HETEROCYCLIC COMPOUNDS AND USES THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priorty to United Sates Provisional Application Numbers 61/409,080, filed November 1, 2010, 61/411,829, filed November 9, 2010, 61/412,330, filed November 10, 2010, and 61/534,323, filed September 13, 2011, 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 mutant-selective epidermal growth factor receptor (EGFR) kinase inhibitors. 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] Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to a tyrosine residue located on a protein substrate. Receptor tyrosine kinases act to transmit signals from the outside of a cell to the inside by activating secondary messaging effectors via a phosphorylation event. A variety of cellular processes are promoted by these signals, including proliferation, carbohydrate utilization, protein synthesis, angiogenesis, cell growth, and cell survival.

[0004] There is strong precedent for involvement of the EGFR in human cancer because over 60% of all solid tumors overexpress at least one of these proteins or their ligands. Overexpression of EGFR is commonly found in breast, lung, head and neck, bladder tumors.

[0005] Activating mutations in the tyrosine kinase domain of EGFR have been identified in patients with non-small cell lung cancer (Lin, N. U.; Winer, E. P., Breast Cancer Res 6: 204-210, 2004). The reversible inhibitors Tarceva (erlotinib) and Iressa (gefitinib) currently are first-line therapy for non-small cell lung cancer patients with activating mutations. The most common activating mutations are L858R and delE746-A750.

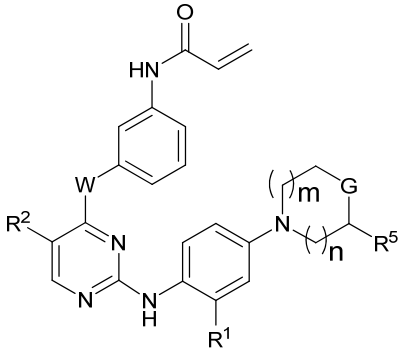
[0006] Additionally, in the majority of patients that relapse, acquired drug resistance, such as by mutation of gatekeeper residue T790M, has been detected in at least half of such clinically

resistant patients. Moreover, T790M may also be pre-existing, there may be an independent, oncogenic role for the T790M mutation. For example, there are patients with the L858R/T790M mutation who never received gefitinib treatment. In addition, germline EGFR T790M mutations are linked with certain familial lung cancers.

[0007] Current drugs in development, including second generation covalent inhibitors, such as BIBW2992, HKI-272 and PF-0299804, are effective against the T790M resistance mutation but exhibit dose-limiting toxicities due to concurrent inhibition of WT EGFR. Accordingly, there remains a need to find mutant-selective EGFR kinase inhibitors useful as therapeutic agents.

SUMMARY

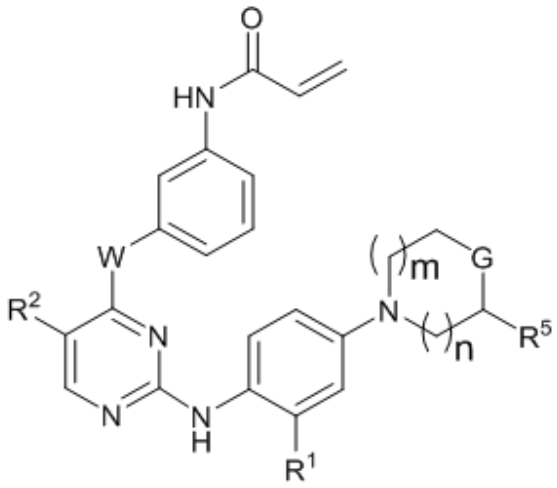
[0008] It has now been found that compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are effective as mutant-selective EGFR kinase inhibitors. Such compounds have general formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein each of n, m, W, G, R^1 R^2, and R^5 is as defined and described herein.

[0008a] In one aspect, the present disclosure refers to a use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by a structural formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

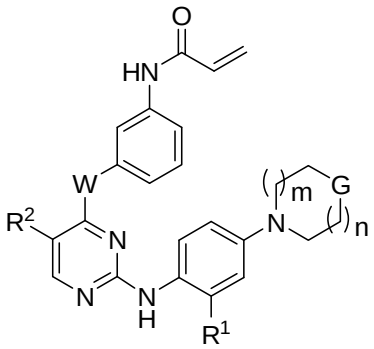
R^2 is $–CF_3$, Cl, or Br;

G is $–NR^3$- or $-S(O)_2$-;

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH; and

R^5 is hydrogen or -C(O)OR.

[0008b] In another aspect, the present disclosure refers to a use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by structural formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $–CF_3$, Cl, or Br;

G is $–NR^3$-; and

[0009] R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH.Compounds of the present disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating cancers associated with one or more EGFR mutations. Such diseases, disorders, or conditions include those described herein.

[0010] Compounds provided by this disclosureare also useful for the study of kinases in biological and pathological phenomena; the study of intracellular signal transduction pathways mediated by such kinases; and the comparative evaluation of new kinase inhibitors.

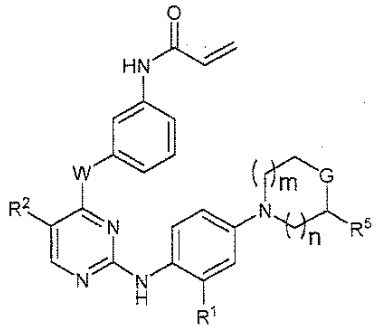
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts MS analysis confirming covalent modification of EGFR T790M/L858R by compound **I-4**.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

1. General Description of Compounds of the Invention

[0011] In certain embodiments, the present invention provides a compound of formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $-CF_3$, Cl, or Br;

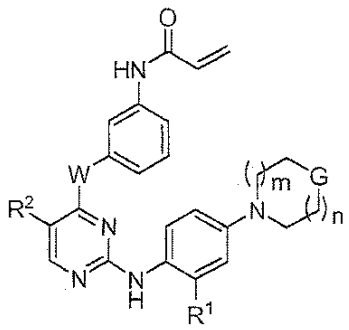
G is –O-, $-NR^3$-, $-S(O)_2$-, or $-CH(OR^4)$-;

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $-SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $-SO_2$-C_{1-4} alkylene-OH;

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

R^5 is hydrogen or -C(O)OR.

[0012] In certain embodiments, the present invention provides a compound of formula **I**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $-CF_3$, Cl, or Br;

G is –O-, $-NR^3$-, or $-CH(OR^4)$-;

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $-SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $-SO_2$-C_{1-4} alkylene-OH; and

R^4 is hydrogen, C_{1-4} alkyl, or C_{1-4} fluoroalkyl.

[0013] As used herein, the term "C_{1-4} alkylene" refers to a bivalent, straight or branched saturated hydrocarbon chain having 1-4 carbon atoms.

[0014] In some embodiments, n is 0 and G is $-CH(OR^4)$-.

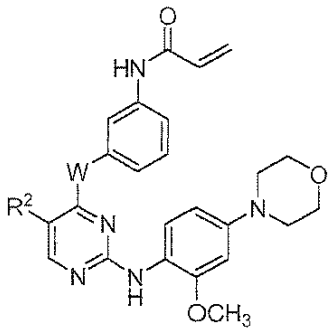
[0015] In some embodiments, m is 0 and G is $-CH(OR^4)$-.

[0016] In some embodiments, the present invention provides a compound of formula **I** or **I-a**, wherein W is –NH-.

[0017] In certain embodiments, the present invention provides a compound of formula **I** or **I-a**, wherein W is –NH- and R^2 is $-CF_3$.

[0018] In certain embodiments, the present invention provides a compound of formula **I** or **I-a**, wherein W is –O- and R^2 is –Cl.

[0019] In certain embodiments, the present invention provides a compound of formula **I-a** wherein G is –O- thereby forming a compound of formula **II**:



II

or a pharmaceutically acceptable salt thereof, wherein W and R^2 are as defined above for formula **I** and **I-a**.

[0020] In some embodiments, the present invention provides a compound of formula **II**, wherein W is –NH-.

[0021] In certain embodiments, the present invention provides a compound of formula **II**, wherein W is –NH- and R^2 is $-CF_3$.

[0022] In some embodiments, the present invention provides a compound of formula **I**, **I-a**, or **II** wherein at least one; or both of the following characteristics apply:

(a) W is –O– or –NH-; and

(b) R^2 is $-CF_3$ or Cl.

[0023] In some embodiments, the present invention provides a compound of formula **I**, **I-a**, or **II** wherein at least one; or both of the following characteristics apply:

(a) W is –O–; and

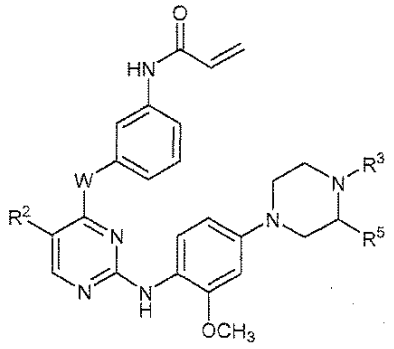
(b) R^2 is $-CF_3$ or Cl.

[0024] In some embodiments, the present invention provides a compound of formula **I**, **I-a**, or **II** wherein at least one; or both of the following characteristics apply:

(a) W is –NH-; and

(b) R^2 is $-CF_3$ or Cl.

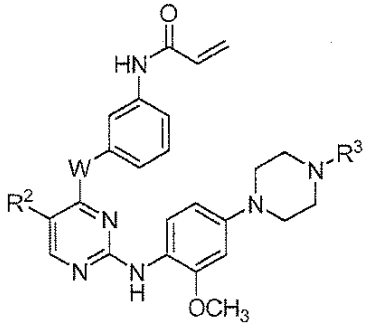
[0025] In certain embodiments, the present invention provides a compound of formula **I** wherein G is $-NR^3$- thereby forming a compound of formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein W, R^2, and R^3 are as defined above for formula **I**.

[0026] In certain embodiments, the present invention provides a compound of formula **I-a** wherein G is $-NR^3-$ thereby forming a compound of formula **III-a**:



III-a

or a pharmaceutically acceptable salt thereof, wherein W, R^2, and R^3 are as defined above for formula **I**.

[0027] As defined above, the R^3 group of formula **III** or **III-a** is $-C(O)-C_{1-4}$ alkyl, $-SO_2-C_{1-4}$ alkyl, $-C(O)-C_{1-4}$ alkylene-OH or $-SO_2-C_{1-4}$ alkylene-OH. One of ordinary skill in the art will appreciate that the R^3 substituent on the piperazine nitrogen renders that nitrogen "non-basic." It will be appreciated that such a non-basic nitrogen moiety is not amenable to acting as a proton-acceptor as compared, for example, to the corresponding secondary amine or alkyl substituted derivative thereof.

[0028] In some embodiments, the present invention provides a compound of formula **III** or **III-a**, wherein W is –NH-.

[0029] In certain embodiments, the present invention provides a compound of formula **III** or **III-a**, wherein W is –NH- and R^2 is $–CF_3$.

[0030] In certain embodiments, the present invention provides a compound of formula **III** or **III-a**, wherein W is –O- and R^2 is –Cl.

[0031] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –O– or –NH-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$ or $–SO_2CH_3$.

[0032] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –NH-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$.

[0033] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –NH–;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–SO_2CH_3$.

[0034] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –O-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$.

[0035] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –O-;

(b) R^2 is Cl; and

(c) R^3 is $–C(O)CH_3$.

[0036] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

(a) W is –O–;

(b) R^2 is $-CF_3$ or Cl; and

(c) R^3 is $-SO_2CH_3$.

[0037] In some embodiments, the present invention provides a compound of formula **III** or **III-a** wherein at least one; at least two; or all three of the following characteristics apply:

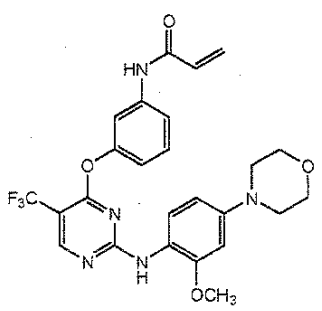
(a) W is –O-;

(b) R^2 is Cl; and

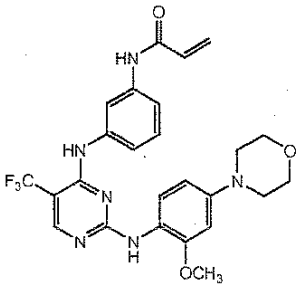
(c) R^3 is $-SO_2CH_3$.

[0038] Exemplary compounds of formula **I** are set forth in Table 1, below.

