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(54) Title: FUSED PYRIMIDINE COMPOUNDS, COMPOSITIONS AND MEDICINAL APPLICATIONS THEREOF

(57) Abstract: The present disclosure relates to a class of fused pyrimidine compounds of Formula I, their stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates, and hydrates thereof. The present disclosure also relates to a process of preparation of these fused pyrimidine compounds, and to pharmaceutical compositions containing them.

FUSED PYRIMIDINE COMPOUNDS, COMPOSITIONS AND MEDICINAL APPLICATIONS THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of Indian patent application number 201941039277 filed on September 27, 2019, which application is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] Lung cancer accounts for the greatest number of cancer deaths, and approximately 85% of lung cancer cases are non-small cell lung cancer (NSCLC). The development of targeted therapies for lung cancer has primarily focused on tumors displaying specific oncogenic drivers, namely mutations in epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Three generations of tyrosine kinase inhibitors (TKIs) have been developed for cancers with the most frequently observed EGFR mutations, however, other oncogenic drivers in the EGFR family of receptor tyrosine kinases have received less research and development focus and several oncogenic drivers, including insertions in the exon 20 gene of EGFR, have no currently approved therapeutics to treat their cancers.

[0003] The mutation, amplification and/or overexpression of human epidermal growth factor receptor 2 (HER2), another member of the human epidermal growth factor receptor family of receptor tyrosine kinases, has been implicated in the oncogenesis of several cancers, including lung, breast, ovarian, and gastric cancers. Although targeted therapies such as trastuzumab and lapatinib have shown clinical efficacy especially in breast tumors, their utility in lung cancer has been limited. It is likely that this variation is due to tissue-specific factors, including the low potency of kinase inhibitors like lapatinib for the mutagenic alterations in HER2 that are observed in the lung cancer patient population, including insertions in the exon 20 gene of HER2.

[0004] Given that many patients with mutations in EGFR and HER2 do not derive clinical benefit from currently available therapies against these targets, there remains a significant unmet need for the development of novel therapies for the treatment of cancers associated with EGFR and HER2 mutations.

SUMMARY OF THE INVENTION

[0005] In one aspect, provided herein is a compound of Formula I:

Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

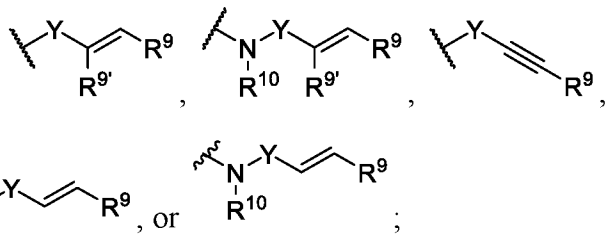
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  ;

Y is $–C(=O)–$, $–S(=O)–$, or $–S(=O)_2–$;

R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, haloalkyl, cycloalkyl, heteroalkyl, or (alkyl)heterocycloalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{11})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

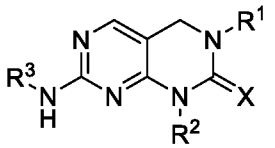
each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $–N(R^{13})_2$, $–S(=O)_2NH_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{15})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0006] In another aspect, provided herein is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

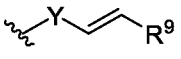
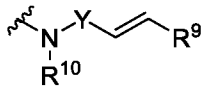
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  or  ;

Y is $–C(=O)–$, $–S(=O)–$, or $–S(=O)_2–$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{11})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $–N(R^{13})_2$, $–S(=O)_2NH_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0007] In some embodiments, n is 0 or 1.

[0008] In some embodiments, R^5 is phenyl, naphthyl, anthracenyl, phenanthrenyl, chrysenyl, pyrenyl, C-linked pyridyl, C-linked pyrimidinyl, C-linked pyrazolyl, or C-linked imidazolyl. In some embodiments, R^5 is unsubstituted. In some embodiments, R^5 is substituted with 1 or 2 $R^{5'}$.

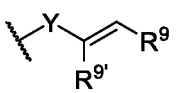
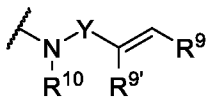
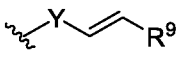
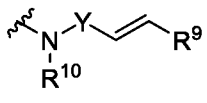
[0009] In some embodiments, each R^4 is independently hydrogen, alkyl, halo, haloalkyl, or alkoxy. In some embodiments, each R^4 is independently hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, trifluoromethyl, trifluoroethyl, pentafluoroethyl, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^4 is independently hydrogen, methyl, fluoro, trifluoromethyl, methoxy, or trifluoromethoxy.

[0010] In some embodiments, each $R^{5'}$ is independently aryl, heteroaryl, alkyl, heterocycloalkyl, halo, cyano, hydroxy, $-N(R^6)_2$, or alkoxy. In some embodiments, each $R^{5'}$ is independently phenyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, methyl, ethyl, *tert*-butyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, fluoro, chloro, cyano, hydroxy, $-N(R^6)_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each $R^{5'}$ is independently phenyl, imidazolyl, pyridinyl, methyl, *tert*-butyl, pyrrolidinyl, morpholinyl, fluoro, cyano, hydroxy, $-N(R^6)_2$, or methoxy.

[0011] In some embodiments, each R^6 is independently alkyl or aryl. In some embodiments, each R^6 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl. In some embodiments, each R^6 is independently methyl or phenyl.

[0012] In some embodiments, X is S. In some embodiments, X is O.

[0013] In some embodiments, R^2 is monocyclic. In some embodiments, R^2 is phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or triazinyl. In some embodiments, R^2 is phenyl, cyclohexyl, or pyrrolyl.

[0014] In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R^7 is  .

[0015] In some embodiments, Y is $-C(=O)-$. In some embodiments, Y is $-S(=O)_2-$.

[0016] In some embodiments, R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, heteroalkyl, haloalkyl, or (alkyl)heterocycloalkyl. In some embodiments, R^9 is hydrogen, halo, or

heteroalkyl. In some embodiments, R^9 and $R^{9'}$ are independently hydrogen, fluoro, chloro, methyl, hydroxyethyl, methoxyethyl, methoxymethyl, dimethylaminomethyl, 1-piperidinylmethyl, 1-morpholinylmethyl, or fluoromethyl. In some embodiments, R^9 is hydrogen, fluoro, chloro, hydroxyethyl, or methoxyethyl.

[0017] In some embodiments, R^{10} is hydrogen, methyl, ethyl *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, trifluoromethyl, or cyclopropyl. In some embodiments, R^{10} is hydrogen or methyl.

[0018] In some embodiments, R^2 is substituted with 1 or 2 R^8.

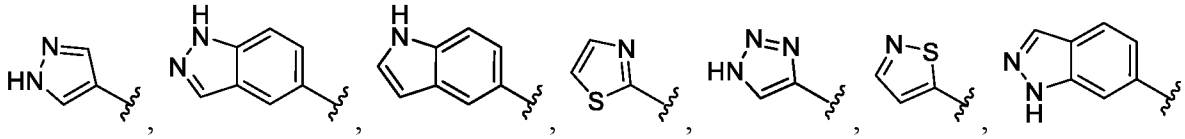
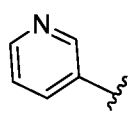
[0019] In some embodiments, each R^8 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, heteroalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^8 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, fluoro, chloro, $-N(R^{11})_2$, hydroxyethyl, methoxyethyl, or cyano.

[0020] In some embodiments, each R^{11} is independently alkyl or aryl. In some embodiments, each R^{11} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl, naphthyl, anthracenyl, or phenanthrenyl. In some embodiments, each R^{11} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl. In some embodiments, each R^{11} is independently methyl or phenyl.

[0021] In some embodiments, R^2 is unsubstituted.

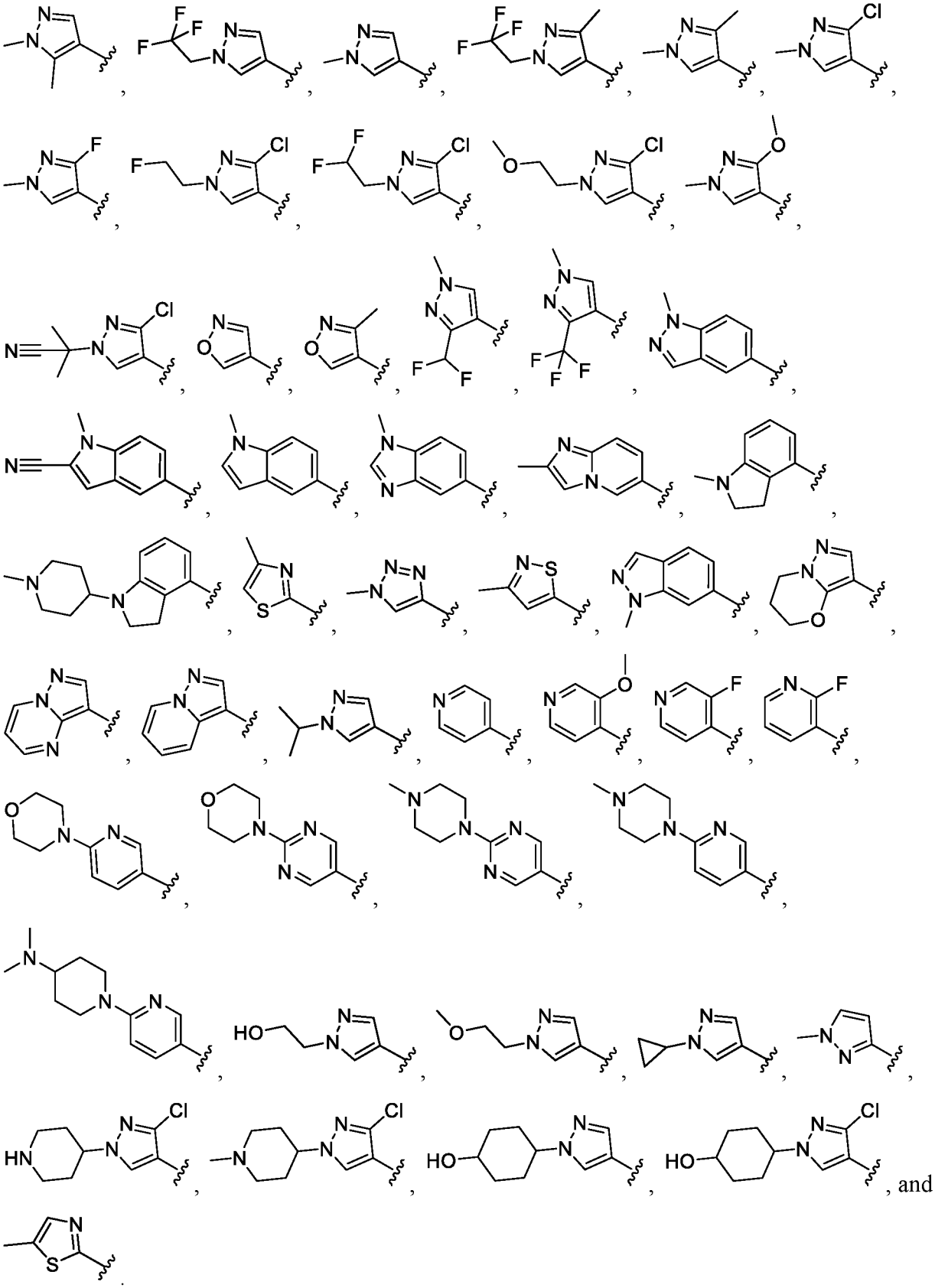
[0022] In some embodiments, R^3 is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, indolyl, indazolyl, benzimidazolyl, azaindolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, or naphthyridinyl. In some embodiments, R^3 is imidazolyl, triazolyl, indolyl, indazolyl, thiazolyl, isothiazolyl, or pyridinyl.

[0023] In some embodiments, R^3 is selected from:

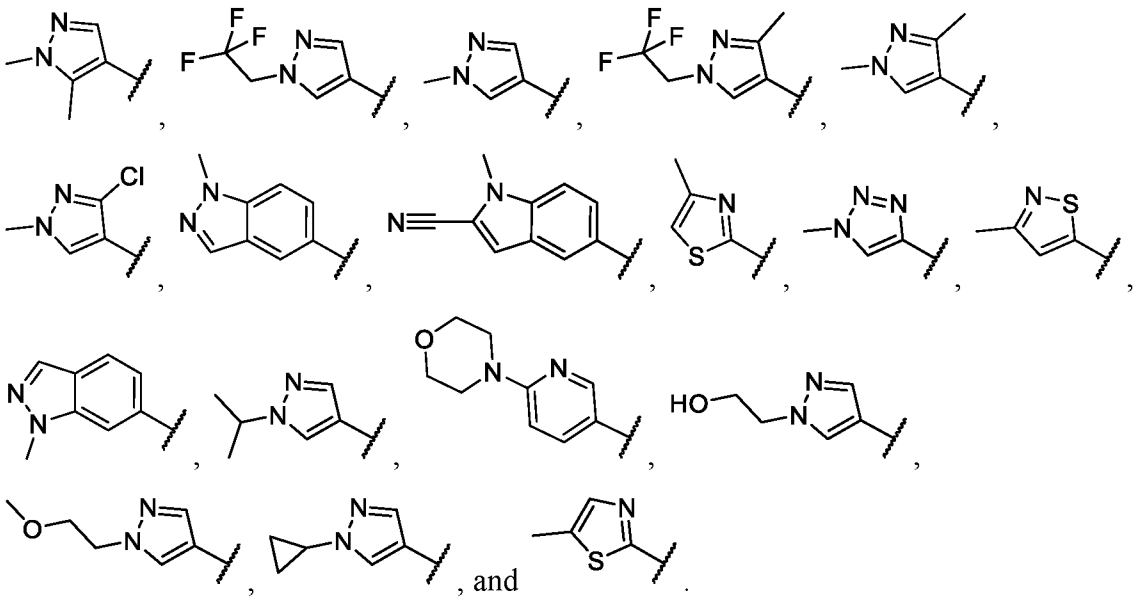



, wherein R^3 is substituted with 0 to 3 R^{12}.

[0024] In some embodiments, R^3 is selected from:



[0025] In some embodiments, R^3 is selected from:



[0026] In some embodiments, R^3 is unsubstituted. In some embodiments, R^3 is substituted with at least 1 R^{12}. In some embodiments, R^3 is substituted with at least 2 R^{12}.

[0027] In some embodiments, each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, or cycloalkyl. In some embodiments, each R^{12} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, fluoro, chloro, cyano, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, $-N(R^{13})_2$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{12} is independently methyl, *iso*-propyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, chloro, cyano, morpholinyl, or cyclopropyl. In some embodiments, each R^{12} is independently methyl, hydroxyethyl, methoxyethyl, trifluoroethyl, or chloro. In some embodiments, each R^{12} is independently methyl or chloro.

[0028] In some embodiments, each R^{13} is independently alkyl or cycloalkyl. In some embodiments, each R^{13} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{13} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{13} is independently methyl, cyclopropyl, or cyclohexyl.

[0029] In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is unsubstituted. In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is substituted with 1 or 2 R^{14}.

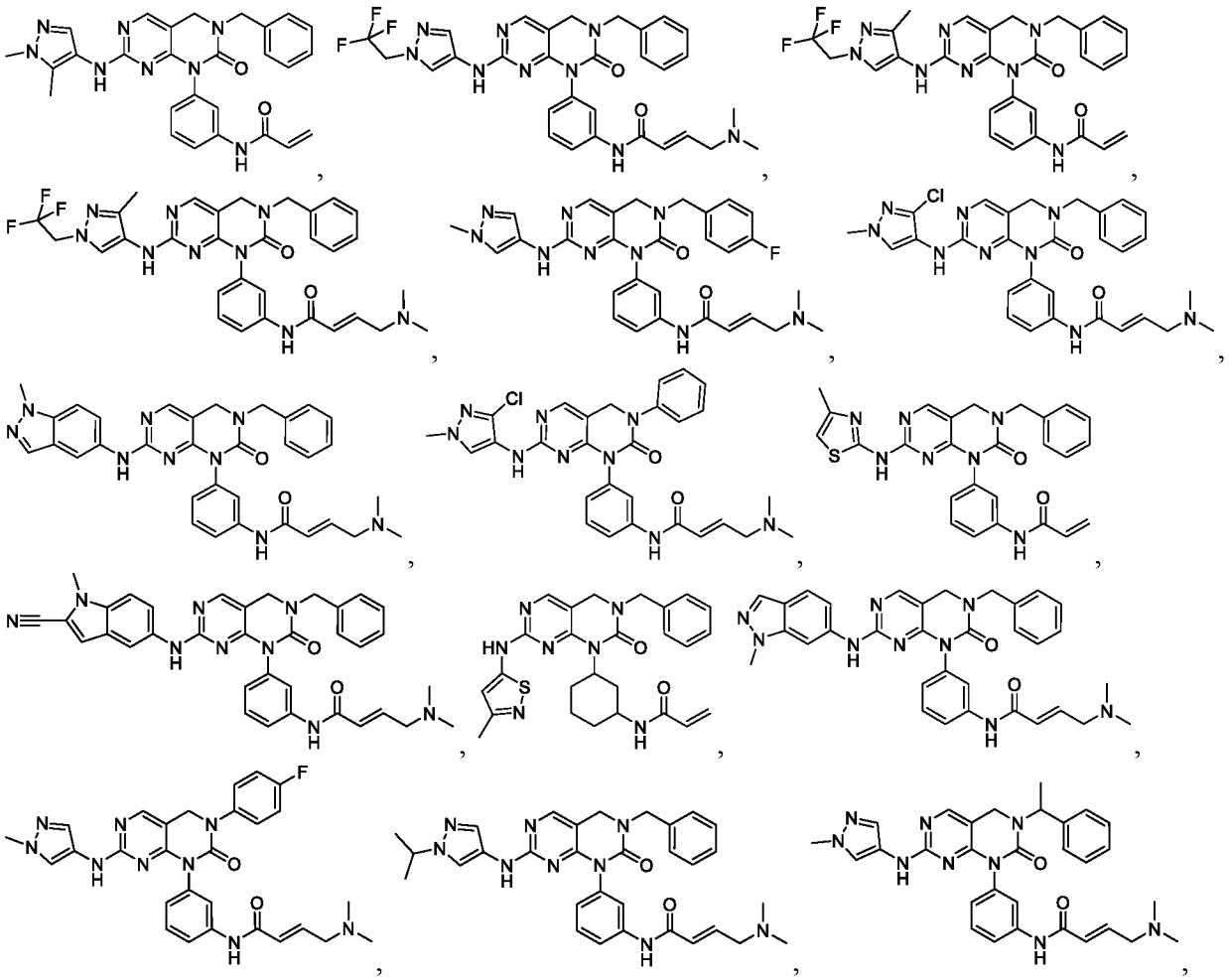
[0030] In some embodiments, each R^{14} is independently alkyl, cycloalkyl, heterocycloalkyl, halo, cyano, $-N(R^{15})_2$, or alkoxy. In some embodiments, each R^{14} is independently methyl,

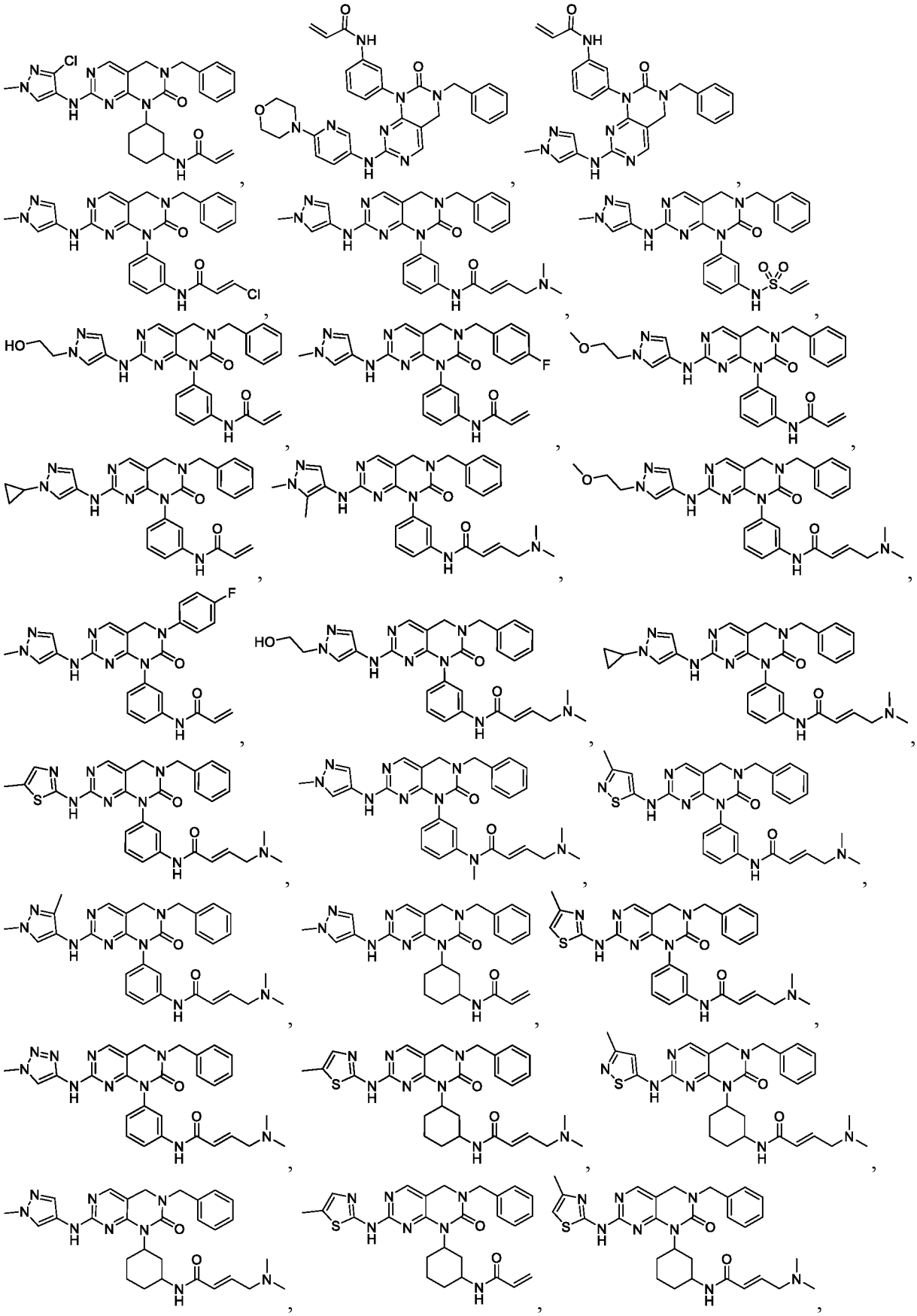
ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, fluoro, chloro, cyano, $-N(R^{15})_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^{14} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, pyrrolidinyl, piperidinyl, morpholinyl, fluoro, chloro, $-N(R^{15})_2$, or methoxy.

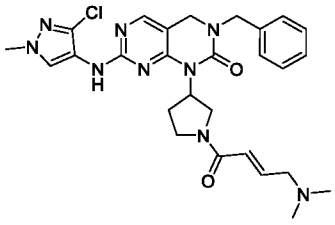
[0031] In some embodiments, each R^{15} is independently alkyl or cycloalkyl. In some embodiments, each R^{15} is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

[0032] In some embodiments, each R^{13} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{13} is independently methyl, cyclopropyl, or cyclohexyl.

