or **VIII-d**:



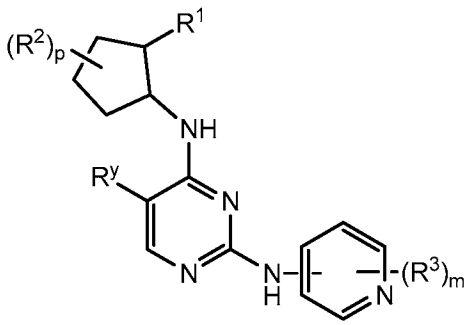
VIII-a



VIII-b



VIII-c



VIII-d

or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 21 or 22, wherein R^y is haloaliphatic.

24. The compound according to claim 23, wherein R^y is $-CF_3$.

25. The compound according to claim 21 or 22, wherein R^y is halogen.

26. The compound according to claim 23, wherein R^y is –Cl.

27. The compound according to any one of claims 21 through 26, wherein at least one R^3 is –OMe.

28. The compound according to claim 1, wherein R^1 is –L-Y, wherein:

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)-;

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 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.

29. The compound according to claim 28, wherein:

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.

30. The compound according to claim 29, wherein 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)-.

31. The compound according to claim 30 wherein 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)-.

32. The compound according to claim 29, wherein L is -NRC(O)CH=CH-, -NRC(O)CH=CHCH$_2$N(CH$_3$)-, -NRC(O)CH=CHCH$_2$O-, -CH$_2$NRC(O)CH=CH-, -NRSO$_2$CH=CH-, -NRSO$_2$CH=CHCH$_2$-, -NRC(O)(C=N$_2$)-, -NRC(O)(C=N$_2$)C(O)-, -NRC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NRC(O)-, -CH$_2$CH$_2$NRC(O)-, or -CH$_2$NRC(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.

33. The compound according to claim 32, wherein 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)-, or -NHC(O)C(=CH$_2$)CH$_2$-, -CH$_2$NHC(O)-, -CH$_2$CH$_2$NHC(O)-, or -CH$_2$NHC(O)cyclopropylene-.

34. The compound according to claim 29, wherein 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)-.

35. The compound according to claim 1, wherein R^1 is –L-Y, wherein:

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_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-,

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 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.

36. The compound according to claim 35, wherein Y is hydrogen or C_{1-6} aliphatic optionally substituted with oxo, halogen, NO_2, or CN.

37. The compound according to claim 36, wherein L is -C≡C-, -C≡CCH_2N(isopropyl)-, -NHC(O)C≡CCH_2CH_2-, -CH_2-C≡C-CH_2-, -C≡CCH_2O-, -CH_2C(O)C≡C-, -C(O)C≡C-, or -CH_2OC(=O)C≡C-.

38. The compound according to claim 1, wherein R^1 is –L-Y, wherein:

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_2N(R)-, –S-, -S(O)-, -SO_2-, -OC(O)-, or -C(O)O-;

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 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.

39. The compound according to claim 1, wherein R^1 is –L-Y, wherein:

L is a covalent bond, -C(O)-, -N(R)C(O)-, or a bivalent C_{1-8} saturated or unsaturated, straight or branched, hydrocarbon chain; and

Y is selected from the following (*i*) through (*xvii*):

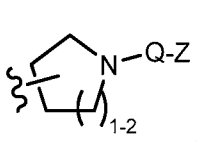
(*i*) C_{1-6} alkyl substituted with oxo, halogen, NO_2, or CN;

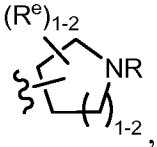
(*ii*) C_{2-6} alkenyl optionally substituted with oxo, halogen, NO_2, or CN; or

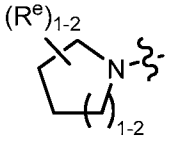
(*iii*) C_{2-6} alkynyl optionally substituted with oxo, halogen, NO_2, or CN; or

(*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; 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; or

(*vi*) 

, 

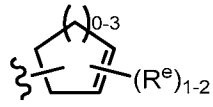
, or 

, wherein each R, Q, Z; or

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

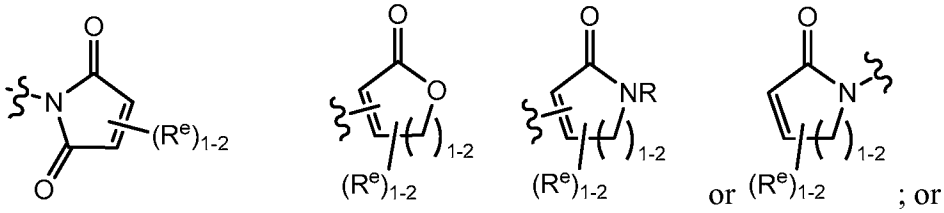
(*viii*) a partially unsaturated 3-6 membered monocyclic ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur, wherein said ring is substituted with 1-4 R^e groups; or

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

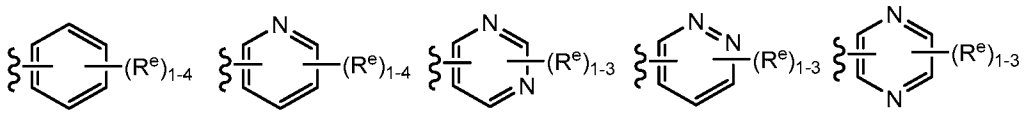
(*x*) 