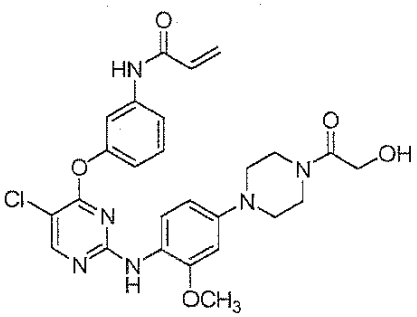
Table 1. Exemplary Compounds



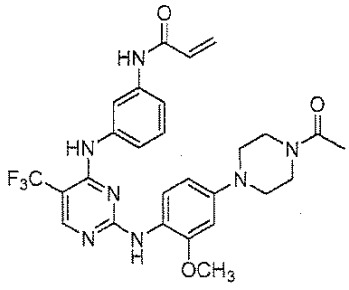
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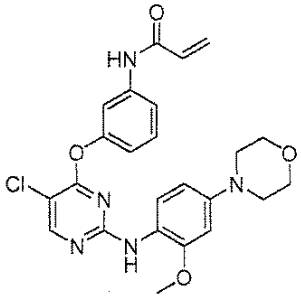
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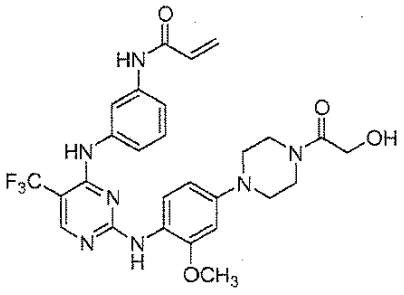
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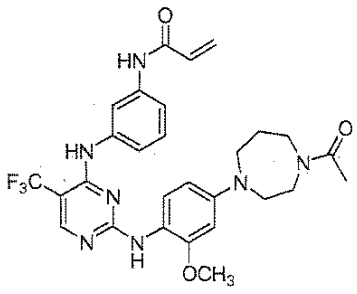
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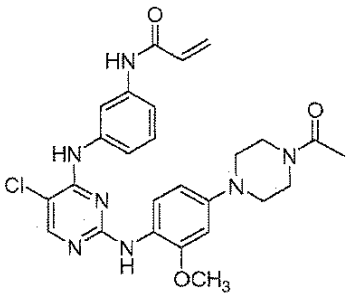
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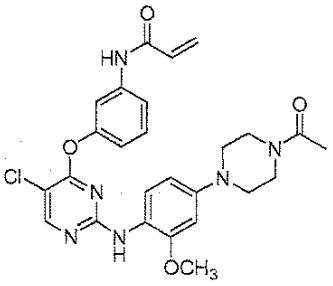
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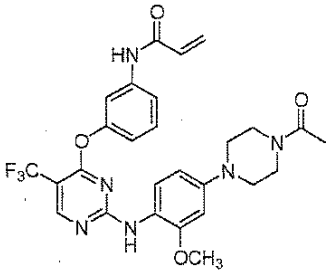
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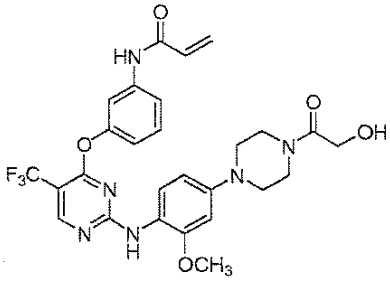
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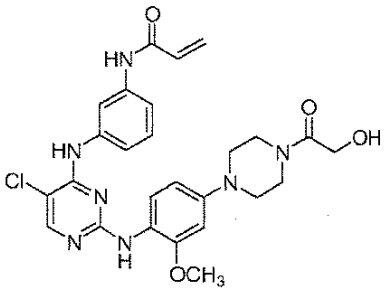
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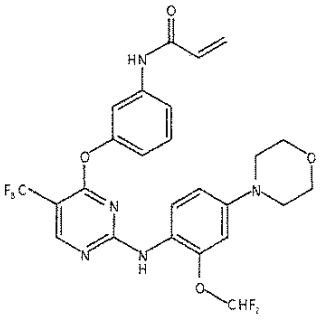
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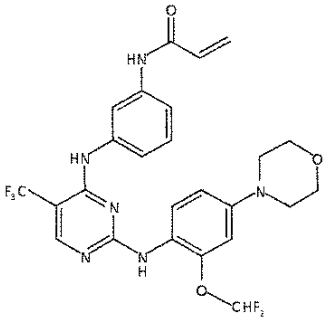
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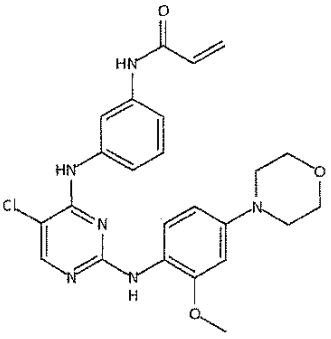
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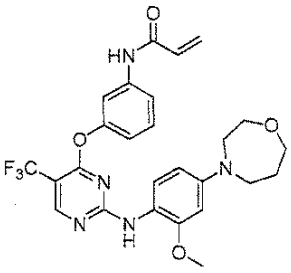
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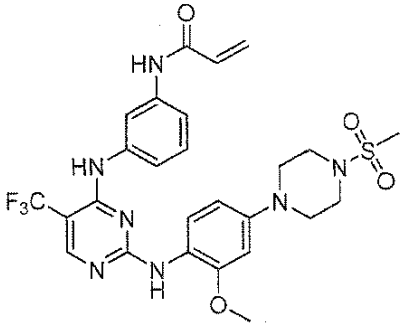
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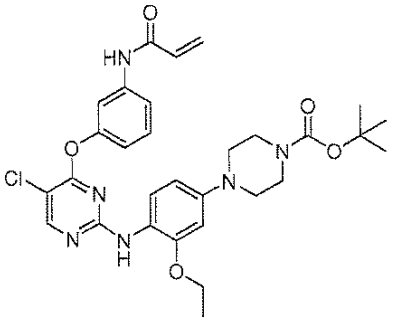
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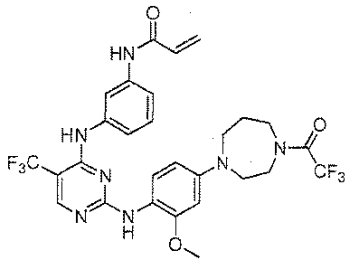
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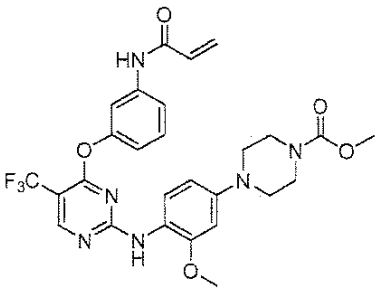
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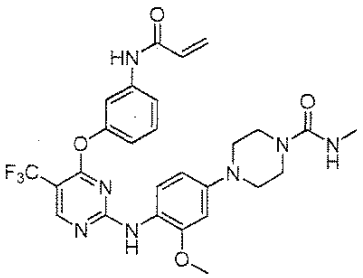
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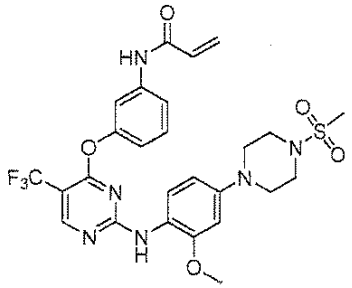
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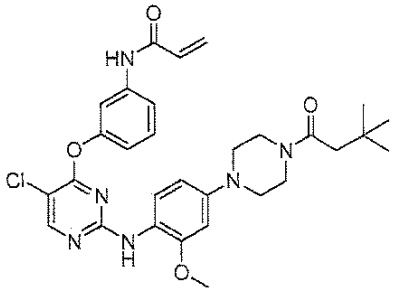
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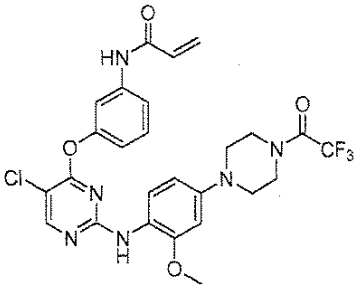
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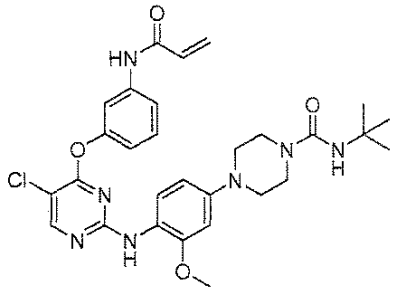
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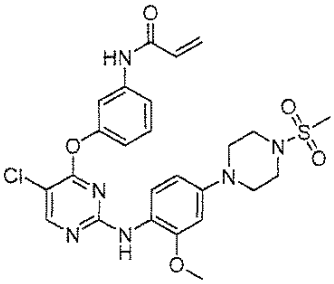
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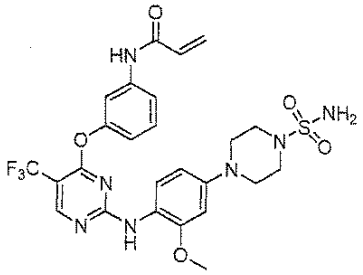
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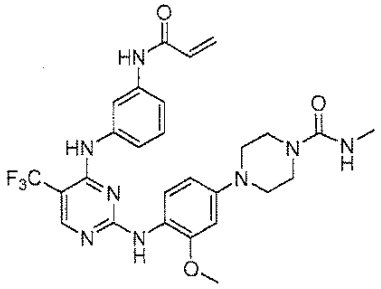
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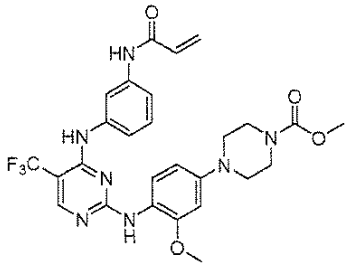
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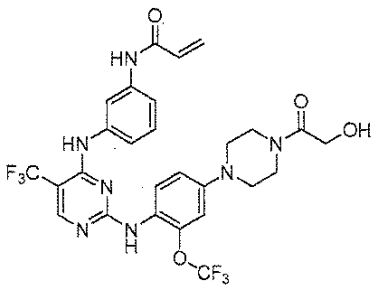
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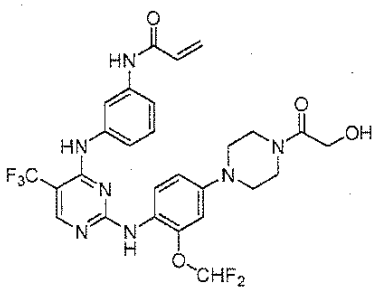
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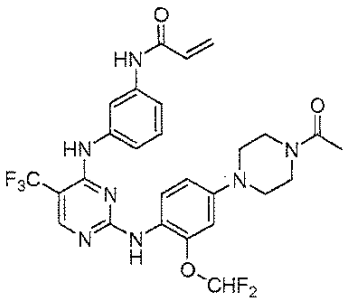
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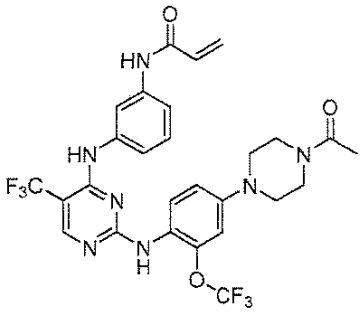
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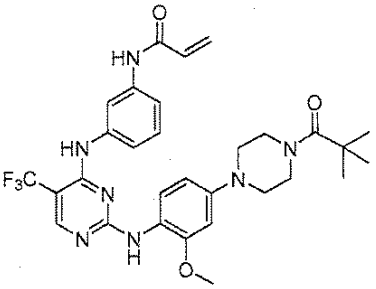
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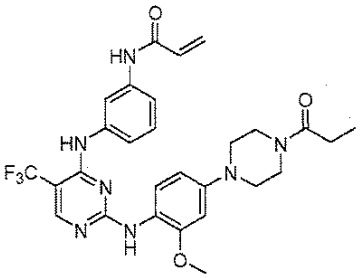
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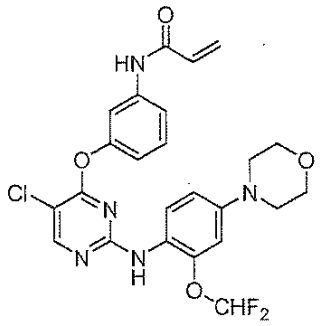
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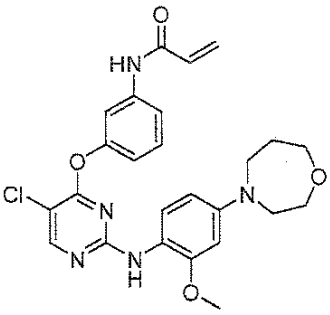
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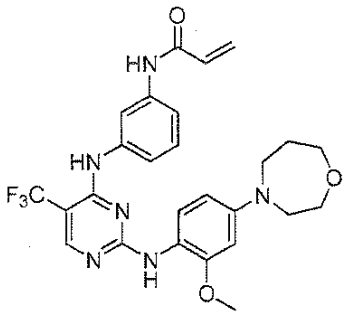
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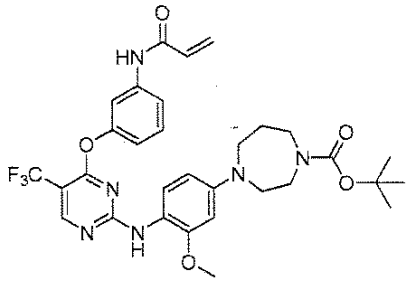
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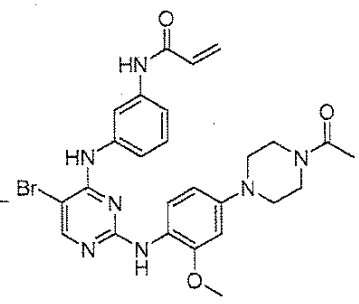
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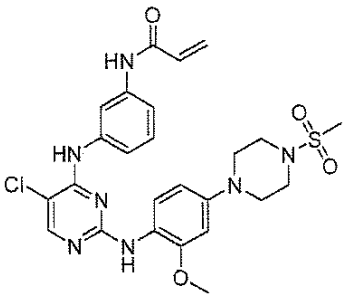
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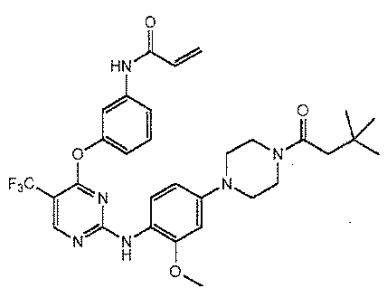
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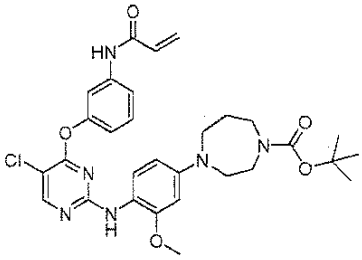
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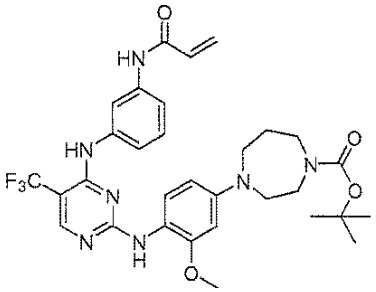
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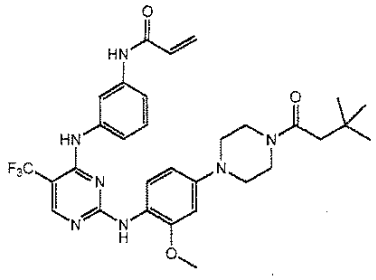
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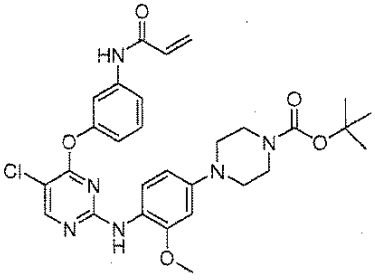
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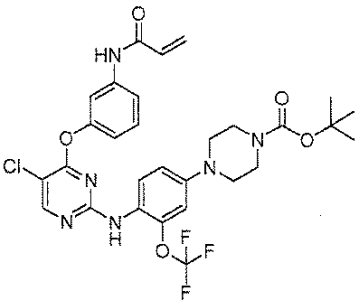
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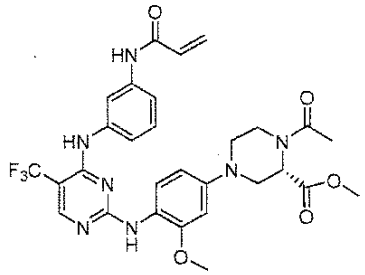
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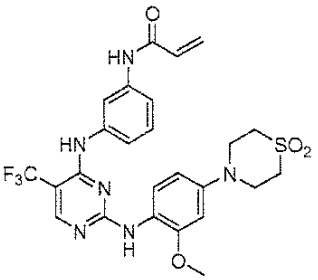
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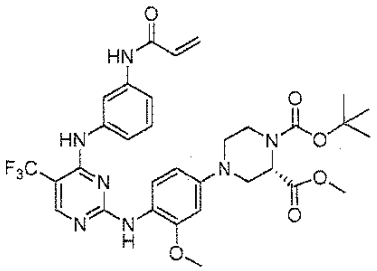
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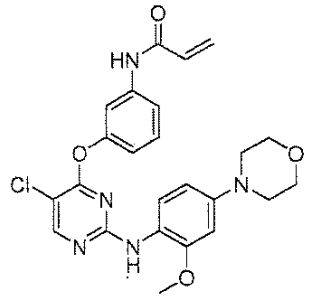
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I-50

[0039] In certain embodiments, the present invention provides a compound set forth in Table 1, above, or a pharmaceutically acceptable salt thereof.

[0040] In certain embodiments, a provided compound does not have the structure



I-5

[0041] 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.

[0042] Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}alkyl)_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, loweralkyl sulfonate and aryl sulfonate.

2. *Description of Exemplary Embodiments*

[0043] As described in detail herein, *infra*, provided compounds are selective inhibitors of at least one mutation of EGFR. It has been surprisingly found that provided compounds are selective inhibitors of at least one mutation of EGFR as compared to wild-type ("WT") EGFR. In certain embodiments, an at least one mutation of EGFR is T790M. In certain embodiments, the at least one mutation of EGFR is a deletion mutation. In some embodiments, the at least one mutation of EGFR is an activating mutation. In certain embodiments, a provided compound selectively inhibits at least one resistant mutation and at least one activating mutation as compared to WT EGFR. In some embodiments, a provided compound selectively inhibits at least one deletion mutation and/or at least one point mutation, and is sparing as to WT EGFR inhibition.

[0044] A mutation of EGFR can be selected from T790M (resistant or oncogenic), L858R (activating), delE746-A750 (activating), G719S (activating), or a combination thereof.

[0045] As used herein, the term "selectively inhibits," as used in comparison to inhibition of WT EGFR, means that a provided compound inhibits at least one mutation of EGFR (i.e., at least one deletion mutation, at least one activating mutation, at least one restistant mutation, or a combination of at least one deletion mutation and at least one point mutation) in at least one assay described herein (e.g., biochemical or cellular). In some embodiments, the term "selectively inhibits," as used in comparison to WT EGFR inhibition means that a provided compound is at least 50 times more potent, at least 45 times, at least 40, at least 35, at least 30, at least 25, or at least 20 times more potent as an inhibitor of at least one mutation of EGFR, as defined and described herein, as compared to WT EGFR.

[0046] As used herein, the term "sparing as to WT EGFR" means that a selective inhibitor of at least one mutation of EGFR, as defined and described above and herein, inhibits EGFR at the upper limit of detection of at least one assay as described herein (e.g., biochemical or cellular as described in detail in **Examples 56-58**). In some embodiments, the term "sparing as to WT EGFR" means that a provided compound inhibits WT EGFR with an IC_{50} of at least 10 μM, at least 9 μM, at least 8 μM, at least 7 μM, at least 6 μM, at least 5 μM, at least 3 μM, at least 2 μM, or at least 1 μM.

[0047] In certain embodiments, a provided compound selectively inhibits (a) at least one activating mutation; and (b) T790M; and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one

activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[0048] In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

[0049] Without wishing to be bound by any particular theory, it is believed that administration of a provided compound to a patient having at least one activating mutation may preempt formation of the T790M resistance mutation. Thus, in certain embodiments, the present invention provides a method for inhibiting an activating mutation in a patient comprising administering to the patient a provided compound or composition thereof, as described herein.

[0050] One of ordinary skill in the art will appreciate that certain patients have an oncogenic form of the T790M mutation, i.e., the T790M mutation is present prior to administration to the patient any EGFR inhibitor and is therefore oncogenic. Accordingly, in some embodiments, the present invention provides a method for inhibiting oncogenic T790M in a patient comprising administering to the patient a provided compound or composition thereof, as described herein.

[0051] Tarceva (erlotinib) and Iressa (gefitinib) are first-line therapies for patients with activating mutations but exhibit dose-limiting toxicities due to concurrent inhibition of WT EGFR. In addition, drugs currently in development, including second generation covalent inhibitors, such as BIBW2992, HKI-272 and PF-0299804, are effective against the T790M resistance mutation but exhibit dose-limiting toxicities due to concurrent inhibition of WT EGFR.

[0052] It has been surprisingly found that provided compounds selectively inhibit each of the EGFR activating and deletion mutations. Moreover, provided compounds are sparing for WT EGFR and associated dose-limiting toxicities.

[0053] This stands in contrast to other known EGFR inhibitors (*e.g.*, BIBW2992 and HKI-272) which are only somewhat effective against mutants but retain activity against WT EGFR and are therefore limited by toxicities associated with inhibition of WT EGFR. Table 2, below, sets forth GI_{50} values of Tarceva, BIBW2992 and HKI-272 as compared with provided compounds **I-2** and **I-4** (where compound numbers correspond to compound numbers in Table 1, *supra*). The data shown in Table 2 correspond to GI_{50} values obtained in the cellular proliferation assay described in detail in **Example 58**, where A431 cells express WT EGFR,

HCC827 express EGFR having the deletion mutation delE746-A750, and H1975 cells express EGFR having a double mutation L858R/T790M.

Table 2. Comparative GI_{50} Values (nM)

Cell Line	Tarceva	BIBW2992	HKI-272	I-2	I-4
A431	298	20	4	>1000	500-1000
HCC827	12	<5	78	10-100	10-100
H1975	>5000	196	13	10-100	10-100

[0054] In some embodiments, a provided compound is at least 50, at least 45 times, at least 40, at least 35, at least 30, at least 25, or at least 20 times more potent for at least one mutation of EGFR as compared to WT EGFR, as determined by the biochemical assay described in detail in **Example 56**, *infra*. In certain embodiments, a provided compound is at least 20, at least 15, or at least 10 times more potent for at least one mutation of EGFR as compared to WT EGFR, as determined by the cellular assay described in detail in **Example 58**, *infra*.

[0055] In some embodiments, a provided compound is at least 50, at least 45 times, at least 40, at least 35, at least 30, at least 25, or at least 20 times more potent for at least one deletion mutation of EGFR as compared to WT EGFR, as determined by the biochemical assay described in detail in **Example 56**, *infra*. In certain embodiments, a provided compound is at least 20, at least 15, or at least 10 times more potent for at least one deletion mutation of EGFR as compared to WT EGFR, as determined by the cellular assay described in detail in **Example 58**, *infra*.

[0056] In some embodiments, a provided compound is at least 50, at least 45 times, at least 40, at least 35, at least 30, at least 25, or at least 20 times more potent for L858R and/or T790M mutation of EGFR as compared to WT EGFR, as determined by the biochemical assay described in detail in **Example 56**, *infra*. In certain embodiments, a provided compound is at least 20, at least 15, or at least 10 times more potent for L858R and/or T790M mutation of EGFR as compared to WT EGFR, as determined by the cellular assay described in detail in **Example 58**, *infra*.

[0057] In some embodiments, a provided compound is at least 20, at least 15, or at least 10 times more potent for double mutant in H1975 cells, as compared to WT EGFR, in the signaling assay described in detail in **Example 57**.

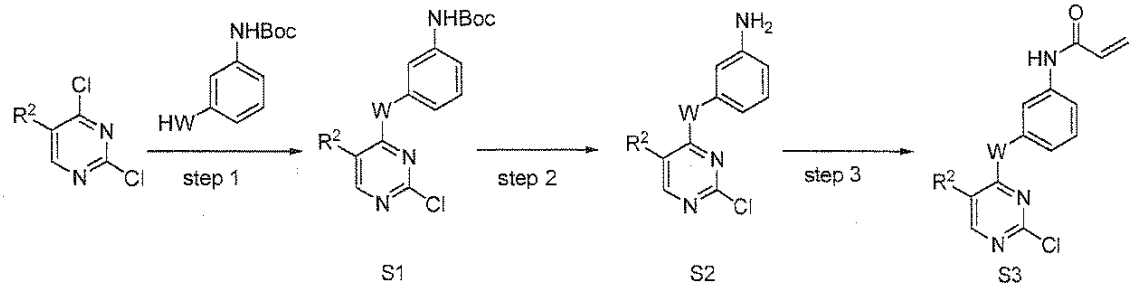
[0058] In certain embodiments, a provided compound inhibits at least one mutation of EGFR selectively as compared to WT EGFR and as compared to other protein kinases (e.g., ErbB2, ErbB4, a TEC-kinase, and/or JAK3). It will be appreciated that the acrylamide moiety, depicted in formula I, is a warhead group for covalently binding to a key cysteine residue in the binding domain of at least one mutation of EGFR selectively as compared to WT EGFR and other protein kinases. Protein kinases having a cysteine residue in the binding domain are known to one of ordinary skill in the art. Such protein kinases having a cysteine residue in the binding domain include the TEC-family of protein kinases (including TEC, BTK, ITK, BMX, JAK3, and RLK). In certain embodiments, the cysteine residue is conserved across a protein kinase sub-family, such as ErbB1 (commonly referred to as EGFR), ErbB2, and ErbB4.

[0059] Without wishing to be bound by any particular theory, it is believed that provided compounds irreversibly inhibit (i.e., covalently modify) at least one mutation of EGFR selectively as compared to WT EGFR and other protein kinases. In some embodiments, a provided compound irreversibly inhibits at least one mutation of EGFR selectively as compared to at least one protein kinase selected from ErbB1, ErbB2, ErbB4, TEC, BTK, ITK, BMX, JAK3, or RLK.

[0060] Notwithstanding, in certain embodiments, provided compounds do not appreciably inhibit, either reversibly or irreversibly, other protein kinases. In some embodiments, a provided compound is selective for inhibiting at least one mutatnt of EGFR as compared to off-target protein kinases thereby avoiding effects and toxicities associated with inhibition thereof.

3. Synthesis and Intermediates

[0061] In certain embodiments, a provided compound is synthesized using one or more of the following steps and intermediates.



wherein R^2 and W are as defined and described in classes and subclasses herein.

[0062] An R^2-substituted 2,4-dichloropyrimidine is allowed to react with, for example, a Boc-protected 3-aminophenol in step 1 to form Intermediate S1. In certain embodiments, step 1 is performed under basic conditions. In some embodiments, step 1 is performed in the presence of a tertiary amine. In certain embodiments, step 1 is performed in the presence of Hunig's base. In some embodiments, step 1 is perfomed in a protic solvent. In some embodiments, step 1 is performed in an alcohol solvent. In certain embodiments, step 1 is performed in n-butanol.

[0063] In step 2, Intermediate S1 is deprotected to form Intermediate S2. In some embodiments, Intermediate S1 is deprotected using acid. In certain embodiments, Intermediate S1 is deprotected in the presence of trifluoroacetic acid.

[0064] In step 3, Intermediate S2 is acylated with an acryloyl group to form Intermediate S3. In certain embodiments, acryoyl chloride is the acylating agent. In certain embodiments, step 3 is performed in a halogenated solvent. In certain embodiments, step 3 is performed in dichloromethane.

[0065] Intermediate S3 can be reacted with various anilines to form compounds as described herein.

4. Uses, Formulation and Administration

Pharmaceutically Acceptable Compositions

[0066] According to another embodiment, the invention provides a composition comprising a compound of this invention, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle. An amount of compound in a composition of this invention is such that is effective to measurably inhibit a protein kinase, particularly to inhibit at least one mutant of EGFR selectively as compared to WT EGFR, in a biological sample or in a patient. In certain embodiments, an at least one mutant of EGFR is T790M. In certain embodiments, the at least one mutant of EGFR is a deletion mutation of EGFR. In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

[0067] In certain embodiments, an amount of compound in a provided composition is such that is effective to measurably inhibit at least one mutation of EGFR selectively as compared to WT EGFR.

[0068] In certain embodiments, an amount of compound in a provided composition is such that is effective to measurably inhibit at least one mutation of EGFR selectively as compared to WT EGFR and other protein kinases (e.g., ErbB2, ErbB4, a TEC-kinase, and/or JAK3).