[0033] In some embodiments, the compound of Formula I is selected from:



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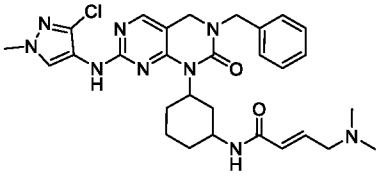
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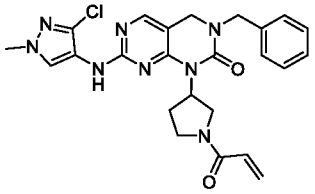
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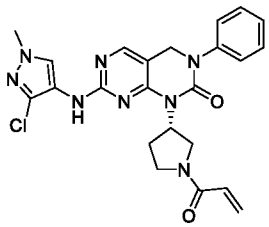
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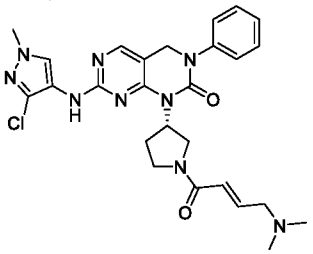
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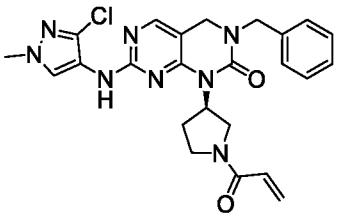
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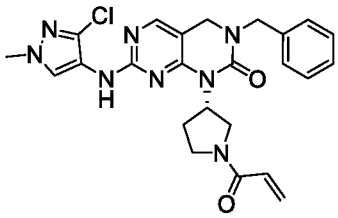
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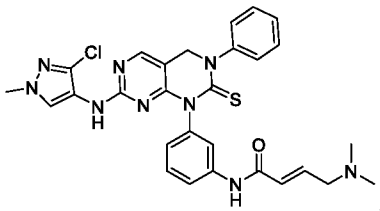
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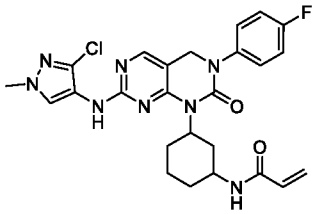
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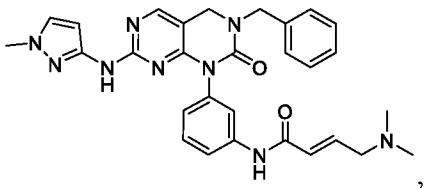
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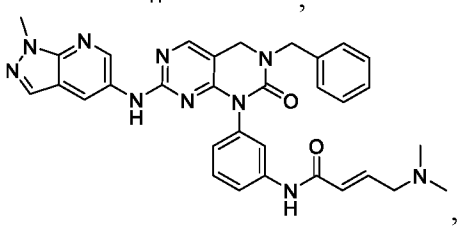
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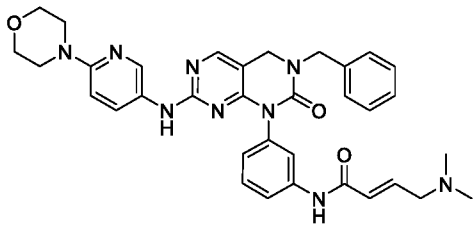
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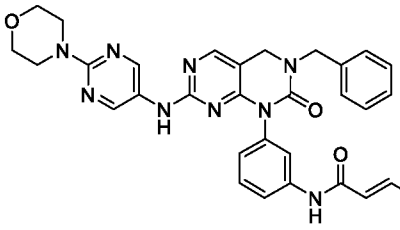
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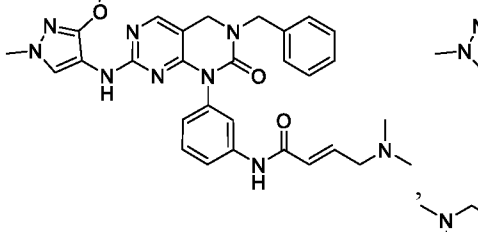
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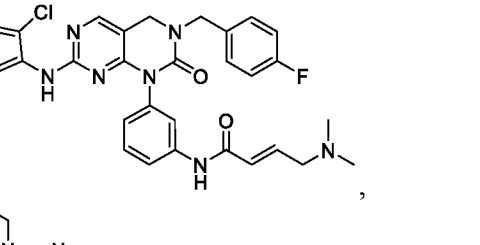
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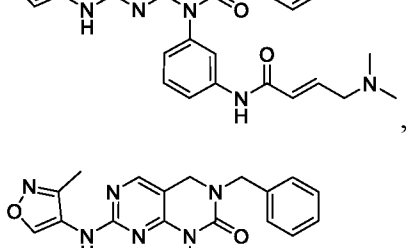
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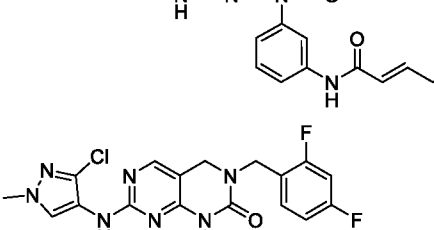
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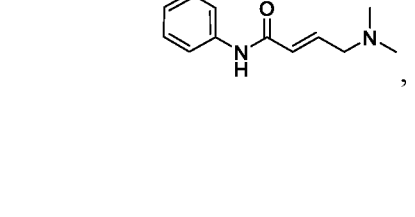
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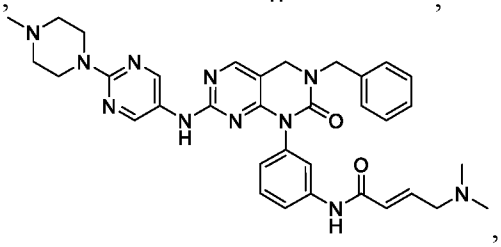
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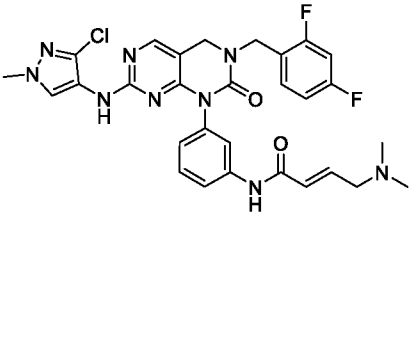
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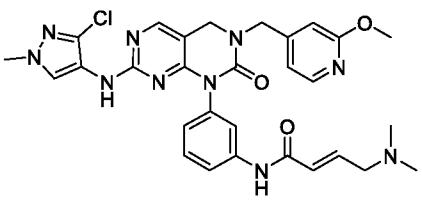
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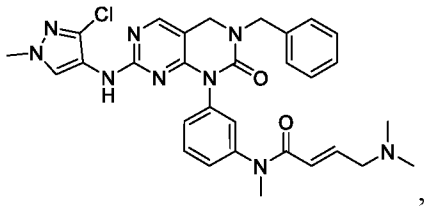
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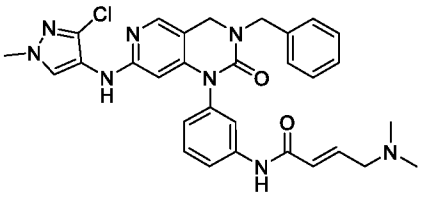
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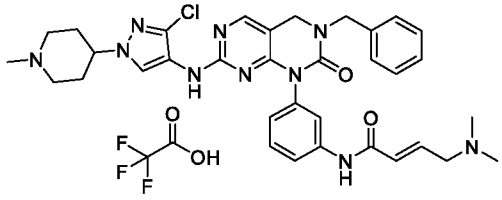
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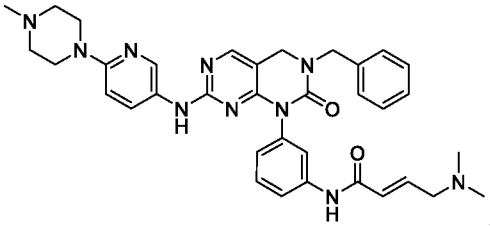
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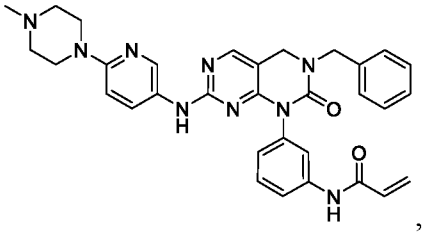
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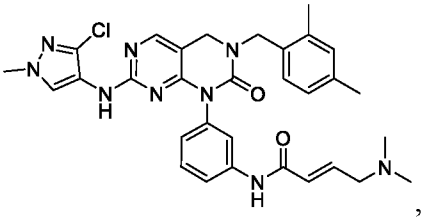
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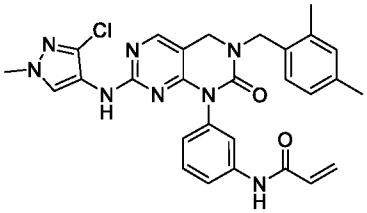
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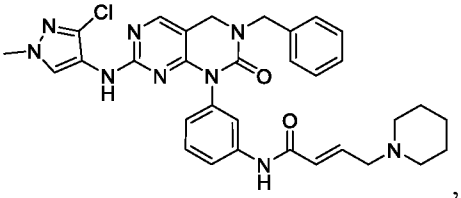
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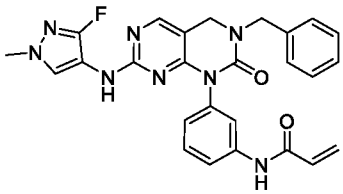
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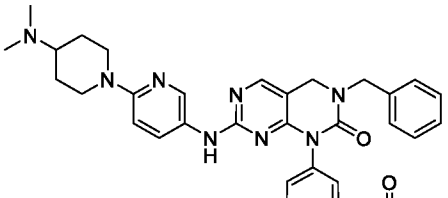
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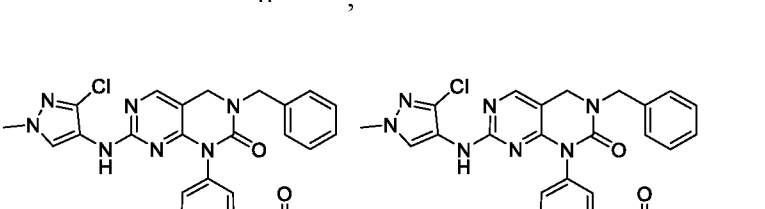
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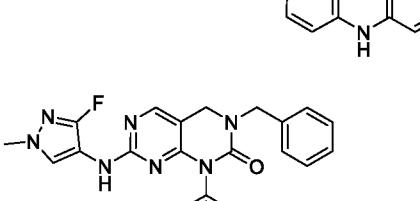
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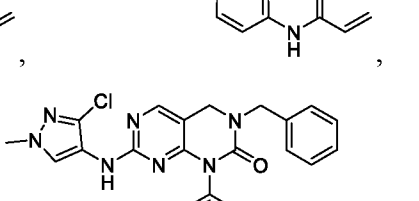
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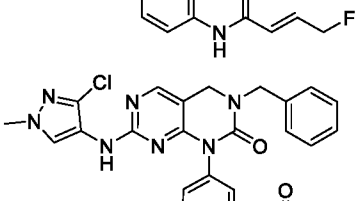
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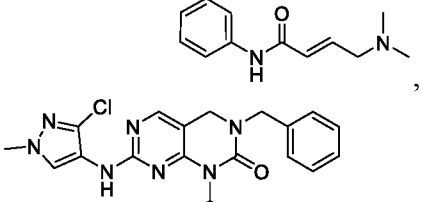
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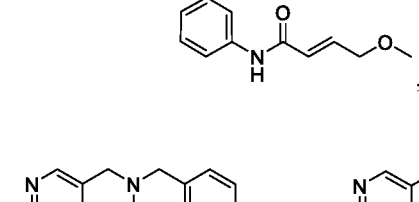
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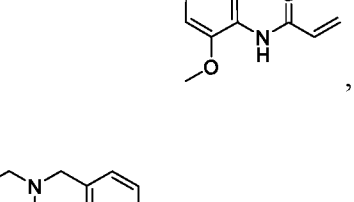
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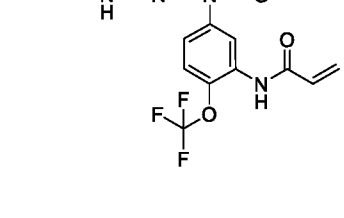
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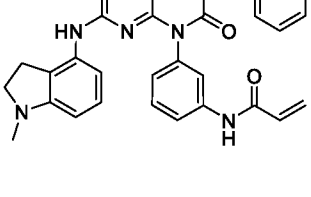
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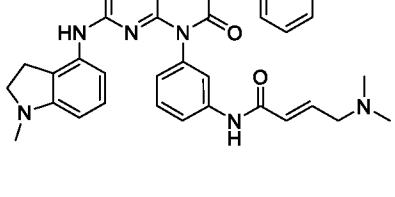
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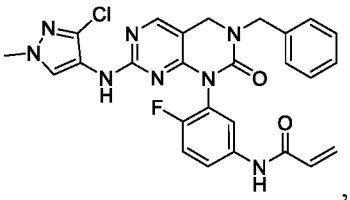
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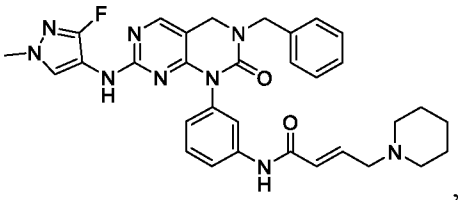
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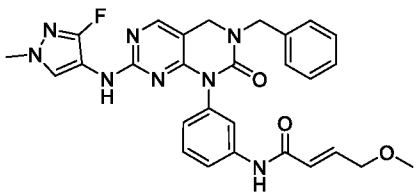
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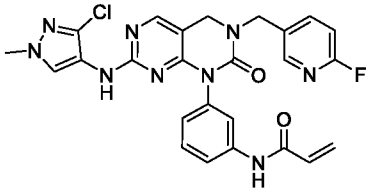
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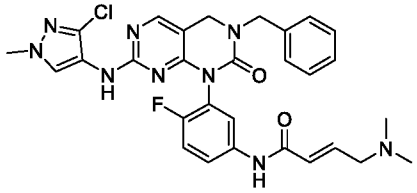
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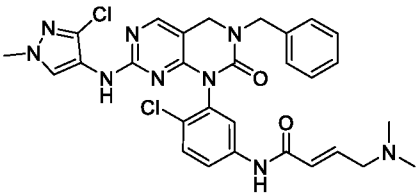
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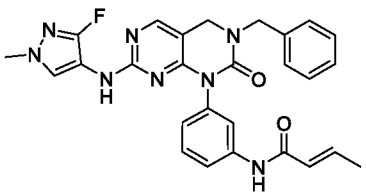
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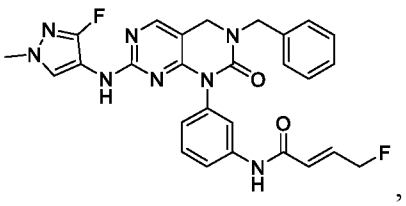
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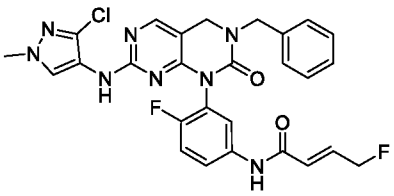
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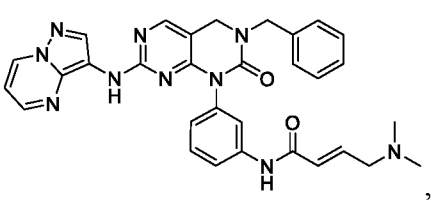
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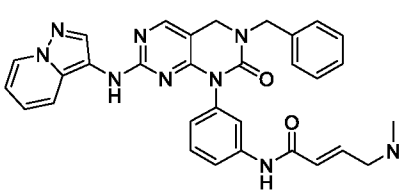
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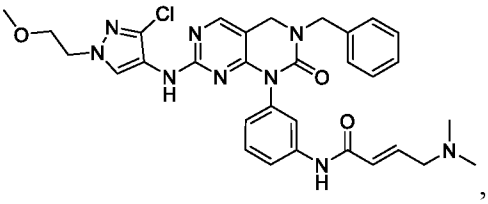
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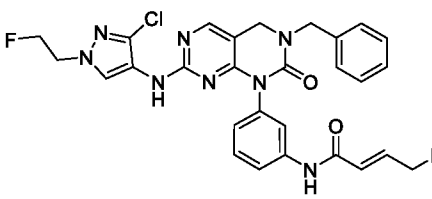
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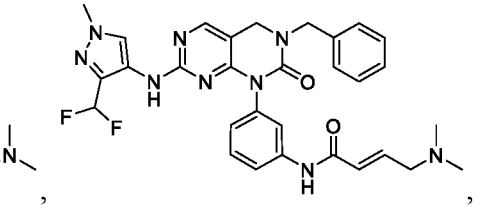
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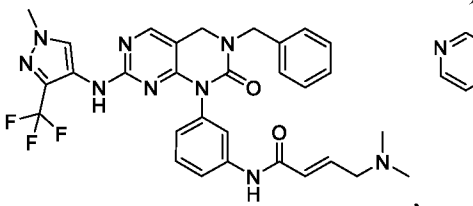
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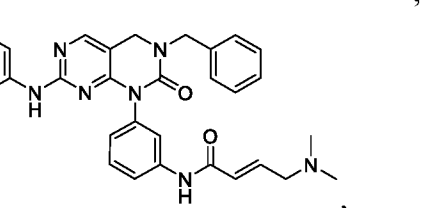
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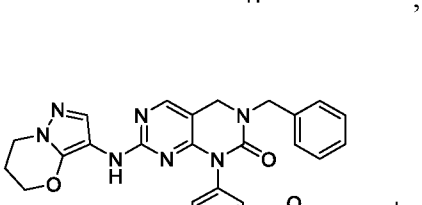
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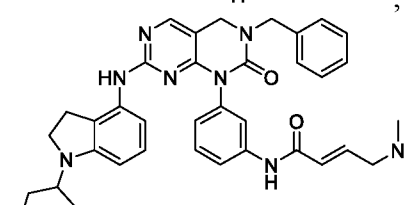
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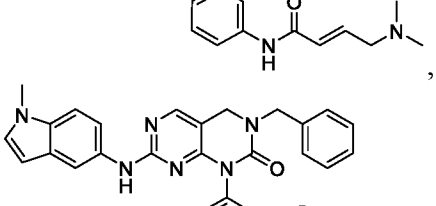
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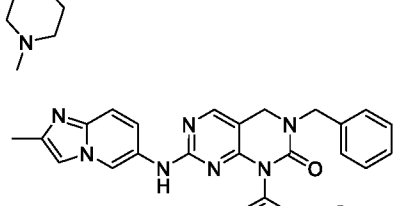
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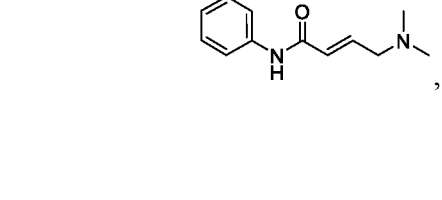
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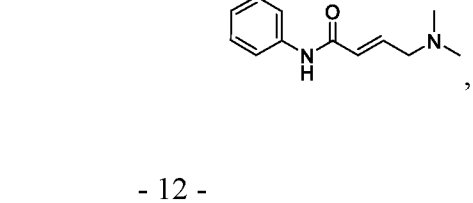
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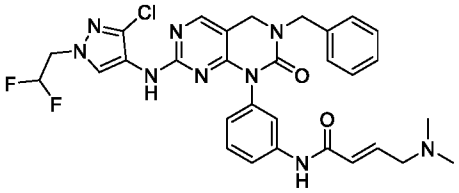
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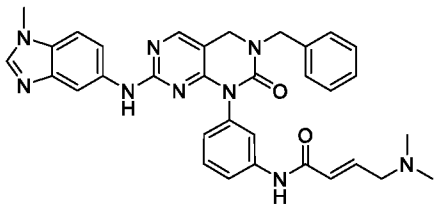
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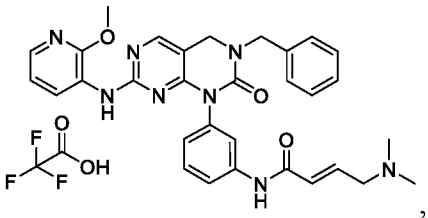
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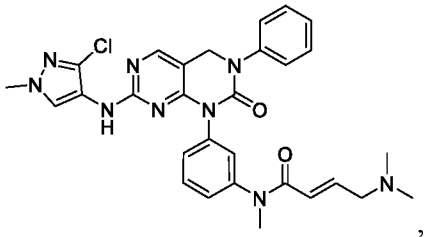
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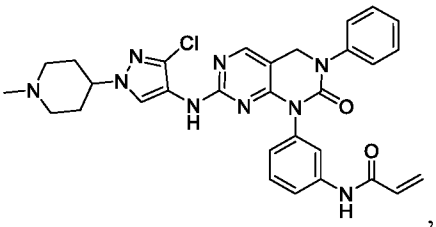
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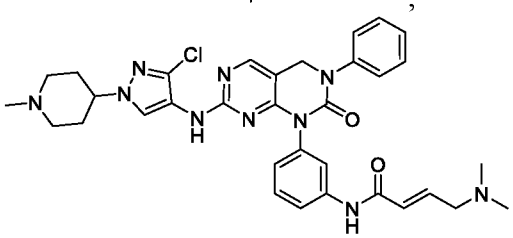
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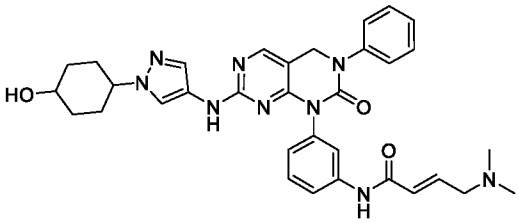
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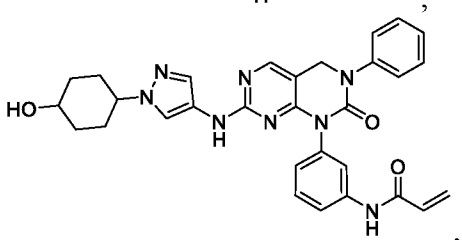
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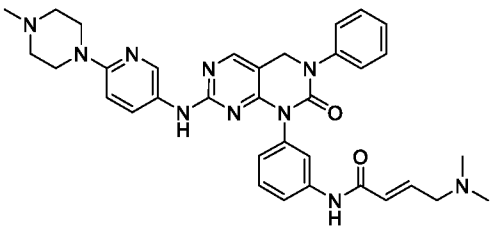
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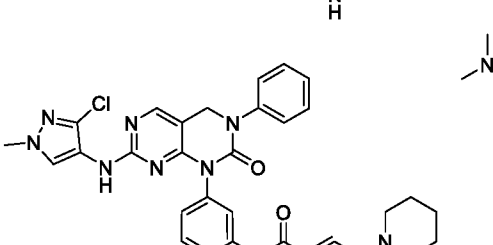
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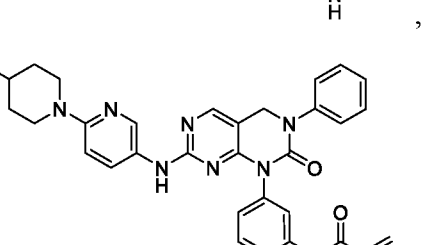
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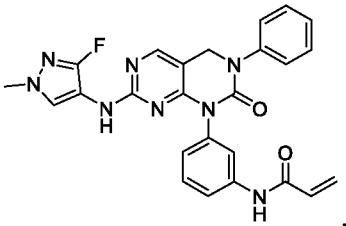
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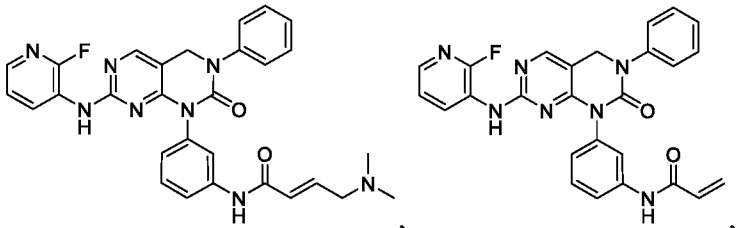

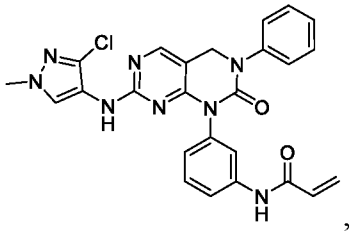
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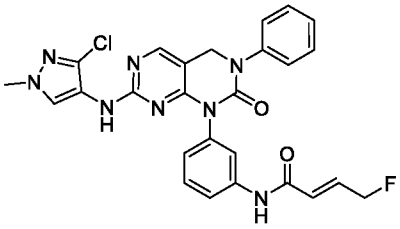
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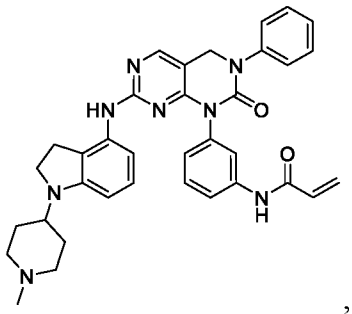
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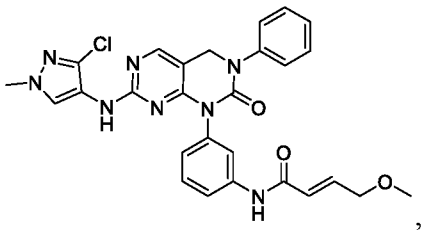
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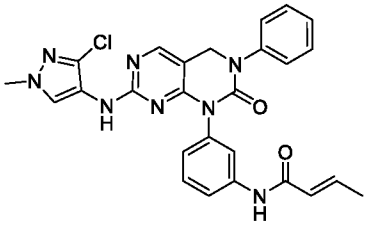
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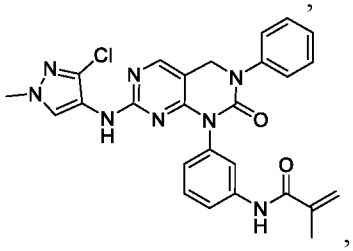
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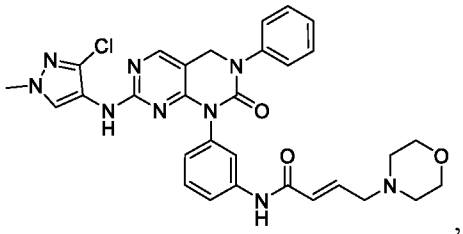
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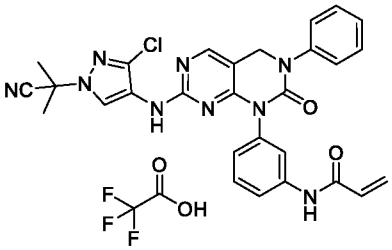
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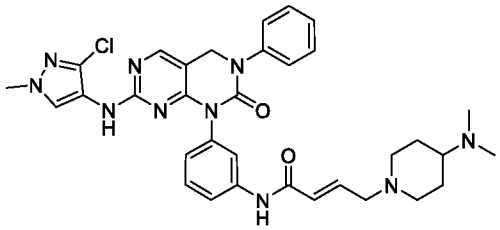
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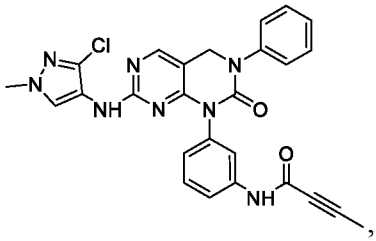
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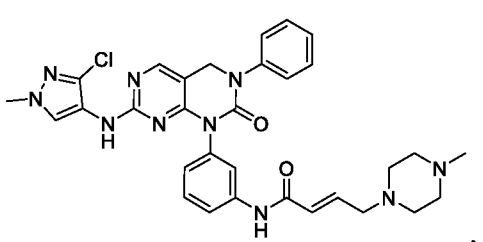
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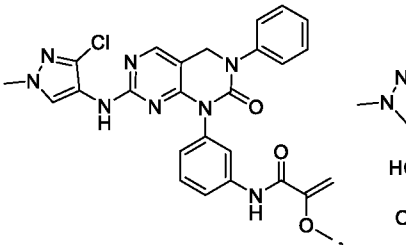
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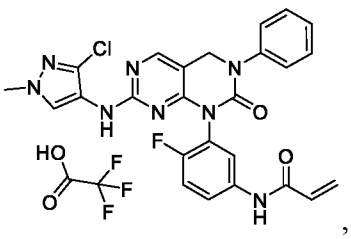
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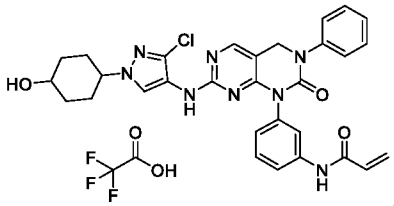
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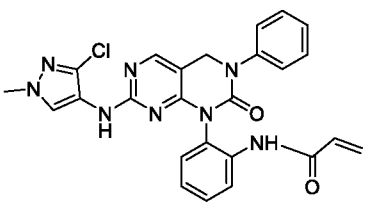
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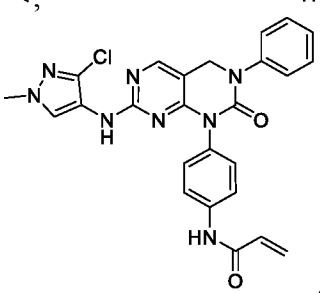
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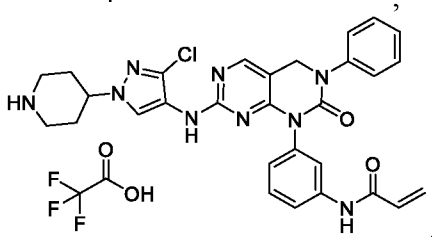
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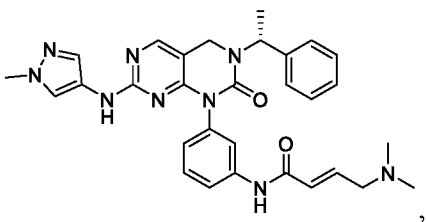
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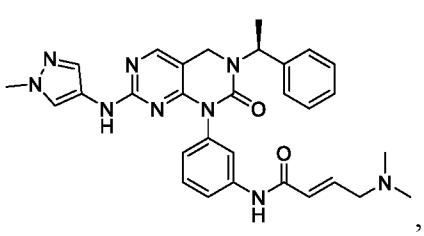