; 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; or

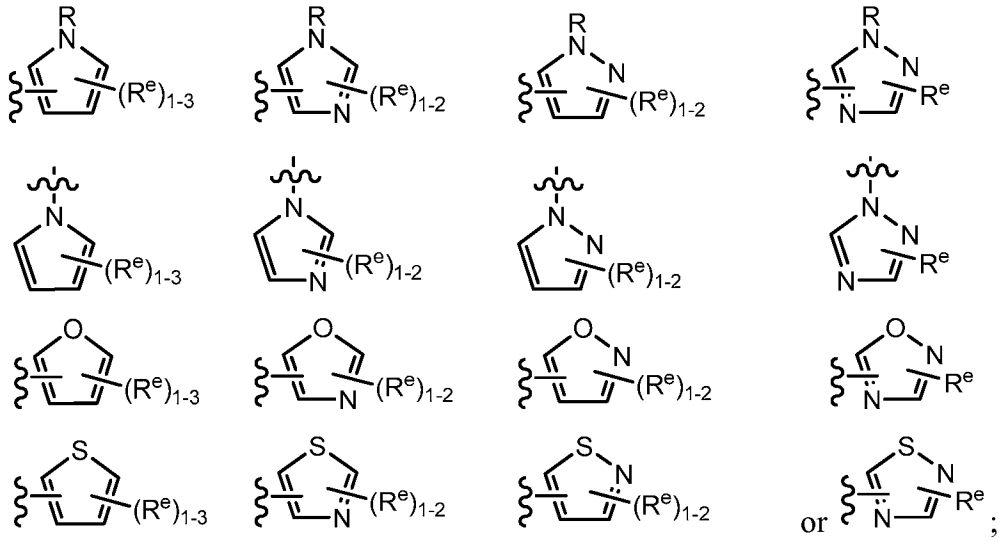
(*xii*)  ; or

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

(*xiv*) 

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; or

(*xvi*)  ;

(*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:

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;

each R^e 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:

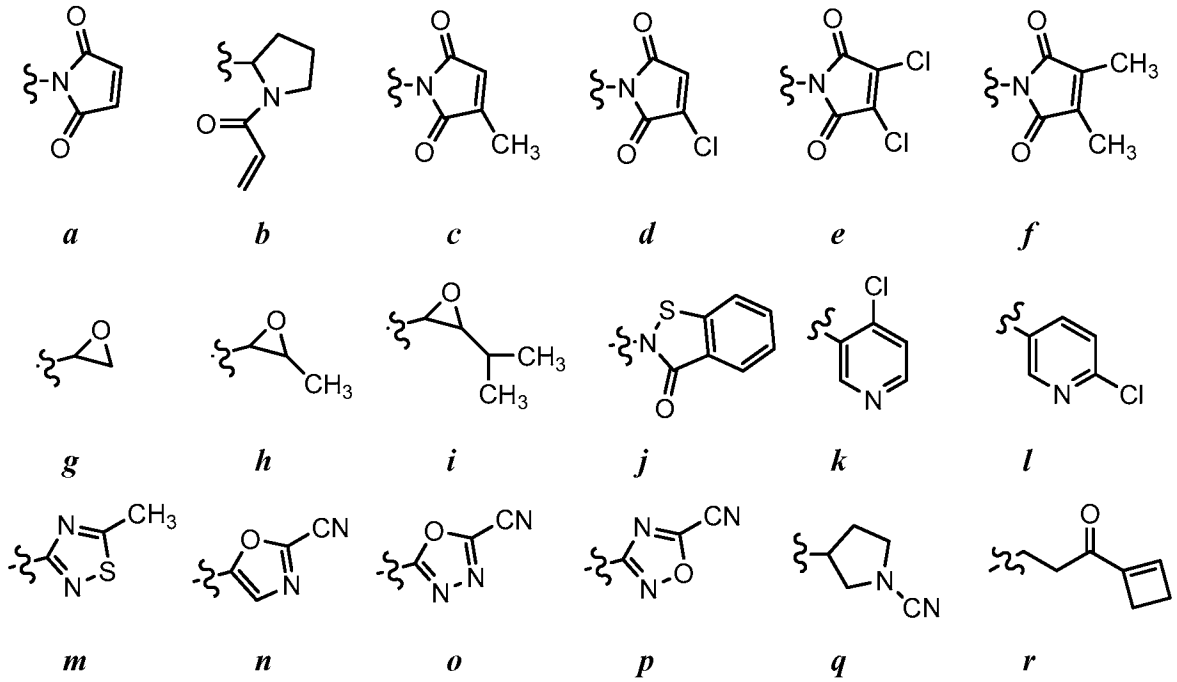
Q is a covalent bond or a bivalent C_{1-6} saturated or unsaturated, straight or branched, hydrocarbon chain, wherein one or two methylene units of Q are optionally and independently replaced by –N(R)-, -S-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -SO-, or -SO_2-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, or –SO_2N(R)-;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

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

40. The compound according to claim 39, wherein 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-.

41. The compound according to claim 40, wherein L is a covalent bond.

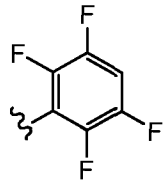
42. The compound according to any of claims 39, 40, and 41, wherein Y is selected from:



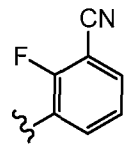
a *b* *c* *d* *e* *f*

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

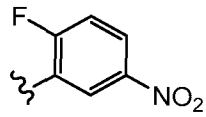
m *n* *o* *p* *q* *r*



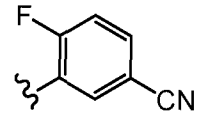
s



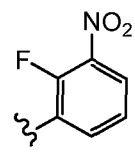
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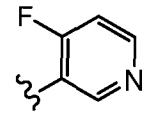
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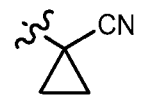
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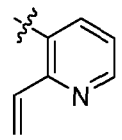
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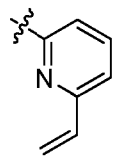
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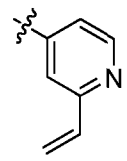
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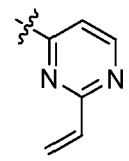
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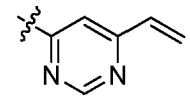
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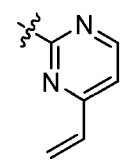
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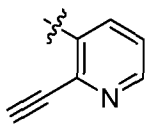
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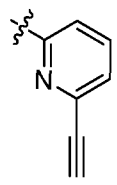
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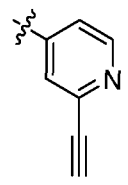
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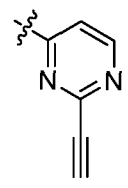
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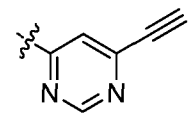
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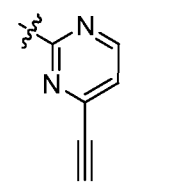
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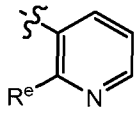
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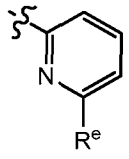
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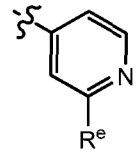
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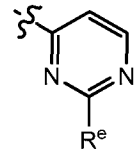
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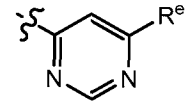
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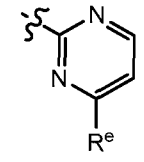
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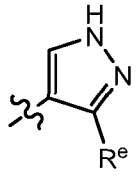
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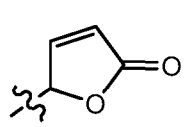
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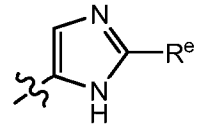
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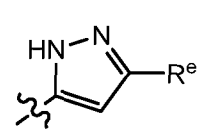
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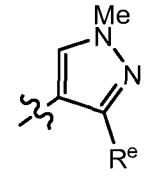
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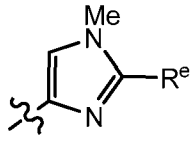
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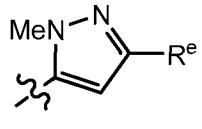
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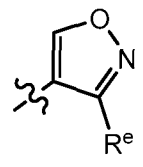
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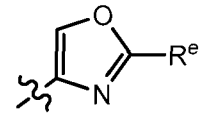
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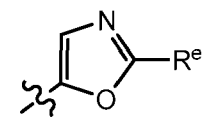
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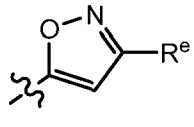
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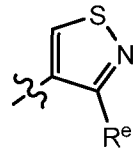
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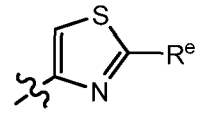
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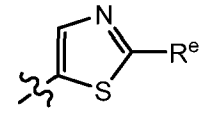
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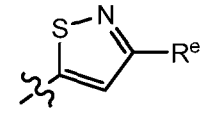
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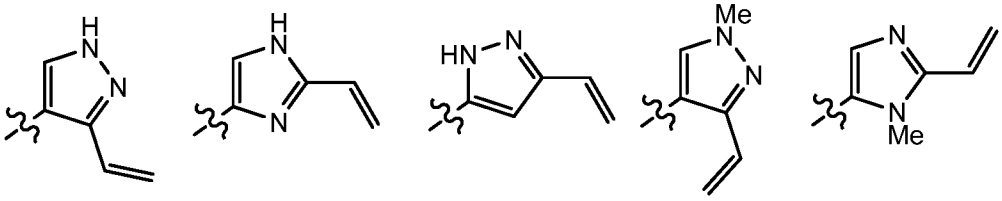
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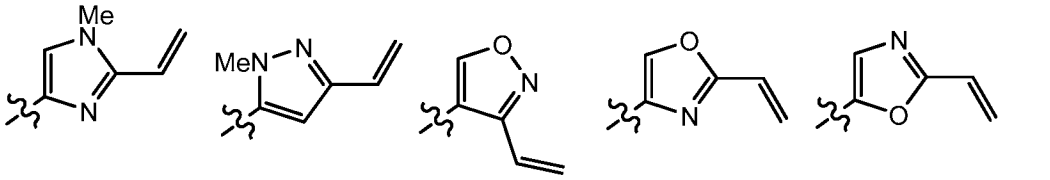
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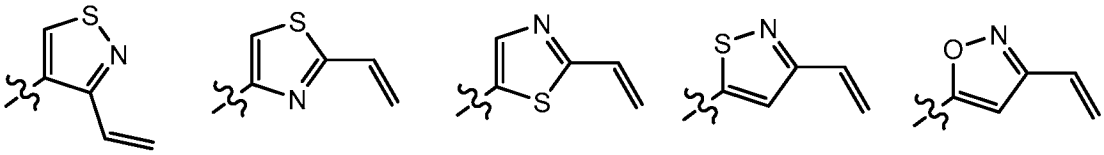
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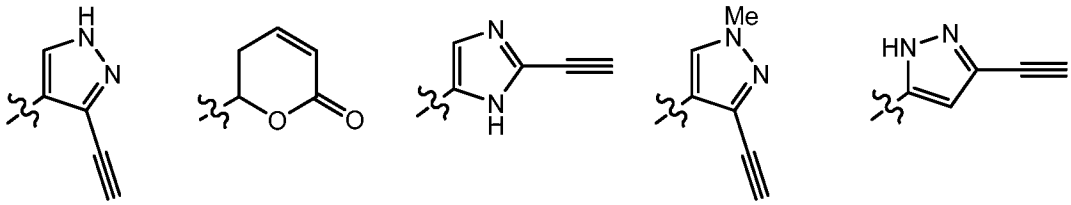
ggg *hhh* *iii* *jjj* *kkk*