[0069] In certain embodiments, the amount of compound in a provided composition is such that is effective to measurably inhibit at least one mutant of EGFR selectively as compared to WT EGFR, 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.

[0070] In certain embodiments, the amount of compound in a provided composition is such that is effective to measurably inhibit at least one mutant of EGFR selectively as compared to WT EGFR, 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.

[0071] In certain embodiments, the amount of compound in a provided composition is such that is effective to measurably inhibit at least one mutant of EGFR selectively as compared to WT EGFR and other protein kinases (e.g., ErbB2, ErbB4, a TEC-kinase, and/or JAK3), 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.

[0072] The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0073] 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.

[0074] 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.

[0075] 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, 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.

[0076] 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.

[0077] 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.

[0078] 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.

[0079] 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.

[0080] 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.

[0081] 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.

[0082] 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.

[0083] In certain embodiments, pharmaceutically acceptable compositions of this invention are formulated for oral administration.

[0084] 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.

[0085] 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

[0086] Compounds and compositions described herein are generally useful for the selective inhibition of at least one mutant of EGFR as compared to WT EGFR. In certain embodiments, an at least one mutant of EGFR is T790M. In certain embodiments, the at least one mutant of EGFR is a deletion mutation of EGFR, an activating mutation of EGFR, or a combination thereof. In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

[0087] In certain embodiments, a provided compound selectively inhibits (a) at least one activating mutation, (b) T790M, and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[0088] In some embodiments, the at least one mutation of EGFR is L858R and/or T790M.

[0089] The activity of a compound utilized in this invention as a selective inhibitor of at least one mutant of EGFR as compared to WT EGFR, may be assayed *in vitro*, *in vivo* or in a cell line. *In vitro* assays include assays that determine inhibition of the phosphorylation activity and/or the subsequent functional consequences, or ATPase activity of activated EGFR (WT or mutant). Alternate *in vitro* assays quantitate the ability of the inhibitor to bind to EGFR (WT or mutant). Inhibitor binding may be measured by radiolabeling the inhibitor prior to binding, isolating the inhibitor/EGFR (WT or mutant) complex and determining the amount of radiolabel bound. Alternatively, inhibitor binding may be determined by running a competition experiment where new inhibitors are incubated with EGFR (WT or mutant) bound to known radioligands. Detailed conditions for assaying a compound utilized in this invention as an inhibitor of EGFR (WT or mutant), are set forth in the Examples below.

[0090] Protein tyrosine kinases are a class of enzymes that catalyze the transfer of a phosphate group from ATP or GTP to a tyrosine residue located on a protein substrate. Receptor tyrosine kinases act to transmit signals from the outside of a cell to the inside by activating secondary messaging effectors via a phosphorylation event. A variety of cellular processes are promoted by these signals, including proliferation, carbohydrate utilization, protein synthesis, angiogenesis, cell growth, and cell survival.

[0091] As used herein, the terms "treatment," "treat," and "treating" refer to reversing, alleviating, delaying the onset of, or inhibiting the progress of a disease or disorder, or one or more symptoms thereof, as described herein. In some embodiments, treatment may be administered after one or more symptoms have developed. In other embodiments, treatment may be administered in the absence of symptoms. For example, treatment may be administered to a susceptible individual prior to the onset of symptoms (e.g., in light of a history of symptoms and/or in light of genetic or other susceptibility factors). Treatment may also be continued after symptoms have resolved, for example to prevent or delay their recurrence.

[0092] Provided compounds are inhibitors of at least one mutant of EGFR and are therefore useful for treating one or more disorders associated with activity of one of more EGFR mutants (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof). Thus, in certain embodiments, the present invention provides a method for treating a mutant EGFR-mediated disorder comprising the step of administering to a patient in need thereof a compound of the present invention, or pharmaceutically acceptable composition thereof.

[0093] As used herein, the term "mutant EGFR-mediated" disorders or conditions as used herein means any disease or other deleterious condition in which at least one mutant of EGFR is known to play a role. In certain embodiments, an at least one mutant of EGFR is T790M. In some embodiments, the at least one mutant of EGFR is a deletion mutation. In certain embodiments, the at least one mutant of EGFR is an activating mutation. In some embodiments, the at least one mutant of EGFR is L858R and/or T790M. In certain embodiments, a provided compound selectively inhibits (a) at least one activating mutation, (b) T790M, and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[0094] Accordingly, another embodiment of the present invention relates to treating or lessening the severity of one or more diseases in which at least one mutant of EGFR is known to play a role. Specifically, the present invention relates to a method of treating or lessening the severity of a disease or condition selected from a proliferative disorder, wherein said method comprises administering to a patient in need thereof a compound or composition according to the present invention.

[0095] In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from a cancer. In some embodiments, the cancer is associated with a solid tumor. In certain embodiments, the cancer is breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, bladder cancer, or non-small cell lung cancer. In some embodiments, the present invention provides a method for treating or lessening the severity of one or more disorders selected from squamous cell carcinoma, salivary gland carcinoma, ovarian carcinoma, or pancreatic cancer.

[0096] In certain embodiments, the present invention provides a method for treating or lessening the severity of neurofibromatosis type I (NF1), neurofibromatosis type II (NF2) Schwann cell neoplasms (e.g. MPNST's), or Schwannomas.

[0097] The compounds and compositions, according to the method of the present invention, may be administered using any amount and any route of administration effective for treating or lessening the severity of a cancer. The exact amount required will vary from subject to subject, depending on the species, age, and general condition of the subject, the severity of the infection,

the particular agent, its mode of administration, and the like. Compounds of the invention are preferably formulated in dosage unit form for ease of administration and uniformity of dosage. The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgment. The specific effective dose level for any particular patient or organism will depend upon a variety of factors including the disorder being treated and the severity of the disorder; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed, and like factors well known in the medical arts. The term "patient", as used herein, means an animal, preferably a mammal, and most preferably a human.

[0098] Pharmaceutically acceptable compositions of this invention can be administered to humans and other animals orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, or drops), bucally, as an oral or nasal spray, or the like, depending on the severity of the infection being treated. In certain embodiments, the compounds of the invention may be administered orally or parenterally at dosage levels of about 0.01 mg/kg to about 50 mg/kg or 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.

[0099] 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.

[00100] 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.

[00101] Injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, terminal (heat) sterilization, or sterilization via ionizing radiationor 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.

[00102] 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.

[00103] 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.

[00104] 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, 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.

[00105] 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. In some embodiments, a solid composition is a liquid filled hard gelatin capsule or solid dispersion.

[00106] 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.

[00107] 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.

[00108] According to another embodiment, the invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutations, or combination 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 at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination 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.

[00109] In certain embodiments, a provided compound selectively inhibits in a biological sample (a) at least one activating mutation, (b) T790M, and (c) is sparing as to WT. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, an activating

mutation is delE746-A750. In some embodiments, an activating mutation is L858R. In some embodiments, an activating mutation is G719S.

[00110] 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.

[00111] Inhibition of at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination 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.

[00112] Another embodiment of the present invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination 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 present invention provides a method for inhibiting (a) at least one activating mutation, and (b) T790M in a patient, and (c)is sparing as to WT, wherein said method comprises administering to the patient a provided compound, or composition thereof. In some embodiments, an at least one activating mutation is a deletion mutation. In some embodiments, an at least one activating mutation is a point mutation. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is delE746-A750. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is L858R. In some embodiments, the present invention provides a method for inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is G719S.

[00113] According to another embodiment, the invention relates to a method of inhibiting at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination 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 at least one mutant of EGFR activity (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination thereof) 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 present invention provides a method for irreversibly inhibiting (a) at least one activating mutation, and (b) T790M in a patient, and (c) is sparing as to WT, wherein said method comprises administering to the patient a provided compound, or composition thereof. In some embodiments, an irreversibly inhibited at least one activating mutation is a deletion mutation. In some embodiments, an irreversibly inhibited at least one activating mutation is a point mutation. In some embodiments, the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is delE746-A750. In some embodiments, the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is L858R. In some embodiments, the the present invention provides a method for irreversibly inhibiting at least one mutant of EGFR in a patient, wherein an activating mutation is G719S.

[00114] In other embodiments, the present invention provides a method for treating a disorder mediated by one or more of at least one mutant of EGFR (e.g., a deletion mutation, an activating mutation, a resistant mutation, or combination 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.

[00115] Depending upon the particular condition, or disease, to be treated, additional therapeutic agents, which are normally administered to treat that condition, may also be present in the compositions of this invention. As used herein, additional therapeutic agents that are normally administered to treat a particular disease, or condition, are known as "appropriate for the disease, or condition, being treated."

[00116] For example, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with chemotherapeutic agents to treat proliferative diseases and cancer. Examples of known chemotherapeutic agents include, but are not limited to, Adriamycin, dexamethasone, vincristine, cyclophosphamide, fluorouracil, topotecan, taxol, interferons, platinum derivatives, taxane (e.g., paclitaxel), vinca alkaloids (e.g., vinblastine), anthracyclines (e.g., doxorubicin), epipodophyllotoxins (e.g., etoposide), cisplatin, an mTOR inhibitor (e.g., a rapamycin), methotrexate, actinomycin D, dolastatin 10, colchicine, emetine, trimetrexate, metoprine, cyclosporine, daunorubicin, teniposide, amphotericin, alkylating agents (e.g., chlorambucil), 5-fluorouracil, campthothecin, cisplatin, metronidazole,

and Gleevec™, among others. In other embodiments, a compound of the present invention is administered in combination with a biologic agent, such as Avastin or VECTIBIX.

[00117] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with an antiproliferative or chemotherapeutic agent selected from any one or more of abarelix, aldesleukin, alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic trioxide, asparaginase, azacitidine, BCG Live, bevacuzimab, fluorouracil, bexarotene, bleomycin, bortezomib, busulfan, calusterone, capecitabine, camptothecin, carboplatin, carmustine, celecoxib, cetuximab, chlorambucil, cladribine, clofarabine, cyclophosphamide, cytarabine, dactinomycin, darbepoetin alfa, daunorubicin, denileukin, dexrazoxane, docetaxel, doxorubicin (neutral), doxorubicin hydrochloride, dromostanolone propionate, epirubicin, epoetin alfa, erlotinib, estramustine, etoposide phosphate, etoposide, exemestane, filgrastim, floxuridine fludarabine, fulvestrant, gefitinib, gemcitabine, gemtuzumab, goserelin acetate, histrelin acetate, hydroxyurea, ibritumomab, idarubicin, ifosfamide, imatinib mesylate, interferon alfa-2a, interferon alfa-2b, irinotecan, lenalidomide, letrozole, leucovorin, leuprolide acetate, levamisole, lomustine, megestrol acetate, melphalan, mercaptopurine, 6-MP, mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, nandrolone, nelarabine, nofetumomab, oprelvekin, oxaliplatin, paclitaxel, palifermin, pamidronate, pegademase, pegaspargase, pegfilgrastim, pemetrexed disodium, pentostatin, pipobroman, plicamycin, porfimer sodium, procarbazine, quinacrine, rasburicase, rituximab, sargramostim, sorafenib, streptozocin, sunitinib maleate, talc, tamoxifen, temozolomide, teniposide, VM-26, testolactone, thioguanine, 6-TG, thiotepa, topotecan, toremifene, tositumomab, trastuzumab, tretinoin, ATRA, uracil mustard, valrubicin, vinblastine, vincristine, vinorelbine, zoledronate, or zoledronic acid.

[00118] Other examples of agents the inhibitors of this invention may also be combined with include, without limitation: treatments for Alzheimer's Disease such as donepezil hydrochloride (Aricept®) and rivastigmine (Exelon®); treatments for Parkinson's Disease such as L-DOPA/carbidopa, entacapone, ropinrole, pramipexole, bromocriptine, pergolide, trihexephendyl, and amantadine; agents for treating Multiple Sclerosis (MS) such as beta interferon (e.g., Avonex® and Rebif®), glatiramer acetate (Copaxone®), and mitoxantrone; treatments for asthma such as albuterol and montelukast (Singulair®); agents for treating schizophrenia such as zyprexa, risperdal, seroquel, and haloperidol; anti-inflammatory agents such as corticosteroids,

TNF blockers, IL-1 RA, azathioprine, cyclophosphamide, and sulfasalazine; immunomodulatory and immunosuppressive agents such as cyclosporin, tacrolimus, rapamycin, mycophenolate mofetil, interferons, corticosteroids, cyclophophamide, azathioprine, and sulfasalazine; neurotrophic factors such as acetylcholinesterase inhibitors, MAO inhibitors, interferons, anti-convulsants, ion channel blockers, riluzole, and anti-Parkinsonian agents; agents for treating cardiovascular disease such as beta-blockers, ACE inhibitors, diuretics, nitrates, calcium channel blockers, and statins; agents for treating liver disease such as corticosteroids, cholestyramine, interferons, and anti-viral agents; agents for treating blood disorders such as corticosteroids, anti-leukemic agents, and growth factors; and agents for treating immunodeficiency disorders such as gamma globulin.

[00119] In certain embodiments, compounds of the present invention, or a pharmaceutically acceptable composition thereof, are administered in combination with a monoclonal antibody or an siRNA therapeutic.

[00120] Those additional agents may be administered separately from an inventive compound-containing composition, as part of a multiple dosage regimen. Alternatively, those agents may be part of a single dosage form, mixed together with a compound of this invention in a single composition. If administered as part of a multiple dosage regime, the two active agents may be submitted simultaneously, sequentially or within a period of time from one another normally within five hours from one another.

[00121] As used herein, the term "combination," "combined," and related terms refers to the simultaneous or sequential administration of therapeutic agents in accordance with this invention. For example, a compound of the present invention may be administered with another therapeutic agent simultaneously or sequentially in separate unit dosage forms or together in a single unit dosage form. Accordingly, the present invention provides a single unit dosage form comprising a provided compound, an additional therapeutic agent, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[00122] The amount of both, an inventive compound and additional therapeutic agent (in those compositions which comprise an additional therapeutic agent as described above)) that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Preferably, compositions of this

invention should be formulated so that a dosage of between 0.01 - 100 mg/kg body weight/day of an inventive can be administered.

[00123] In those compositions which comprise an additional therapeutic agent, that additional therapeutic agent and the compound of this invention may act synergistically. Therefore, the amount of additional therapeutic agent in such compositions will be less than that required in a monotherapy utilizing only that therapeutic agent. In such compositions a dosage of between 0.01 – 1,000 μg/kg body weight/day of the additional therapeutic agent can be administered.

[00124] The amount of additional therapeutic agent present in the compositions of this invention will be no more than the amount that would normally be administered in a composition comprising that therapeutic agent as the only active agent. Preferably the amount of additional therapeutic agent in the presently disclosed compositions will range from about 50% to 100% of the amount normally present in a composition comprising that agent as the only therapeutically active agent.

[00125] The compounds of this invention, or pharmaceutical compositions thereof, may also be incorporated into compositions for coating an implantable medical device, such as prostheses, artificial valves, vascular grafts, stents and catheters. Vascular stents, for example, have been used to overcome restenosis (re-narrowing of the vessel wall after injury). However, patients using stents or other implantable devices risk clot formation or platelet activation. These unwanted effects may be prevented or mitigated by pre-coating the device with a pharmaceutically acceptable composition comprising a kinase inhibitor. Implantable devices coated with a compound of this invention are another embodiment of the present invention.

EXEMPLIFICATION

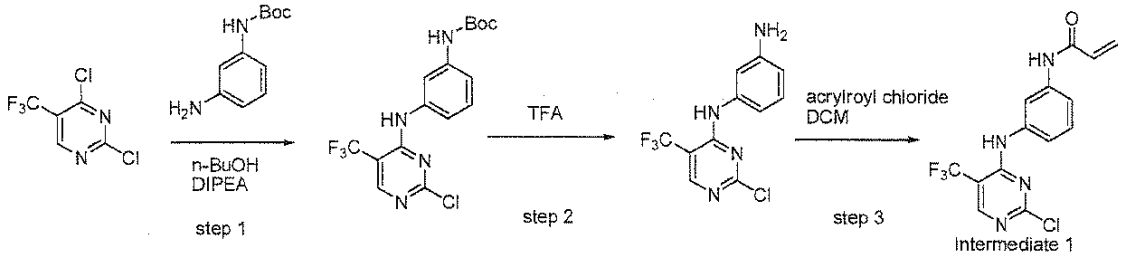
[00126] As depicted in the Examples below, in certain exemplary embodiments, compounds are prepared according to the following general procedures. It will be appreciated that, although the general methods depict the synthesis of certain compounds of the present invention, the following general methods, and other methods known to one of ordinary skill in the art, can be applied to all compounds and subclasses and species of each of these compounds, as described herein.

[00127] Compound numbers utilized in the Examples below correspond to compound numbers set forth in Table 1, *supra*.

[00128] Provided compounds are prepared according to methods known to one of ordinary skill in the art and include methods described in detail in US 20100029610, published February 4, 2010, the entirety of which is hereby incorporated herein by reference.

EXAMPLE 1
Intermediate 1

Scheme 1



Step 1:

[00129] In a 25 mL 3-neck RBF previously equipped with a magnetic stirrer, Thermo pocket and $CaCl_2$ guard tube, N-Boc-1,3-diaminobenzene (0.96 g) and n-butanol (9.00 mL) were charged. Reaction mixture was cooled to 0 °C. 2,4-Dichloro-5-trifluoromethylpyrimidine (1.0 g) was added dropwise to the above reaction mixture at 0 °C. The DIPEA (0.96 mL) was dropwise added to the above reaction mixture at 0 °C and the reaction mixture was stirred for 1 hr at 0 °C to 5 °C. Finally the reaction mixture was allowed to warm to room temperature. Reaction mixture was stirred for another 4 hrs at room temperature. Completion of reaction was monitored by TLC using hexane: ethyl acetate (7: 3). The solid precipitated out was filtered off and washed with 1-butanol (2 mL). Solid was dried under reduced pressure at 40 °C for 1 hr. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.48 (S, 9 H), 7.02 (m, 1 H), 7.26 (m, 2 H), 7.58 (S, 1 H), 8.57 (S, 1 H), 9.48 (S, 1 H), 9.55 (S, 1 H).

Step 2:

[00130] To the above crude (3.1 g) in DCM (25 mL) was added TFA (12.4 mL) slowly at 0 °C. The reaction mixture was allowed to warm to room temperature. Reaction mixture was stirred for another 10 min at room temperature. The crude was concentrated under reduced pressure.

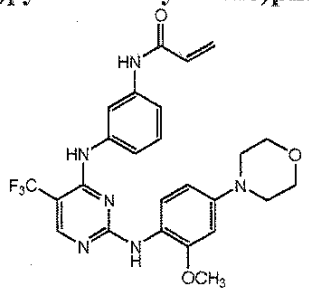
Step 3:

[00131] The concentrated crude was dissolved in DIPEA (2.0 mL) and DCM (25 mL), and then cooled to -30 °C. To the reaction mixture was slowly added acryloyl chloride (0.76 g) at -30

°C. The reaction mass was warmed to room temperature stirred at room temperature for 1.0 hr. The reaction was monitored on TLC using hexane: ethyl acetate (7:3) as mobile phase. Reaction got completed after 1 hr. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.76 (dd, J = 2.0, 10.0 Hz, 1 H), 6.24 (dd, J = 2.0, 17.2 Hz, 1 H), 6.48 (m, 1 H), 7.14 (d, J = 8.8 Hz, 1 H), 7.37 (t, J = 8.0 Hz, 1 H), 7.94 (S, 1 H), 8.59 (S, 1 H), 9.60 (S, 1 H), 10.26 (S, 1 H).

EXAMPLE 2

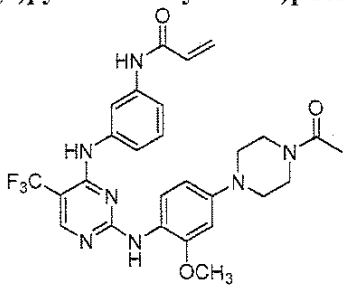
Compound I-2 N-(3-(2-(2-methoxy-4-morpholinophenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00132] To obtain the title compound **I-2**, a mixture of intermediate 1 in Example 1 (16 mg) and 2-methoxy-4-morpholinoaniline in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the title compound as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.4 (S, 1 H), 9.72 (br, 1 H), 9.18 (br, 1 H), 8.49 (br, 1 H), 7.83 (S, 1 H), 7.59 (d, J = 8.4 Hz, 1 H), 7.31-7.48 (m,2 H), 7.41 (t, J = 15.2 Hz, 1 H), 7.12 (br, 1 H), 6.67 (S, 1 H), 6.49 (dd, J = 10.0, 16.8 Hz, 1 H), 6.25 (dd, J = 2.0, 16.8 Hz, 1 H), 5.77 (dd, J = 2.0, 10.0 Hz, 1 H), 3.7-3.9 (m, 7 H), 3.1 (br, 4 H); calculated mass for $C_{25}H_{25}F_3N_6O_3$: 514.2, found: 515.5 ($M+H^+$).