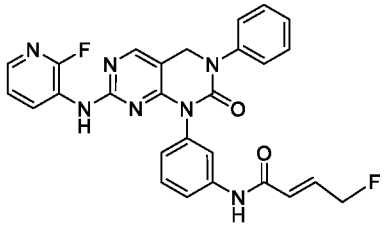

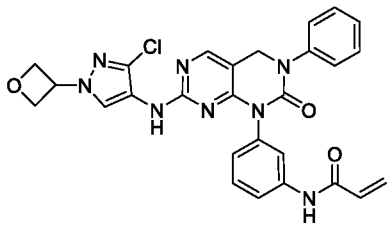

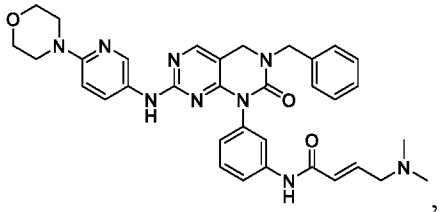

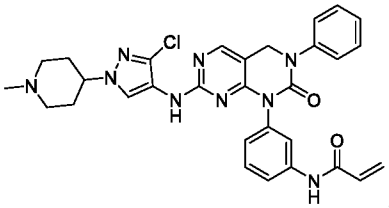

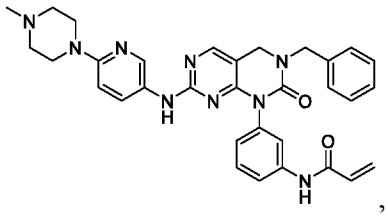

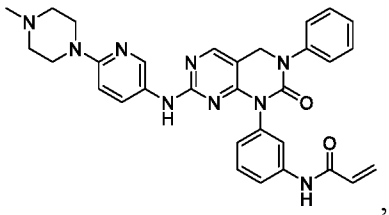

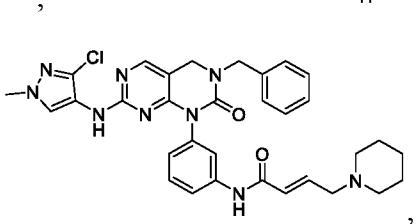

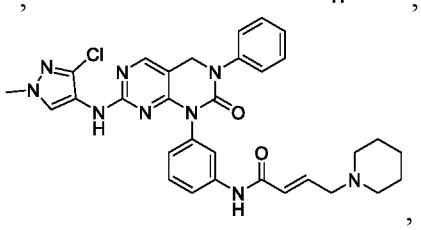

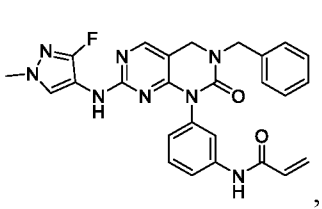

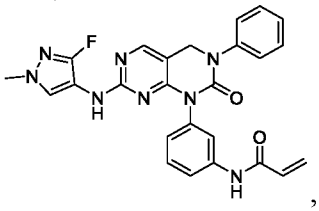

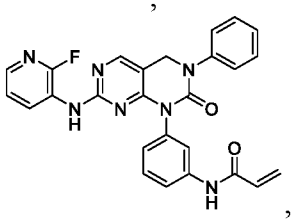

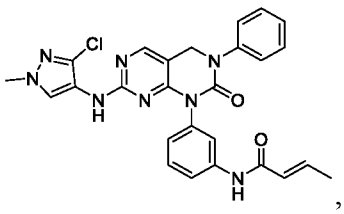

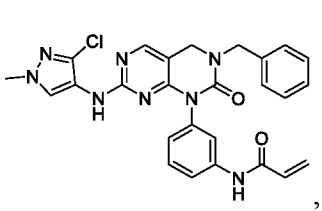

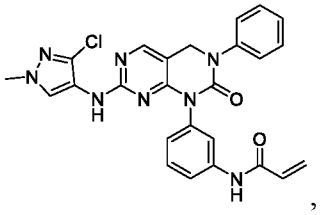

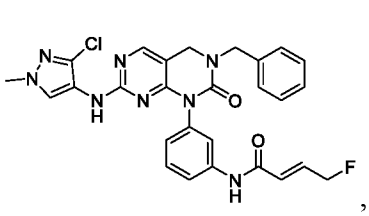

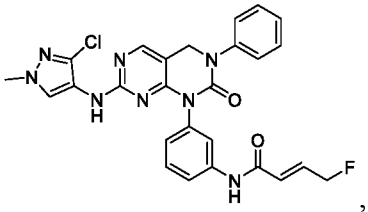

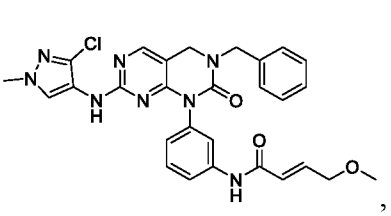

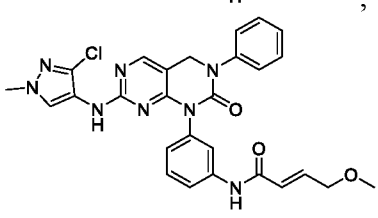

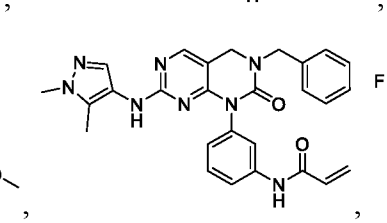

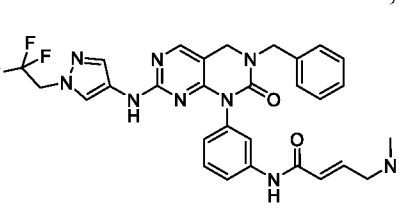

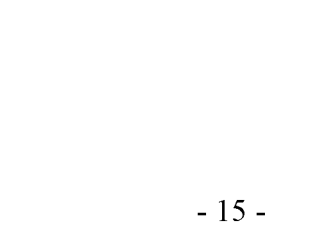

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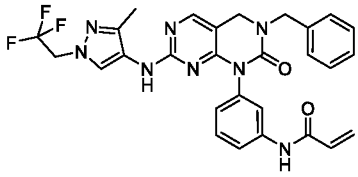
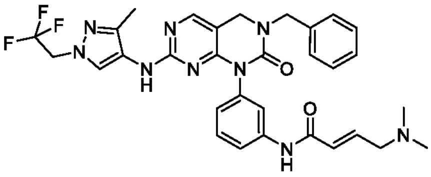
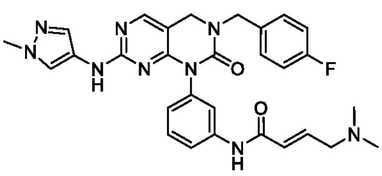
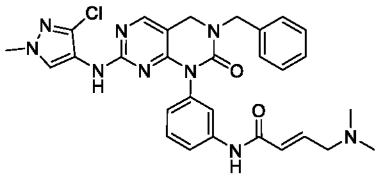
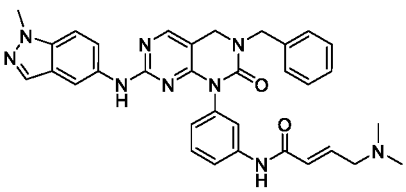
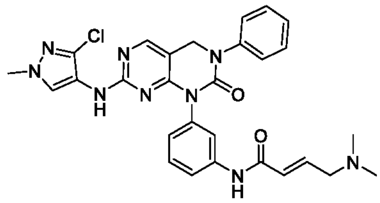
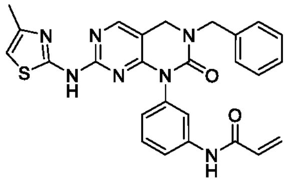
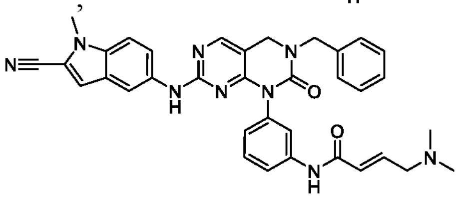
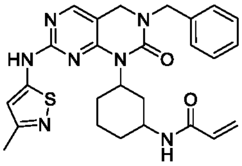
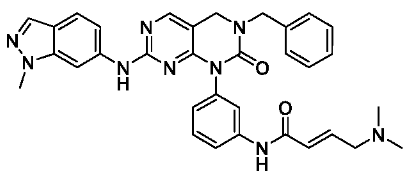
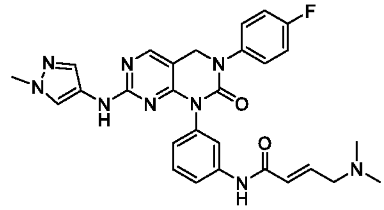
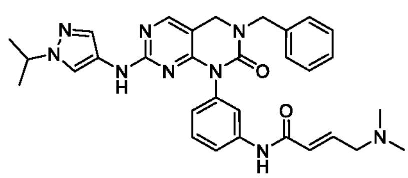
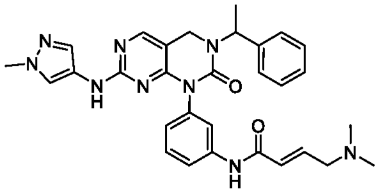
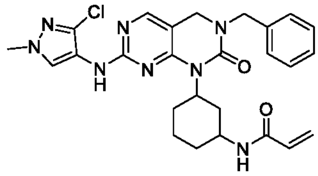
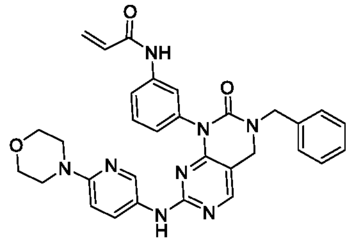
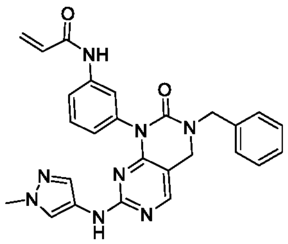
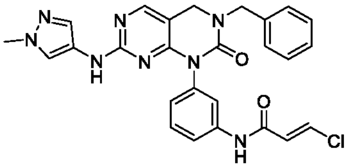
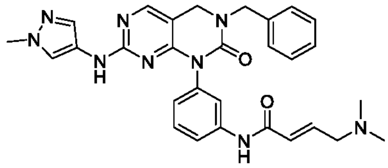
 ,
 ,
 ,

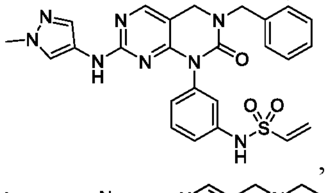
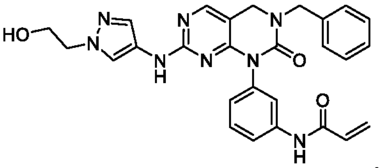
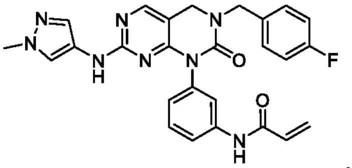
 ,
 ,
 ,

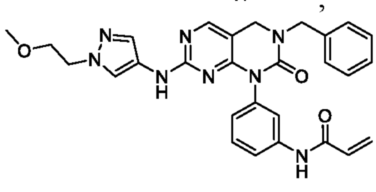
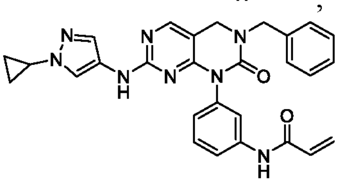
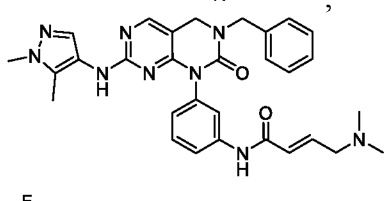
 ,
 ,
 ,

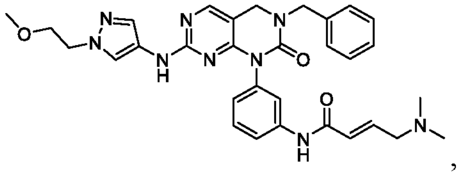
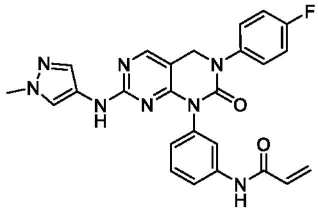
 ,
 ,
 ,

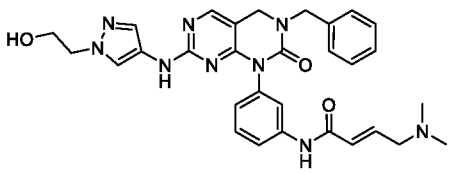
 ,
 ,
 ,

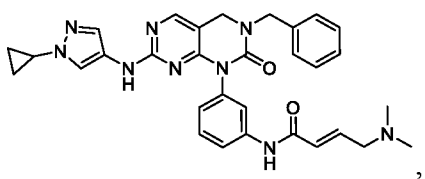
 ,
 ,
 ,

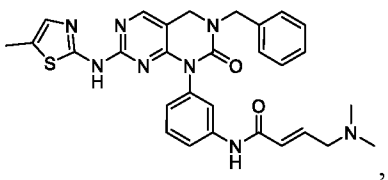
 ,
 ,
 ,

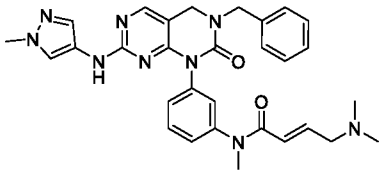
 ,
 ,
 ,

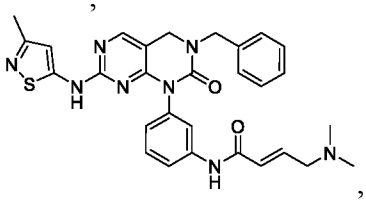
 ,
 ,

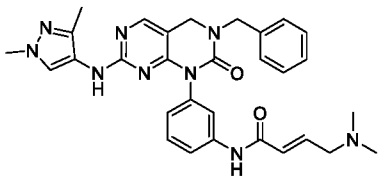


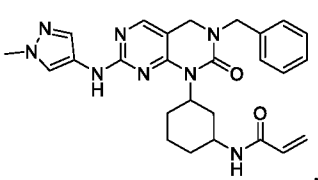


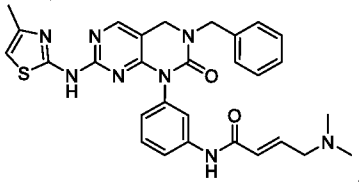


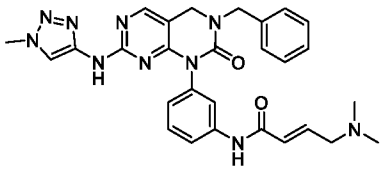


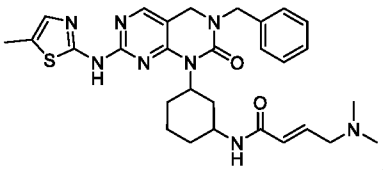


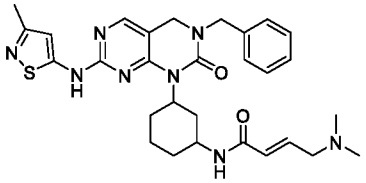


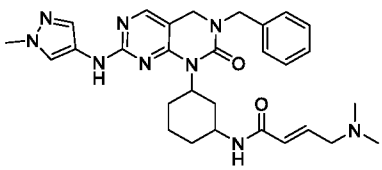


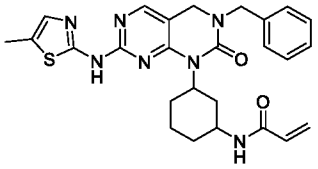


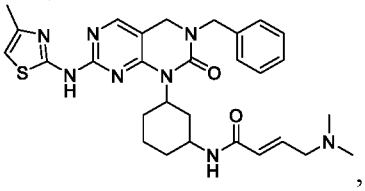


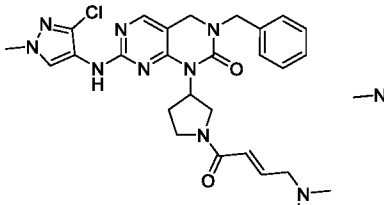


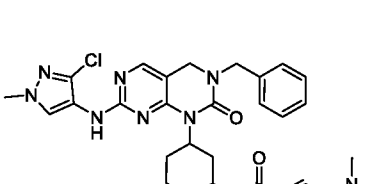


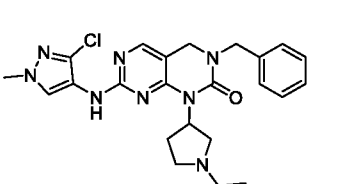


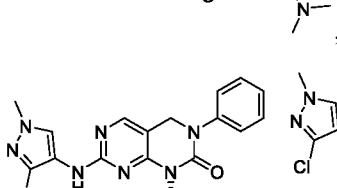


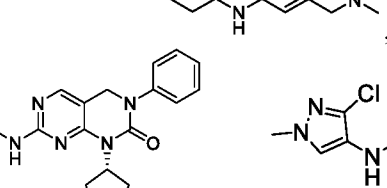


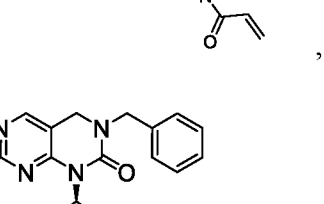


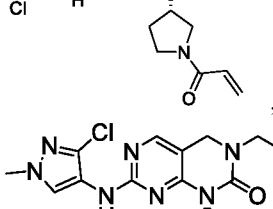


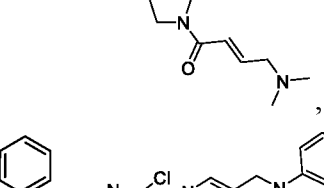


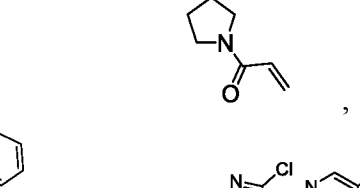


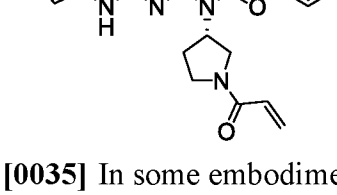


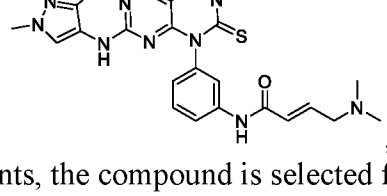


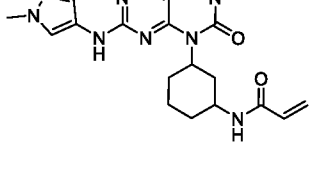












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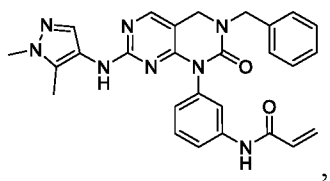
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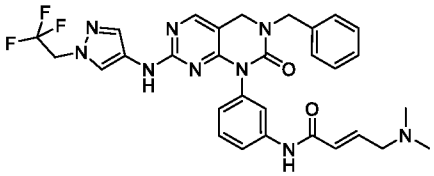
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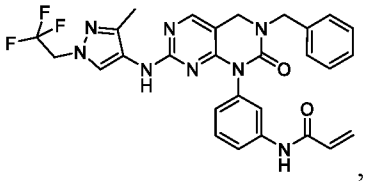
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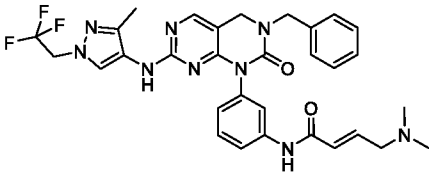
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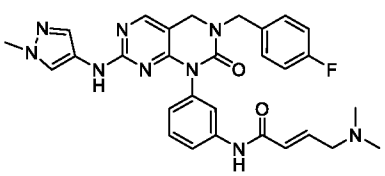
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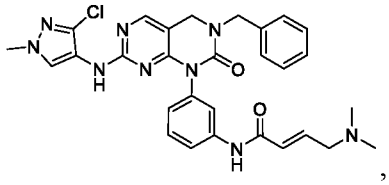
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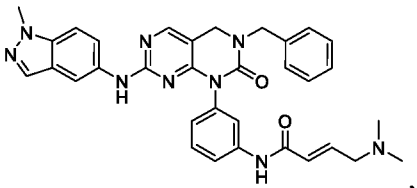
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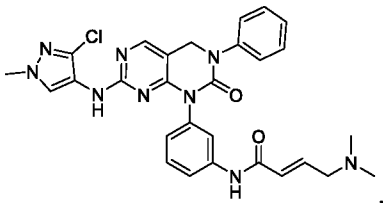
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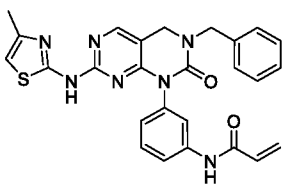
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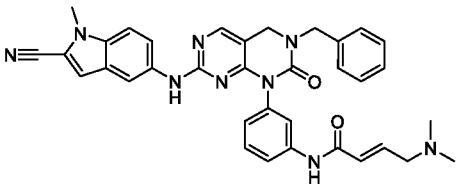
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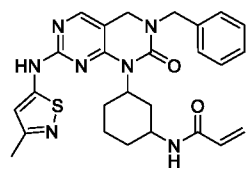
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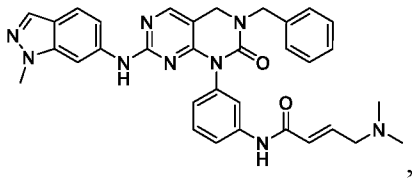
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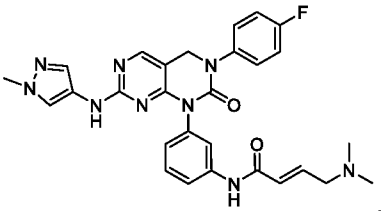
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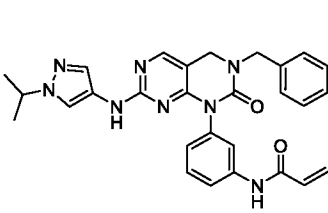
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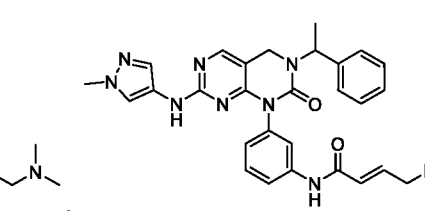
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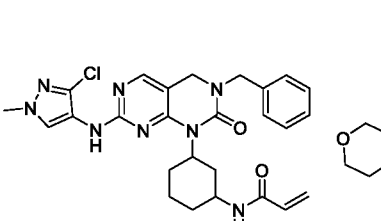
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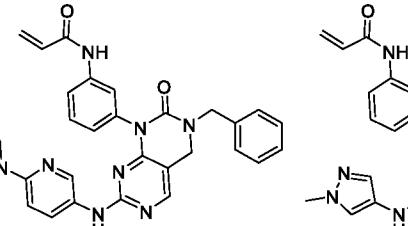
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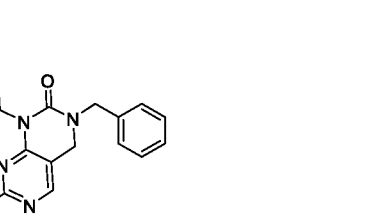
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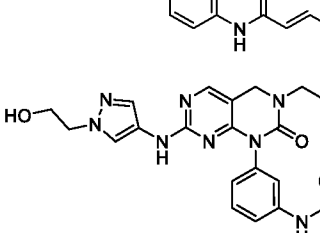
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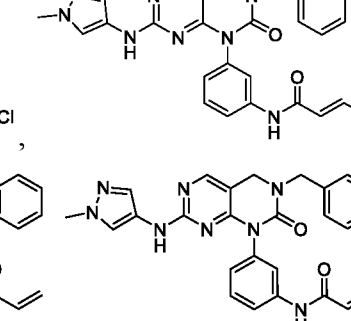
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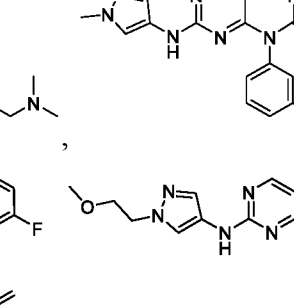
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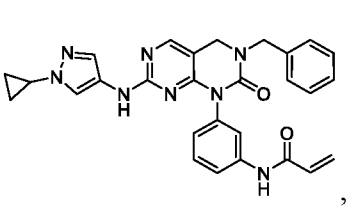
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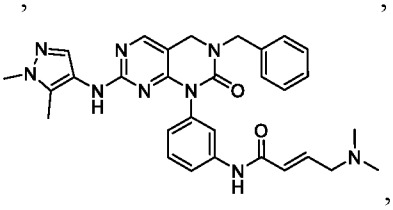
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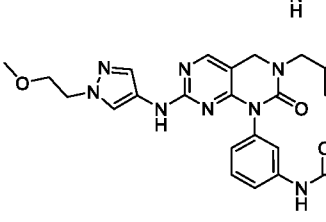
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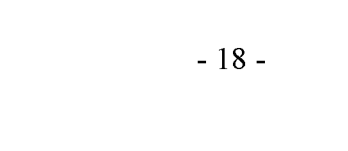
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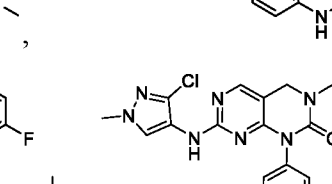
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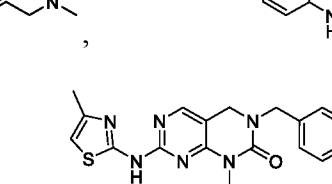
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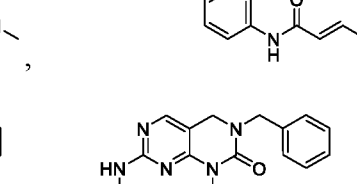
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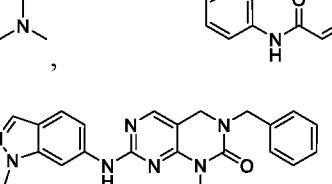
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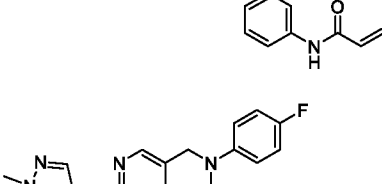
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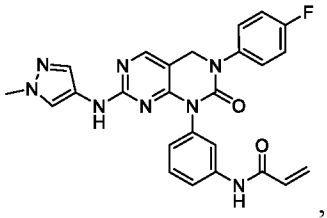