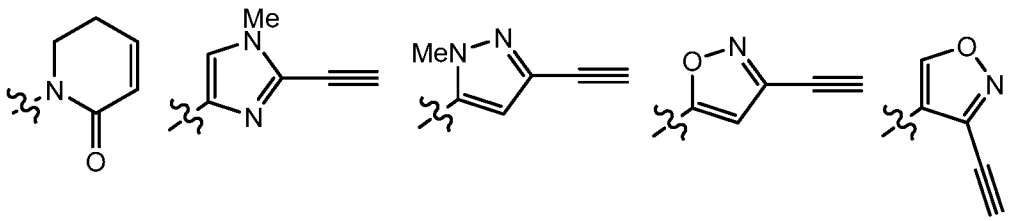
lll *mmm* *nnn* *ooo* *ppp*



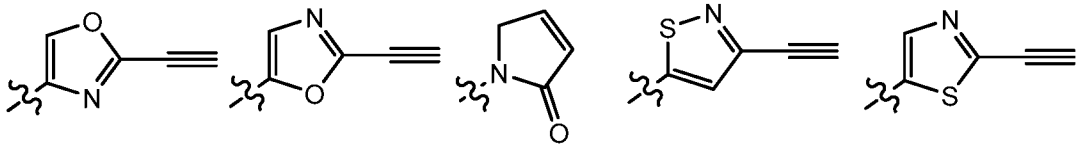
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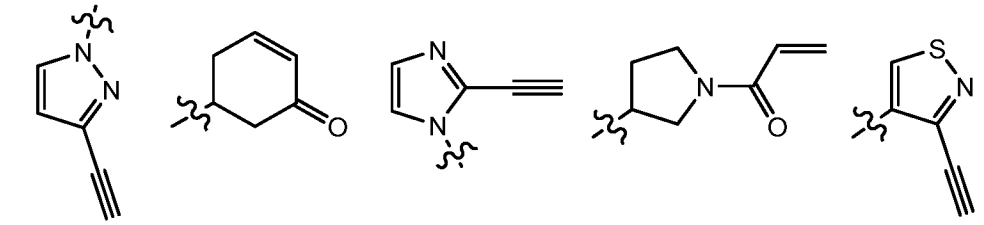
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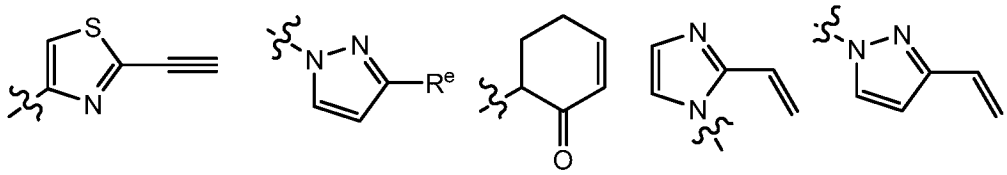
zzz *aaaa* *bbbb* *cccc* *dddd*