EXAMPLE 3

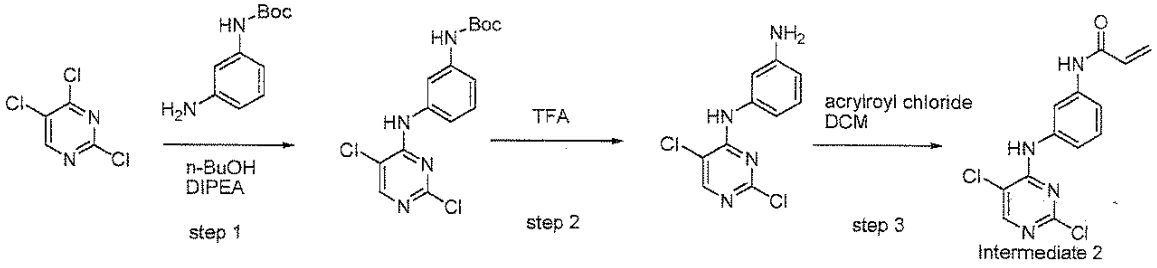
Compound I-4 N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00133] Using 2-methoxy-4-(4-acteylpiperazinyl)aniline and intermediate 1 in Example 1, the title compound **I-4** was prepared as described in Example 2. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.2 (S, 1 H), 8.2 (br, 1 H), 8.30 (S, 1 H), 7.73 (br, 1 H), 7.52 (d, J = 7.8 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.26 (J = 8.2 Hz, 1 H), 7.14 (be, 1 H), 6.60 (S, 1 H), 6.42 (dd, J = 11.4, 16.9 Hz, 1 H), 6.24 (d, J = 16.9 Hz, 1 H), 5.75 (d, J = 11.4 Hz, 1 H), 3.76 (S, 3 H), 3.04 (br, 4 H), 2.04 (S, 3 H); calculated mass for $C_{27}H_{28}F_3N_7O_3$: 555.2, found: 556.2 ($M+H^+$).

EXAMPLE 4
Intermediate 2

Scheme 2



Step 1:

[00134] The title step was executed according to Step 1 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.48 (S, 9 H), 7.16 (d, 1 H), 7.25 (m, 2 H), 7.70 (S, 1 H), 8.37 (S, 1 H), 9.47 (S, 1 H), 9.55 (S, 1 H).

Step 2:

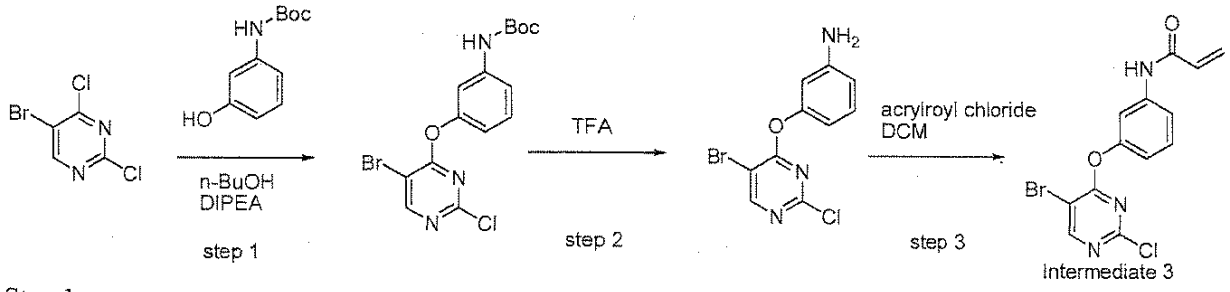
[00135] The title step was executed according to Step 2 in Scheme 1 of Example 1.

Step 3:

[00136] The title step was executed according to Step 3 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.76 (dd, J = 1.6, 10.8, Hz 1 H), 6.25 (dd, J = 1.6, 16.8 Hz, 1 H), 6.46 (m, 1 H), 7.30 (m, 2 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.91 (S, 1 H), 8.38 (S, 1 H), 9.60 (S, 1 H), 10.23 (S, 1 H).

EXAMPLE 5
Intermediate 3

Scheme 3



Step 1:

[00137] The title step was executed according to Step 1 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.47 (S, 9 H), 6.89 (d, J = 7.6 Hz, 1 H), 7.35 (m, 2 H), 7.45 (S, 1 H), 8.89 (S, 1 H), 9.64 (S, 1 H).

Step 2:

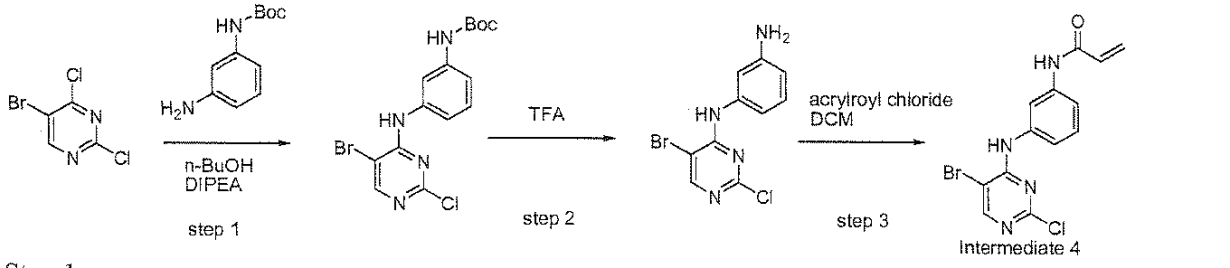
[00138] The title step was executed according to Step 2 in Scheme 1 of Example 1.

Step 3:

[00139] The title step was executed according to Step 3 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.77 (d, J = 10.0 Hz, 1 H), 6.25 (d, J = 17.2 Hz, 1 H), 6.45 (m, 1 H). 7.01 (d, J = 7.2 Hz, 1 H), 7.53 (m, 2 H), 7.73 (S, 1 H), 8.98 (S, 1 H), 10.40 (S, 1 H).

EXAMPLE 6
Intermediate 4

Scheme 4



Step 1:

[00140] The title step was executed according to Step 1 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.50 (S, 9 H), 7.10 (d, J = 6.0 Hz, 1 H), 7.25 (m, 2 H), 8.44 (S, 1 H), 9.32 (S, 1 H), 9.47 (S, 1 H).

Step 2:

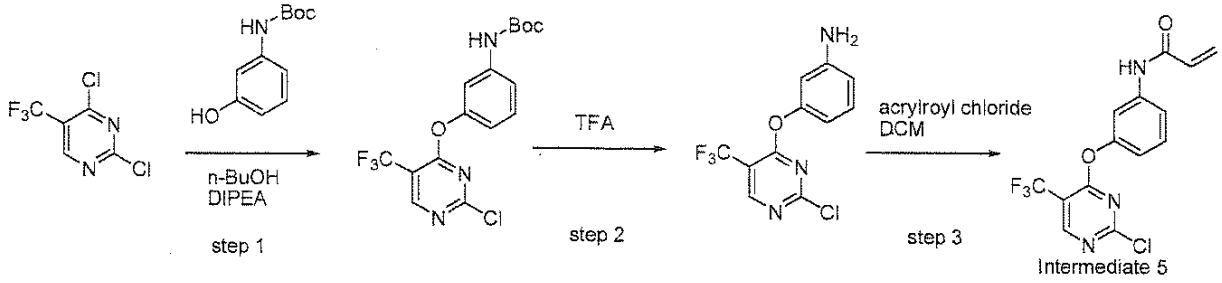
[00141] The title step was executed according to Step 2 in Scheme 1 of Example 1.

Step 3:

[00142] The title step was executed according to Step 3 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.76 (dd, J = 1.6, 10.0 Hz, 1 H), 6.25 (dd, J = 1.6, 16.8 Hz, 1 H), 6.43 (m, 1 H), 7.23 (d, J = 8.0 Hz, 1 H), 7.35 (t, J = 8.0 Hz, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 7.80 (S, 1 H), 8.38 (S, 1 H), 9.36 (S, 1 H), 10.23 (S, 1 H).

EXAMPLE 7
Intermediate 5

Scheme 5



Step 1:

[00143] The title step was executed according to Step 1 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.47 (S, 9 H), 6.90 (d, J = 6.0 Hz, 1 H), 7.35 (m, 2 H), 7.50 (S, 1 H), 9.05 (S, 1 H), 9.65 (S, 1 H).

Step 2:

[00144] The title step was executed according to Step 2 in Scheme 1 of Example 1.

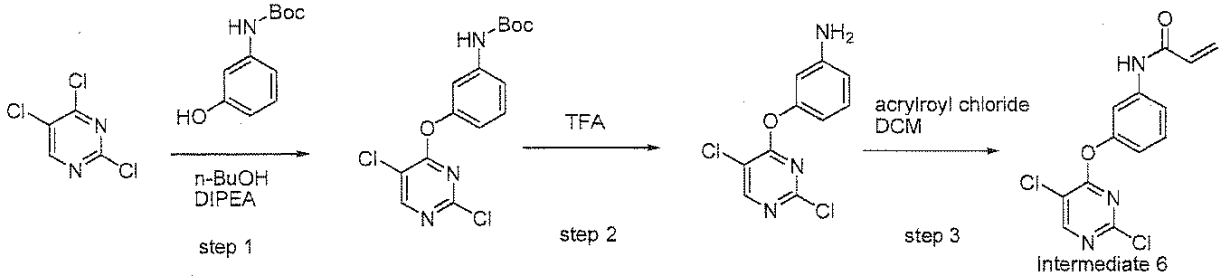
Step 3:

[00145] The title step was executed according to Step 3 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.76 (d, J = 10.0 Hz, 1 H), 6.25 (dd, J = 1.6, 16.8 Hz, 1 H), 6.46 (m, 2 H), 7.01 (d, J = 8.0 Hz, 1 H), 7.08 (t, J = 8.4 Hz, 1H) 7.25 (S, 1 H), 9.44 (S, 1 H), 10.02 (S, 1 H).

EXAMPLE 8

Intermediate 6

Scheme 6



Step 1:

[00146] The title step was executed according to Step 1 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 1.47 (S, 9 H), 6.60 (S, 1 H), 6.86 (d, J = 8.4 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 7.36 (m, 1 H), 7.50 (S, 1 H), 8.40 (S, 1 H).

Step 2:

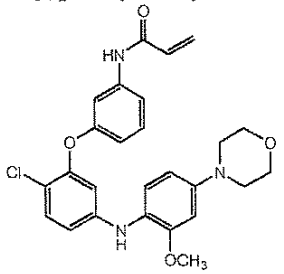
[00147] The title step was executed according to Step 2 in Scheme 1 of Example 1.

Step 3:

[00148] The title step was executed according to Step 3 in Scheme 1 of Example 1. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 5.78 (dd, J = 2.0, 10.0 Hz, 1 H), 6.25 (dd, J = 2.0, 17.2 Hz, 1 H), 6.40 (m, 1 H), 7.02 (d, 1 H), 7.50 (m, 2 H), 7.71 (S, 1 H), 8.40 (S, 1 H), 10.35 (S, 1 H).

EXAMPLE 9

Compound I-5 N-(3-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)

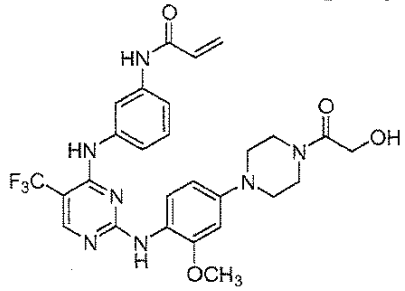


[00149] To obtain the title compound, a mixture of intermediate 6 in Example 8 and 2-methoxy-4-morpholinoaniline in n-butanol with catalytic HCl was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified to give the title compound. ^{1}H-NMR (chloroform-d, 400 MHz) δ 8.23 (S, 1 H), 7.6-7.8 (br, 2 H), 7.4-7.5 (m, 3 H), 7.00 (dd, J = 1.4, 8.2 Hz, 1 H), 6.41 (m, 2 H), 6.23 (m, 2 H), 5.77 (dd, J = 1.4, 10.1 Hz, 1 H), 3.84 (m, 4

H), 3.81 (S, 3 H), 3.04 (m, 4 H); calculated mass for $C_{24}H_{24}ClN_5O_4$: 481.2, found: 482.2 ($M+H^+$).

EXAMPLE 10

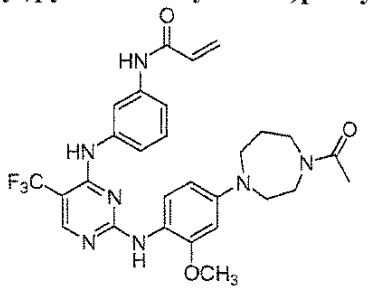
Compound I-6 N-(3-(2-(4-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00150] Using 2-methoxy-4-(4-(2-hydroxyacteyl)piperazinyl)aniline and intermediate 1 of Example 1, the title compound **I-6** was prepared as described in Example 2. ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.33 (S, 1 H), 8.08 (br, 1 H), 7.86 (br, 1 H), 7.60 (br, 1 H), 7.39 (m, 1 H), 6.89 (S, 1 H), 6.22-6.55 (m, 3 H), 5.80 (d, J = 10.0 Hz), 4.24 (S, 2 H), 3.90 (S, 2 H), 3.85 (S, 2 H), 3.64 (S, 1 H), 3.45 (S, 2 H), 3.13 (S, 3 H); calculated mass for $C_{27}H_{28}F_3N_7O_4$: 571.2, found: 572.4 ($M+H^+$).

EXAMPLE 11

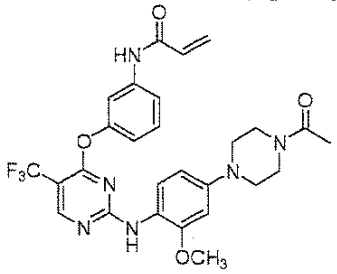
Compound I-7 N-(3-(2-(4-(4-acetyl-1,4-diazepan-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00151] Using 1-(4-(4-amino-3-methoxyphenyl)-1,4-diazepan-1-yl)ethanone and intermediate 1 of Example 1, the title compound **I-7** was prepared as described in Example 2. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.2 (S, 1 H), 9.2 (br, 1 H), 8.7 (br, 1 H), 8.4 (br, 1 H), 7.76 (br, 1 H), 7.49 (d, J = 8.2 Hz, 1 H), 7.27 (br, 2 H), 7.1 (br, 1 H), 6.42 (dd, J = 11.0, 16.5 Hz, 1 H), 6.30 (br,

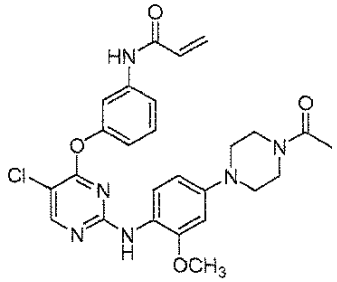
1 H), 6.24 (d, J = 16.5 Hz, 1 H), 5.9 (br, 1 H), 5.74 (d, J = 11.0 Hz, 1 H), 3.3-3.7 (m, 4 H), 1.7-1.95 (m, 5 H); calculated mass for $C_{28}H_{30}F_3N_7O_3$: 569.2, found: 570.2 ($M+H^+$).

EXAMPLE 12
Compound I-10 N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)



[00152] To obtain the title compound, a mixture of intermediate 5 of Example 7 and 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the title compound as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.32 (S, 1 H), 8.92 (S, 1 H), 8.60 (S, 1 H), 7.72 (t, J = 2.3 Hz, 1 H), 7.58 (d, J = 8.7 Hz, 1 H), 7.43 (m, 2 H), 6.98 (m, 1 H), 6.61 (d, J = 2.3, 1 H), 6.42 (m, 2 H), 6.25 (dd, J = 1.8, 16.9 Hz, 1 H), 5.77 (d, J = 1.8, 10.1 Hz, 1 H), 3.7-4.0 (m, 4 H), 3.77 (S, 3 H), 3.1 (m, 4 H), 1.99 (S, 3 H); calculated mass for $C_{27}H_{27}F_3N_6O_4$: 556.2, found: 557.1 ($M+H^+$).

EXAMPLE 13
Compound I-9 N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-yloxy)phenyl)acrylamide)

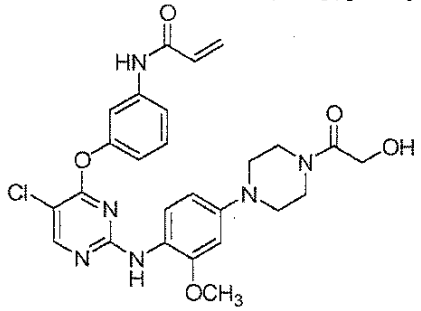


[00153] Using 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone and intermediate 6 of Example 8, the title compound was prepared as described in Example 9. ^{1}H-NMR (chloroform-d, 400 MHz) δ 8.26 (S, 1 H), 8.08 (br, 1 H), 7.93 (br, 1 H), 7.68 (S, 1 H), 7.57 (m, 1 H), 7.45 (m, 2 H), 6.96 (d, J = 7.8 Hz, 1 H), 6.69 (S, 1 H), 6.60 (d, J = 7.4 Hz, 1 H), 6.41 (d, J = 1.4, 17.0 Hz,

1 H), 6.30 (dd, J = 10.1, 16.5 Hz, 1 H), 5.75 (d, J = 1.4, 10.1 Hz, 1 H), 3.97 (m, 2 H), 3.85 (S, 3 H), 3.82 (m, 2 H), 3.29 (m, 2 H), 3.24 (m, 2 H), 2.19 (S, 3 H); calculated mass for $C_{26}H_{27}ClN_6O_4$: 522.2, found: 523.2 ($M+H^+$).

EXAMPLE 14

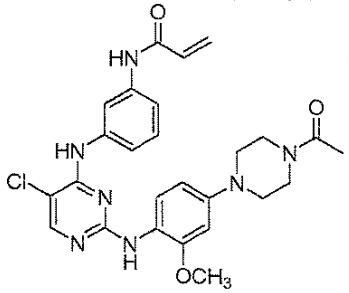
Compound I-3 N-(3-(5-chloro-2-(4-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methoxyphenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00154] Using 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)-2-hydroxyethanone and intermediate 6 of Example 8, the title compound was prepared as described in Example 9. ^{1}H-NMR (chloroform-d, 400 MHz) δ 8.24 (S, 1 H), 7.71 (br, 1 H), 7.63 (m, 1 H), 7.49 (m, 1 H), 7.44 (t, J = 8.2 Hz, 1 H), 7.39 (d, J = 6.9 Hz, 2 H), 7.00 (dd, J = 1.8, 7.8 Hz, 1 H), 6.45 (d, J = 2.8 Hz, 1 H), 6.44 (dd, J = 1.4, 16.9 Hz, 1 H), 6.23 (dd, J = 10.1, 16.9 Hz, 1 H), 5.79 (dd, J = 1.4, 10.1 Hz, 1 H), 4.22 (s, 2 H), 3.82 (S, 3 H), 3.80 (S, 2 H), 3.42 (m, 2 H), 3.06 (m, 4 H); calculated mass for $C_{26}H_{27}ClN_6O_5$: 538.2, found: 539.1 ($M+H^+$).

EXAMPLE 15

Compound I-8 N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)acrylamide)

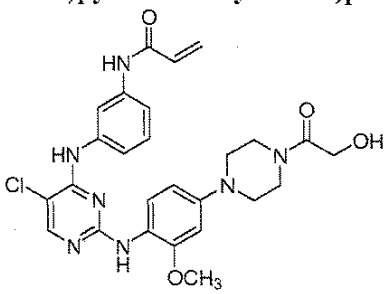


[00155] To obtain the title compound, a mixture of intermediate 2 of Example 4 and 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone in n-butanol with catalytic HCl was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified to give the title compound. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.2 (S, 1 H), 8.86 (S, 1

H), 8.07 (S, 1 H), 7.94 (br, 1 H), 7.70 (S, 1 H), 7.68 (S, 1 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.27 (m, 2 H), 6.63 (d, J = 2.4 Hz, 1 H), 6.46 (dd, J = 10.0, 16.8 Hz, 1 H), 6.31 (br, 1 H), 6.29 (dd, J = 2.0, 16.8 Hz, 1 H), 5.76 (dd, J = 2.0, 10.0 Hz, 1 H), 3.79 (S, 3 H), 3.56 (m, 4 H), 3.0-3.2 (m, 4 H), 2.04 (S, 3 H); calculated mass for $C_{26}H_{28}ClN_7O_3$: 521.2, found: 522.4 ($M+H^+$).