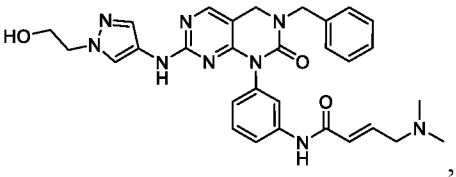

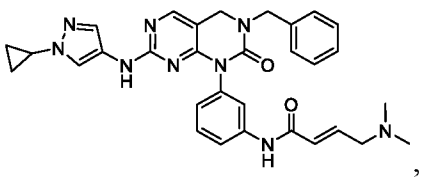

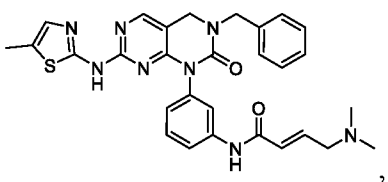

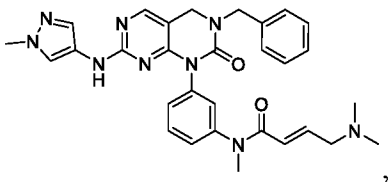

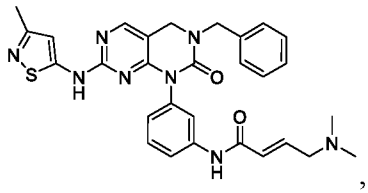

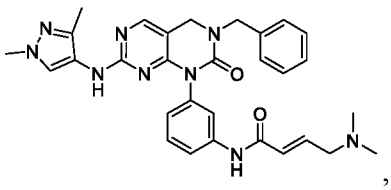

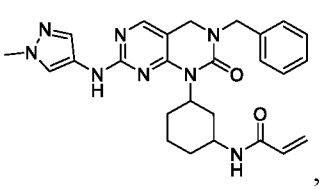

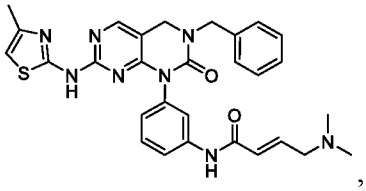

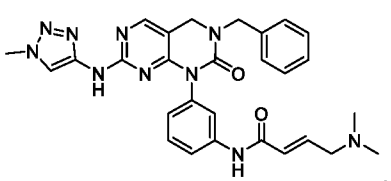

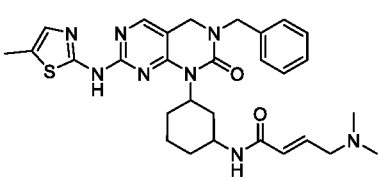

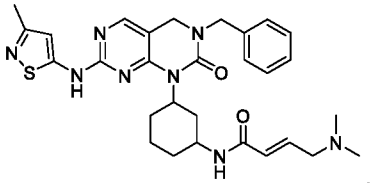

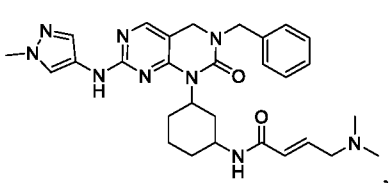

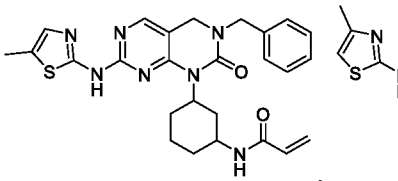

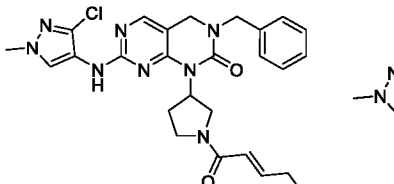

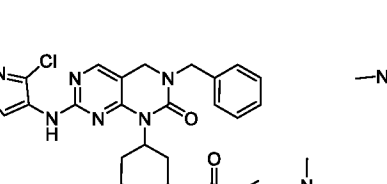

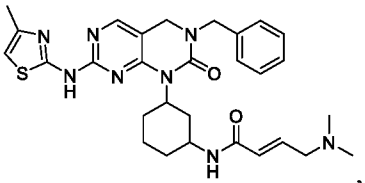

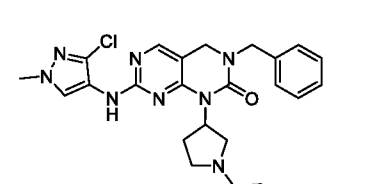

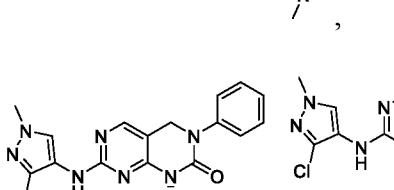

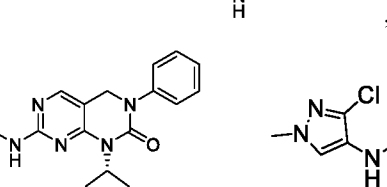

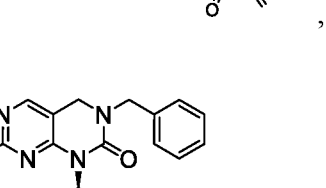

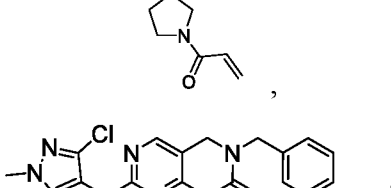

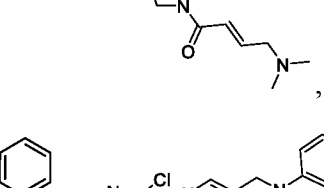

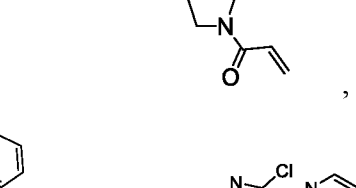

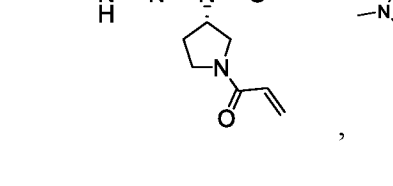

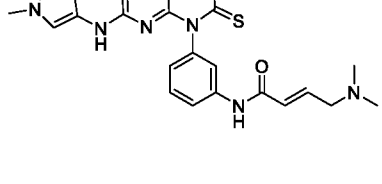

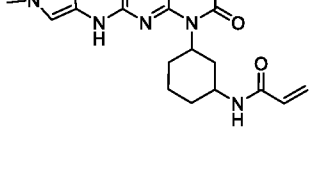

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[0036] In another aspect, provided herein is a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0037] In another aspect, provided herein is a method of inhibiting an epidermal growth factor receptor (EGFR) family kinase mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0038] In another aspect, provided herein is a method of inhibiting a human epidermal growth factor receptor 2 (HER2) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

[0039] In another aspect, provided herein is a method of inhibiting an epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0040] In another aspect, provided herein is a method of inhibiting a drug-resistant epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the drug-resistant EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR.

[0041] In another aspect, provided herein is a method of inhibiting human epidermal growth factor receptor 2 (HER2) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of a HER2 mutant relative to wild-type EGFR. In some embodiments, the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

[0042] In another aspect, provided herein is a method of inhibiting epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of an EGFR mutant relative to wild-type EGFR.

[0043] In some embodiments, the EGFR mutant comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutant is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR.

[0044] In another aspect, provided herein is a method of treating a disease or disorder associated with an epidermal growth factor receptor (EGFR) family kinase in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0045] In some embodiments, the disease or disorder in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

[0046] In some embodiments, the disease or disorder in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR,

or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

[0047] In another aspect, provided herein is a method of treating one or more cancer cells in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0048] In another aspect, provided herein is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0049] In some embodiments, the cancer is selected from bladder cancer, prostate cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, and non-small cell lung cancer. In some embodiments, the cancer is selected from non-small cell lung cancer, prostate cancer, head and neck cancer, breast cancer, colorectal cancer, and glioblastoma.

[0050] In some embodiments, the cancer in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

[0051] In some embodiments, the cancer in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

[0052] In another aspect, the present disclosure provides a method of treating an inflammatory disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0053] In some embodiments, the inflammatory disease is selected from psoriasis, eczema, and atherosclerosis.

[0054] In some embodiments, the inflammatory disease in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

[0055] In some embodiments, the inflammatory disease in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

[0056] The present disclosure discloses a process of preparation of compounds of Formula I, or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, and to pharmaceutical compositions containing them.

[0057] The compounds of the present invention are useful in the treatment, prevention or suppression of diseases and disorders mediated by epidermal growth factor receptor (EGFR).

[0058] These and other features, aspects, and advantages of the present disclosure will become better understood with reference to the following description. This statement is provided to introduce a selection of concepts in simplified form. This statement is not intended to identify key features or essential features of the subject matter, nor is it intended to be used to limit the scope of the subject matter.

INCORPORATION BY REFERENCE

[0059] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0060] In the structural formulae given herein and throughout the present disclosure, the following terms have the indicated meaning, unless specifically stated otherwise.

[0061] The term "optionally substituted" as used herein means that the group in question is either unsubstituted or substituted with one or more of the substituents specified. In some embodiments, when the group in question is substituted with more than one substituent, the substituent is the same. In some embodiments, when the group in question is substituted with more than one substituent, the substituent is different.

[0062] The term "alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having 1, 2, 3, 4, 5, or 6 carbon atoms. This term is exemplified by groups such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, t-butyl, n-hexyl, and the like.

[0063] The term "cycloalkyl" refers to unless otherwise mentioned, carbocyclic groups of from 3 to 6 carbon atoms having a single cyclic ring or multiple condensed rings or spirocyclic rings or bridged rings. This definition encompasses rings that are saturated or partially unsaturated. Such cycloalkyl groups include, by way of example, single ring structures such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, and the like.

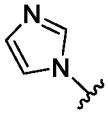
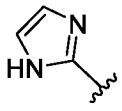
[0064] "Halo" or "Halogen", alone or in combination with any other term means halogens such as chloro (Cl), fluoro (F), bromo (Br) and iodo (I).

[0065] The term "aryl" refers to a radical derived from a hydrocarbon ring system comprising hydrogen, 6 to 30 carbon atoms and at least one aromatic ring. This definition encompasses monocyclic, bicyclic, tricyclic or tetracyclic ring system, as well as fused or bridged ring systems. Aryl radicals include, but are not limited to, aryl radicals derived from the hydrocarbon ring systems of aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals that are optionally substituted.

[0066] The term "phenyl" refers to an aromatic carbocyclic group of 6 carbon atoms having a single ring.

[0067] The term "phenyl alkyl" refers to a monoradical branched or unbranched saturated hydrocarbon chain having 1, 2, 3, 4, 5, or 6 carbon atoms substituted with an aromatic carbocyclic group of 6 carbon atoms having a single ring.

[0068] The term "heteroaryl" refers to an aromatic cyclic group having 5, or 6 carbon atoms and 1, 2, or 3 heteroatoms selected from oxygen, nitrogen and sulfur within at least one ring. An "X-

linked heteroaryl" refers to a heteroaryl connected to the rest of the molecule via an X atom. For example,  is an N-linked imidazolyl, while  is a C-linked imidazolyl.

[0069] The term "heterocycloalkyl" refers to a saturated, partially unsaturated, or unsaturated group having a single ring or multiple condensed rings or spirocyclic rings, or bridged rings unless otherwise mentioned, having from 2 to 10 carbon atoms and from 1 to 3 hetero atoms, selected from nitrogen, sulfur, phosphorus, and/or oxygen within the ring.

[0070] The term "alkenyl" refers to unsaturated aliphatic groups having at least one double bond.

[0071] The term "alkynyl" refers to unsaturated aliphatic groups having at least one triple bond.

[0072] The term "amino" refers to the $–NH_2$ radical.

[0073] The term "cyano" refers to the –CN radical.

[0074] The term "hydroxy" or "hydroxyl" refers to the –OH radical.

[0075] The term "heteroalkyl" refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with an O, N or S atom. Unless stated otherwise specifically in the specification, the heteroalkyl group is optionally substituted as described below. Representative heteroalkyl groups include, but are not limited to $-OCH_2CH_2OMe$, $–OCH_2CH_2OCH_2CH_2NH_2$, and $–OCH_2CH_2OCH_2CH_2OCH_2CH_2N(Me)_2$.

[0076] The term "haloalkyl" refers to an alkyl radical as described above where one or more carbon atoms of the alkyl is replaced with a halogen atom. In some embodiments, the haloalkyl group is optionally substituted as described below. Representative haloalkyl groups include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, difluoroethyl, and trifluoroethyl.

[0077] The term "aminoalkyl" refers to an alkyl group substituted with an amino (NH2) group.

[0078] The term "alkoxy" refers to the group R–O–, where R is optionally substituted alkyl or optionally substituted cycloalkyl, or optionally substituted alkenyl or optionally substituted alkynyl; or optionally substituted cycloalkenyl, where alkyl, alkenyl, alkynyl, cycloalkyl and cycloalkenyl are as defined herein. Representative examples of alkoxy groups include but are not limited to methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, tert-butoxy, sec-butoxy, n-pentoxy, n-hexoxy, 1,2-dimethylbutoxy, trifluoromethoxy, and the like.

[0079] In some embodiments, the compounds of the present disclosure have the ability to crystallize in more than one form, a characteristic known as polymorphism, and all such polymorphic forms ("polymorphs") are encompassed within the scope of the disclosure. Polymorphism generally can occur as a response to changes in temperature or pressure or both,

and can also result from variations in the crystallization process. Polymorphs can be distinguished by various physical characteristics, and typically the X-ray diffraction patterns, solubility behavior, and melting point of the compound are used to distinguish polymorphs.

[0080] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, sulfur, fluorine chlorine, iodine, phosphorus, such as, for example, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{35}S, ^{18}F, ^{36}Cl, ^{123}I, ^{124}I, ^{125}I, ^{131}I, ^{32}P and ^{33}P. In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example, increased in vivo half-life or reduced dosage requirements. In some embodiments, the compounds described herein can exist as isotopic variants. In some embodiments, an isotopic variant of a compound described herein has one or more hydrogen atoms replaced by deuterium.

[0081] In some embodiments, the compounds described herein contain one or more chiral centers and/or double bonds and therefore, exist as stereoisomers, such as double-bond isomers (i.e., geometric isomers), regioisomers, enantiomers or diastereomers. Accordingly, the chemical structures depicted herein encompass all possible enantiomers and stereoisomers of the illustrated or identified compounds including the stereoisomerically pure form (e.g., geometrically pure, enantiomerically pure or diastereomerically pure) and enantiomeric and stereoisomeric mixtures. Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers using separation techniques or chiral synthesis techniques well known to the person skilled in the art. In some embodiments, the compounds also exist in several tautomeric forms including the enol form, the keto form and mixtures thereof. Accordingly, the chemical structures depicted herein encompass all possible tautomeric forms of the illustrated or identified compounds.

[0082] In some embodiments, compounds exist in unsolvated forms as well as solvated forms, including hydrated forms and as N-oxides. In some embodiments, compounds are hydrated, solvated or N-oxides. In some embodiments, certain compounds exist in multiple crystalline or amorphous forms. Also contemplated within the scope of the disclosure are congeners, analogs, hydrolysis products, metabolites and precursor or prodrugs of the compound. In general, unless

otherwise indicated, all physical forms are equivalent for the uses contemplated herein and are intended to be within the scope of the present disclosure.

[0083] "Pharmaceutically acceptable salt" embraces salts with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids, for example hydrochloric, sulfuric, phosphoric, diphosphoric, hydrobromic, hydroiodic and nitric acid and organic acids, for example citric, fumaric, maleic, malic, mandelic, ascorbic, oxalic, succinic, tartaric, benzoic, acetic, methanesulfonic, ethanesulfonic, benzenesulfonic or *p*-toluenesulfonic acid. Pharmaceutically acceptable bases include alkali metal (e.g. sodium or potassium) and alkali earth metal (e.g. calcium or magnesium) hydroxides and organic bases, for example alkyl amines, arylalkyl amines and heterocyclic amines.

[0084] "Pharmaceutical composition" refers to one or more active ingredients, and one or more inert ingredients that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present disclosure encompass any composition comprising a compound of the present disclosure and a pharmaceutically acceptable carrier.

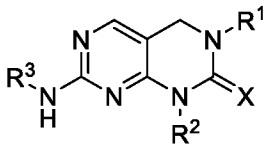
[0085] "Carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of

the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0086] "Combined" or "in combination" or "combination" should be understood as a functional coadministration, encompassing scenarios wherein compounds are administered separately, in different formulations, different modes of administration (for example subcutaneous, intravenous or oral) and different times of administration. In some embodiments, the individual compounds of such combinations are administered sequentially in separate pharmaceutical compositions. In some embodiments, the individual compounds of such combinations are administered simultaneously in combined pharmaceutical compositions.

Compounds

[0087] In one aspect, provided herein is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

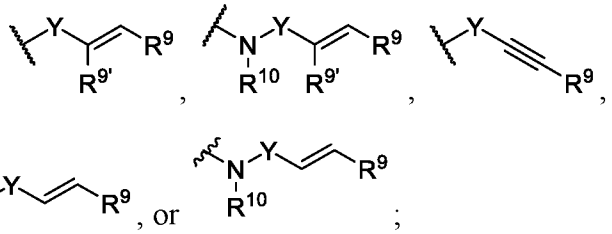
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  ;

Y is $–C(=O)–$, $–S(=O)–$, or $–S(=O)_2–$;

R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, haloalkyl, cycloalkyl, heteroalkyl, or (alkyl)heterocycloalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

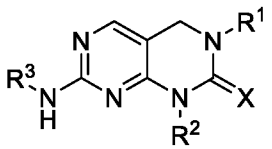
each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0088] In another aspect, provided herein is a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $-(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

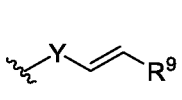
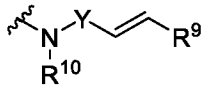
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  or  ;

Y is –C(=O)–, –S(=O)–, or –S(=O)$_2$–;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, –N(R^{11})$_2$, –S(=O)$_2$alkyl, –S(=O)$_2$aryl, –S(=O)$_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, –N(R^{13})$_2$, –S(=O)$_2$NH$_2$, –S(=O)$_2$alkyl, –S(=O)$_2$aryl, –S(=O)$_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, –N(R^{15})$_2$, –S(=O)$_2$alkyl, –S(=O)$_2$aryl, –S(=O)$_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0089] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

R^1 is–(C(R^4)$_2$)$_n$$R^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

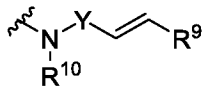
n is 1;

each R^4 is independently hydrogen or alkyl;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is aryl substituted with one R^7;

R^7 is  ;

Y is –C(=O)–, or –S(=O)$_2$–;

R^9 is hydrogen or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo.

[0090] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

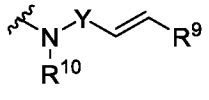
R^1 is–$(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

n is 0;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is aryl substituted with one R^7;

R^7 is  ;

Y is –C(=O)–;

R^9 is hydrogen or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo.

[0091] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

R^1 is–$(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

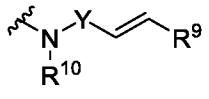
n is 1;

each R^4 is hydrogen;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is cycloalkyl substituted with one R^7;

R^7 is  ;

Y is –C(=O)–;

R^9 is hydrogen or heteroalkyl;

R^{10} is hydrogen;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo.

[0092] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

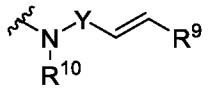
R^1 is–$(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

n is 0;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is cycloalkyl substituted with one R^7;

R^7 is  ;

Y is –C(=O)–;

R^9 is hydrogen;

R^{10} is hydrogen;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo.

[0093] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

R^1 is–$(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

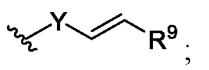
n is 1;

each R^4 is hydrogen;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is heterocycloalkyl substituted with one R^7;

R^7 is  ;

Y is –C(=O)–;

R^9 is hydrogen or heteroalkyl;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo.

[0094] Some embodiments provided herein describe a compound of Formula I or a pharmaceutically acceptable salt thereof, wherein:

X is O;

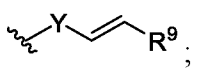
R^1 is–$(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0 or 1 $R^{5'}$;

n is 0;

R^5 is aryl;

each $R^{5'}$ is halo;

R^2 is heterocycloalkyl substituted with one R^7;

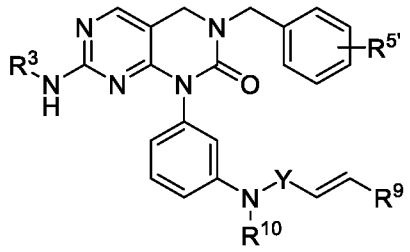
R^7 is  ;

Y is –C(=O)–;

R^9 is hydrogen;

R^3 is heteroaryl substituted with 1 or 2 R^{12}; and

each R^{12} is independently alkyl or halo. Some embodiments provided herein describe a compound of Formula I-A



Formula I-A

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is –C(=O)–, –S(=O)–, or $–S(=O)_2–$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

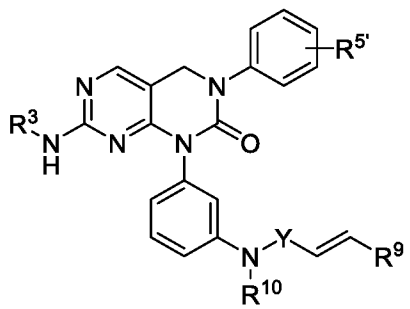
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $–N(R^{13})_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{15})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0095] Some embodiments provided herein describe a compound of Formula I-B



Formula I-B

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is $-C(=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

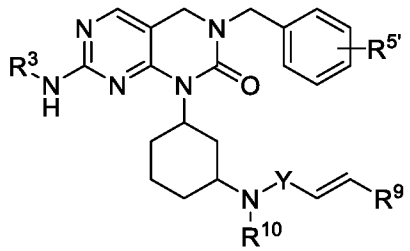
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0096] Some embodiments provided herein describe a compound of Formula I-C



Formula I-C

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is $-C(=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

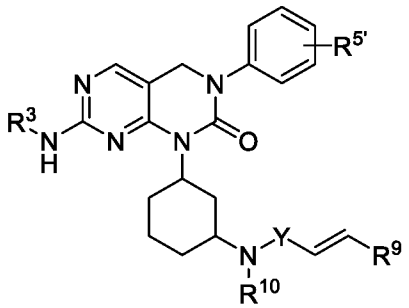
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0097] Some embodiments provided herein describe a compound of Formula I-D



Formula I-D

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is $-C(=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen or alkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

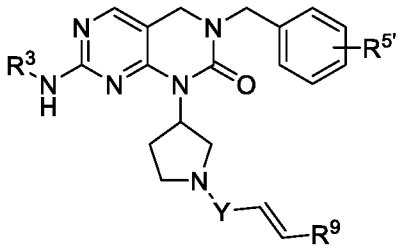
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0098] Some embodiments provided herein describe a compound of Formula I-E



Formula I-E

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is $-C(=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

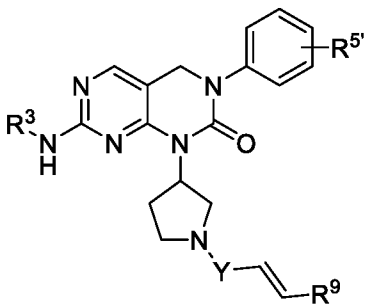
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0099] Some embodiments provided herein describe a compound of Formula I-F



Formula I-F

or a pharmaceutically acceptable salt thereof, wherein:

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

Y is –C(=O)–, –S(=O)–, or –S(=O)$_2$–;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

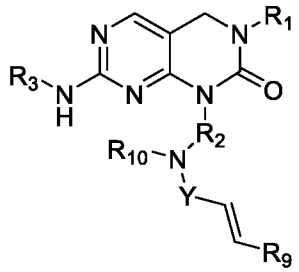
each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, –N(R^{13})$_2$, or cycloalkyl, wherein the heterocycloalkyl or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, –N(R^{15})$_2$, –S(=O)$_2$alkyl, –S(=O)$_2$aryl, –S(=O)$_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0100] Some embodiments provided herein describe a compound of Formula I-G



Formula I-G

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is–(C(R^4)$_2$)$_n$$R^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, –N(R^6)$_2$, –S(=O)$_2$alkyl, –S(=O)$_2$aryl, –S(=O)$_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is substituted with 0, 1, or 2 R^8;

Y is –C(=O)–, –S(=O)–, or –S(=O)$_2$–;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

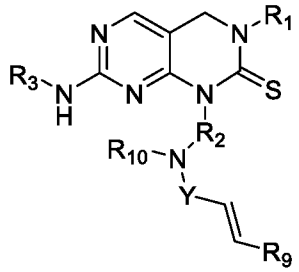
each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0101] Some embodiments provided herein describe a compound of Formula I-H



Formula I-H

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is substituted with 0, 1, or 2 R^8;

Y is $-C(=O)-$, $-S(=O)-$, or $-S(=O)_2-$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

[0102] For any and all of the embodiments, substituents are selected from among a subset of the listed alternatives. For example, in some embodiments, n is 0, 1, 2, or 3. In some embodiments, n is 0, 1, or 2. In some embodiments, n is 0, 1, or 3. In some embodiments, n is 0, 2, or 3. In some embodiments, n is 1, 2, or 3. In some embodiments, n is 0 or 1. In some embodiments, n is 1 or 2. In some embodiments, n is 2 or 3. In some embodiments, n is 0 or 2. In some embodiments, n is 0 or 3. In some embodiments, n is 1 or 3. In some embodiments, n is 0. In some embodiments, n is 1. In some embodiments, n is 2. In some embodiments, n is 3.

[0103] In some embodiments, R^5 is phenyl, naphthyl, anthracenyl, phenanthrenyl, chrysenyl, pyrenyl, C-linked pyridyl, C-linked pyrimidinyl, C-linked pyrazolyl, or C-linked imidazolyl. In some embodiments, R^5 is phenyl, naphthyl, anthracenyl, phenanthrenyl, C-linked pyridyl, C-linked pyrimidinyl, C-linked pyrazolyl, or C-linked imidazolyl. In some embodiments, R^5 is phenyl. In some embodiments, R^5 is naphthyl. In some embodiments, R^5 is anthracenyl. In some embodiments, R^5 is phenanthrenyl. In some embodiments, R^5 is chrysenyl. In some embodiments, R^5 is pyrenyl. In some embodiments, R^5 is C-linked pyridyl. In some embodiments, R^5 is C-linked pyrimidinyl. In some embodiments, R^5 is C-linked pyrazolyl. In some embodiments, R^5 is C-linked imidazolyl.

[0104] In some embodiments, R^5 is unsubstituted. In some embodiments, R^5 is substituted with 0, 1, or 2 $R^{5'}$. In some embodiments, R^5 is substituted with 0 or 1 $R^{5'}$. In some embodiments, R^5 is substituted with 0 or 2 $R^{5'}$. In some embodiments, R^5 is substituted with 1 or 2 $R^{5'}$. In some embodiments, R^5 is substituted with 1 $R^{5'}$. In some embodiments, R^5 is substituted with 2 $R^{5'}$.

[0105] In some embodiments, each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl. In some embodiments, each R^4 is independently hydrogen, alkyl, halo, haloalkyl, or alkoxy. In some embodiments, each R^4 is independently hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, trifluoromethyl, trifluoroethyl, pentafluoroethyl, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^4 is independently hydrogen, methyl, fluoro, trifluoromethyl, methoxy, or trifluoromethoxy. In some embodiments, each R^4 is hydrogen. In some embodiments, each R^4 is independently alkyl. In some embodiments, each R^4 is independently halo. In some embodiments, each R^4 is independently haloalkyl. In some embodiments, each R^4 is hydroxy. In some embodiments, each R^4 is independently alkoxy. In some embodiments, each R^4 is independently heteroalkyl. In some embodiments, each R^4 is methyl. In some embodiments, each R^4 is ethyl. In some embodiments, each R^4 is *n*-propyl. In some embodiments, each R^4 is *iso*-propyl. In some embodiments, each R^4 is *n*-butyl. In some embodiments, each R^4 is *iso*-butyl. In some embodiments, each R^4 is *sec*-butyl. In some embodiments, each R^4 is *tert*-butyl. In some embodiments, each R^4 is fluoro. In some embodiments, each R^4 is chloro. In some embodiments, each R^4 is trifluoromethyl. In some embodiments, each R^4 is trifluoroethyl. In some embodiments, each R^4 is pentafluoroethyl. In some embodiments, each R^4 is methoxy. In some embodiments, each R^4 is ethoxy. In some embodiments, each R^4 is trifluoromethoxy.