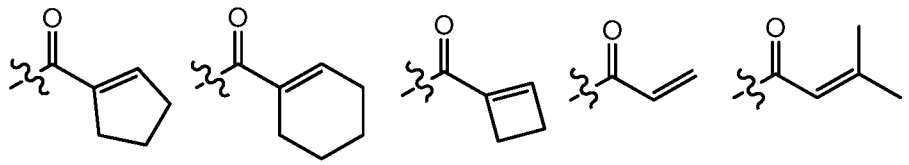
eeee *ffff* *gggg* *hhhh* *iiii*



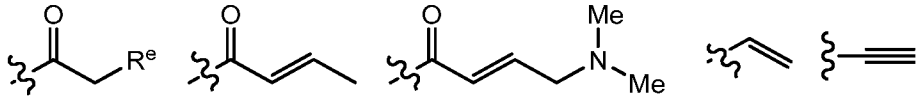
jjjj *kkkk* *llll* *mmmm* *nnnn*



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



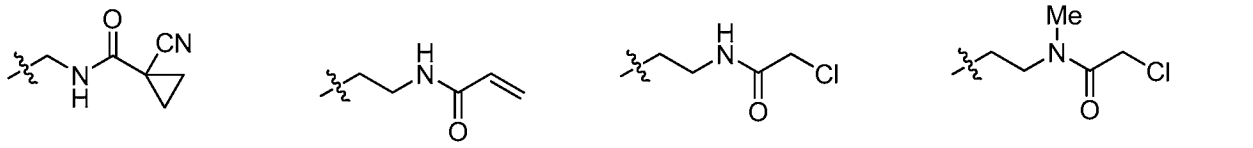
tttt *uuuu* *vvvv* *wwww* *xxxx*



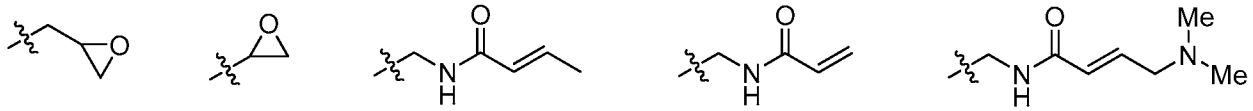
yyyy *zzzz* *aaaaa* *bbbbb* *ccccc*

wherein each R^e is independently selected from halogen.

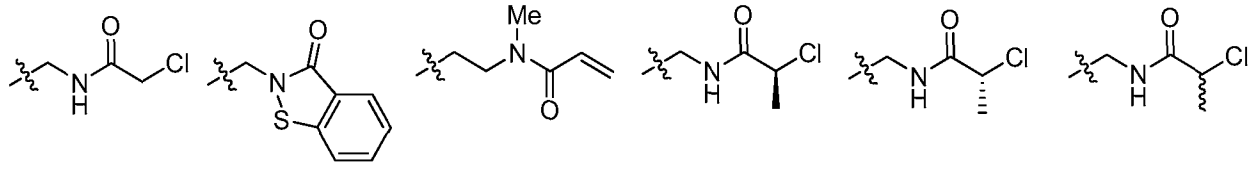
43. The compound according to claim 1, wherein R^1 is selected from:



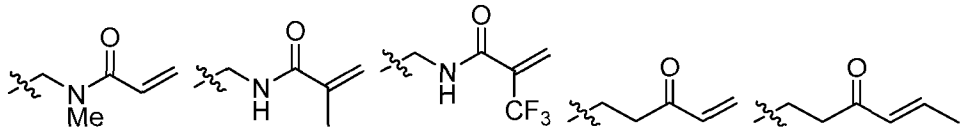
a *b* *c* *d*



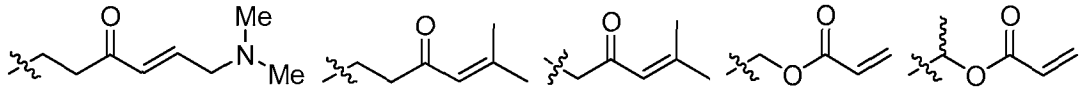
e *f* *g* *h* *i*



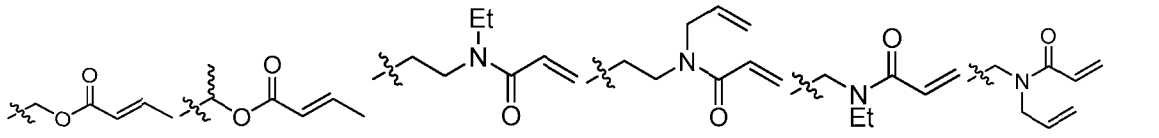
j *k* *l* *m* *n* *o*



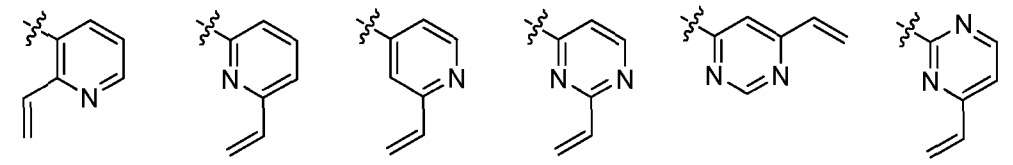
p *q* *r* *s* *t*



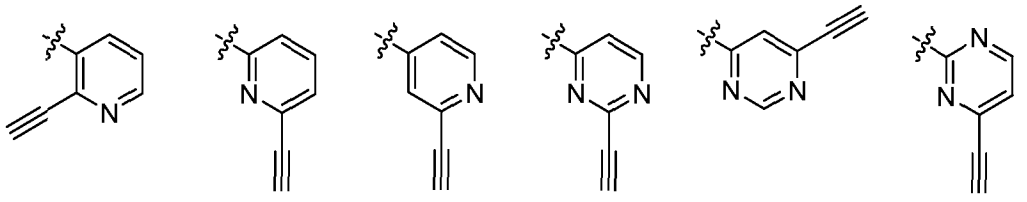
u *v* *w* *x* *y*



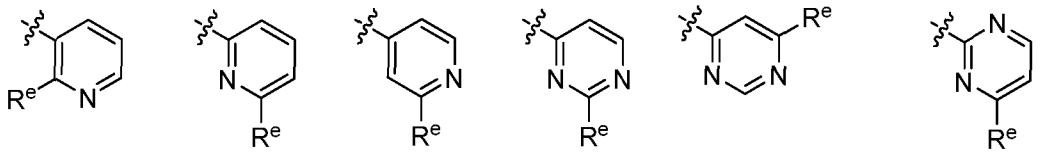
z *aa* *bb* *cc* *dd* *ee*



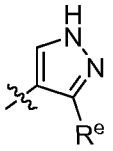
ff *gg* *hh* *ii* *jj* *kk*



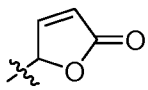
ll *mm* *nn* *oo* *pp* *qq*



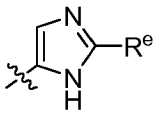
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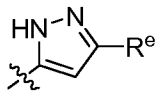
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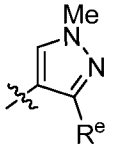
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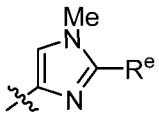
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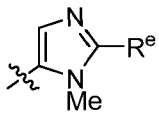
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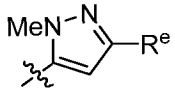
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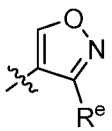
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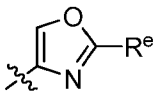
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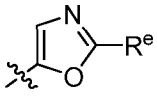
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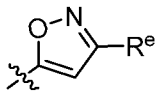
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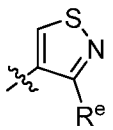
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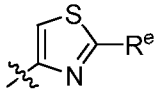
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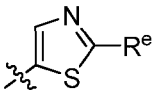
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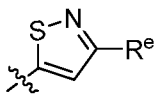
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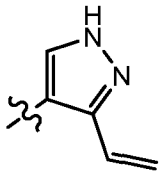
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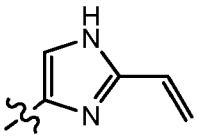
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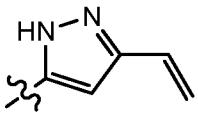
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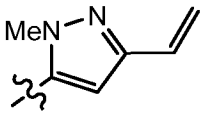
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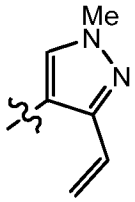


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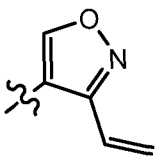


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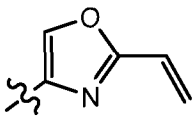




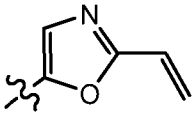
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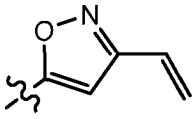
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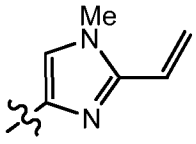
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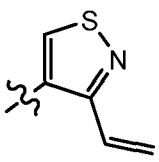
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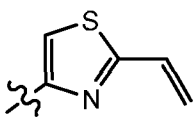
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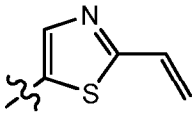
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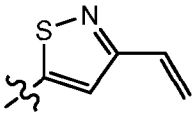
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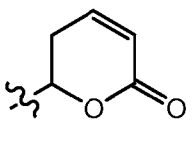
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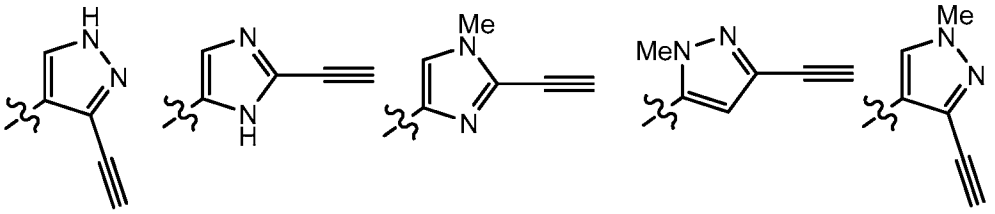
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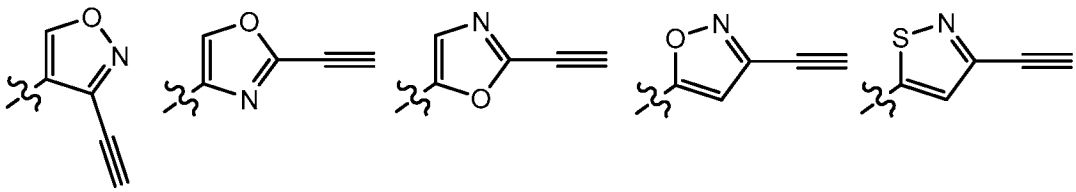
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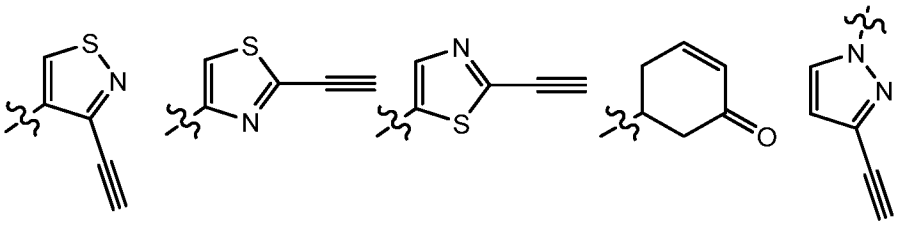
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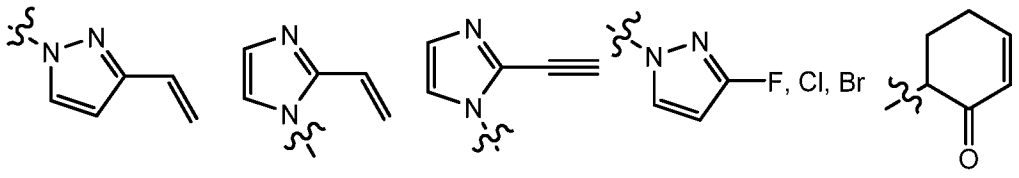
bbbb *cccc* *dddd* *eeee* *ffff*