EXAMPLE 16

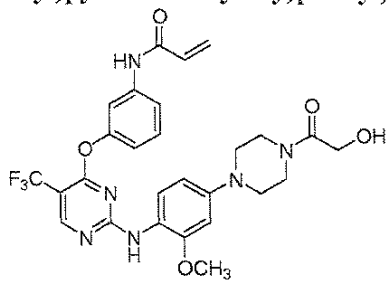
Compound I-12 N-(3-(5-chloro-2-(4-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylamide)



[00156] Using 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)-2-hydroxyethanone and intermediate 2 of Example 4, the title compound was prepared as described in Example 15. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.2 (S, 1 H), 8.86 (S, 1 H), 8.07 (S, 1 H), 7.94 (br, 1 H), 7.70 (m, 2 H), 7.46 (d, J = 7.6 Hz, 1 H), 7.27 (m, 2 H), 6.63 (d, J = 2.4 Hz, 1 H), 6.46 (dd, J = 10.0, 16.8 Hz, 1 H), 6.31 (br, 1 H), 6.29 (dd, J = 2.0, 16.8 Hz, 1 H), 5.76 (dd, J = 2.0, 10.0 Hz, 1 H), 4.66 (t, J = 5.6 Hz, 1 H), 4.14 (t, J = 5.6 Hz, 2 H), 3.79 (S, 3 H), 3.61 (br, 2 H), 3.48 (br, 2 H), 3.05 (m, 4 H), 2.04 (S, 3 H); calculated mass for $C_{26}H_{28}ClN_7O_4$: 537.2, found: 538.4 ($M+H^+$).

EXAMPLE 17

Compound I-11 N-(3-(2-(4-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)

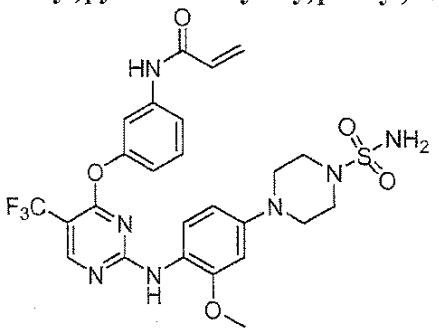


[00157] Using 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)-2-hydroxyethanone and intermediate 5 of Example 7, the title compound was prepared as described in Example 12. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.34 (S, 1 H), 8.84 (S, 1 H), 8.56 (br, 1 H), 7.63 (S, 1 H), 7.53

(d, J = 8.0 Hz, 1 H), 7.41 (m, 1 H), 7.16 (m, 1 H), 6.96 (br, 1 H), 6.57 (br, 1 H), 6.45 (br, 1 H), 6.44 (dd, J = 10.0, 16.8 Hz, 1 H), 6.29 (dd, J = 1.6, 16.8 Hz, 1 H), 5.79 (dd, J = 1.6, 10.0 Hz, 1 H), 4.66 (t, J = 5.6 Hz, 1 H), 4.14 (d, J = 5.6 Hz, 2 H), 3.73 (S, 3 H), 3.60 (br, 2 H), 3.47 (br, 2 H), 3.08 (br, 4 H); calculated mass for $C_{27}H_{27}F_3N_6O_5$: 572.2, found: 573.6 ($M+H^+$).

EXAMPLE 18

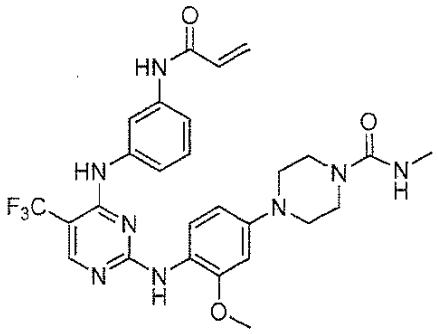
Compound I-27, N-(3-(2-(2-methoxy-4-(4-sulfamoylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)



[00158] A mixture of the intermediate 5 (20 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N-methylmorpholine (20 uL), dioxane (0.5 mL), and sulfamide (50 mg). The reaction mixture was microwaved at 90 °C for 30 minutes. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.30 (s, 1 H), 8.81 (s, 1 H), 8.54 (br, 1 H), 7.62 (s, 1 H), 7.52 (d, J = 8.2 Hz, 1 H), 7.39 (t, J = 8.2 Hz, 1 H), 7.16 (d, J = 8.7 Hz, 1 H), 6.95 (m, 1 H), 6.85 (s, 2 H), 6.58 (m, 1 H), 6.43 (dd, J = 11.4, 17.0 Hz, 1 H), 6.26 (d, J = 17.0 Hz, 1 H), 5.78 (d, J = 11.4 Hz, 1 H), 3.72 (s, 3 H), 3.19 (m, 4 H), 3.06 (m, 4 H); calculated mass for $C_{25}H_{26}F_3N_7O_5S$: 593.2, found: 594.2 ($M+H^+$).

EXAMPLE 19

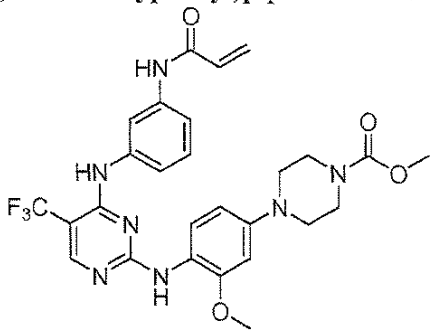
Compound I-28 (4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)-N-methylpiperazine-1-carboxamide)



[00159] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and N-methyl-N-hydroxysuccinyl carbamate (50 mg) at 0 °C. The reaction mixture was stirred room temperature overnight. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{27}H_{29}F_3N_8O_3$: 570.2, found: 571.2 ($M+H^+$).

EXAMPLE 20

Compound I-29 (methyl 4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1-carboxylate)

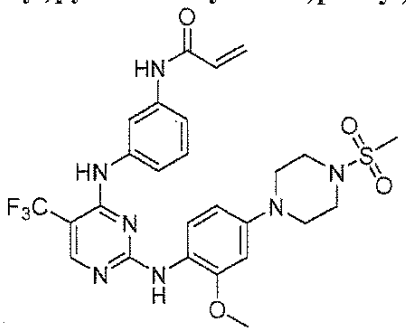


[00160] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was

concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methyl chloroformate (20 uL) at 0 °C. The reaction mixture was stirred room temperature for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{27}H_{28}F_3N_7O_4$: 571.2, found: 572.2 ($M+H^+$).

EXAMPLE 21

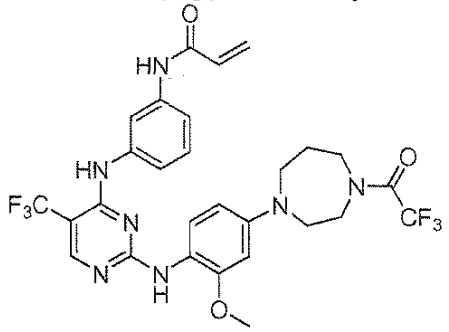
Compound I-17 (N-(3-(2-(2-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00161] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methanesulfonyl chloride (20 uL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.22 (s, 1 H), 9.28 (br, 1 H), 8.72 (br, 1 H), 8.37 (br, 1 H), 7.77 (s, 1 H), 7.52 (d, J = 8.0 Hz, 1 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.30 (t, J = 8.0 Hz, 1 H), 7.12 (br, 1 H), 6.62 (s, 1 H), 6.43 (dd, J = 10.0, 16.8 Hz, 1 H), 6.24 (d, J = 16.8 Hz, 1 H), 6.22 (br, 1 H), 5.76 (d, J = 10.0 Hz, 1 H), 3.77 (s, 3 H), 3.21 (m, 4 H), 3.18 (m, 4 H), 2.92 (s, 3 H); calculated mass for $C_{26}H_{28}F_3N_7O_4S$: 591.2, found: 592.2 ($M+H^+$).

EXAMPLE 22

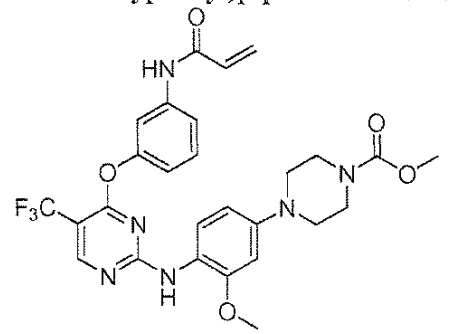
Compound I-19 (N-(3-(2-(2-methoxy-4-(4-(2,2,2-trifluoroacetyl)-1,4-diazepan-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00162] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)-1,4-diazepane-1-carboxylate (21 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and trifluoroacetic anhydride (10 uL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.2 (S, 1 H), 9.1 (br, 1 H), 8.6 (br, 1 H), 8.3 (br, 1 H), 7.75 (br, 1 H), 7.50 (d, J = 8.7 Hz, 1 H), 7.26 (m, 2 H), 7.11 (m, 1 H), 6.42 (dd, J = 10.1, 17.0 Hz, 1 H), 6.34 (m, 1 H), 6.23 (d, J =17.0 Hz, 1 H), 5.74 (dd, J = 1.8, 10.1 Hz,1 H), 3.3-3.8 (m, 8 H), 1.88 (m, 2 H); calculated mass for $C_{28}H_{27}F_6N_7O_3$: 623.2, found: 624.2 ($M+H^+$).

EXAMPLE 23

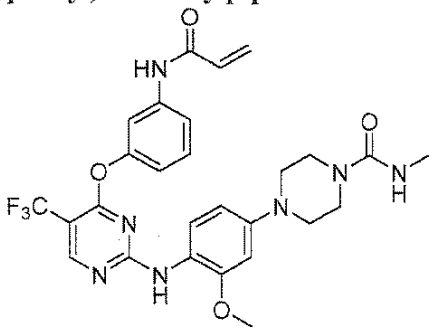
Compound I-20 (methyl 4-(4-(4-(3-acrylamidophenoxy)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1-carboxylate)



[00163] A mixture of the intermediate 5 (20 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methyl chloroformate (20 uL) at 0 °C. The reaction mixture was stirred room temperature for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.30 (s, 1 H), 8.80 (s, 1 H), 8.53 (br, 1 H), 7.60 (s, 1 H), 7.51 (d, J = 8.2 Hz, 1 H), 7.40 (t, J = 8.2 Hz, 1 H), 7.14 (d, J = 9.6 Hz, 1 H), 6.93 (m, 1 H), 6.55 (m, 1 H), 6.40 (dd, J = 10.0, 16.8 Hz, 1 H), 6.24 (dd, J = 1.8, 16.8 Hz, 1 H), 5.76 (dd, J = 1.8, 10.0 Hz, 1 H), 3.70 (s, 3 H), 3.58 (s, 3 H), 3.49 (m, 4 H), 3.05 (m, 4 H); calculated mass for $C_{27}H_{27}F_3N_6O_5$: 572.2, found: 573.2 ($M+H^+$).

EXAMPLE 24

Compound I-21 (4-(4-(4-(3-acrylamidophenoxy)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)-N-methylpiperazine-1-carboxamide)

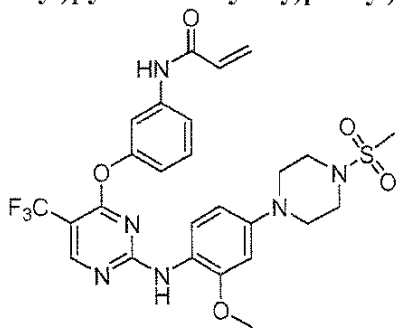


[00164] A mixture of the intermediate 5 (18 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and N-methyl-N-hydroxysuccinyl carbamate (50 mg) at 0 °C.

The reaction mixture was stirred room temperature overnight. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{27}H_{28}F_3N_7O_4$: 571.2, found: 572.2 ($M+H^+$).

EXAMPLE 25

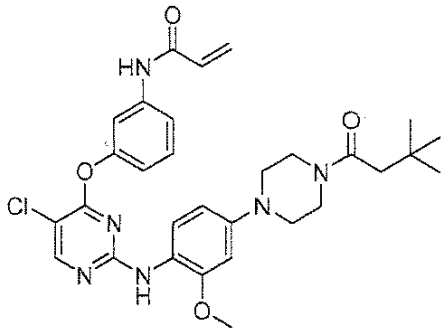
Compound I-22 (N-(3-(2-(2-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)



[00165] A mixture of the intermediate 5 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methanesulfonyl chloride (10 uL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{26}H_{27}F_3N_6O_5S$: 592.2, found: 593.2 ($M+H^+$).

EXAMPLE 26

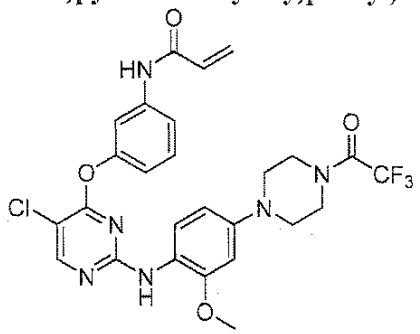
Compound I-23 (N-(3-(5-chloro-2-(4-(4-(3,3-dimethylbutanoyl)piperazin-1-yl)-2-methoxyphenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00166] A mixture of the intermediate 6 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and 3,3-dimethylbutyryl chloride at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.33 (s, 1 H), 8.35 (s, 1 H), 8.15 (s, 1 H), 7.60 (s, 1 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.40 (t, J = 8.2 Hz, 1 H), 7.24 (d, J = 8.7 Hz, 1 H), 6.95 (d, J = 7.8 Hz, 1 H), 6.57 (s, 1 H), 6.42 (dd, J = 10.0, 16.8 Hz, 1 H), 6.25 (d, J = 16.8 Hz, 1 H), 6.18 (m, 1 H), 6.77 (d, J = 10.0 Hz, 1 H), 3.93 (s, 3 H), 3.68 (m, 4 H), 2.99 (m, 4 H), 2.26 (s, 2 H), 0.99 (s, 9 H); calculated mass for $C_{30}H_{35}ClN_6O_4$: 578.2, found: 579.2 ($M+H^+$).

EXAMPLE 27

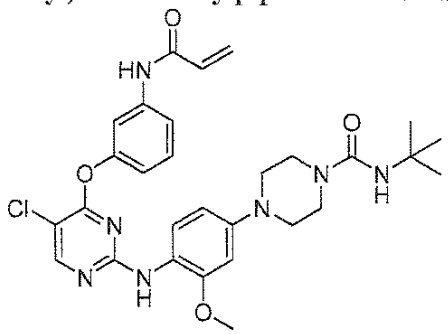
Compound I-24 (N-(3-(5-chloro-2-(2-methoxy-4-(4-(2,2,2-trifluoroacetyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00167] A mixture of the intermediate 6 (20 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and trifluoroacetic anhydride (10 uL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.32 (s, 1 H), 8.35 (s, 1 H), 8.16 (s, 1 H), 7.59 (s, 1 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.40 (t, J = 8.2 Hz, 1 H), 7.24 (d, J = 8.7 Hz, 1 H), 6.96 (d, J = 7.8 Hz, 1 H), 6.57 (d, J = 2.8 Hz, 1 H), 6.41 (dd, J = 10.0, 16.8 Hz, 1 H), 6.24 (dd, J = 1.8, 16.8 Hz, 1 H), 6.19 (m, 1 H), 5.76 (dd, J = 1.8, 10.0 Hz, 1 H), 3.72 (s, 3 H), 3.68 (m, 4 H), 3.13 (m, 4 H); calculated mass for $C_{26}H_{24}ClF_3N_6O_4$: 576.2, found: 577.0 ($M+H^+$).

EXAMPLE 28

Compound I-25 (4-(4-(4-(3-acrylamidophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxyphenyl)-N-tert-butylpiperazine-1-carboxamide)

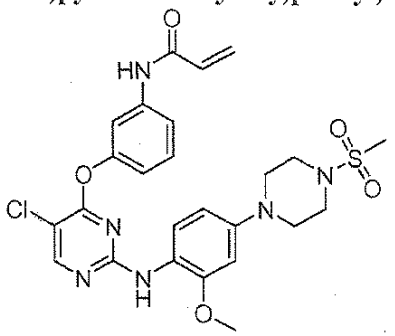


[00168] A mixture of the intermediate 6 (20 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and tert-butyl isocyanate at 0 °C. The reaction mixture was

stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.35 (s, 1 H), 8.37 (s, 1 H), 8.19 (s, 1 H), 7.62 (s, 1 H), 7.56 (d, J = 8.2 Hz, 1 H), 7.41 (t, J = 8.2 Hz, 1 H), 7.28 (d, J = 8.2 Hz, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 6.65 (s, 1 H), 6.43 (dd, J = 10.0, 16.8 Hz, 1 H), 6.29 (s, 1 H), 6.26 (d, J = 16.8 Hz, 1 H), 5.92 (s, 1 H), 5.77 (d, J = 10.0 Hz, 1 H), 3.74 (s, 3 H), 3.41 (s, 4 H), 3.04 (s, 4 H), 1.26 (s, 9 H); calculated mass for $C_{29}H_{34}ClN_7O_4$: 579.2, found: 580.2 ($M+H^+$).

EXAMPLE 29

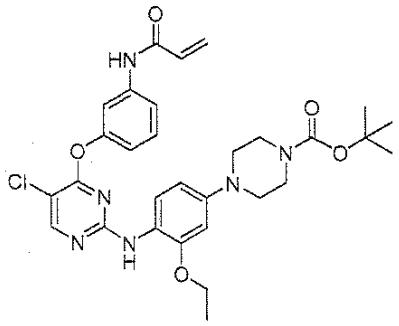
Compound I-26 (N-(3-(5-chloro-2-(2-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00169] A mixture of the intermediate 6 (20 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methanesulfonyl chloride at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{25}H_{27}ClN_6O_5S$: 558.2, found: 559.2 ($M+H^+$).

EXAMPLE 30

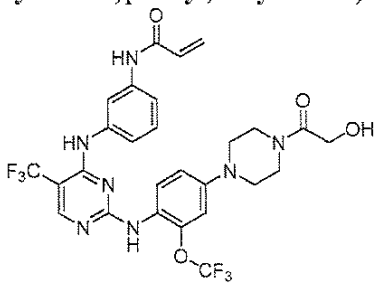
Compound I-18 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-chloropyrimidin-2-ylamino)-3-ethoxyphenyl)piperazine-1-carboxylate)



[00170] A mixture of the intermediate 6 (16 mg) and tert-butyl 4-(4-amino-3-ethoxyphenyl)piperazine-1-carboxylate (21 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{30}H_{35}ClN_6O_5$: 594.2, found: 595.5 ($M+H^+$).

EXAMPLE 31

Compound I-30 (N-(3-(2-(4-(4-(2-hydroxyacetyl)piperazin-1-yl)-2-(trifluoromethoxy)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)

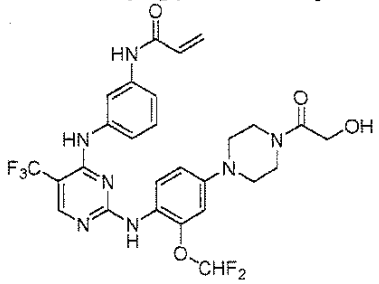


[00171] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-trifluoromethoxyphenyl)piperazine-1-carboxylate (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), N,N-dimethylformamide (1.0 mL), HATU, and glycolic acid at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.14 (s, 1 H), 8.99 (s, 1 H), 8.61 (s, 1 H), 8.29 (s, 1 H), 7.71 (s, 1 H), 7.44 (s, 1

H), 7.42 (s, 1 H), 7.18 (m, 2 H), 6.85 (s, 1 H), 6.75 (m, 1 H), 6.45 (dd, J = 10.0, 16.8 Hz, 1 H), 6.26 (d, J = 16.8 Hz, 1 H), 5.77 (d, J = 10.0 Hz, 1 H), 4.66 (t, J = 5.6 Hz, 1 H), 4.14 (d, J = 5.6 Hz, 2 H), 3.61 (br, 2 H), 3.49 (br, 2 H), 3.11 (br, 4 H); calculated mass for $C_{27}H_{25}F_6N_7O_4$: 625.2, found: 625.8 ($M+H^+$).

EXAMPLE 32

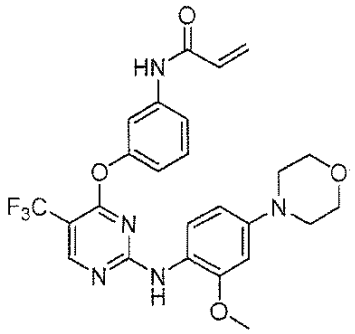
Compound I-31 (N-(3-(2-(2-(difluoromethoxy)-4-(4-(2-hydroxyacetyl)piperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00172] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-difluoromethoxyphenyl)piperazine-1-carboxylate (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), N,N-dimethylformamide (1.0 mL), HATU, and glycolic acid at 0 °C. The reaction mixture was stirred at room temperature for 30 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{27}H_{26}F_5N_7O_4$: 607.2, found: 607.8 ($M+H^+$).