[0106] In some embodiments, each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^6)_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy. In some embodiments, each $R^{5'}$ is independently aryl, heteroaryl, alkyl, heterocycloalkyl, halo, cyano, hydroxy, $-N(R^6)_2$, or alkoxy. In some embodiments, each $R^{5'}$ is independently aryl. In some embodiments, each $R^{5'}$ is independently heteroaryl. In some embodiments, each $R^{5'}$ is independently alkyl. In some embodiments, each $R^{5'}$ is independently cycloalkyl. In some embodiments, each $R^{5'}$ is independently heterocycloalkyl. In some embodiments, each $R^{5'}$ is independently halo. In some embodiments, each $R^{5'}$ is independently heteroalkyl. In some embodiments, each $R^{5'}$ is independently haloalkyl. In some embodiments, each $R^{5'}$ is cyano. In some embodiments, each $R^{5'}$ is hydroxy. In some embodiments, each $R^{5'}$ is amino. In some embodiments, each $R^{5'}$ is independently $-N(R^6)_2$. In some embodiments, each $R^{5'}$ is independently $-S(=O)_2$alkyl. In some embodiments, each $R^{5'}$ is independently $-S(=O)_2$aryl. In some embodiments, each $R^{5'}$ is independently$-S(=O)_2$heteroaryl. In some embodiments, each $R^{5'}$ is independently alkoxy. In some embodiments, each $R^{5'}$ is independently phenyl, naphthyl, anthracenyl, phenanthrenyl, chrysenyl, pyrenyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, indolyl, indazolyl, benzimidazolyl, azaindolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl,

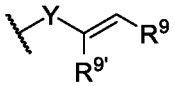
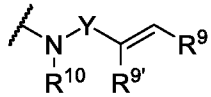
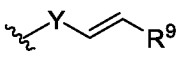
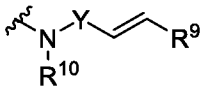
pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, naphthyridinyl, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, fluoro, chloro, cyano, hydroxy, $-N(R^6)_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each $R^{5'}$ is independently phenyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, methyl, ethyl, *tert*-butyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, fluoro, chloro, cyano, hydroxy, $-N(R^6)_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each $R^{5'}$ is independently phenyl, imidazolyl, pyridinyl, methyl, *tert*-butyl, pyrrolidinyl, morpholinyl, fluoro, cyano, hydroxy, $-N(R^6)_2$, or methoxy. In some embodiments, each $R^{5'}$ is phenyl. In some embodiments, each $R^{5'}$ is naphthyl. In some embodiments, each $R^{5'}$ is anthracenyl. In some embodiments, each $R^{5'}$ is phenanthrenyl. In some embodiments, each $R^{5'}$ is chrysenyl. In some embodiments, each $R^{5'}$ is pyrenyl. In some embodiments, each $R^{5'}$ is pyrrolyl. In some embodiments, each $R^{5'}$ is imidazolyl. In some embodiments, each $R^{5'}$ is pyrazolyl. In some embodiments, each $R^{5'}$ is triazolyl. In some embodiments, each $R^{5'}$ is tetrazolyl. In some embodiments, each $R^{5'}$ is indolyl. In some embodiments, each $R^{5'}$ is indazolyl. In some embodiments, each $R^{5'}$ is benzimidazolyl. In some embodiments, each $R^{5'}$ is azaindolyl. In some embodiments, each $R^{5'}$ is thiazolyl. In some embodiments, each $R^{5'}$ is isothiazolyl. In some embodiments, each $R^{5'}$ is oxazolyl. In some embodiments, each $R^{5'}$ is isoxazolyl. In some embodiments, each $R^{5'}$ is pyridinyl. In some embodiments, each $R^{5'}$ is pyrimidinyl. In some embodiments, each $R^{5'}$ is pyridazinyl. In some embodiments, each $R^{5'}$ is pyrazinyl. In some embodiments, each $R^{5'}$ is triazinyl. In some embodiments, each $R^{5'}$ is quinolinyl. In some embodiments, each $R^{5'}$ is isoquinolinyl. In some embodiments, each $R^{5'}$ is quinoxalinyl. In some embodiments, each $R^{5'}$ is quinazolinyl. In some embodiments, each $R^{5'}$ is cinnolinyl. In some embodiments, each $R^{5'}$ is naphthyridinyl. In some embodiments, each $R^{5'}$ is methyl. In some embodiments, each $R^{5'}$ is ethyl. In some embodiments, each $R^{5'}$ is *n*-propyl. In some embodiments, each $R^{5'}$ is *iso*-propyl. In some embodiments, each $R^{5'}$ is *n*-butyl. In some embodiments, each $R^{5'}$ is *iso*-butyl. In some embodiments, each $R^{5'}$ is *sec*-butyl. In some embodiments, each $R^{5'}$ is *tert*-butyl. In some embodiments, each $R^{5'}$ is azetidinyl. In some embodiments, each $R^{5'}$ is oxetanyl. In some embodiments, each $R^{5'}$ is pyrrolidinyl. In some embodiments, each $R^{5'}$ is imidazolidinyl. In some embodiments, each $R^{5'}$ is tetrahydrofuranyl. In some embodiments, each $R^{5'}$ is piperidinyl. In some embodiments, each $R^{5'}$ is piperazinyl. In some embodiments, each $R^{5'}$ is tetrahydropyranyl. In some embodiments, each $R^{5'}$ is morpholinyl. In some embodiments, each $R^{5'}$ is fluoro. In some embodiments, each $R^{5'}$ is chloro. In some embodiments, each $R^{5'}$ is

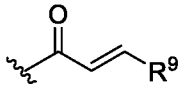
methoxy. In some embodiments, each $R^{5'}$ is ethoxy. In some embodiments, each $R^{5'}$ is trifluoromethoxy.

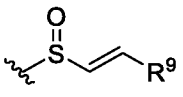
[0107] In some embodiments, each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl. In some embodiments, each R^6 is independently alkyl or aryl. In some embodiments, each R^6 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl, naphthyl, anthracenyl, phenanthrenyl, chrysenyl, or pyrenyl. In some embodiments, each R^6 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl. In some embodiments, each R^6 is independently methyl or phenyl. In some embodiments, each R^6 is methyl. In some embodiments, each R^6 is ethyl. In some embodiments, each R^6 is *n*-propyl. In some embodiments, each R^6 is *iso*-propyl. In some embodiments, each R^6 is *n*-butyl. In some embodiments, each R^6 is *iso*-butyl. In some embodiments, each R^6 is *sec*-butyl. In some embodiments, each R^6 is *tert*-butyl. In some embodiments, each R^6 is phenyl. In some embodiments, each R^6 is naphthyl. In some embodiments, each R^6 is anthracenyl. In some embodiments, each R^6 is phenanthrenyl. In some embodiments, each R^6 is chrysenyl. In some embodiments, each R^6 is pyrenyl.

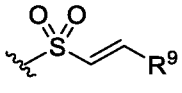
[0108] In some embodiments, X is S. In some embodiments, X is O.

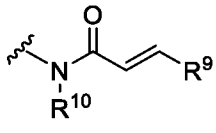
[0109] In some embodiments, R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. In some embodiments, R^2 is aryl. In some embodiments, R^2 is heteroaryl. In some embodiments, R^2 is cycloalkyl. In some embodiments, R^2 is heterocycloalkyl. In some embodiments, R^2 is monocyclic. In some embodiments, R^2 is phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or triazinyl. In some embodiments, R^2 is phenyl, cyclohexyl, or pyrrolyl. In some embodiments, R^2 is phenyl. In some embodiments, R^2 is cyclopropyl. In some embodiments, R^2 is cyclobutyl. In some embodiments, R^2 is cyclopentyl. In some embodiments, R^2 is cyclohexyl. In some embodiments, R^2 is pyrrolyl. In some embodiments, R^2 is imidazolyl. In some embodiments, R^2 is pyrazolyl. In some embodiments, R^2 is triazolyl. In some embodiments, R^2 is tetrazolyl. In some embodiments, R^2 is thiazolyl. In some embodiments, R^2 is isothiazolyl. In some embodiments, R^2 is oxazolyl. In some embodiments, R^2 is isoxazolyl. In some embodiments, R^2 is pyridinyl. In some embodiments, R^2 is pyrimidinyl. In some embodiments, R^2 is pyridazinyl. In some embodiments, R^2 is pyrazinyl. In some embodiments, R^2 is triazinyl.

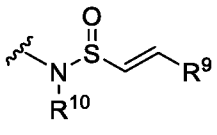
[0110] In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R^7 is  . In some embodiments, R^7 is  . In

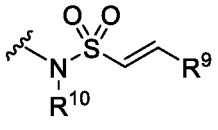


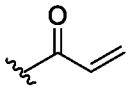


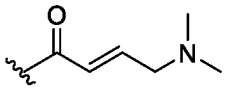


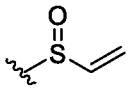


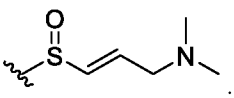


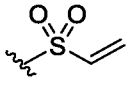


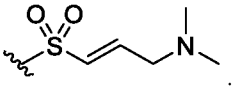


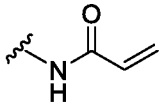


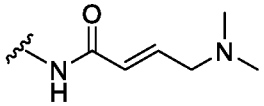


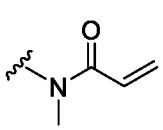


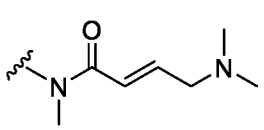


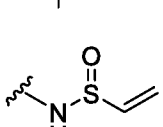


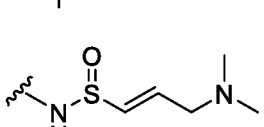


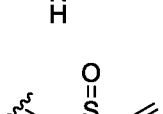


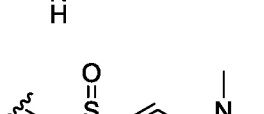


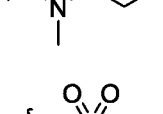


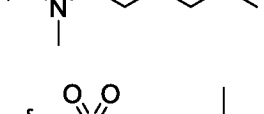


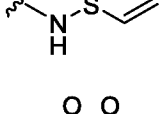


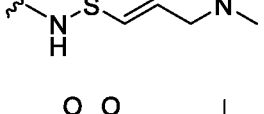


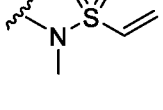


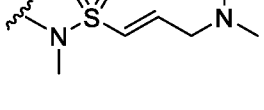












some embodiments, R^7 is . In some embodiments, R^7 is .

[0111] In some embodiments, Y is –C(=O)–. In some embodiments, Y is –S(=O)–. In some embodiments, Y is $–S(=O)_2–$.

[0112] In some embodiments, R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, heteroalkyl, haloalkyl, or (alkyl)heterocycloalkyl. In some embodiments, R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl. In some embodiments, R^9 is hydrogen, halo, or heteroalkyl. In some embodiments, R^9 and $R^{9'}$ are independently hydrogen, fluoro, chloro, methyl, hydroxyethyl,

methoxyethyl, methoxymethyl, dimethylaminomethyl, 1-piperidinylmethyl, 1-morpholinylmethyl, or fluoromethyl. In some embodiments, R^9 is hydrogen, fluoro, chloro, hydroxyethyl, or methoxyethyl. In some embodiments, R^9 is hydrogen. In some embodiments, R^9 is fluoro. In some embodiments, R^9 is chloro. In some embodiments, R^9 is hydroxyethyl. In some embodiments, R^9 is methoxyethyl. In some embodiments, R^9 is methyl. In some embodiments, R^9 is methoxymethyl. In some embodiments, R^9 is dimethylaminomethyl. In some embodiments, R^9 is 1-piperidinylmethyl. In some embodiments, R^9 is 1-morpholinomethyl. In some embodiments, R^9 is fluoromethyl. In some embodiments, $R^{9'}$ is hydrogen. In some embodiments, $R^{9'}$ is fluoro. In some embodiments, $R^{9'}$ is chloro. In some embodiments, $R^{9'}$ is hydroxyethyl. In some embodiments, $R^{9'}$ is methoxyethyl. In some embodiments, $R^{9'}$ is methyl. In some embodiments, $R^{9'}$ is methoxymethyl. In some embodiments, $R^{9'}$ is dimethylaminomethyl. In some embodiments, $R^{9'}$ is 1-piperidinylmethyl. In some embodiments, $R^{9'}$ is 1-morpholinomethyl. In some embodiments, $R^{9'}$ is fluoromethyl.

[0113] In some embodiments, R^{10} is hydrogen or alkyl. In some embodiments, R^{10} is hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, or *tert*-butyl. In some embodiments, R^{10} is hydrogen. In some embodiments, R^{10} is methyl. In some embodiments, R^{10} is ethyl. In some embodiments, R^{10} is *n*-propyl. In some embodiments, R^{10} is *iso*-propyl. In some embodiments, R^{10} is *n*-butyl. In some embodiments, R^{10} is *iso*-butyl. In some embodiments, R^{10} is *sec*-butyl. In some embodiments, R^{10} is *tert*-butyl.

[0114] In some embodiments, R^2 is unsubstituted. In some embodiments, R^2 is substituted with 1 or 2 R^8. In some embodiments, R^2 is substituted with 1 R^8. In some embodiments, R^2 is substituted with 2 R^8.

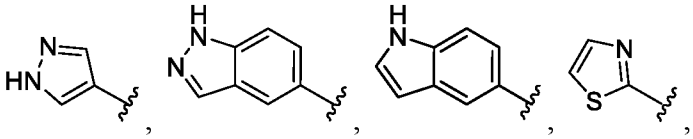
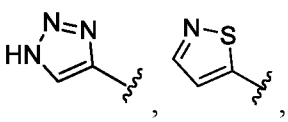
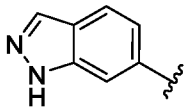
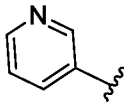
[0115] In some embodiments, each R^8 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, heteroalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^8 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, fluoro, chloro, $-N(R^{11})_2$, hydroxyethyl, methoxyethyl, or cyano. In some embodiments, each R^8 is methyl. In some embodiments, each R^8 is ethyl. In some embodiments, each R^8 is *n*-propyl. In some embodiments, each R^8 is *iso*-propyl. In some embodiments, each R^8 is *n*-butyl. In some embodiments, each R^8 is *iso*-butyl. In some embodiments, each R^8 is *sec*-butyl. In some embodiments, each R^8 is *tert*-butyl. In some embodiments, each R^8 is fluoro. In some embodiments, each R^8 is chloro. In some embodiments, each R^8 is independently $-N(R^{11})_2$. In some embodiments, each R^8 is hydroxyethyl. In some embodiments, each R^8 is methoxyethyl. In some embodiments, each R^8 is cyano.

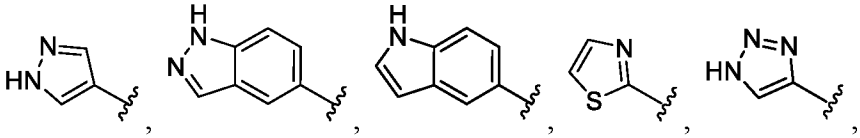
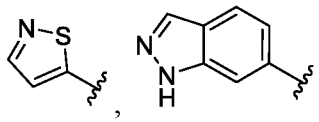
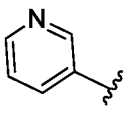
[0116] In some embodiments, each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{11} is independently alkyl or aryl. In some embodiments, each R^{11} is

independently alkyl. In some embodiments, each R^{11} is independently cycloalkyl. In some embodiments, each R^{11} is independently aryl. In some embodiments, each R^{11} is independently heteroaryl. In some embodiments, each R^{11} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl, naphthyl, anthracenyl, phenanthrenyl, chrysenyl, or pyrenyl. In some embodiments, each R^{11} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl. In some embodiments, each R^{11} is independently methyl or phenyl. In some embodiments, each R^{11} is methyl. In some embodiments, each R^{11} is ethyl. In some embodiments, each R^{11} is *n*-propyl. In some embodiments, each R^{11} is *iso*-propyl. In some embodiments, each R^{11} is *n*-butyl. In some embodiments, each R^{11} is *iso*-butyl. In some embodiments, each R^{11} is *sec*-butyl. In some embodiments, each R^{11} is *tert*-butyl. In some embodiments, each R^{11} is phenyl. In some embodiments, each R^{11} is naphthyl. In some embodiments, each R^{11} is anthracenyl. In some embodiments, each R^{11} is phenanthrenyl. In some embodiments, each R^{11} is chrysenyl. In some embodiments, each R^{11} is pyrenyl.

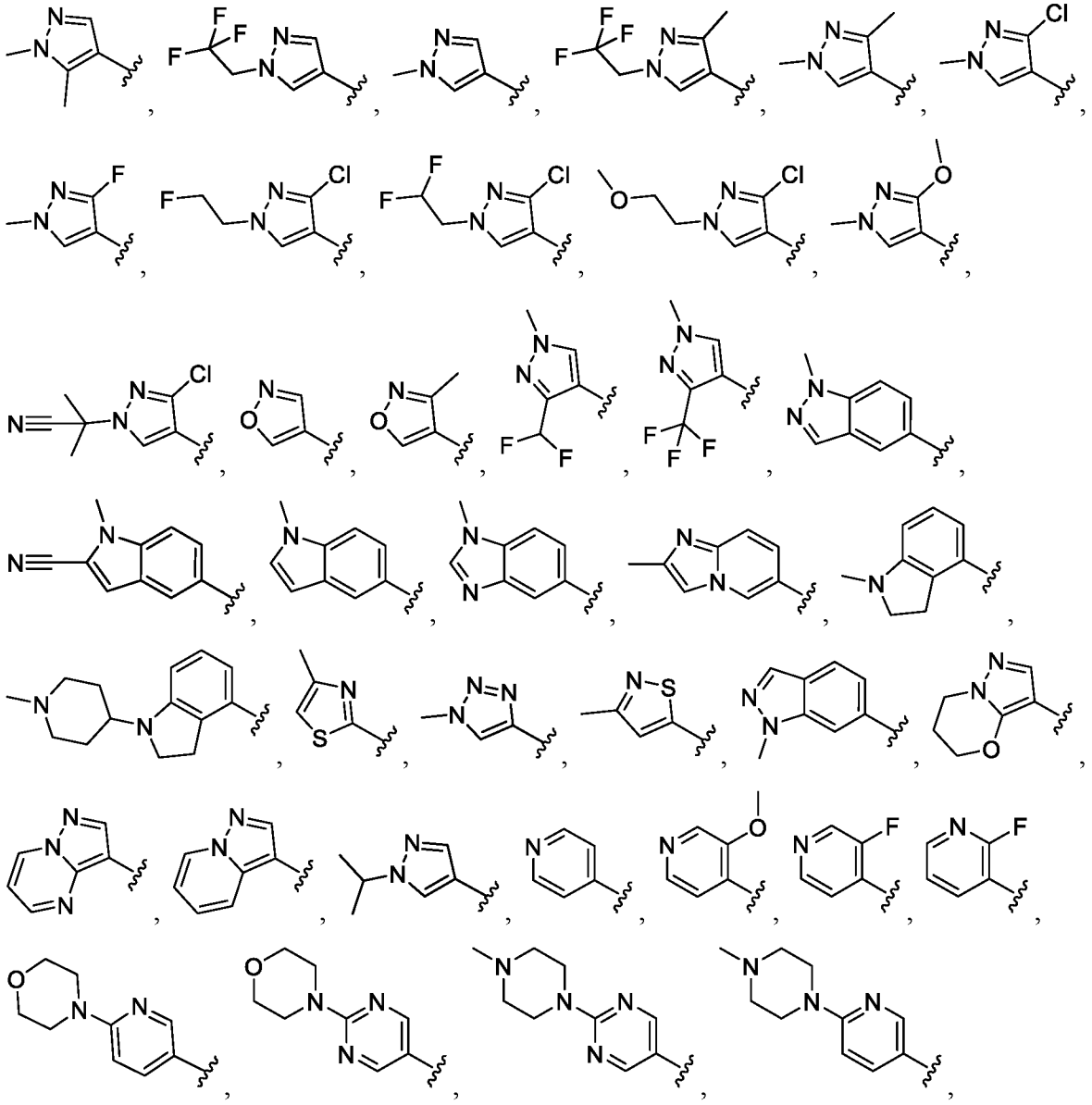
[0117] In some embodiments, R^3 is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, indolyl, indazolyl, benzimidazolyl, azaindolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, or naphthyridinyl. In some embodiments, R^3 is pyrazolyl, triazolyl, indolyl, indazolyl, thiazolyl, isothiazolyl, or pyridinyl. In some embodiments, R^3 is pyrrolyl. In some embodiments, R^3 is imidazolyl. In some embodiments, R^3 is pyrazolyl. In some embodiments, R^3 is triazolyl. In some embodiments, R^3 is tetrazolyl. In some embodiments, R^3 is indolyl. In some embodiments, R^3 is indazolyl. In some embodiments, R^3 is benzimidazolyl. In some embodiments, R^3 is azaindolyl. In some embodiments, R^3 is thiazolyl. In some embodiments, R^3 is isothiazolyl. In some embodiments, R^3 is oxazolyl. In some embodiments, R^3 is isoxazolyl. In some embodiments, R^3 is pyridinyl. In some embodiments, R^3 is pyrimidinyl. In some embodiments, R^3 is pyridazinyl. In some embodiments, R^3 is pyrazinyl. In some embodiments, R^3 is triazinyl. In some embodiments, R^3 is quinolinyl. In some embodiments, R^3 is isoquinolinyl. In some embodiments, R^3 is quinoxalinyl. In some embodiments, R^3 is quinazolinyl. In some embodiments, R^3 is cinnolinyl. In some embodiments, R^3 is naphthyridinyl.

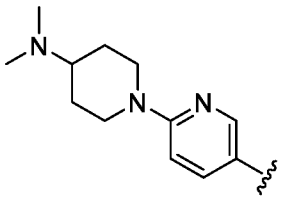
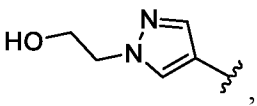
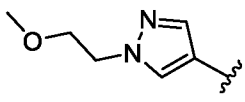
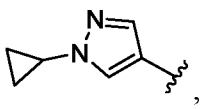
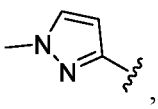
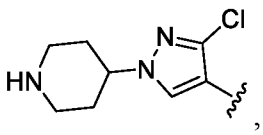
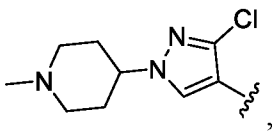
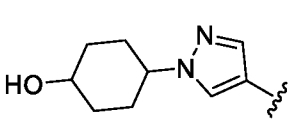
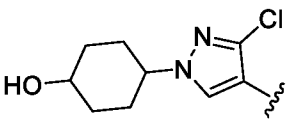
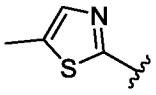
[0118] In some embodiments, R^3 is unsubstituted. In some embodiments, R^3 is substituted with at least 1 R^{12}. In some embodiments, R^3 is substituted with at least 2 R^{12}. In some embodiments, R^3 is substituted with 1 R^{12}. In some embodiments, R^3 is substituted with 2 R^{12}. In some embodiments, R^3 is substituted with 3 R^{12}.

[0119] In some embodiments, R^3 is  ,  , ,  , or  , wherein R^3 is substituted with 0 to 3 R^{12}.

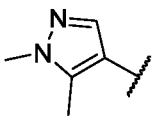
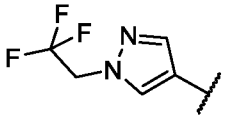
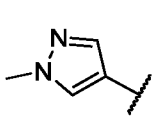
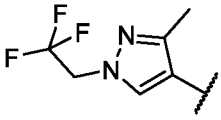
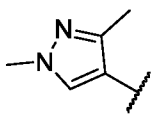
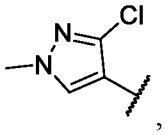
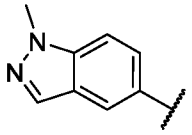
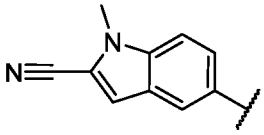
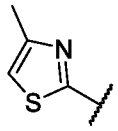
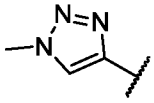
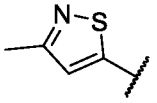
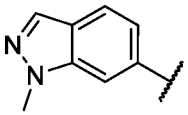
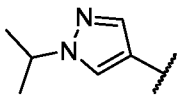
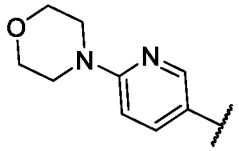
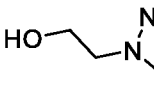
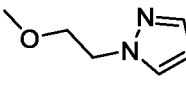
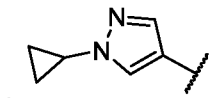
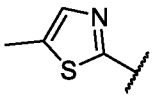
In some embodiments, R^3 is  ,  , , or  , wherein R^3 is substituted with 1 or 2 R^{12}.

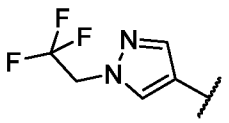
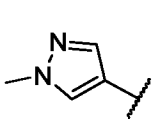
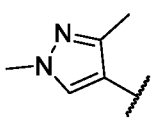
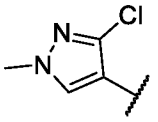
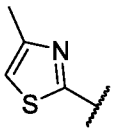
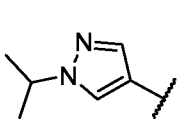
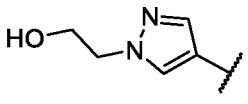
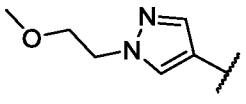
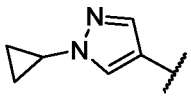
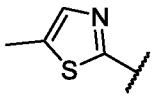
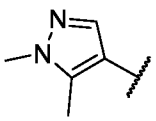
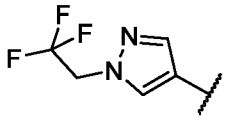
[0120] In some embodiments, R^3 is selected from:

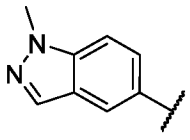


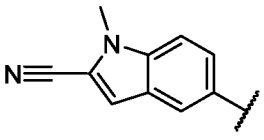
 ,  ,  ,  ,  ,
 ,  ,  ,  , and
 .