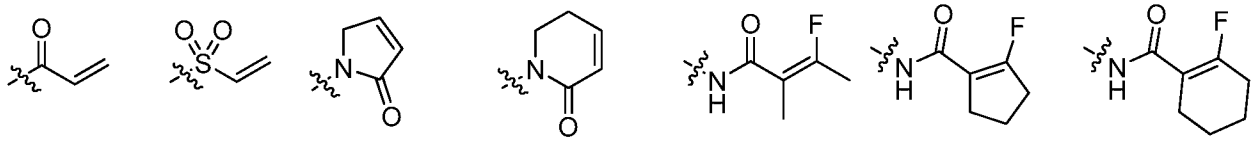
gggg *hhhh* *iiii* *jjjj* *kkkk*



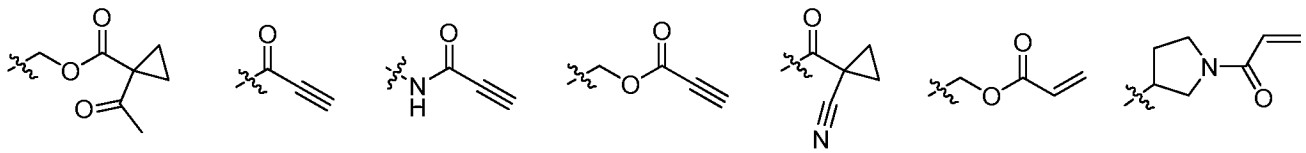
llll *mmmm* *nnnn* *oooo* *pppp*



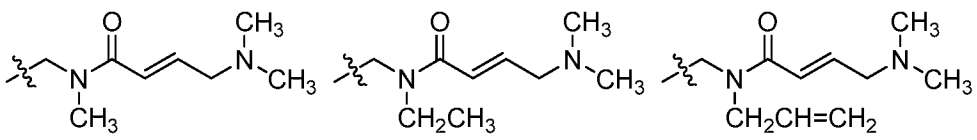
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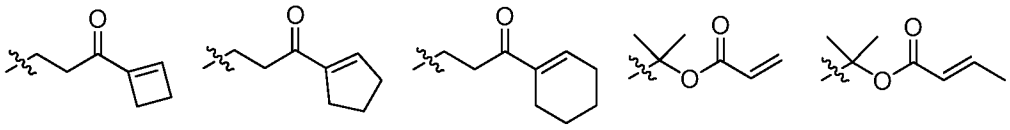
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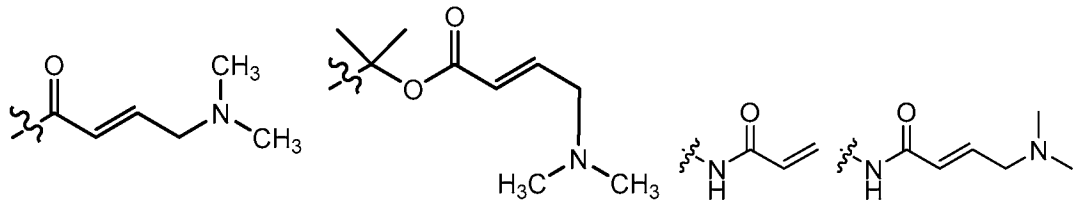
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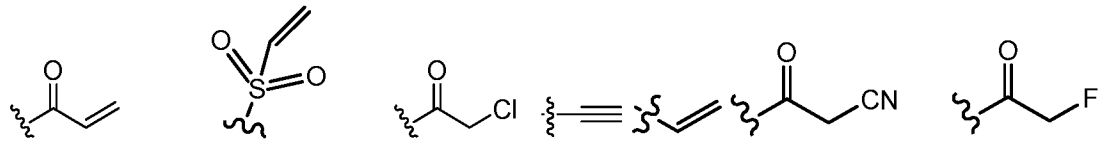
jjjjj *kkkkk* *lllll*