EXAMPLE 33

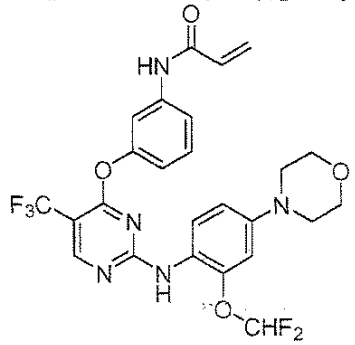
Compound I-1 (N-(3-(2-(2-methoxy-4-morpholinophenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)



[00173] A mixture of the intermediate 5 (16 mg) and 2-methoxy-4-morpholinoaniline (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.35 (S, 1 H), 8.83 (S, 1 H), 8.55 (br, 1 H), 7.63 (S, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.40 (m, 1 H), 7.16 (d, J = 8.8 Hz, 1 H), 6.96 (br, 1 H), 6.54 (br, 1 H), 6.43 (m, 1 H), 6.27 (dd, J = 1.7, 16.8 Hz, 1 H), 5.77 (dd, J = 1.7, 10.4 Hz, 1 H), 3.72 (br, 7 H), 3.04 (br, 4 H); calculated mass for $C_{25}H_{24}F_3N_5O_4$: 515.2, found: 516.7 ($M+H^+$).

EXAMPLE 34

Compound I-13 (N-(3-(2-(2-(difluoromethoxy)-4-morpholinophenylamino)-5-(trifluoromethyl)pyrimidin-4-yloxy)phenyl)acrylamide)

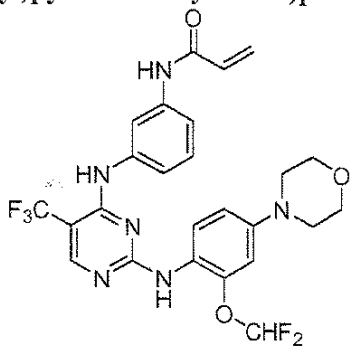


[00174] A mixture of the intermediate 5 (16 mg) and 2-difluoromethoxy-4-morpholinoaniline (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C.

The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.33 (s, 1 H), 9.34 (s, 1 H), 8.55 (br, 1 H), 7.63 (s, 1 H), 7.51 (br, 1 H), 7.40 (br, 1 H), 7.19 (d, J = 9.2 Hz, 1 H), 6.96 (br, 1 H), 6.65 (br, 1 H), 6.43 (dd, J = 10.0, 16.8 Hz, 1 H), 6.27 (dd, J = 2.0, 16.8 Hz, 1 H), 5.79 (dd, J = 2.0, 10.0 Hz, 1 H), 3.73 (t, J = 4.4 Hz, 1 H), 3.06 (m, 4 H); calculated mass for $C_{25}H_{22}F_5N_5O_4$: 551.2, found: 551.7 ($M+H^+$).

EXAMPLE 35

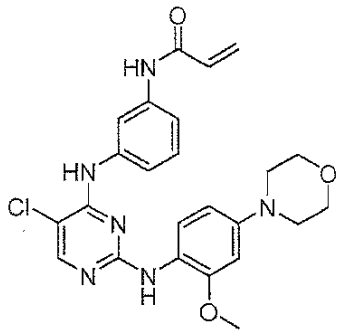
Compound I-14 (N-(3-(2-(2-(difluoromethoxy)-4-morpholinophenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00175] A mixture of the intermediate 1 (16 mg) and 2-difluoromethoxy-4-morpholinoaniline (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.14 (s, 1 H), 8.63 (s, 1 H), 8.28 (s, 1 H), 7.71 (s, 1 H), 7.46 (d, J = 7.2 Hz, 1 H), 7.38 (s, 1 H), 7.15 (m, 2 H), 6.91 (m,1 H), 6.67 (m, 2 H), 6.44 (dd, J = 10.0, 16.8 Hz, 1 H), 6.25 (d, J = 16.8 Hz, 1 H), 5.76 (d, J = 10.0 Hz, 1 H), 3.73 (t, J = 4.4 Hz, 1 H), 3.05 (br, 4 H); calculated mass for $C_{25}H_{23}F_5N_6O_3$: 550.2, found: 550.9 ($M+H^+$).

EXAMPLE 36

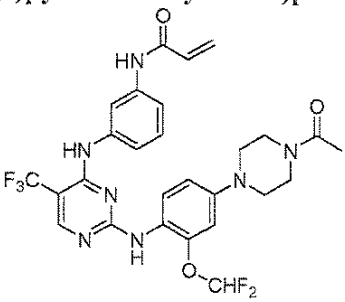
Compound I-15 (N-(3-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)acrylamide)



[00176] A mixture of the intermediate 2 (16 mg) and 2-difluoromethoxy-4-morpholinoaniline (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ C10.16 (s, 1 H), 8.85 (s, 1 H), 8.07 (s, 1 H), 7.95 (br, 1 H), 7.68 (m, 2 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.27 (m, 2 H), 6.60 (d, J = 2.4 Hz, 1 H), 6.45 (dd, J = 10.0, 16.8 Hz, 1 H), 6.26 (m, 2 H), 5.76 (dd, J = 2.0, 10.0 Hz, 1 H), 3.79 (s, 3 H), 3.73 (m, 4 H), 3.03 (m, 4 H); calculated mass for $C_{24}H_{25}ClN_6O_3$: 480.2, found: 481.4 ($M+H^+$).

EXAMPLE 37

Compound I-32 (N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-(difluoromethoxy)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)

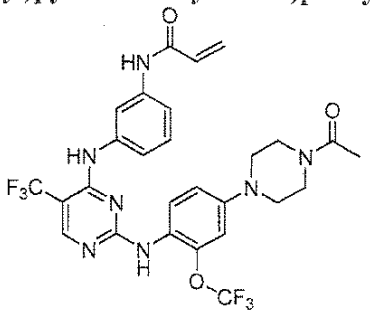


[00177] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-difluoromethoxyphenyl)piperazine-1-carboxylate (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and acetic anhydride (50 uL). The reaction mixture was stirred room temperature overnight. The crude was concentrated under reduced pressure and purified

using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.13 (s, 1 H), 8.63 (s, 2 H), 8.29 (s, 1 H), 7.71 (s, 1 H), 7.47 (d, J = 7.2 Hz, 1 H), 7.39 (m, 1 H), 7.16 (m, 2 H), 6.91 (s, 1 H), 6.69 (s, 1 H), 9.59 (m, 1 H), 6.44 (dd, J = 10.0, 16.8 Hz, 1 H), 6.26 (d, J = 16.8 Hz, 1 H), 5.77 (d, J = 10.0 Hz, 1 H), 3.57 (s, 4 H), 3.10 (s, 2 H), 3.04 (s, 2 H), 2.05 (s, 3 H); calculated mass for $C_{27}H_{26}F_5N_7O_3$: 591.2, found: 591.8 ($M+H^+$).

EXAMPLE 38

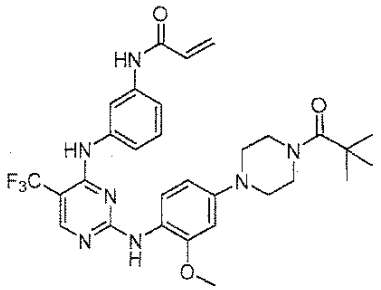
Compound I-33 (N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-(trifluoromethoxy)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00178] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-trifluoromethoxyphenyl)piperazine-1-carboxylate (22 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and acetic anhydride (30 uL). The reaction mixture was stirred room temperature overnight. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.15 (s, 1 H), 9.00 (s, 1 H), 8.62 (s, 1 H), 8.29 (s, 1 H), 7.71 (s, 1 H), 7.43 (s, 2 H), 7.18 (m, 2 H), 6.84 (s, 1 H), 6.75 (br, 1 H), 6.45 (dd, J = 10.0, 16.8 Hz, 1 H), 6.26 (d, J = 16.8 Hz, 1 H), 5.77 (d, J = 10.0 Hz, 1 H), 3.57 (br, 4 H), 3.13 (br, 2 H), 3.06 (br, 2 H), 2.05 (s, 3 H); calculated mass for $C_{27}H_{25}F_6N_7O_3$: 609.2, found: 610.0 ($M+H^+$).

EXAMPLE 39

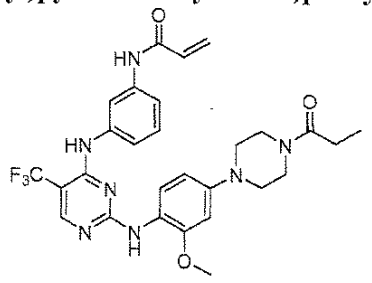
Compound I-34 (N-(3-(2-(2-methoxy-4-(4-pivaloylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00179] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and pivaloyl chloride (20 uL) at 0 °C. The reaction mixture was stirred room temperature for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{30}H_{34}F_3N_7O_3$: 597.3, found: 598.3 ($M+H^+$).

EXAMPLE 40

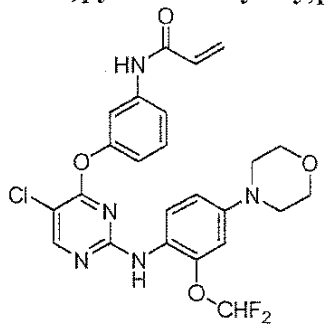
Compound I-35 (N-(3-(2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00180] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20

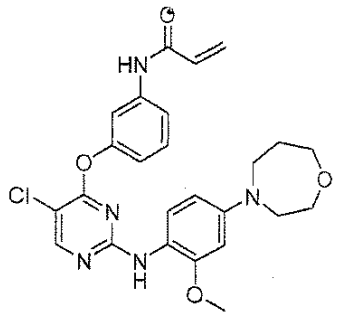
uL), dichloromethane (1.0 mL), and propionyl chloride (10 uL) at 0 °C. The reaction mixture was stirred room temperature for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{27}H_{28}F_3N_7O_3$: 555.2, found: 556.2 ($M+H^+$).

EXAMPLE 41
Compound I-36 (N-(3-(5-chloro-2-(2-(difluoromethoxy)-4-morpholinophenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00181] A mixture of the intermediate 6 (20 mg) and 2-difluoromethoxy-4-morpholinoaniline (22 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.33 (s, 1 H), 8.71 (s, 1 H), 8.35 (s, 1 H), 7.62 (t, J = 2.0 Hz, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.40 (t, J = 8.0 Hz, 1 H), 7.23 (d, J = 8.8 Hz, 1 H), 6.97 (dd, J = 64.8, 66.4 Hz, 1 H), 6.95 (s, 1 H), 6.64 (d, J = 2.0 Hz, 1 H), 6.59 (br, 1 H), 6.44 (dd, J = 10.0, 16.8 Hz, 1 H), 6.27 (dd, J = 2.0, 16.8 Hz, 1 H), 5.79 (dd, J = 2.0, 10.0 Hz, 1 H), 3.72 (m, 4 H), 3.03 (m, 4 H); calculated mass for $C_{24}H_{22}ClF_2N_5O_4$: 517.1, found: 517.7 ($M+H^+$).

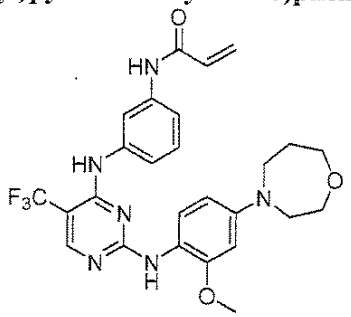
EXAMPLE 42
Compound I-37 (N-(3-(5-chloro-2-(2-methoxy-4-(1,4-oxazepan-4-yl)phenylamino)pyrimidin-4-yloxy)phenyl)acrylamide)



[00182] A mixture of the intermediate 6 (20 mg) and 2-methoxy-4-(1,4-oxazepan-4-yl)aniline (21 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{25}H_{26}ClN_5O_4$: 495.2, found: 495.8 ($M+H^+$).

EXAMPLE 43

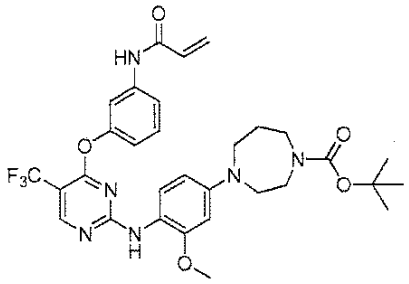
Compound I-38 (N-(3-(2-(2-methoxy-4-(1,4-oxazepan-4-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00183] A mixture of the intermediate 1 (16 mg) and 2-methoxy-4-(1,4-oxazepan-4-yl)aniline (21 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{26}H_{27}F_3N_6O_3$: 528.2, found: 528.8 ($M+H^+$).

EXAMPLE 44

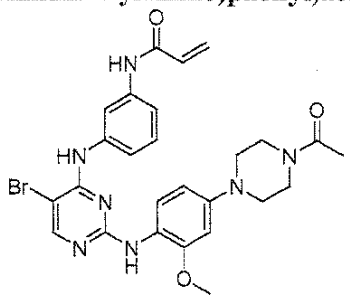
Compound I-39 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)-1,4-diazepane-1-carboxylate)



[00184] A mixture of the intermediate 5 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)-1,4-diazepane-1-carboxylate (21 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{26}H_{27}F_3N_6O_3$: 528.2, found: 528.8 ($M\text{-}Boc+H^+$).

EXAMPLE 45

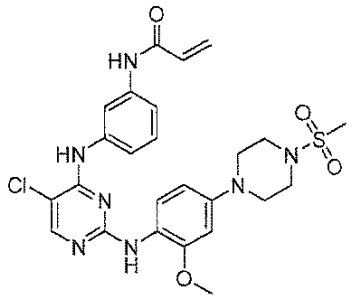
Compound I-40 (N-(3-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-bromopyrimidin-4-ylamino)phenyl)acrylamide)



[00185] A mixture of intermediate 4 and 1-(4-(4-amino-3-methoxyphenyl)piperazin-1-yl)ethanone (18 mg) in n-butanol (1 mL) with catalytic HCl was microwaved for 20 min at 150 °C. The crude was concentrated under reduced pressure and purified to give the title compound. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.15 (s, 1 H), 8.60 (br, 1 H), 8.15 (s, 1 H), 7.89 (br, 1 H), 7.67 (m, 2 H), 7.47 (d, J = 6.8 Hz, 1 H), 7.26 (m, 2 H), 6.63 (d, J = 2.4 Hz, 1 H), 6.45 (dd, J = 10.0, 16.8 Hz, 1 H), 6.28 (m, 1 H), 6.26 (dd, J = 2.0, 16.8 Hz, 1 H), 5.76 (dd, J = 2.0, 10.0 Hz, 1 H), 3.79 (s, 3 H), 3.56 (m, 4 H), 3.06 (m, 2 H), 3.03 (m, 2 H), 2.05 (s, 3 H); calculated mass for $C_{26}H_{28}BrN_7O_3$: 565.1, found: 566.3 ($M+H^+$).

EXAMPLE 46

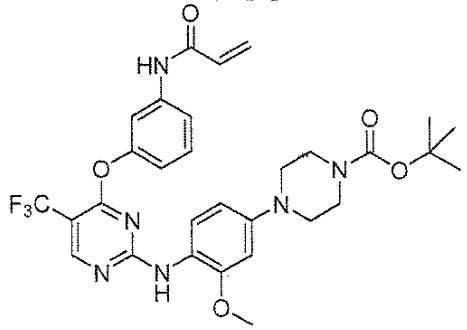
Compound I-41 (N-(3-(5-chloro-2-(2-methoxy-4-(4-(methylsulfonyl)piperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)acrylamide)



[00186] A mixture of the intermediate 2 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1.0 mL) with catalytic trifluoroacetic acid was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and methanesulfonyl chloride (10 uL) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.16 (s, 1 H), 8.86 (s, 1 H), 8.08 (s, 1 H), 7.95 (s, 1 H), 7.70 (m, 2 H), 7.44 (d, J = 7.6 Hz, 1 H), 7.28 (m, 2 H), 6.64 (d, J = 2.4 Hz, 1 H), 6.46 (dd, J = 10.0, 16.8 Hz, 1 H), 6.32 (m, 1 H), 6.26 (dd, J = 2.0, 16.8 Hz, 1 H), 5.77 (dd, J = 2.0, 10.0 Hz, 1 H), 3.80 (s, 3 H), 3.30 (m, 4 H), 3.25 (m, 2 H), 3.17 (m, 2 H), 2.93 (s, 3 H); calculated mass for $C_{25}H_{28}ClN_7O_4S$: 557.2, found: 558.4 ($M+H^+$).

EXAMPLE 47

Compound I-42 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1-carboxylate)

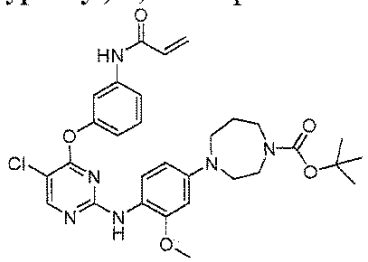


[00187] A mixture of the intermediate 5 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic

trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{30}H_{33}F_3N_6O_5$: 614.3, found: 615.2 ($M+H^+$).

EXAMPLE 48

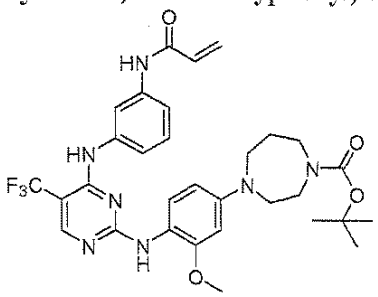
Compound I-43 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxyphenyl)-1,4-diazepane-1-carboxylate)



[00188] A mixture of the intermediate 6 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)-1,4-diazepane-1-carboxylate (21 mg) in n-butanol (1 mL) with catalytic HCl was microwaved for 20 min at 100 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{30}H_{35}ClN_6O_5$: 594.2, found: 594.8 ($M+H^+$).

EXAMPLE 49

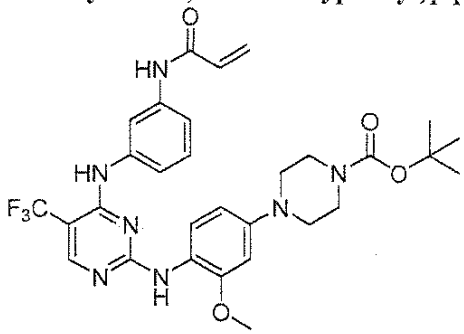
Compound I-44 (tert-butyl 4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)-1,4-diazepane-1-carboxylate)



[00189] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)-1,4-diazepane-1-carboxylate (21 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{31}H_{36}F_3N_7O_4$: 627.3, found: 628.0 ($M+H^+$).

EXAMPLE 50

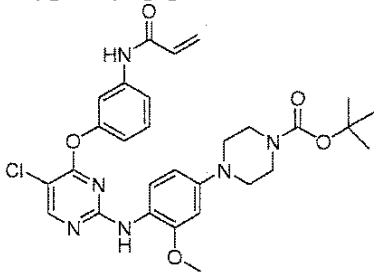
Compound I-45 (tert-butyl 4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1-carboxylate)



[00190] A mixture of the intermediate 1 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{30}H_{34}F_3N_7O_4$: 613.3, found: 614.1 ($M+H^+$).

EXAMPLE 51

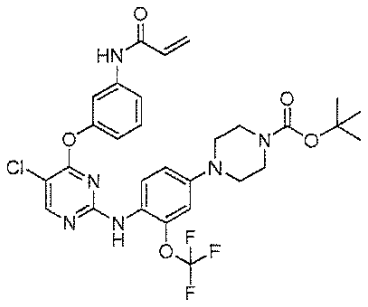
Compound I-46 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-chloropyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1-carboxylate)



[00191] A mixture of the intermediate 6 (16 mg) and tert-butyl 4-(4-amino-3-methoxyphenyl)piperazine-1-carboxylate (20 mg) in n-butanol (1 mL) with catalytic HCl was microwaved for 20 min at 120 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{29}H_{33}ClN_6O_5$: 580.2, found: 581.2 ($M+H^+$).

EXAMPLE 52

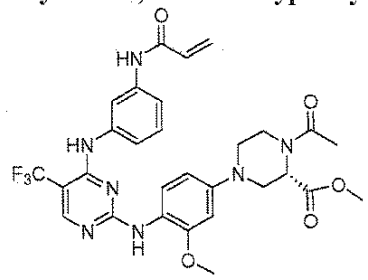
Compound I-47 (tert-butyl 4-(4-(4-(3-acrylamidophenoxy)-5-chloropyrimidin-2-ylamino)-3-(trifluoromethoxy)phenyl)piperazine-1-carboxylate)



[00192] A mixture of the intermediate 6 (16 mg) and tert-butyl 4-(4-amino-3-trifluoromethoxyphenyl)piperazine-1-carboxylate (22 mg) in n-butanol (1.0 mL) with catalytic HCl was microwaved for 20 min at 120 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{29}H_{30}ClF_3N_6O_5$: 634.2, found: 635.4 ($M+H^+$).