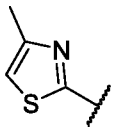
[0121] In some embodiments, R^3 is selected from:

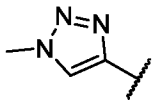
 ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  ,  ,
 ,  ,  ,  ,  , and
 . In some embodiments, R^3 is selected from:

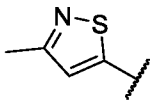
 ,  ,  ,  ,  ,  ,
 ,  ,  , and  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is . In some embodiments, R^3 is . In some embodiments, R^3 is . In some

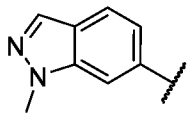


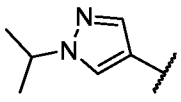


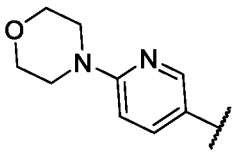


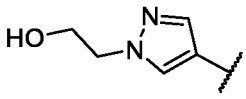


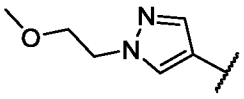


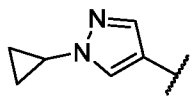


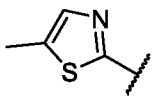


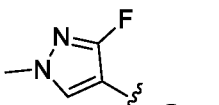


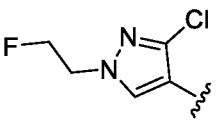


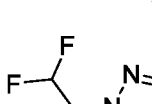


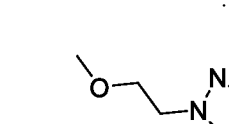


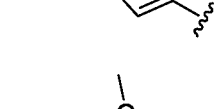


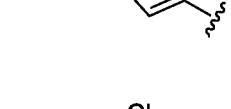


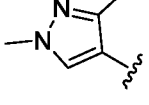


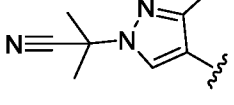


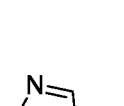


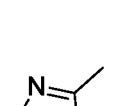


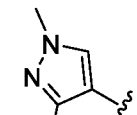


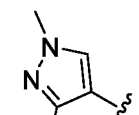


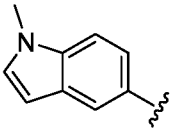


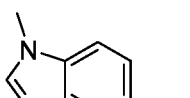


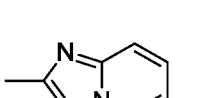


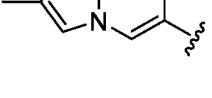


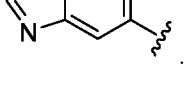




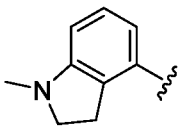
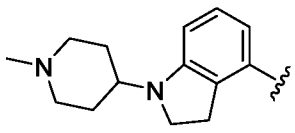
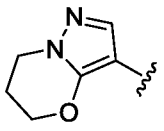
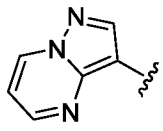
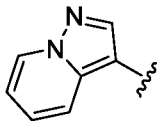
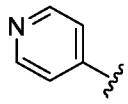
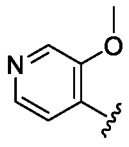
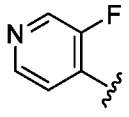
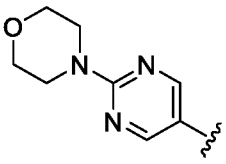
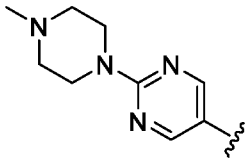
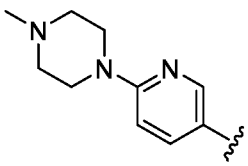
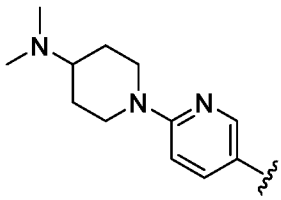
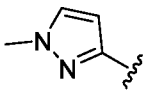
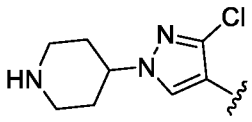
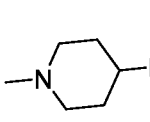
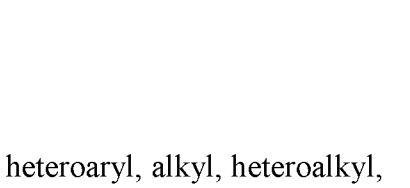
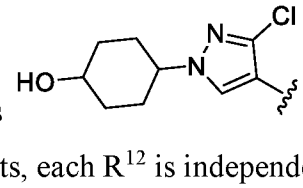








embodiments, R^3 is . In some embodiments, R^3 is . In some

embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is  . In some embodiments, R^3 is . In some embodiments, R^3 is  .

[0122] In some embodiments, each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or cycloalkyl. In some embodiments, each R^{12} is independently alkyl, heteroalkyl, haloalkyl, halo, cyano, heterocycloalkyl, $-N(R^{13})_2$, or cycloalkyl. In some embodiments, each R^{12} is independently aryl. In some embodiments, each R^{12} is independently heteroaryl. In some embodiments, each R^{12} is independently alkyl. In some embodiments, each R^{12} is independently heteroalkyl. In some embodiments, each R^{12} is independently haloalkyl. In some embodiments, each R^{12} is independently halo. In some embodiments, each R^{12} is cyano. In

some embodiments, each R^{12} is independently alkoxy. In some embodiments, each R^{12} is independently heterocycloalkyl. In some embodiments, each R^{12} is independently $-N(R^{13})_2$. In some embodiments, each R^{12} is independently $-S(=O)_2NH_2$. In some embodiments, each R^{12} is independently $-S(=O)_2$alkyl. In some embodiments, each R^{12} is independently $-S(=O)_2$aryl. In some embodiments, each R^{12} is independently $-S(=O)_2$heteroaryl. In some embodiments, each R^{12} is independently cycloalkyl. In some embodiments, each R^{12} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, fluoro, chloro, cyano, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, $-N(R^{13})_2$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{12} is independently methyl, *iso*-propyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, chloro, cyano, morpholinyl, or cyclopropyl. In some embodiments, each R^{12} is independently methyl, hydroxyethyl, methoxyethyl, trifluoroethyl, or chloro. In some embodiments, each R^{12} is independently methyl or chloro. In some embodiments, each R^{12} is methyl. In some embodiments, each R^{12} is ethyl. In some embodiments, each R^{12} is *n*-propyl. In some embodiments, each R^{12} is *iso*-propyl. In some embodiments, each R^{12} is *n*-butyl. In some embodiments, each R^{12} is *iso*-butyl. In some embodiments, each R^{12} is *sec*-butyl. In some embodiments, each R^{12} is *tert*-butyl. In some embodiments, each R^{12} is hydroxyethyl. In some embodiments, each R^{12} is methoxyethyl. In some embodiments, each R^{12} is trifluoromethyl. In some embodiments, each R^{12} is trifluoroethyl. In some embodiments, each R^{12} is pentafluoroethyl. In some embodiments, each R^{12} is fluoro. In some embodiments, each R^{12} is chloro. In some embodiments, each R^{12} is azetidinyl. In some embodiments, each R^{12} is oxetanyl. In some embodiments, each R^{12} is pyrrolidinyl. In some embodiments, each R^{12} is imidazolidinyl. In some embodiments, each R^{12} is tetrahydrofuranyl. In some embodiments, each R^{12} is piperidinyl. In some embodiments, each R^{12} is piperazinyl. In some embodiments, each R^{12} is tetrahydropyranyl. In some embodiments, each R^{12} is morpholinyl. In some embodiments, each R^{12} is cyclopropyl. In some embodiments, each R^{12} is cyclobutyl. In some embodiments, each R^{12} is cyclopentyl. In some embodiments, each R^{12} is cyclohexyl.

[0123] In some embodiments, each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{13} is independently alkyl or cycloalkyl. In some embodiments, each R^{13} is independently alkyl. In some embodiments, each R^{13} is independently cycloalkyl. In some embodiments, each R^{13} is independently aryl. In some embodiments, each R^{13} is independently heteroaryl. In some embodiments, each R^{13} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In

some embodiments, each R^{13} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{13} is independently methyl, cyclopropyl, or cyclohexyl. In some embodiments, each R^{13} is methyl. In some embodiments, each R^{13} is ethyl. In some embodiments, each R^{13} is *n*-propyl. In some embodiments, each R^{13} is *iso*-propyl. In some embodiments, each R^{13} is *n*-butyl. In some embodiments, each R^{13} is *iso*-butyl. In some embodiments, each R^{13} is *sec*-butyl. In some embodiments, each R^{13} is *tert*-butyl. In some embodiments, each R^{13} is cyclopropyl. In some embodiments, each R^{13} is cyclobutyl. In some embodiments, each R^{13} is cyclopentyl. In some embodiments, each R^{13} is cyclohexyl.

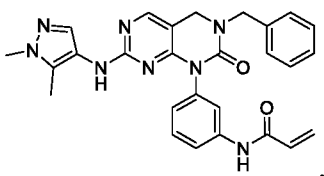
[0124] In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is unsubstituted. In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is substituted with 1 or 2 R^{14}. In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is substituted with 1 R^{14}. In some embodiments, the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is substituted with 2 R^{14}.

[0125] In some embodiments, each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy. In some embodiments, each R^{14} is independently alkyl, cycloalkyl, heterocycloalkyl, halo, cyano, $-N(R^{15})_2$, or alkoxy. In some embodiments, each R^{14} is independently aryl. In some embodiments, each R^{14} is independently heteroaryl. In some embodiments, each R^{14} is independently alkyl. In some embodiments, each R^{14} is independently cycloalkyl. In some embodiments, each R^{14} is independently heterocycloalkyl. In some embodiments, each R^{14} is independently halo. In some embodiments, each R^{14} is independently heteroalkyl. In some embodiments, each R^{14} is independently haloalkyl. In some embodiments, each R^{14} is cyano. In some embodiments, each R^{14} is hydroxy. In some embodiments, each R^{14} is amino. In some embodiments, each R^{14} is independently $-N(R^{15})_2$. In some embodiments, each R^{14} is independently $-S(=O)_2$alkyl. In some embodiments, each R^{14} is independently $-S(=O)_2$aryl. In some embodiments, each R^{14} is independently $-S(=O)_2$heteroaryl. In some embodiments, each R^{14} is independently alkoxy. In some embodiments, each R^{14} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, fluoro, chloro, cyano, $-N(R^{15})_2$, methoxy, ethoxy, or trifluoromethoxy. In some embodiments, each R^{14} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, pyrrolidinyl, piperidinyl, morpholinyl, fluoro, chloro, $-N(R^{15})_2$, or methoxy. In some embodiments, each R^{14} is methyl. In some embodiments, each R^{14} is ethyl. In some embodiments, each R^{14} is *n*-propyl. In some embodiments, each R^{14} is *iso*-propyl. In some embodiments, each R^{14} is *n*-butyl. In some

embodiments, each R^{14} is *iso*-butyl. In some embodiments, each R^{14} is *sec*-butyl. In some embodiments, each R^{14} is *tert*-butyl. In some embodiments, each R^{14} is cyclopropyl. In some embodiments, each R^{14} is cyclobutyl. In some embodiments, each R^{14} is cyclopentyl. In some embodiments, each R^{14} is cyclohexyl. In some embodiments, each R^{14} is azetidinyl. In some embodiments, each R^{14} is oxetanyl. In some embodiments, each R^{14} is pyrrolidinyl. In some embodiments, each R^{14} is imidazolidinyl. In some embodiments, each R^{14} is tetrahydrofuranyl. In some embodiments, each R^{14} is piperidinyl. In some embodiments, each R^{14} is piperazinyl. In some embodiments, each R^{14} is tetrahydropyranyl. In some embodiments, each R^{14} is morpholinyl. In some embodiments, each R^{14} is fluoro. In some embodiments, each R^{14} is chloro. In some embodiments, each R^{14} is methoxy. In some embodiments, each R^{14} is ethoxy. In some embodiments, each R^{14} is trifluoromethoxy.

[0126] In some embodiments, each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl. In some embodiments, each R^{15} is independently alkyl or cycloalkyl. In some embodiments, each R^{15} is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl. In some embodiments, each R^{15} is methyl. In some embodiments, each R^{15} is ethyl. In some embodiments, each R^{15} is *n*-propyl. In some embodiments, each R^{15} is *iso*-propyl. In some embodiments, each R^{15} is *n*-butyl. In some embodiments, each R^{15} is *iso*-butyl. In some embodiments, each R^{15} is *sec*-butyl. In some embodiments, each R^{15} is *tert*-butyl. In some embodiments, each R^{15} is cyclopropyl. In some embodiments, each R^{15} is cyclobutyl. In some embodiments, each R^{15} is cyclopentyl. In some embodiments, each R^{15} is cyclohexyl.