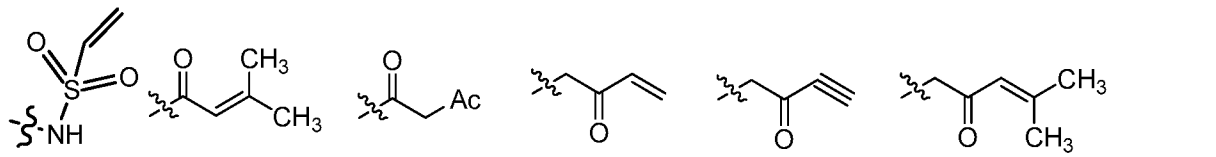
mmmmm *nnnnn* *ooooo* *ppppp* *qqqqq*



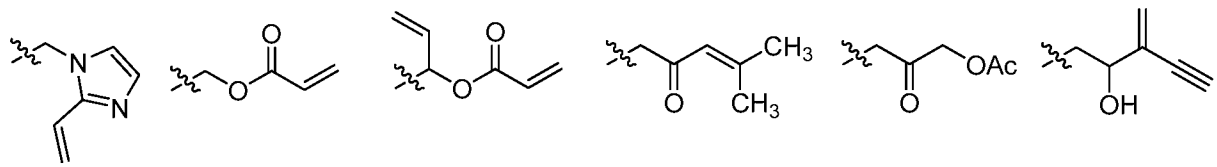
rrrrr *sssss* *ttttt* *uuuuu*



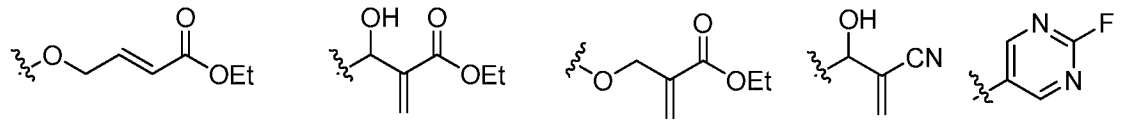
vvvvv *wwwww* *xxxxx* *yyyyy* *zzzzz* *aaaaaa* *bbbbbbb*



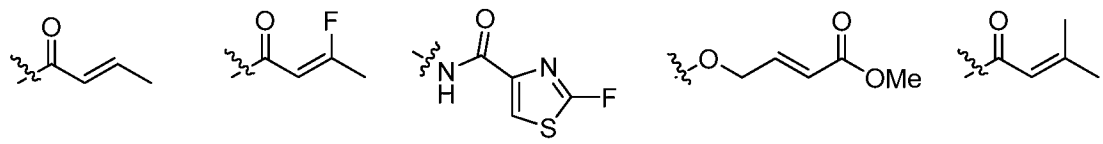
ccccccc *ddddddd* *eeeeeee* *fffffff* *ggggggg* *hhhhhhh*



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



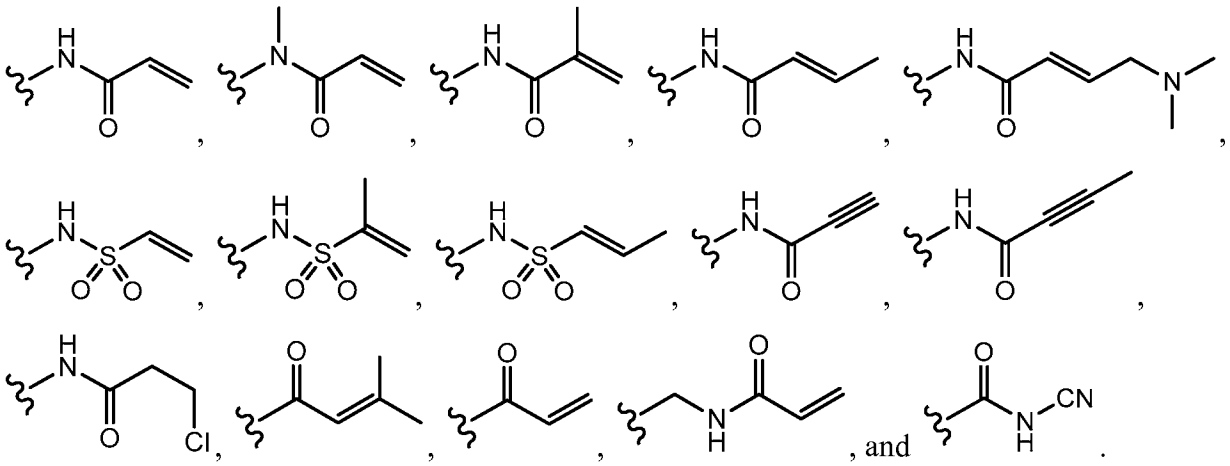
oooooo *pppppp* *qqqqqq* *rrrrrr* *ssssss*



tttttt *uuuuuu* *vvvvvv* *wwwwww* or *xxxxxx*

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

44. The compound according to claim 1, wherein R^1 is selected from:



45. A compound selected from those depicted in Table 3.

46. A composition comprising a compound according to claim 1, and a pharmaceutically acceptable adjuvant, carrier, or vehicle.

47. A method for inhibiting one or both of ERK1 and ERK2, or a mutant thereof, activity in a patient or in a biological sample comprising the step of administering to said patient or contacting said biological sample with a compound according to claim 1.

48. The method according to claim 47, wherein the one or both of ERK1 and ERK2, or a mutant thereof, activity is inhibited irreversibly.

49. The method according to claim 48, wherein the one or both of ERK1 and ERK2, or a mutant thereof, activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1.

50. The method according to claim 48, wherein the one or both of ERK1 and ERK2, or a mutant thereof, activity is inhibited irreversibly by covalently modifying Cys 166 of ERK2.

51. The method according to claim 48, wherein the one or both of ERK1 and ERK2, or a mutant thereof, activity is inhibited irreversibly by covalently modifying Cys 183 of ERK1 and Cys 166 of ERK2.

52. A method for treating a disease, disorder, or condition mediated by one or both of ERK1 and ERK2 in a patient in need thereof, comprising the step of administering to said patient a compound according to claim 1.

53. A method for overcoming drug resistance to Raf and Mek inhibitors, comprising the step of administering to said patient an inhibitor compound of one or both of ERK1 and ERK2 according to claim 1.

54. The method according to claim 52, wherein the disease, disorder, or condition is a cancer, tumor, or neoplastic disorder.

55. The method according to claim 52, wherein the disease, disorder, or condition is a carcinoma selected from breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, non-small cell lung cancer, squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, melanoma, or pancreatic cancer.