EXAMPLE 53

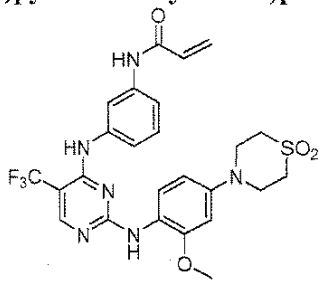
Compound I-48 ((S)-methyl 1-acetyl-4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-2-carboxylate)



[00193] A mixture of the intermediate 1 (16 mg) and (S)-1-tert-butyl 2-methyl 4-(4-amino-3-methoxyphenyl)piperazine-1,2-dicarboxylate (23 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier). The intermediate was dissolved in dichloromethane (1.0 mL) and treated with TFA (0.3 mL). After 10 minutes, the mixture was concentrated under reduced pressure. To the residue were added N,N-diethylisopropylamine (20 uL), dichloromethane (1.0 mL), and acetic anhydride (20 uL). The reaction mixture was stirred room temperature overnight. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{29}H_{30}F_3N_7O_5$: 613.2, found: 614.2 ($M+H^+$).

EXAMPLE 54

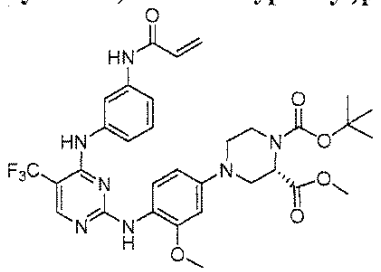
Compound I-49 (N-(3-(2-(2-methoxy-4,4-dioxo-4-thiomorpholinophenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)acrylamide)



[00194] A mixture of the intermediate 1 (18 mg) and 2-methoxy-4-S,S-dioxothiomorpholino-aniline (24 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. ^{1}H-NMR (DMSO-d6, 400 MHz) δ 10.16 (s, 1 H), 8.66 (br, 1 H), 8.29 (s, 1 H), 8.13 (s, 1 H), 7.77 (br, 1 H), 7.51 (s, 1 H), 7.49 (s, 1 H), 7.26 (t, J = 8.0 Hz, 1 H), 7.18 (br, 1 H), 6.64 (d, J = 2.0 Hz, 1 H), 6.44 (dd, J = 10.0, 16.8 Hz, 1 H), 6.31 (m, 1 H), 6.26 (dd, J = 2.0, 16.8 Hz, 1 H), 5.77 (dd, J = 2.0, 10.0 Hz, 1 H), 3.79 (s, 3 H), 3.70 (m, 4 H), 3.12 (m, 4 H); calculated mass for $C_{25}H_{25}F_3N_6O_8S$: 562.2, found: 562.8 ($M+H^+$).

EXAMPLE 55

Compound I-50 ((S)-1-tert-butyl 2-methyl 4-(4-(4-(3-acrylamidophenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)-3-methoxyphenyl)piperazine-1,2-dicarboxylate)



[00195] A mixture of the intermediate 1 (20 mg) and (S)-1-tert-butyl 2-methyl 4-(4-amino-3-methoxyphenyl)piperazine-1,2-dicarboxylate (26 mg) in dioxane (1.0 mL) with catalytic trifluoroacetic acid was stirred overnight at 50 °C. The crude was concentrated under reduced pressure and purified using HPLC (TFA modifier) to give the desired as a TFA salt. Calculated mass for $C_{32}H_{36}F_3N_7O_6$: 671.3, found: 672.3 ($M+H^+$).

Biological Examples

[00196] Described below are assays used to measure the biological activity of provided compounds as selective inhibitors of mutant EGFR as compared to WT EGFR (and other protein kinases).

EXAMPLE 56

Omnia Assay Protocol for Potency Assessment Against EGFR (WT) and EGFR (T790M/L858R) Active Enzymes

[00197] Below describes the biochemical assay protocol using EGFR-WT and EGFR-T790M/L858R.

[00198] The mechanics of the assay platform are best described by the vendor (Invitrogen, Carlsbad, CA) on their website at the following URL: www.invitrogen.com/content.cfm?pageid=11338 or www.invitrogen.com/site/us/en/home/Products-and-Services/Applications/Drug-Discovery/Target-and-Lead-Identification-and-Validation/KinaseBiology/KB-Misc/Biochemical-Assays/Omnia-Kinase-Assays.html.

[00199] Briefly, 10X stocks of EGFR-WT (PV3872) from Invitrogen and EGFR-T790M/L858R (40350) from BPS Bioscience, San Diego, CA, 1.13X ATP (AS001A) and appropriate Tyr-Sox conjugated peptide substrates (KCZ1001) were prepared in 1X kinase reaction buffer consisting of 20 mM Tris, pH 7.5, 5 mM $MgCl_2$, 1 mM EGTA, 5 mM β-glycerophosphate, 5% glycerol (10X stock, KB002A) and 0.2 mM DTT (DS001A). 5 µL of each enzyme were pre-incubated in a Corning (#3574) 384-well, white, non-binding surface microtiter plate (Corning, NY) for 30 min. at 25°C with a 0.5 µL volume of 50% DMSO and serially diluted compounds prepared in 50% DMSO. Kinase reactions were started with the addition of 45 µL of the ATP/Tyr-Sox peptide substrate mix and monitored every 71 seconds for 60 minutes at $\lambda_{ex}360/\lambda_{em}485$ in a Synergy^4 plate reader from BioTek (Winooski, VT). At the conclusion of each assay, progress curves from each well were examined for linear reaction kinetics and fit statistics (R^2, 95% confidence interval, absolute sum of squares). Initial velocity (0 minutes to ~30 minutes) from each reaction was determined from the slope of a plot of relative fluorescence units *vs* time (minutes) and then plotted against inhibitor concentration to estimate IC_{50} from log[Inhibitor] vs Response, Variable Slope model in GraphPad Prism from GraphPad Software (San Diego, CA).

[00200] [EGFR-WT] = 5 nM, [ATP] = 15 uM, [Y12-Sox] = 5 uM (ATP K_{Mapp} ~ 12 uM); and [EGFR-T790M/L858R] = 2.5 nM, [ATP] = 20 uM, [Y12-Sox] = 5 uM (ATP K_{Mapp} ~ 20 uM).

[00201] Table 3 shows the activity of selected compounds of this invention in the EGFR inhibition assay described above. Table 3 shows mutant EGFR data as compared to WT EGFR and provides the selectivity ratio of WT to mutant for each test compound. The compound numbers correspond to the compound numbers in Table 1.

Table 3. EGFR (Mutant and Wild Type) Biochemical Inhibition Data

Compound #	WT EGFR IC_{50} (nM)	EGFR (T790M/L858R) IC_{50} (nM)	Ratio WT/mutant
I-1	30-100	1-10	>40
I-2	10-30	<1	>20
I-3	1-10	<1	>5
I-4	1-10	<1	>10
I-5	10-30	1-10	>25
I-6	1-10	<1	>5
I-7	10-30	<1	>15
I-8	10-30	1-10	>10
I-9	1-10	<1	>5
I-10	1-10	1-10	>1
I-11	10-30	<1	>25
I-12	10-30	<1	>15
I-13	30-100	<1	>35
I-14	10-30	<1	>25
I-15	30-100	1-10	>15
I-17	10-30	<1	>30
I-18	>1000	10-30	>50
I-19	100-300	1-10	>50
I-20	10-30	1-10	>5
I-21	10-30	<1	>35
I-22	30-100	<1	>50
I-23	100-300	1-10	>25
I-24	30-100	1-10	>15
I-26	10-30	<1	>25
I-27	1-10	1-10	>5
I-28	1-10	<1	>10
I-29	10-30	<1	>30
I-30	30-100	<1	>50
I-31	<1	<1	1
I-32	<1	<1	>1
I-33	1-10	<1	>10
I-34	30-100	<1	>40

Compound #	WT EGFR IC_{50} (nM)	EGFR (T790M/L858R) IC_{50} (nM)	Ratio WT/mutant
I-35	1-10	<1	>10
I-36	10-30	<1	>25
I-37	30-100	1-10	>25
I-38	10-30	<1	>50
I-39	>1000	10-30	>50
I-40	10-30	1-10	>20
I-41	30-100	1-10	>20
I-42	300-1000	300-1000	>1
I-43	300-1000	1-10	>50
I-44	300-1000	1-10	>50
I-45	30-100	1-10	>20
I-46	100-300	<1	>50
I-47	>1000	10-30	>50
I-48	10-30	<1	>25
I-49	1-10	<1	>1

EXAMPLE 57

Cell Culture and Antibodies

[00202] A431 human epidermoid carcinoma, H1975 human NSCLC and HCC827 human NSCLC adenocarcinoma cells were obtained from the American Type Culture Center (Manassas, VA). A431 cells were grown in DMEM (Invitrogen, Carlsbad, CA) supplemented with 10% FBS (HyClone, South Logan, UT) and 1% Penicillin-Streptomycin (P/S, Lonza, Walkersville, MD). H1975 and HCC827 cells were grown in complete RPMI 1640 (Invitrogen) supplemented with 10% FBS and 1% P/S. All cells were maintained and propagated as monolayer cultures at 37°C in a humidified 5% CO_2 incubator.

[00203] All primary antibodies were obtained from Cell Signaling (Danvers, MA) and used at 1:1000. Secondary antibodies were used at 1:10,000. Goat anti-mouse IgG IRDye 800CW antibody was obtained from LiCor Biosciences (Lincoln, NE) and goat anti-rabbit IgG Alexa Fluor 680 was obtained from Invitrogen.

Immunoblotting

[00204] Cells were grown in 12-well plates (Corning, Coring, NY) to 90% confluence and then incubated in low-serum (0.1% FBS) media for 16-18 hr. Cells were then treated with 5, 1.25, 0.31, 0.078, 0.020 or 0.005μM test compound in low-serum (0.1% FBS) media for 1 hr. A431 cells were then stimulated with 50 ng/ml EGF (Peprotech, Rocky Hill, NJ) for 15 min.

After treatment, cell monolayers were washed with cold PBS (Invitrogen) and immediately lysed by scrapping into 60 uL cold Cell Extraction Buffer (Invitrogen) supplemented with Complete Protease inhibitors (Roche, Indianapolis, IN) and PhosphoSTOP (Roche) phosphatase inhibitors.

[00205] Lysate protein concentrations were determined by BCA Assay (Pierce, Rockford, IL) and 50 ug of each lysate was separated by 4-12% gradient SDS-PAGE (Invitrogen), transferred to nitrocellulose membrane (Biorad, Hercules, CA) and probed with specific antibodies. Phospho-protein signals were quantitated using Odyssey Infrared Imaging (Li-Cor Biosciences).

[00206] To assess phosphor-EGFR signaling, blots were probed with rabbit anti-Phospho-EGFR (Y1068) and mouse total anti-EGFR antibodies. Phospho-EGFR signal was normalized to total EGFR expression for each sample. Results are indicated as % DMSO control. Normalized data was fitted using a sigmoidal curve analysis program (Graph Pad Prism version 5) with variable Hill slope to determine the EC_{50} values.

[00207] Table 4 shows mutant EGFR data in H1975 (double mutation L858R/T790M) and HCC827 (delE746-A750 deletion mutation) cells as compared to WT EGFR (A431 cells). The compound numbers recited in Table 4 correspond to the compound numbers in Table 1.

Table 4. EGFR (Mutant and Wild Type) Signaling (1 hr)

Compound #	WT EGFR EC_{50} (nM)	H1975 EC_{50} (nM)	Ratio WT/mutant	HCC827 EC_{50} (nM)	Ratio WT/mutant
I-1	>1000	10-100	>50	-	-
I-2	>1000	10-100	>50	-	-
I-3	>1000	500-1000	>5	-	-
I-4	>1000	10-100	>50	100-500	>25
I-5	>1000	10-100	>30	-	-
I-6	>1000	10-100	>20	-	-
I-7	>1000	100-500	>5	-	-
I-8	>1000	>1000	>1	-	-
I-9	>1000	-	-	-	-
I-11	>1000	100-500	>15	-	-
I-12	>1000	>1000	>1	-	-
I-13	-	10-100	-	-	-
I-14	500-1000	10-100	>15	10-100	>15
I-17	>1000	10-100	>30	100-500	>5
I-21	>1000	100-500	>5	-	-
I-22	>1000	100-500	>35	-	-
I-26	>1000	100-500	>40	-	-
I-27	>1000	-	-	-	-
I-29	>1000	-	-	-	-

Compound #	WT EGFR EC_{50} (nM)	H1975 EC_{50} (nM)	Ratio WT/mutant	HCC827 EC_{50} (nM)	Ratio WT/mutant
I-33	>1000	10-100	>50	-	-
I-34	>1000	100-500	>35	-	-
I-35	>1000	<10	>50	-	-
I-40	>1000	>1000	>1	-	-
I-41	>1000	>1000	>1	-	-
I-44	>1000	500-1000	>5	-	-
I-45	>1000	100-500	>10	-	-
I-46	>1000	100-500	>10	<10	>50
I-48	>1000	10-100	>50	-	-
I-49	>1000	10-100	>20	-	-

EXAMPLE 58

Cell Proliferation

[00208] Cells were plated in Growth Media supplemented with 5% FBS and 1% P/S at a density of 3,000 cells per well in 96 well tissue culture plates (Corning). Cells were allowed to settle down for 4 hr and then treated with 5, 1.25, 0.31, 0.078, 0.020 or 0.005μM test compound for 72 hr. Cell viability was determined by CellTiter Glo (Promega, Madison, WI) and results were converted to cell numbers using a standard curve. Growth inhibition (GI50) values were determined by Graph Pad Prism.

[00209] The result of this experiment is depicted in Table 5, where it shows mutant selective inhibition in H1975 (double mutation L858R/T790M) and HCC827 (delE746-A750 deletion mutation) cells but not in WT-EGFR A431 cells.

Table 5. EGFR (Mutant and Wild Type) Cell Proliferation

Compound #	WT EGFR GI_{50} (nM)	H1975 GI_{50} (nM)	Ratio WT/mutant	HCC827 GI_{50} (nM)	Ratio WT/mutant
I-1	>1000	10-100	>15	10-100	>15
I-2	>1000	10-100	>20	10-100	>40
I-3	>1000	100-500	>5	10-100	>45
I-4	500-1000	10-100	>10	10-100	>35
I-5	>1000	100-500	>5	10-100	>20
I-6	500-1000	10-100	>10	10-100	>40
I-7	>1000	100-500	>1	100-500	>10
I-8	500-1000	100-500	>1	10-100	>20
I-9	>1000	100-500	>5	10-100	>50
I-10	>1000	500-1000	>1	100-500	>20

Compound #	WT EGFR GI_{50} (nM)	H1975 GI_{50} (nM)	Ratio WT/mutant	HCC827 GI_{50} (nM)	Ratio WT/mutant
I-11	>1000	100-500	>5	10-100	>45
I-12	500-1000	100-500	>1	10-100	>30
I-13	>1000	100-500	>10	10-100	>50
I-14	>1000	100-500	>5	10-100	>10
I-15	>1000	500-1000	>1	100-500	>10
I-17	>1000	100-500	>10	10-100	>15
I-18	>1000	500-1000	>1	100-500	>5
I-19	>1000	100-500	>5	100-500	>10
I-20	>1000	100-500	>5	100-500	>15
I-21	500-1000	100-500	>1	10-100	>20
I-22	>1000	100-500	>10	10-100	>35
I-23	>1000	500-1000	>1	100-500	>20
I-24	500-1000	100-500	>1	10-100	>40
I-26	>1000	>1000	>1	10-100	>35
I-27	>1000	100-500	>1	10-100	>10
I-28	>1000	500-1000	>5	10-100	>50
I-29	>1000	10-100	>10	10-100	>15
I-30	>1000	100-500	>1	10-100	>25
I-33	>1000	10-100	>30	100-500	>15
I-34	>1000	100-500	>5	10-100	>50
I-35	>1000	10-100	>10	10-100	>25
I-36	>1000	100-500	>25	10-100	>50
I-37	>1000	500-1000	>1	100-500	>10
I-38	>1000	>1000	>1	500-1000	>5
I-39	>1000	>1000	<1	>1000	>1
I-40	500-1000	100-500	>5	10-100	>10
I-41	>1000	100-500	>1	10-100	>20
I-44	>1000	500-1000	>5	500-1000	>5
I-45	>1000	100-500	>1	100-500	>10
I-46	>1000	500-1000	>1	100-500	>10
I-48	>1000	10-100	>10	10-100	>15
I-49	>1000	100-500	>10	10-100	>25
I-50	>1000	100-500	>10	10-100	>50

EXAMPLE 59

Washout Experiment in H1975 cells containing EGFR deletion/T790M mutation

[00210] Cells were plated in Growth Media supplemented with 10% FBS and 1% P/S at a density of 2.0 x 10 5 cells per well in 12 well tissue culture plates. Cells were allowed to settle down for 4 hrs and then maintained in low-serum (0.1% FBS) media overnight.

[00211] The following morning the media was removed and the cells were treated with 500 nM test compound in low-serum media for 1 hr. The cells were washed free of compound 2X with PBS (Invitrogen). One set of cells were immediately lysed as indicated above as the 0 hr time point. The remaining cells were incubated with complete RPMI-1640 growth media (10% FBS) for 1, 3, 6 and 24 hr. For the first 1 hr, cells were washed 2X with PBS every 30 min. DMSO (0.5%) controls were collected at the 0, 3, 6 and 24 hr time points.

[00212] Compounds **I-2** and **I-4** demonstrate prolonged duration of action after compound removal. pEGFR phosphorylation is inhibited by 80-100% 1 hr after compound removal. pEGFR remained 60-90% inhibited for at least 8 hours after compound was removed, but activity was restored to 40-60% by new protein synthesis at 24h.

EXAMPLE 60

Mass Spectrometry for Mutant EGFR

[00213] Compound **I-4** modifies EGFR T790M/L858R singly and completely, as confirmed by whole protein MS analysis. Intact EGFR T790M/L858R (BPS, 40350) was incubated for 60 min. at a 10-fold excess of Compound **I-4** to protein. 5 µL aliquots of the samples 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 (10mg/ml in 0.1%TFA:Acetonitrile 50:50). Panel A shows the mass spec trace of the intact EGFR T790M/L858R protein (m/z = 88,389 Da). Panel B shows the mass spec trace of EGFR T790M/L858R incubated with Compound **I-4** (mw=555.56) for 30 min. The centroid mass (m/z= 88,820 Da) shows a mass shift of 431Da (78%), indicating complete modification of EGFR T790M/L858R by Compound **I-4**.

[00214] Compounds **I-1** and **I-3** were similarly tested and found to covalently modify the protein.

EXAMPLE 61

H1975 Tumor *in vivo* study

[00215] Female nu/nu mice were implanted with $1x10^7$ H1975 tumor cells in 50% Matrigel subcutaneously (0.2ml injection volume) in the flank. Tumor measurements were recorded three times per week. Tumors were pair matched when they reached an average size of 100-150mg. Group size was 10 mice. Test compound was administered intraperitoneal, 25mg/kg daily for 21

days. % Tumor inhibition values were determined at 15 days, the time at which the control group reached a maximum tumor volume. Tumor volume was followed until tumors reached $1500mm^3$ or 60 days.

[00216] Tumor inhibition values for provided compounds are shown in **Table 6**, below.

Table 6.

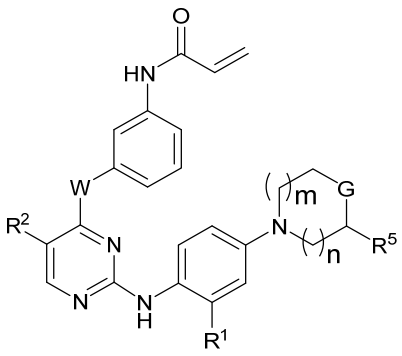
Compound #	% Tumor inhibition
I-1	>66
I-2	>66
I-4	>66
I-5	>33

[00217] While a number of embodiments of this invention are described herein, it is apparent that the basic examples may be altered to provide other embodiments that utilize the compounds and methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims rather than by the specific embodiments that have been represented by way of example.