[0127] In some embodiments, the compound of Formula I is selected from: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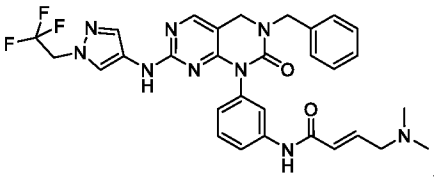
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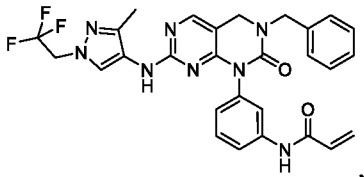
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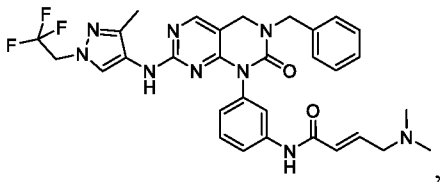
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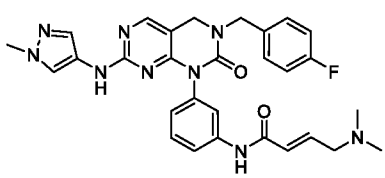
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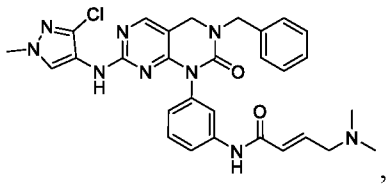
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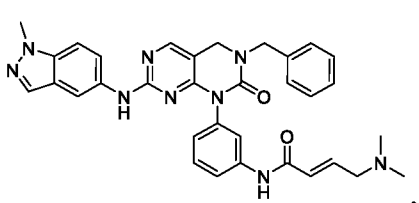
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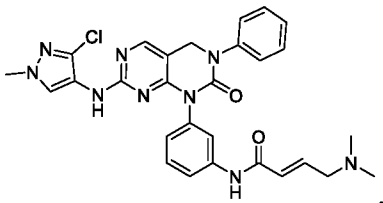
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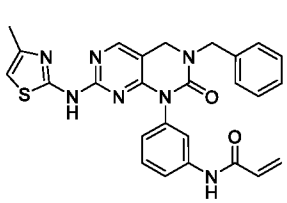
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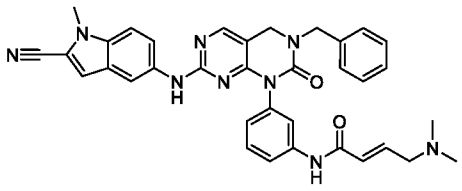
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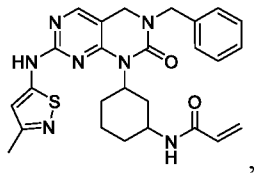
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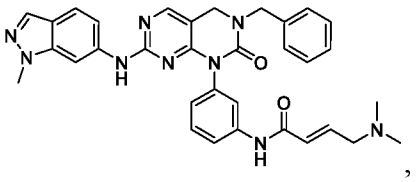
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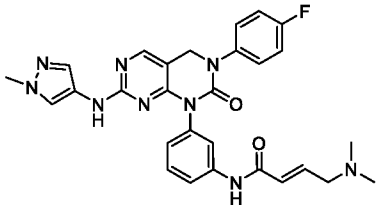
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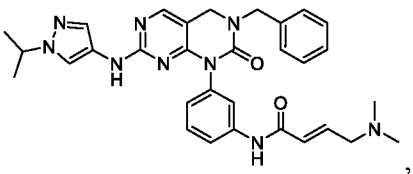
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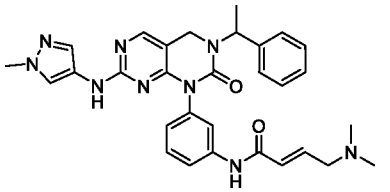
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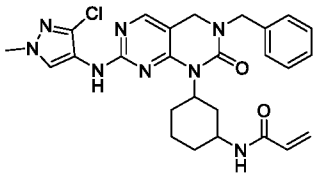
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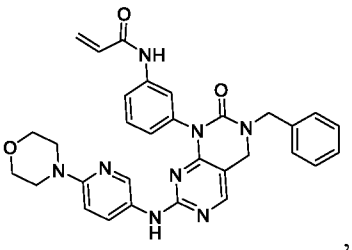
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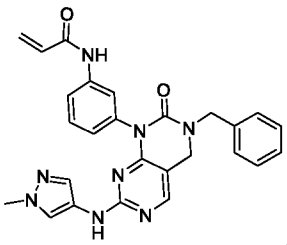
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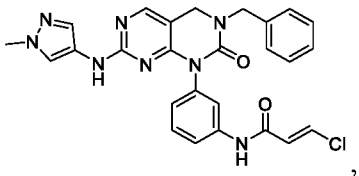
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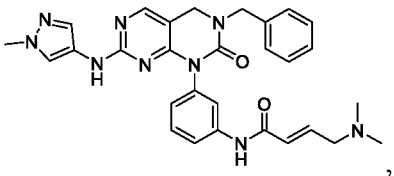
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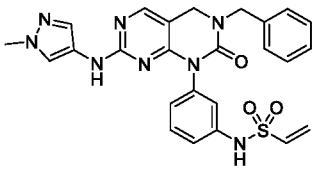
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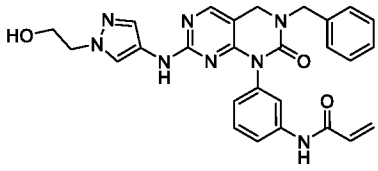
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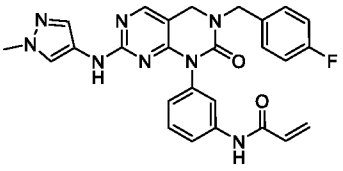
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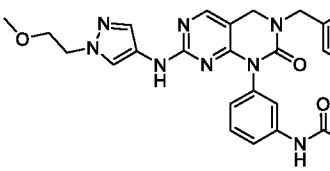
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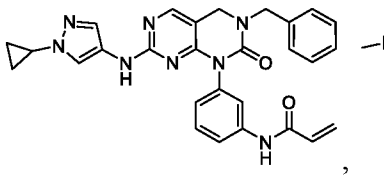
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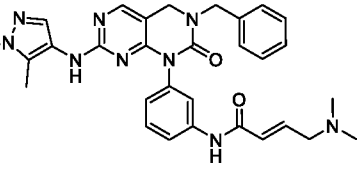
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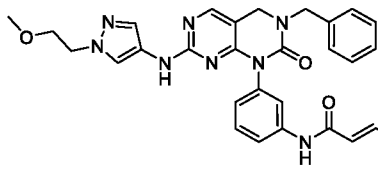
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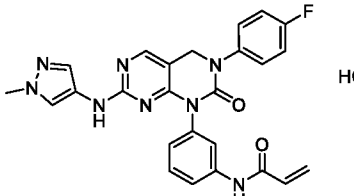
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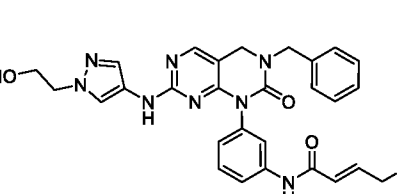
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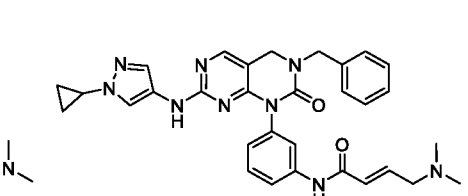
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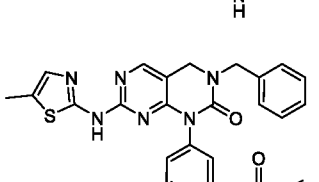
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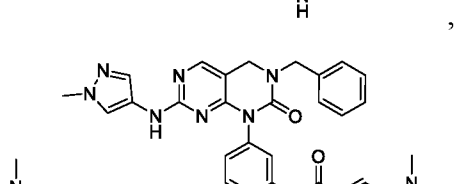
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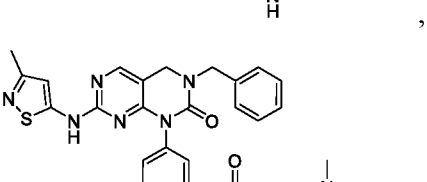
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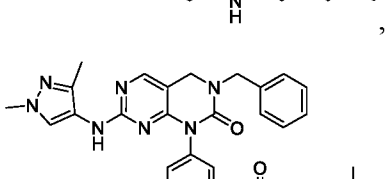
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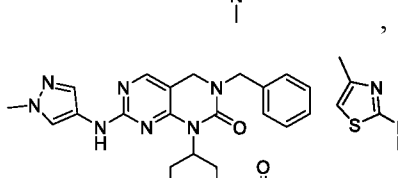
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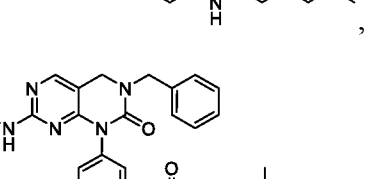
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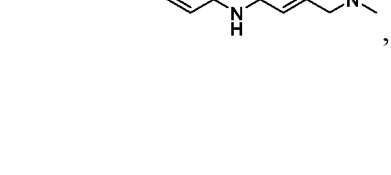
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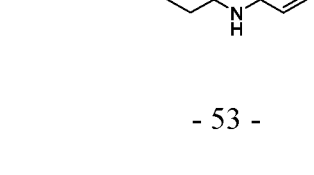
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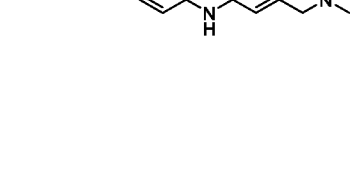
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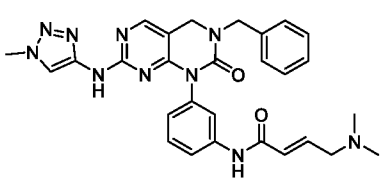
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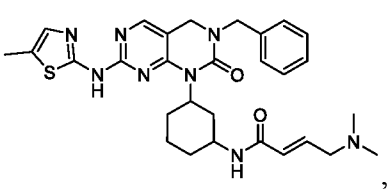
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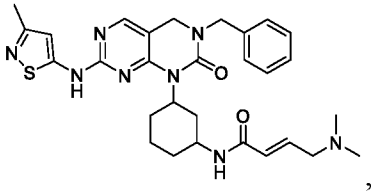
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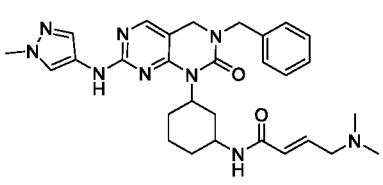
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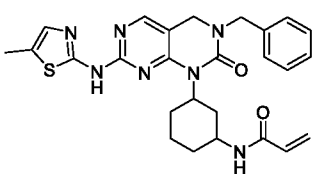
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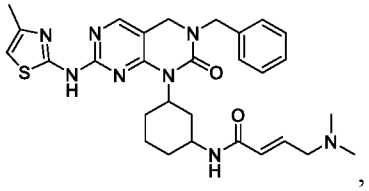
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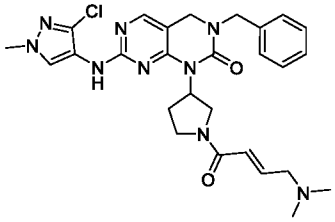
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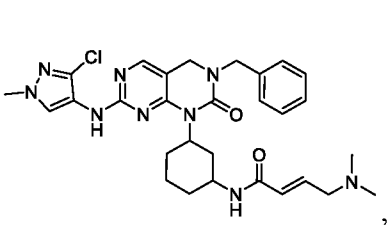
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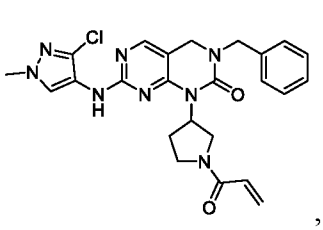
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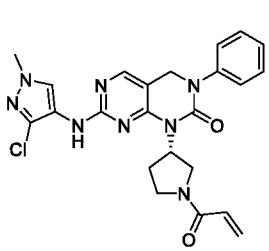
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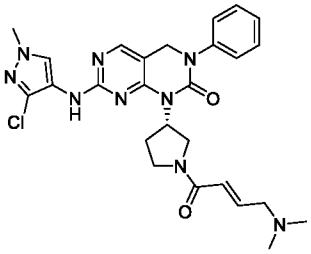
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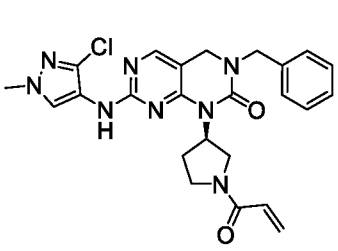
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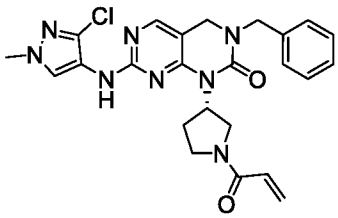
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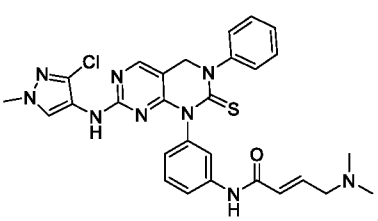
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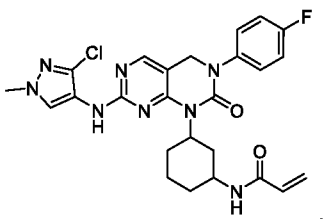
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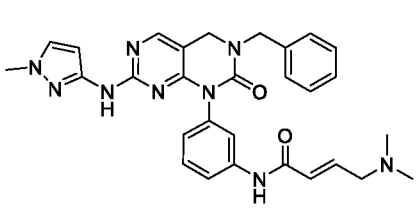
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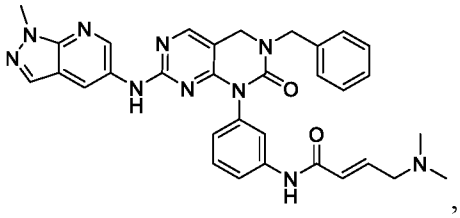
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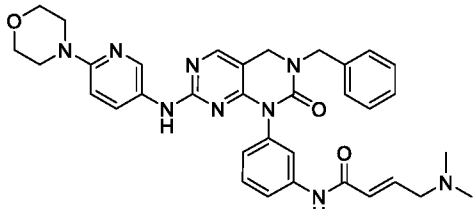
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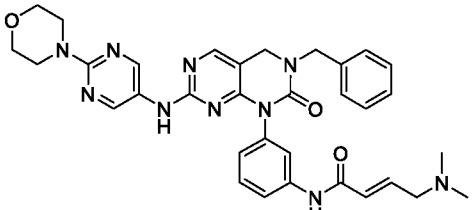
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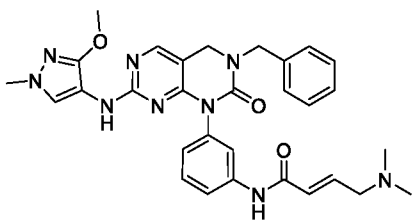
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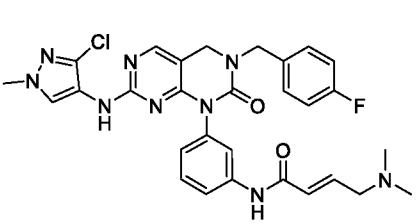
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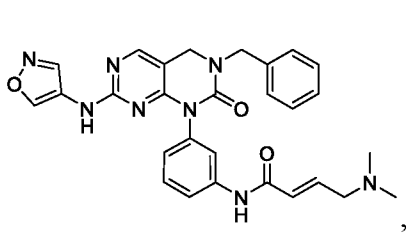
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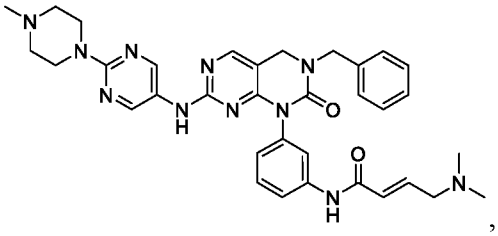
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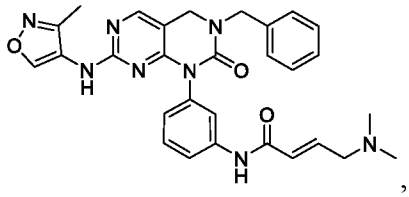
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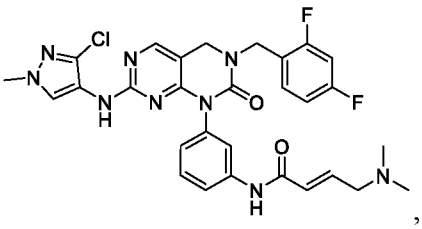
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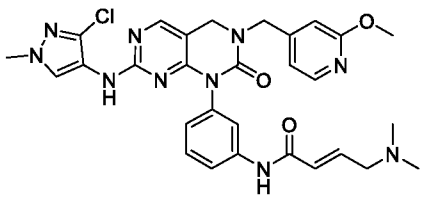
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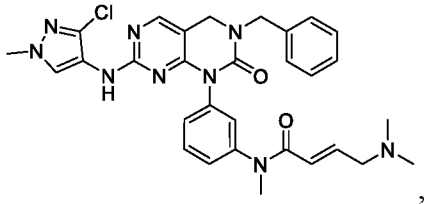
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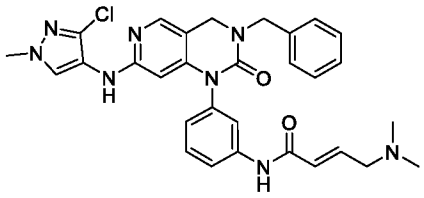
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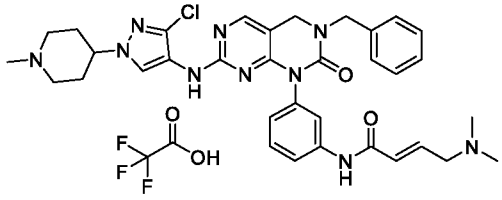
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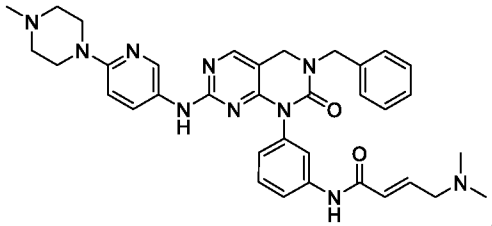
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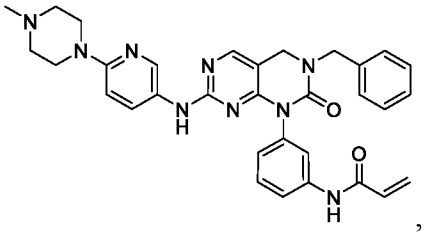
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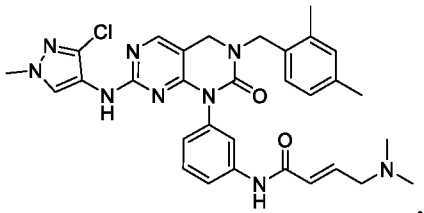
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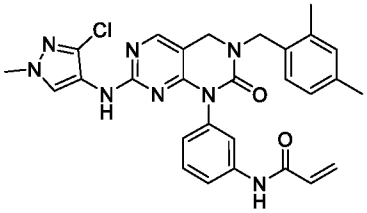
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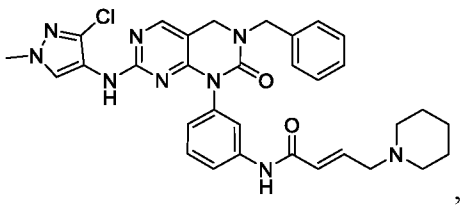
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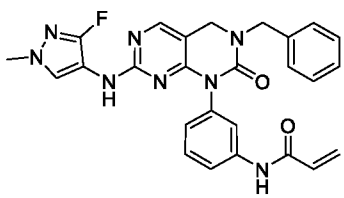
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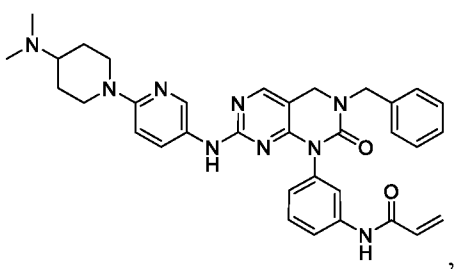
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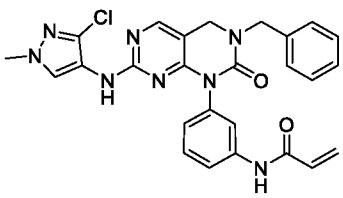
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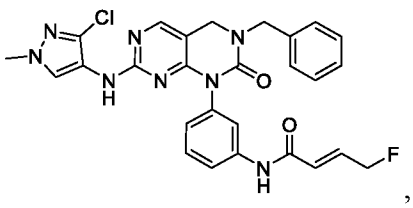
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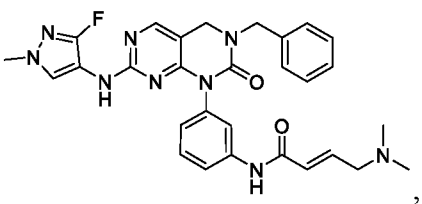
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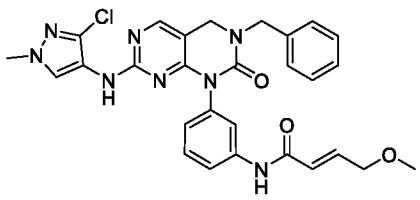
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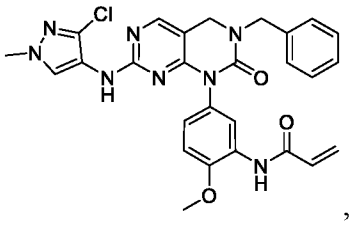
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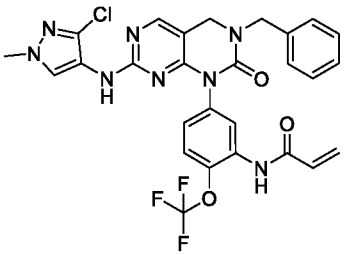
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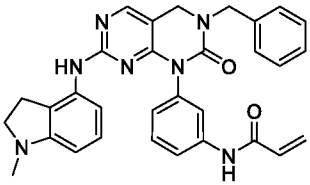
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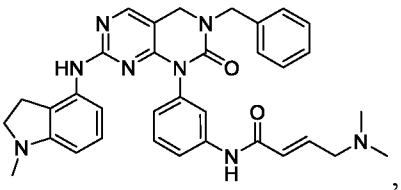
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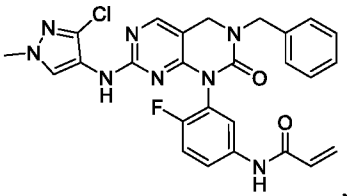
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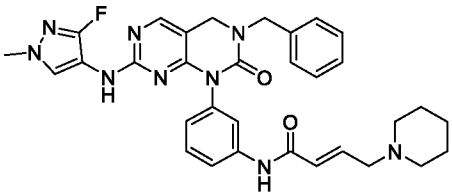
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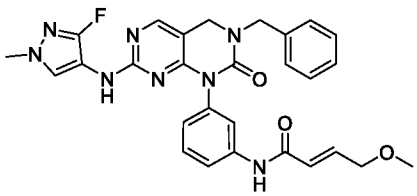
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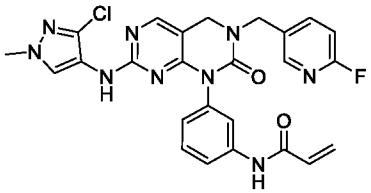
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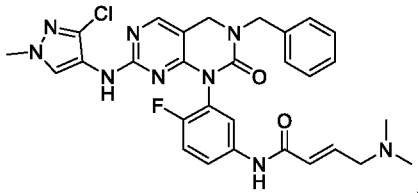
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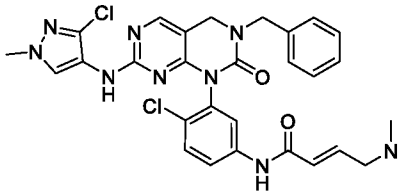
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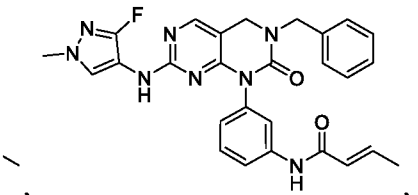
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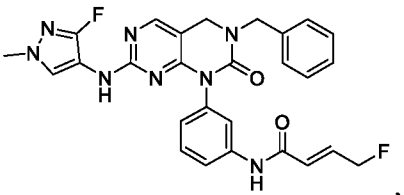
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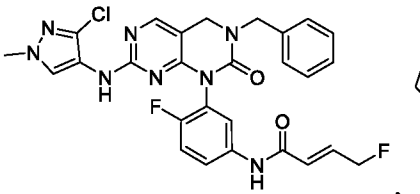
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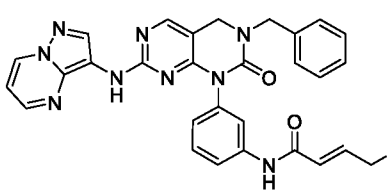
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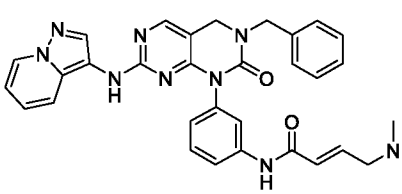
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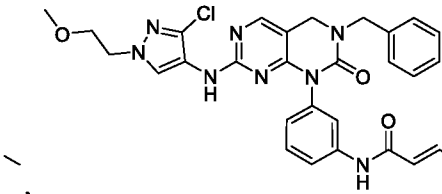
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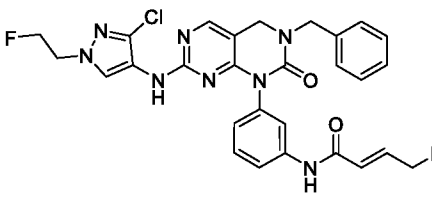
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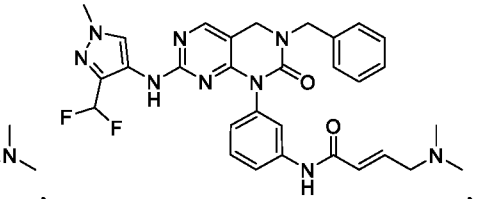
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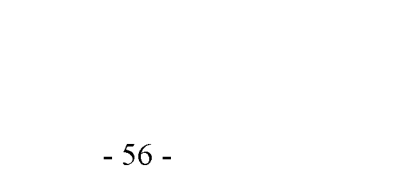
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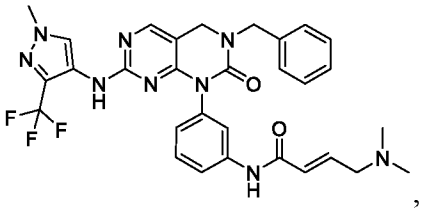
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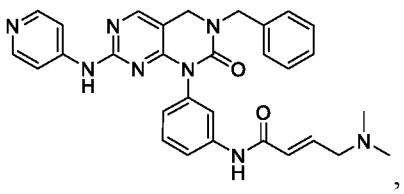
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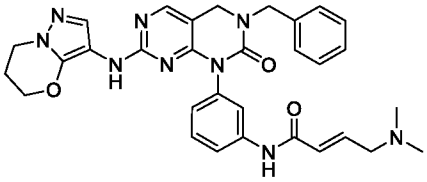
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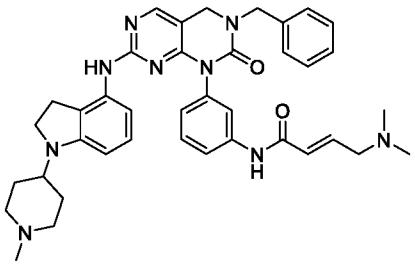
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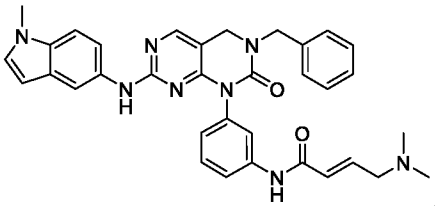
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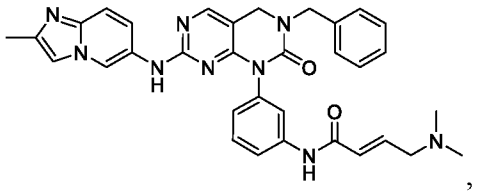
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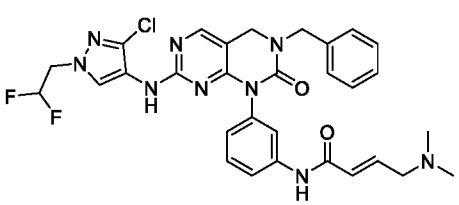
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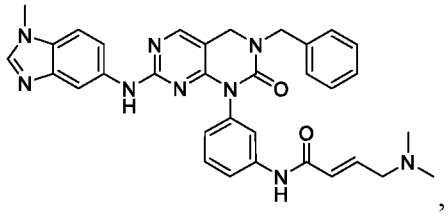
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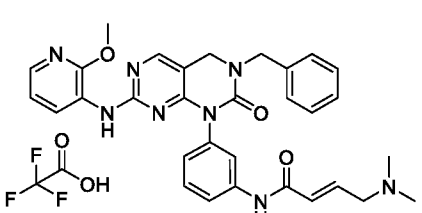
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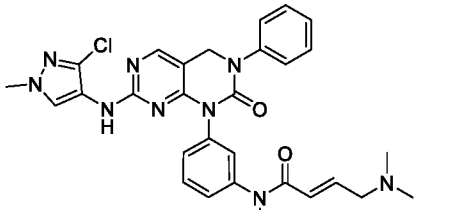
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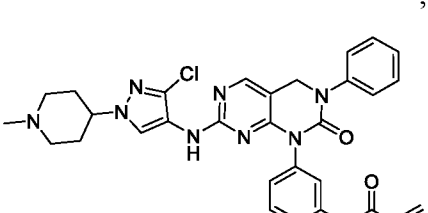
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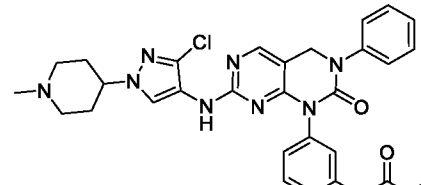
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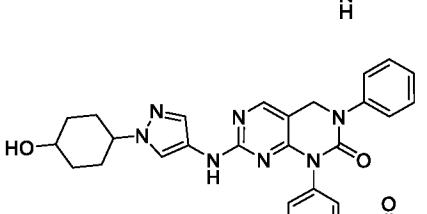
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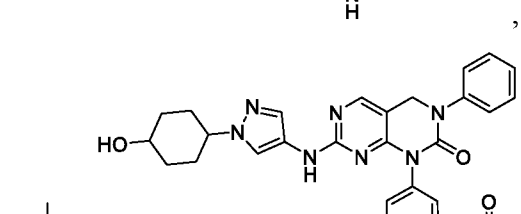
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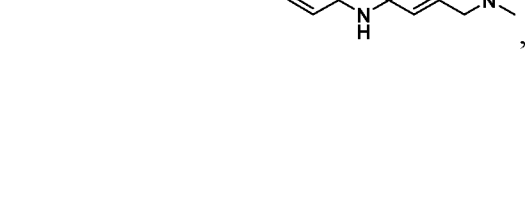
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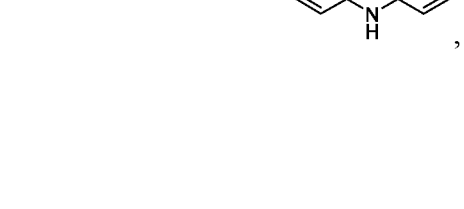
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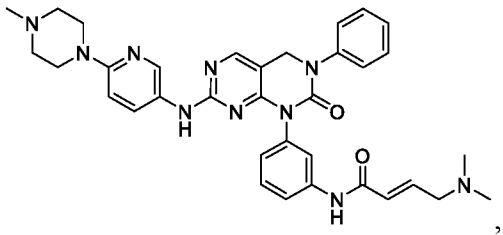
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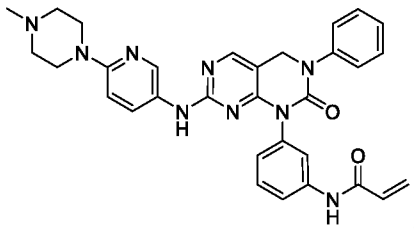
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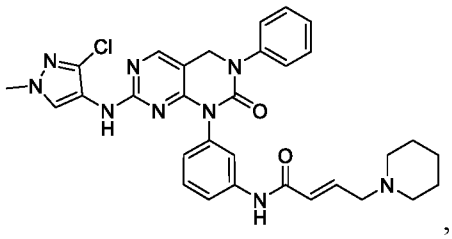
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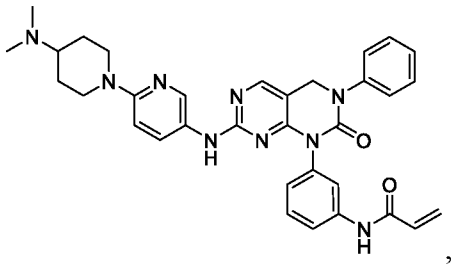
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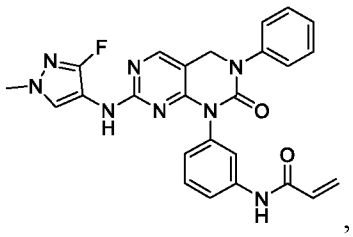
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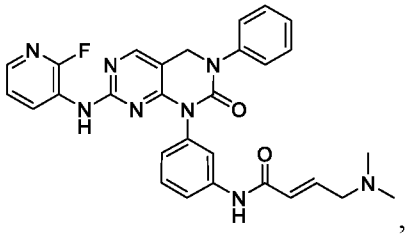
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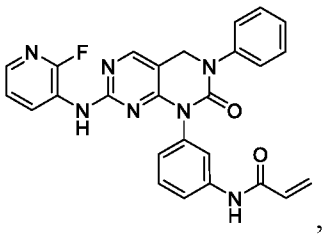
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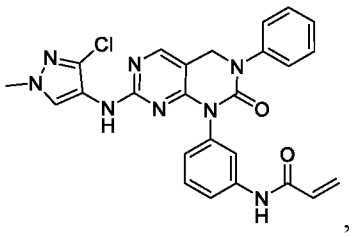
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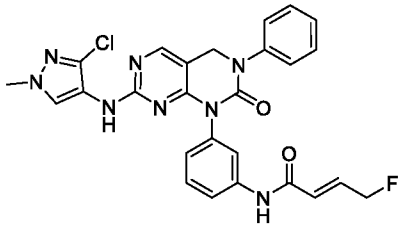
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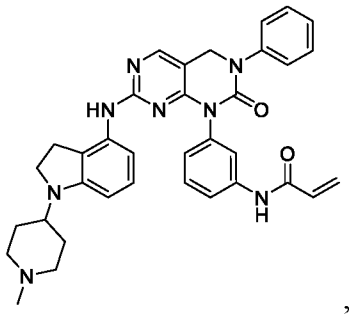
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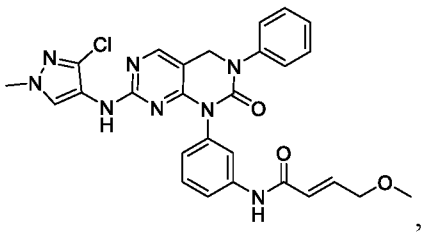
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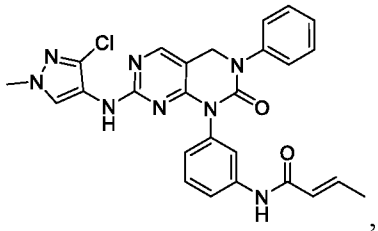
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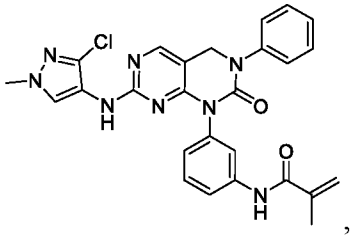
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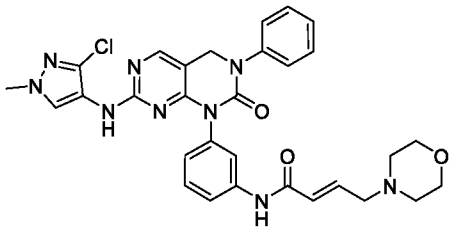
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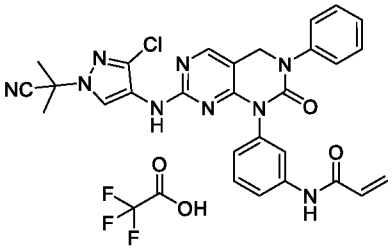
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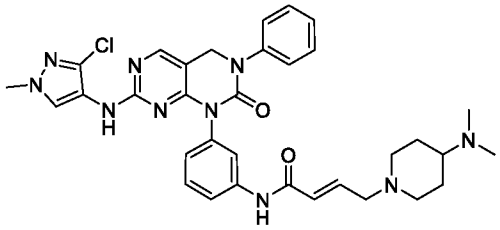
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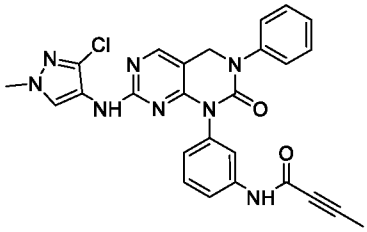
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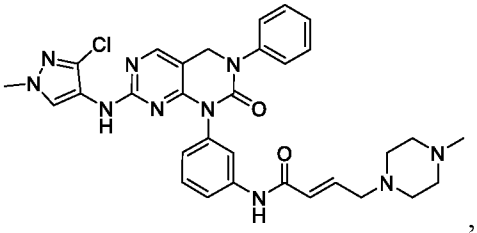
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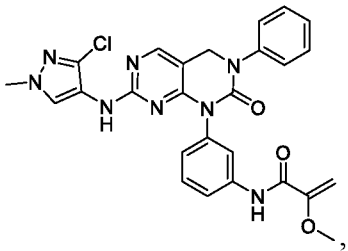
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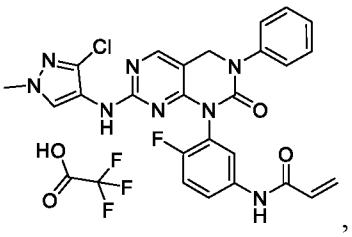
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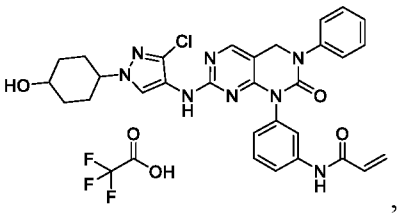
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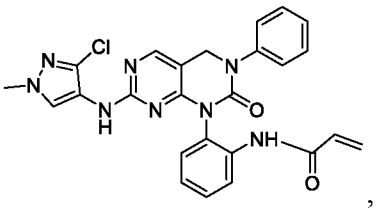
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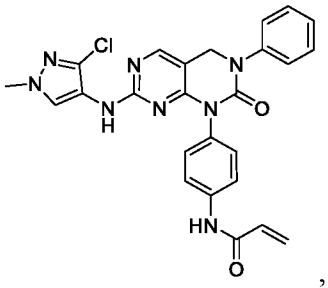
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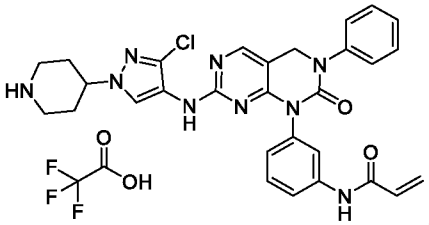
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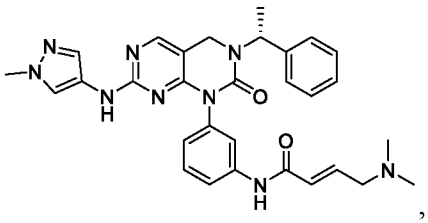
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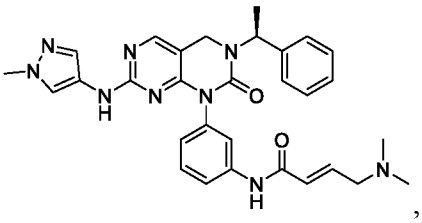
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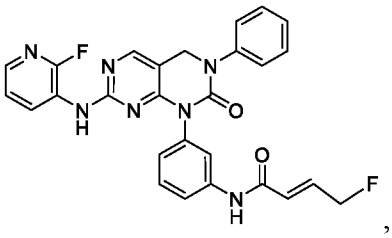
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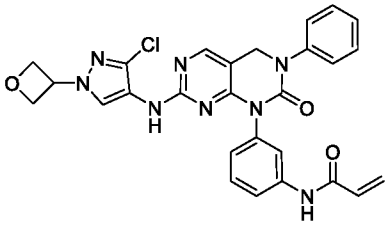
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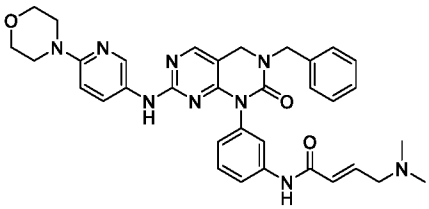
[0128] In some embodiments, the compound of Formula I is selected from: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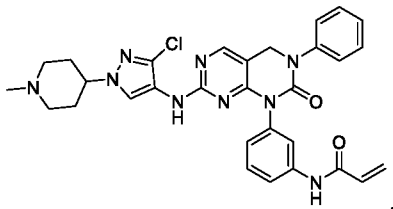
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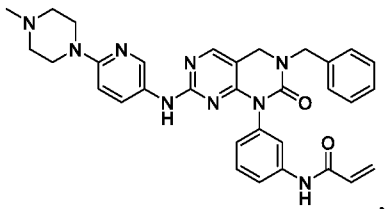
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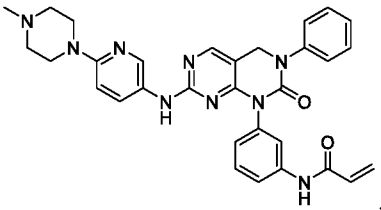
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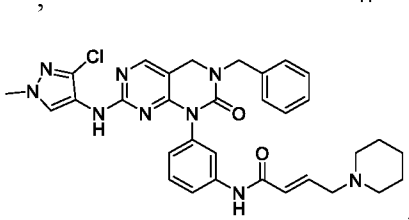
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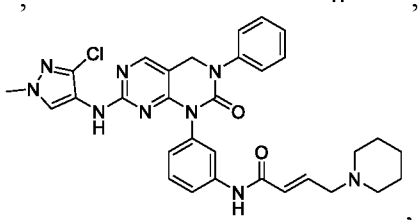
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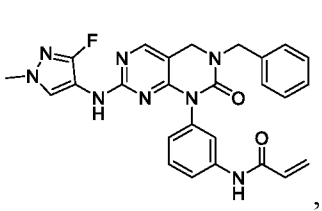
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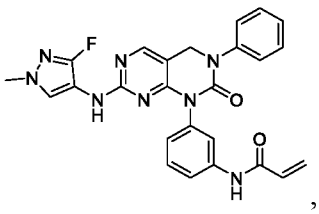
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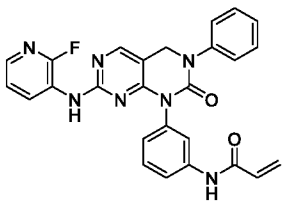
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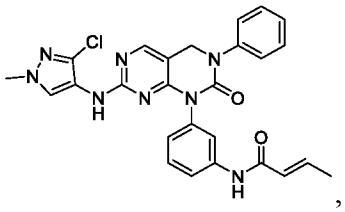
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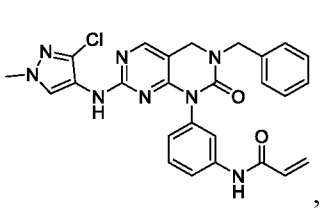
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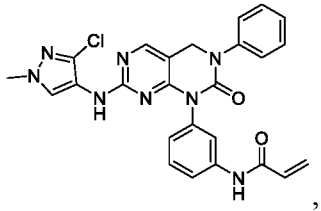
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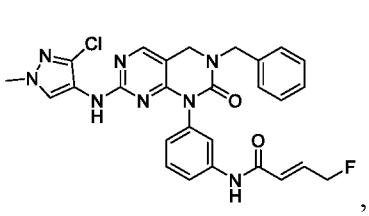
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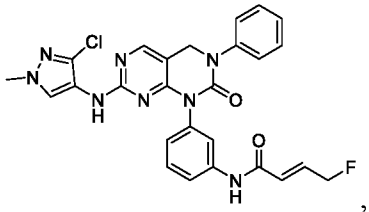
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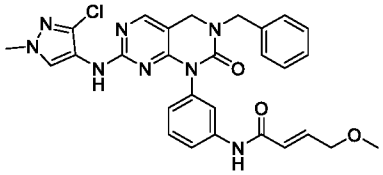
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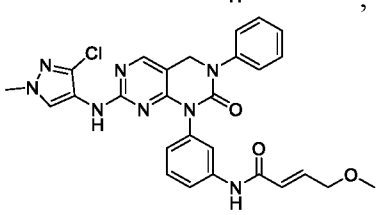
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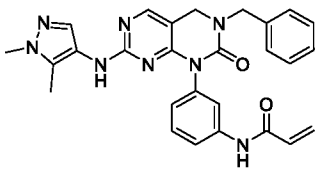
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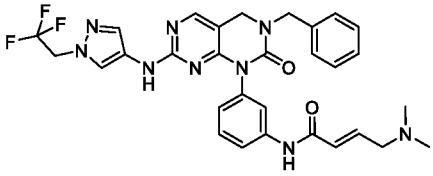
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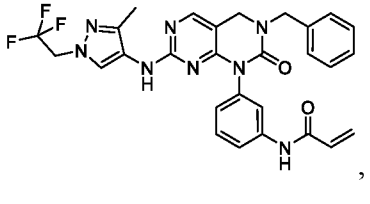
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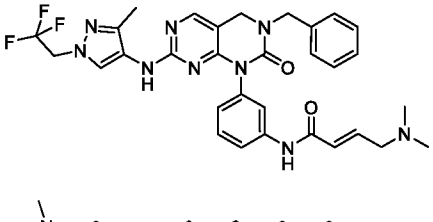
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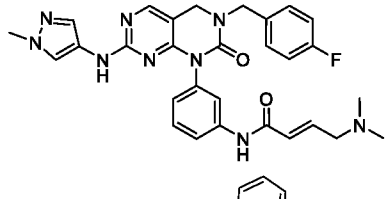
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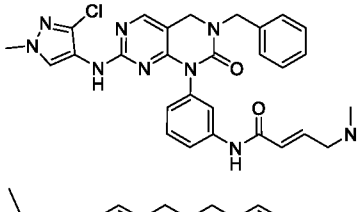
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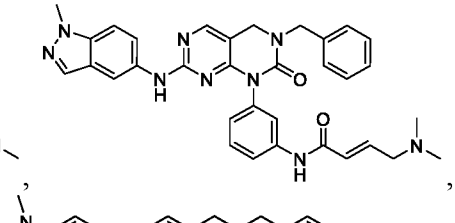
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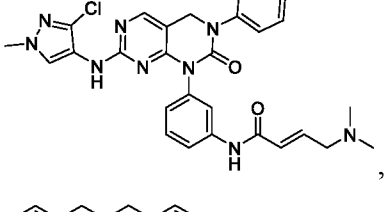
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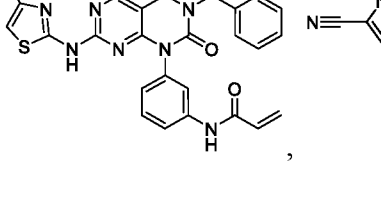
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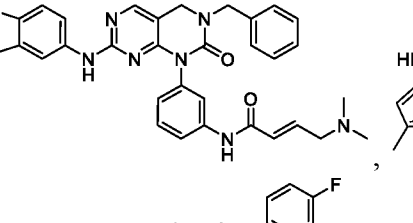
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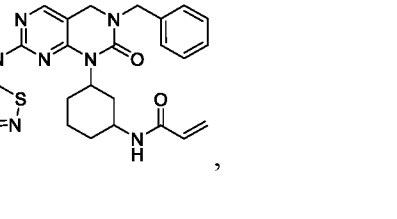
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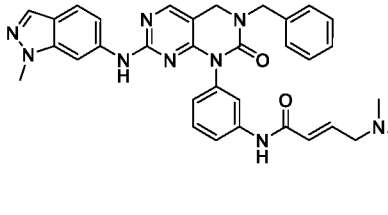
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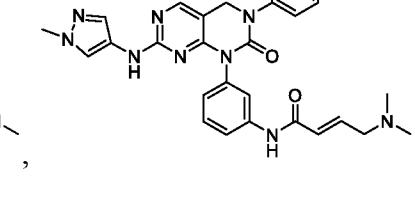
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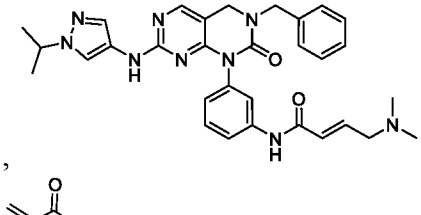
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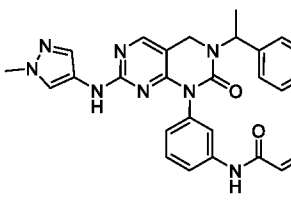
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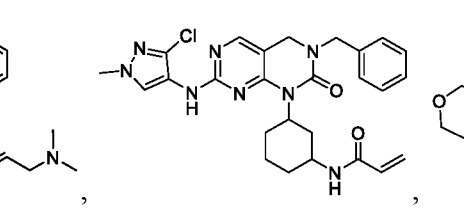
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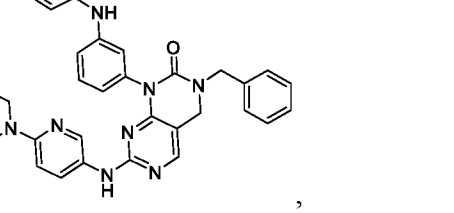
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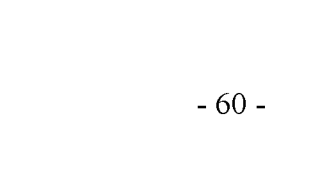
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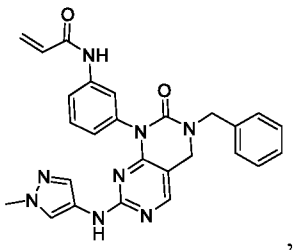
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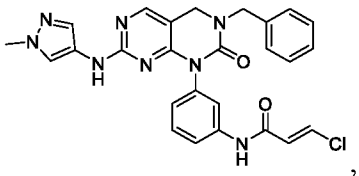
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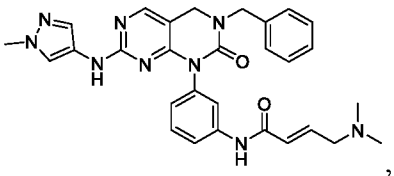
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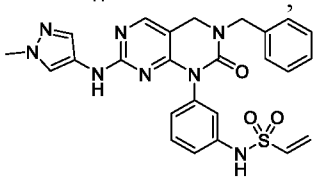
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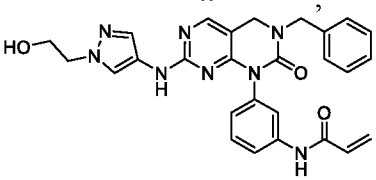
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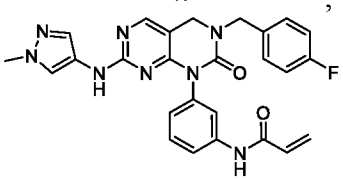
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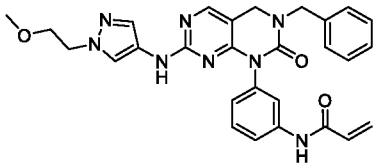
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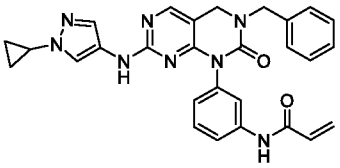
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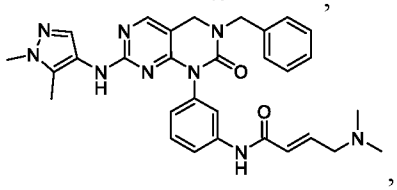
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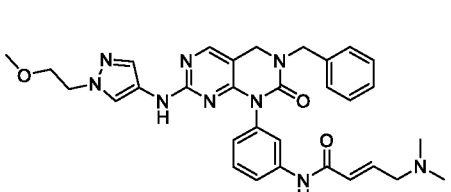
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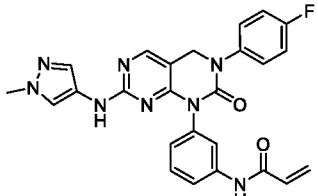
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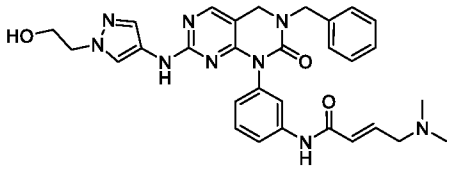
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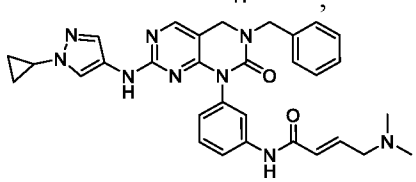
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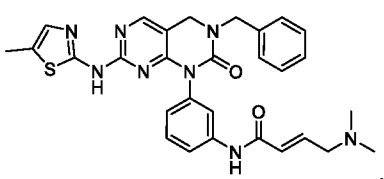
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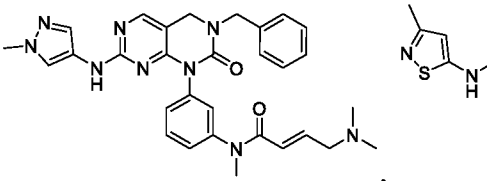
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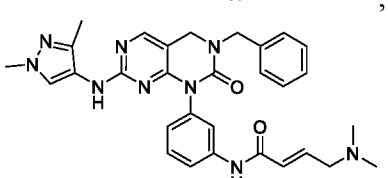
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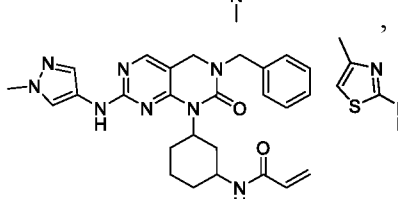
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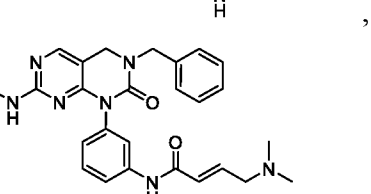
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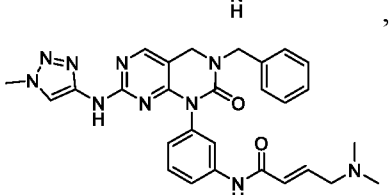
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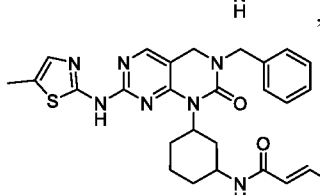
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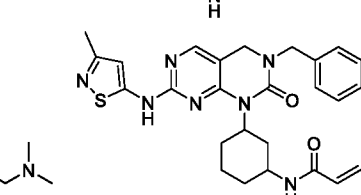
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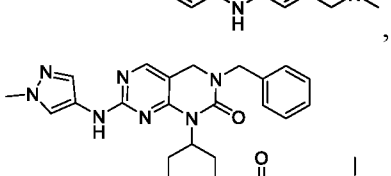
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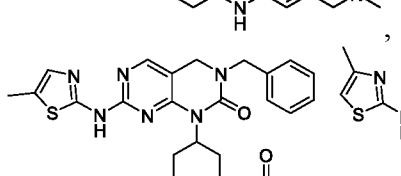
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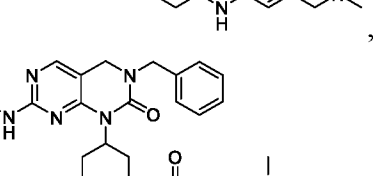
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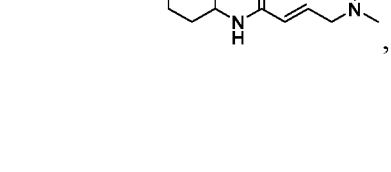
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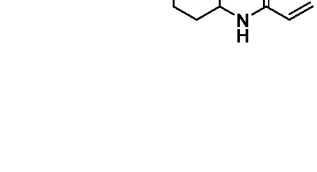
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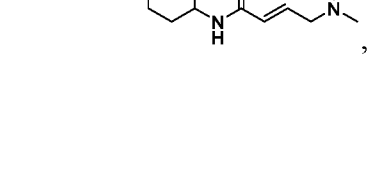
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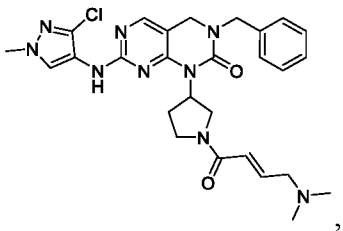
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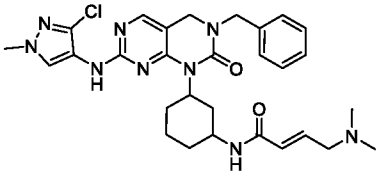
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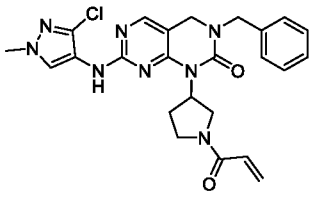
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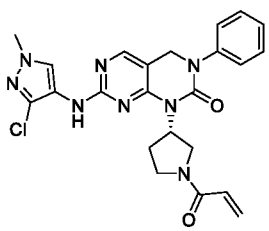
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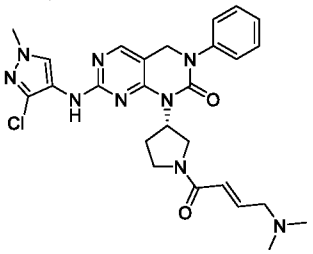
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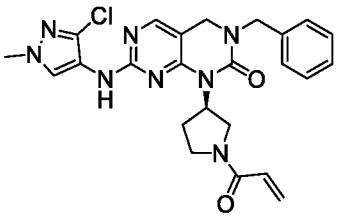
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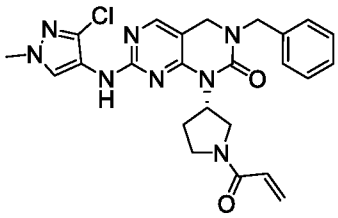
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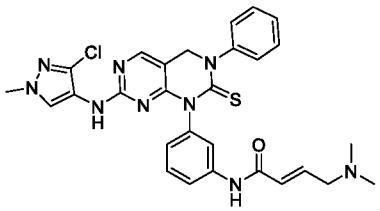
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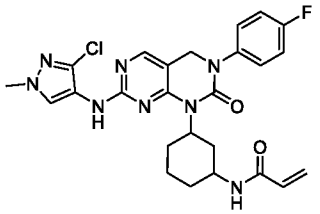
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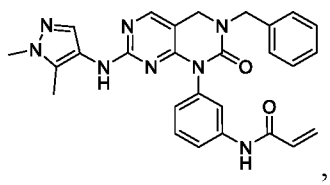
[0129] In some embodiments, the compound of Formula I is selected from: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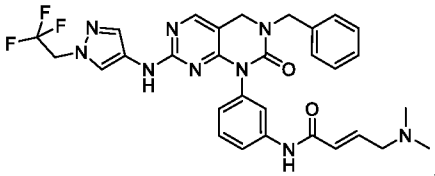
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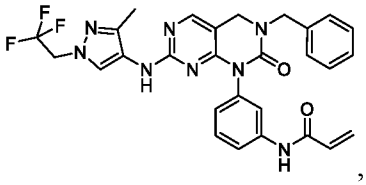
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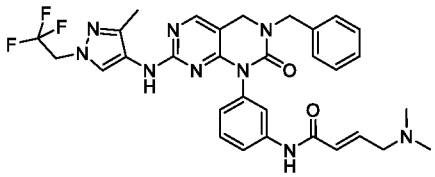
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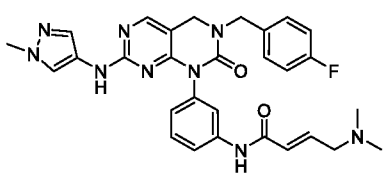
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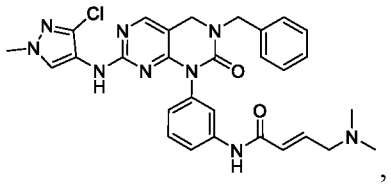
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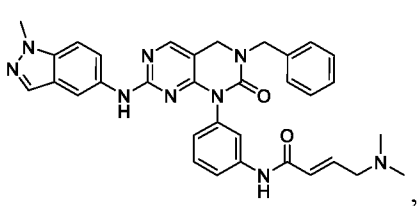
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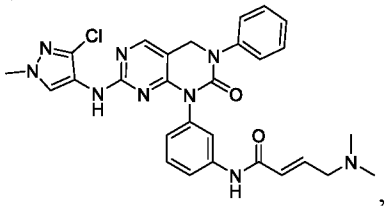
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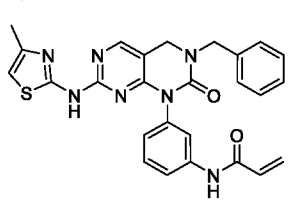
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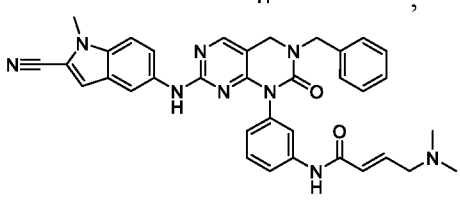
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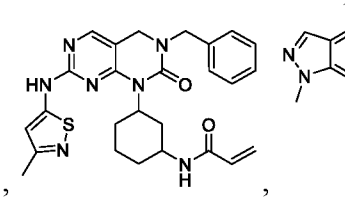
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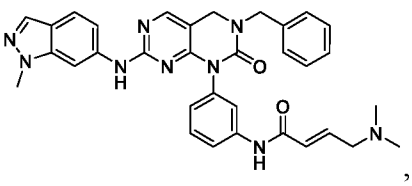
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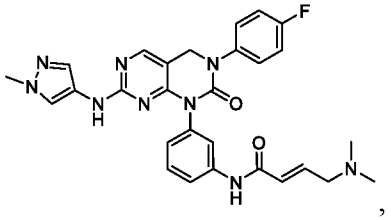
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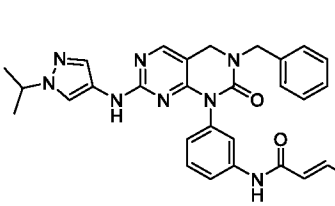
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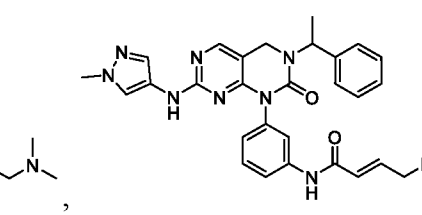
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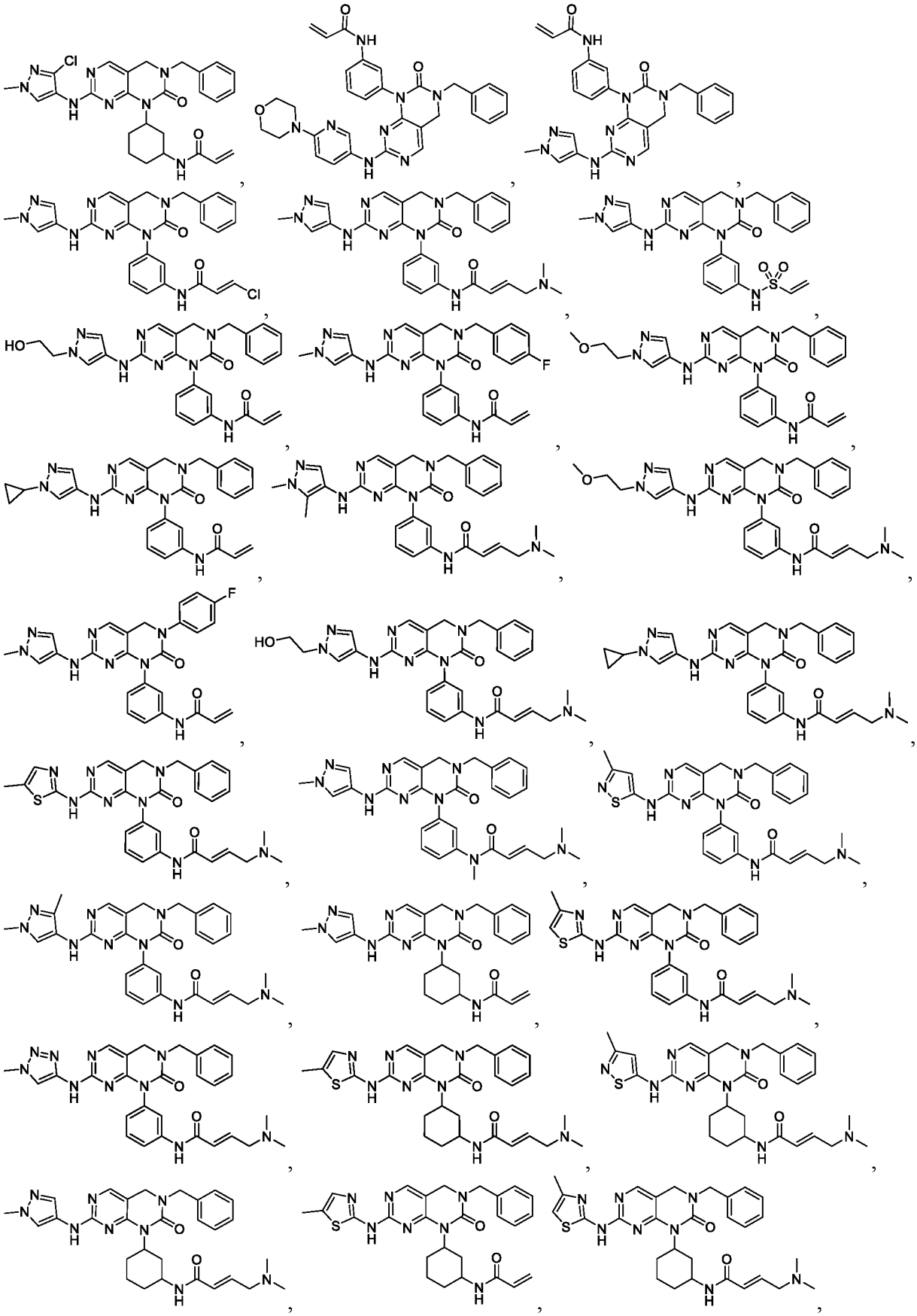