CLAIMS

We claim:

1. Use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by a structural formula **I**:



I

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

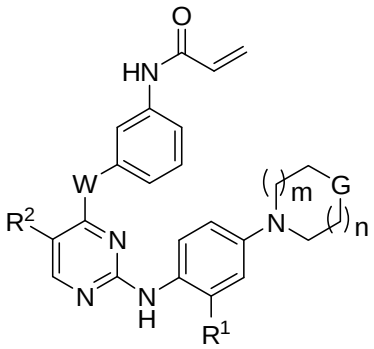
R^2 is $–CF_3$, Cl, or Br;

G is $–NR^3$- or $-S(O)_2$-;

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH; and

R^5 is hydrogen or -C(O)OR.

2. Use of a compound in the manufacture of a medicament for treatment of a mutant EGFR-mediated proliferative disorder, wherein the compound is represented by structural formula **I-a**:



I-a

or a pharmaceutically acceptable salt thereof, wherein:

n is 0, 1, or 2;

m is 0, 1, or 2, wherein m and n are not simultaneously 0;

W is –O– or –NH-;

R^1 is –OR;

each R is independently C_{1-4} alkyl or C_{1-4} fluoroalkyl;

R^2 is $–CF_3$, Cl, or Br;

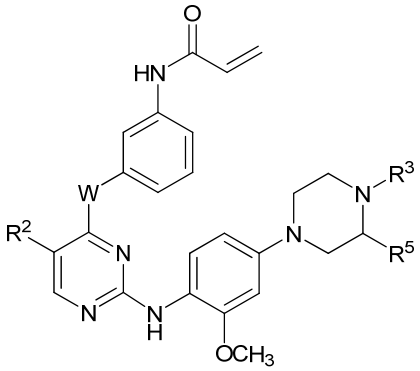
G is $–NR^3$-; and

R^3 is –C(O)-R, -C(O)OR, -C(O)NHR, $–SO_2$-R, $-SO_2NH_2$, -C(O)-C_{1-4} alkylene-OH or $–SO_2$-C_{1-4} alkylene-OH.

3. Use according to claim 1 or 2, wherein W is –NH-.

4. Use according to claim 3, wherein R^2 is $–CF_3$.

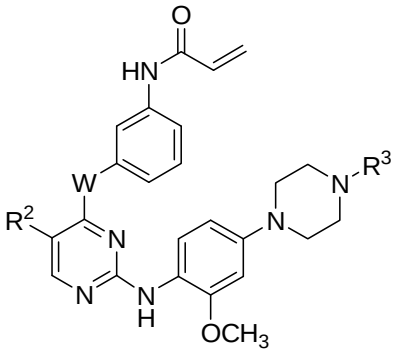
5. Use according to claim 1, wherein the compound is represented by structural formula **III**:



III

or a pharmaceutically acceptable salt thereof, wherein W, R^2, R^3 and R^5 are as defined in claim 1.

6. Use according to claim 1, wherein the compound is represented by structural formula **III-a**:



III-a

or a pharmaceutically acceptable salt thereof, wherein W, R^2 and R^3 are as defined in claim 1.

7. Use according to claim 5 or 6, wherein W is –NH-.

8. Use according to claim 5 or 6, wherein R^2 is $–CF_3$.

9. Use according to claim 5 or 6, wherein at least one of definitions (a) and (b) apply:
(a) R^2 is $–CF_3$ or Cl; and
(b) R^3 is $–C(O)CH_3$ or $–SO_2CH_3$.

10. Use according to claim 9, wherein both definitions (a) and (b) apply.

11. Use according to claim 5 or 6, wherein at least one of definitions (a), (b), and (c) apply:
(a) W is –NH-;
(b) R^2 is $–CF_3$ or Cl; and
(c) R^3 is $–C(O)CH_3$.

12. Use according to claim 11, wherein at least two of definitions (a), (b), and (c) apply.

13. Use according to claim 12, wherein all three of definitions (a), (b), and (c) apply.

14. Use according to claim 5 or 6, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –NH–;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–SO_2CH_3$.

15. Use according to claim 14, wherein at least two of definitions (a), (b), and (c) apply.

16. Use according to claim 15, wherein all three of definitions (a), (b), and (c) apply.

17. Use according to claim 5 or 6, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O-;

(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–C(O)CH_3$.

18. Use according to claim 17, wherein at least two of definitions (a), (b), and (c) apply.

19. Use according to claim 18, wherein all three of definitions (a), (b), and (c) apply.

20. Use according to claim 5 or 6, wherein at least one of definitions (a), (b), and (c) apply:

(a) W is –O–;

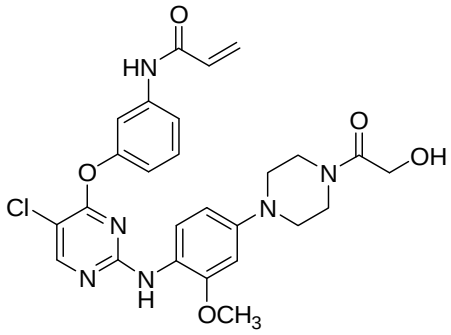
(b) R^2 is $–CF_3$ or Cl; and

(c) R^3 is $–SO_2CH_3$.

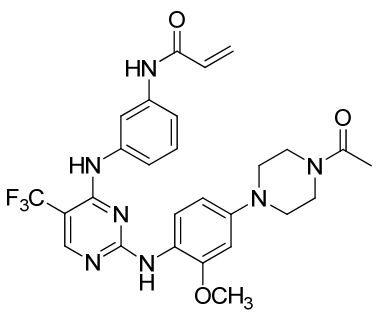
21. Use according to claim 20, wherein at least two of definitions (a), (b), and (c) apply.

22. Use according to claim 21, wherein all three of definitions (a), (b), and (c) apply.

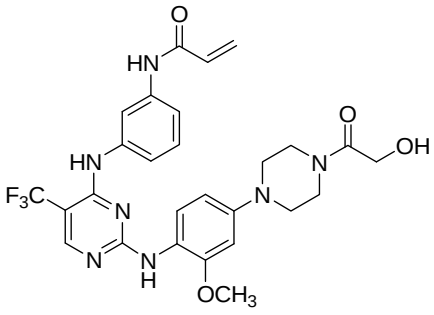
23. Use according to claim 1, wherein the compound is selected from:



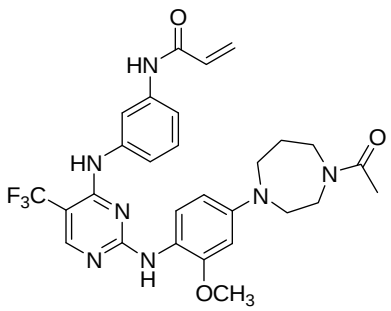
I-3



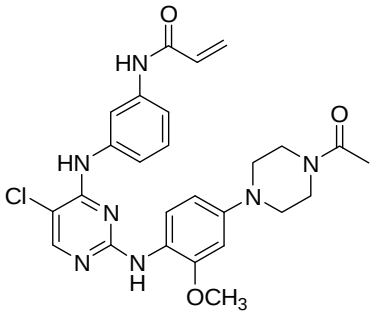
I-4



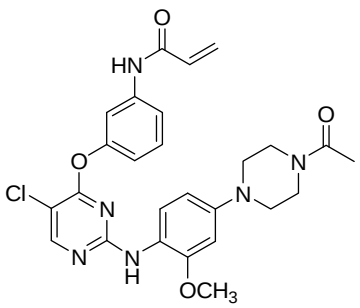
I-6



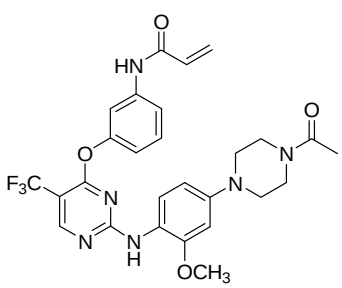
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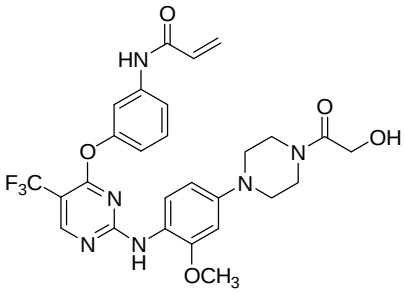
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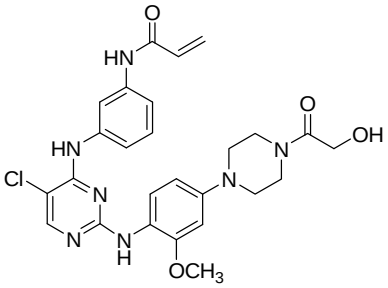
I-9



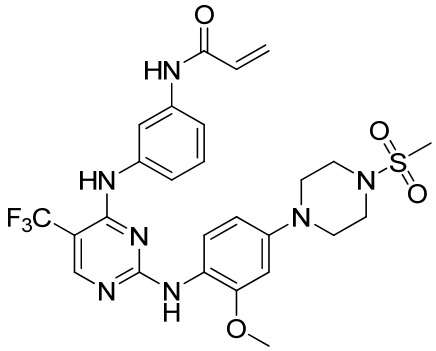
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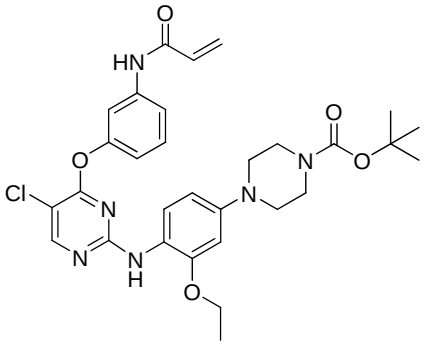
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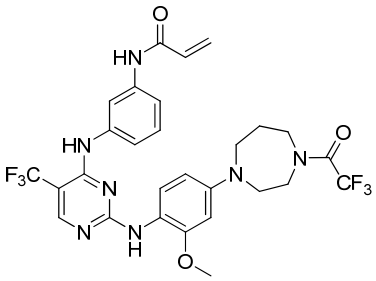
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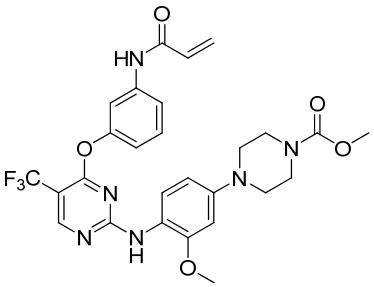
I-17



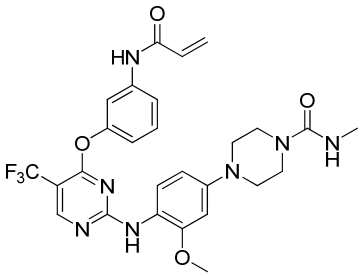
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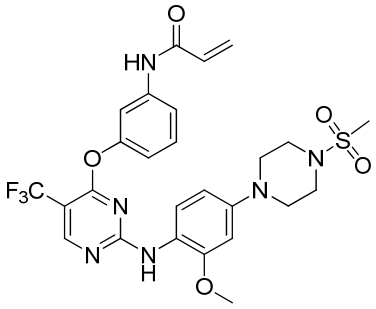
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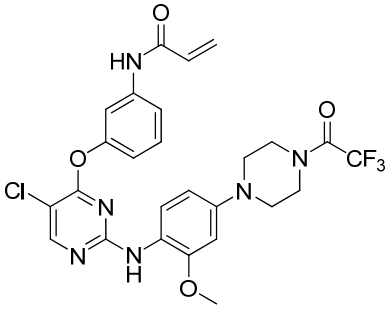
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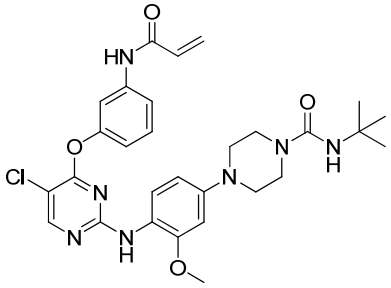
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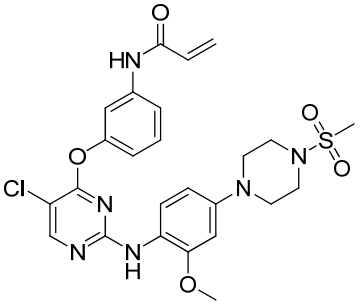
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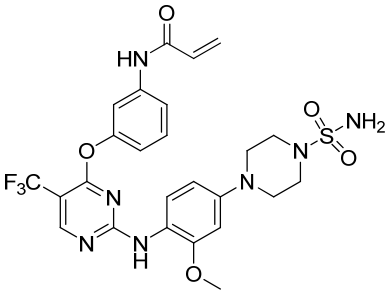
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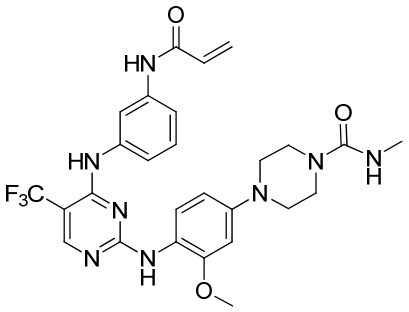
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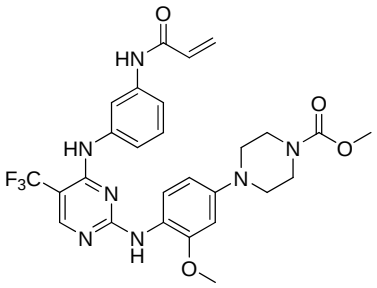
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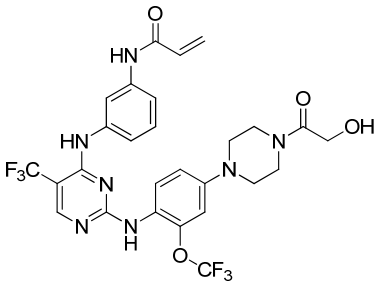
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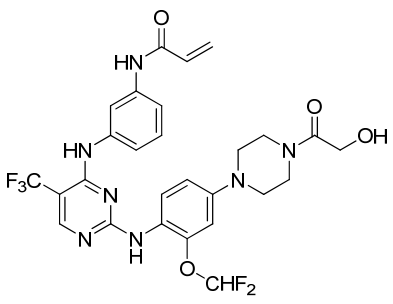
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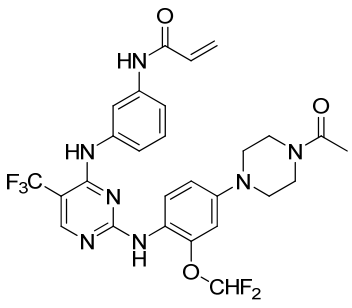
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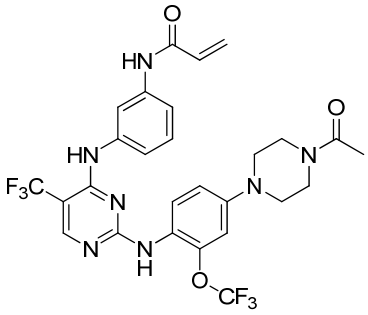
I-30



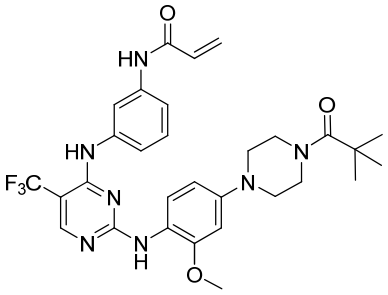
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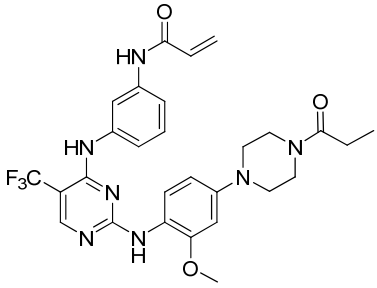
I-32



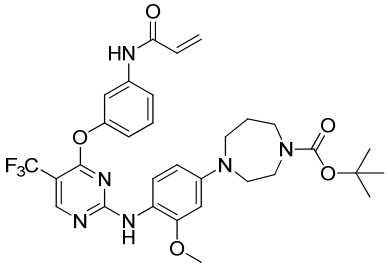
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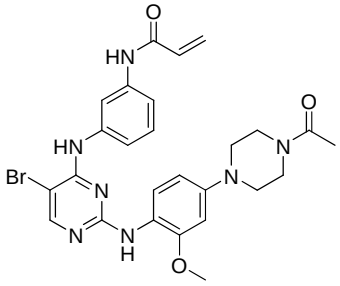
I-34



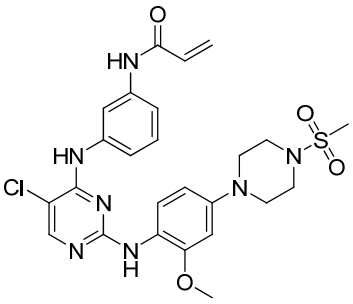
I-35



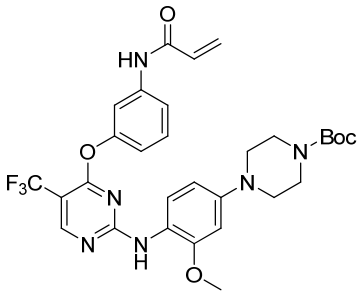
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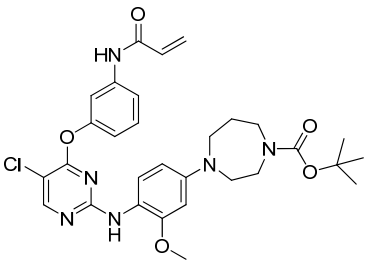
I-40



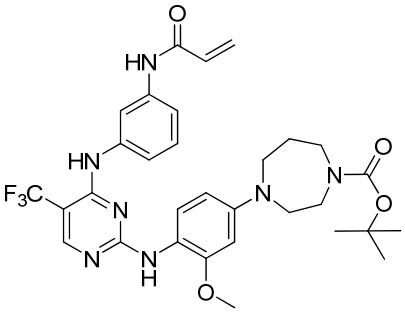
I-41



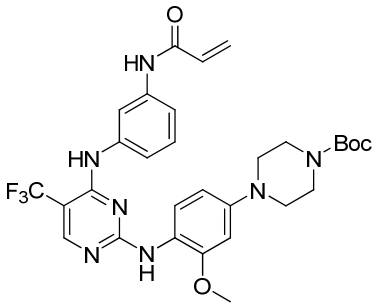
I-42



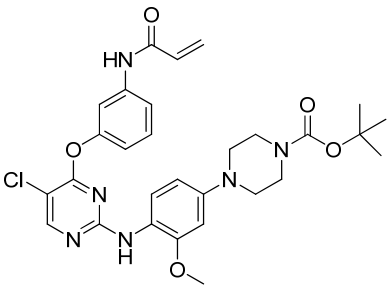
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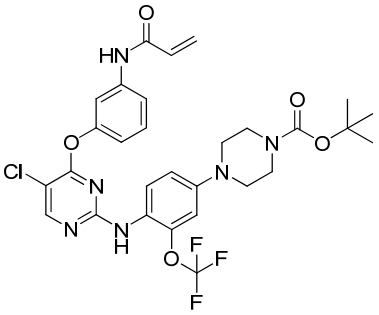
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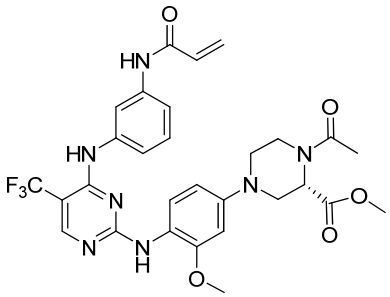
I-45



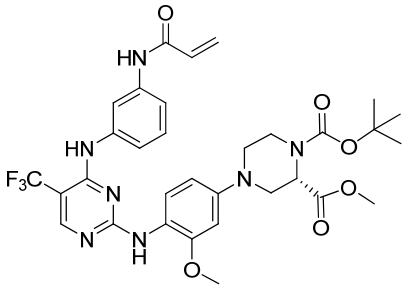
I-46



I-47



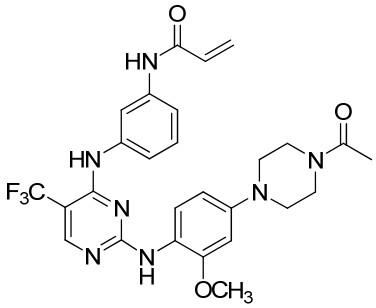
I-48



I-50

or a pharmaceutically acceptable salt thereof.

24. Use according to claim 1, wherein the compound is of formula:



I-4

or a pharmaceutically acceptable salt thereof.

25. Use according to claim 1, wherein the mutant EGFR-mediated proliferative disorder is a cancer selected from breast cancer, glioblastoma, lung cancer, cancer of the head and neck, colorectal cancer, and bladder cancer.

26. Use according to claim 25, wherein the cancer is a lung cancer.

27. Use according to claim 26, wherein the lung cancer is non-small cell lung cancer.