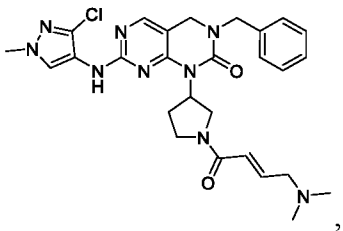
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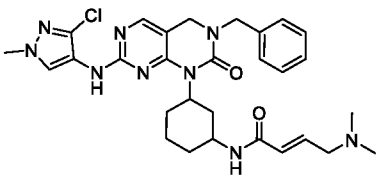
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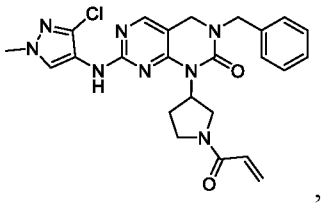
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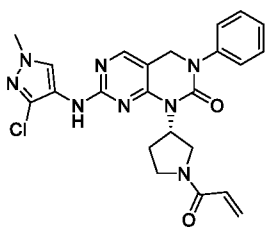
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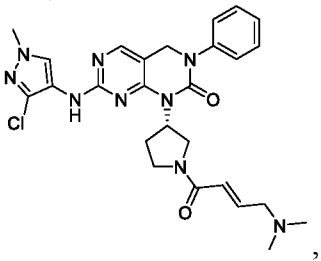
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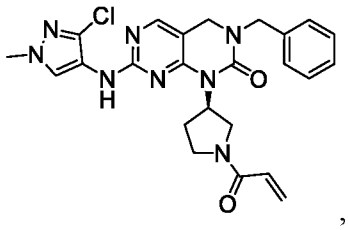
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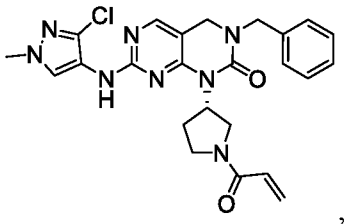
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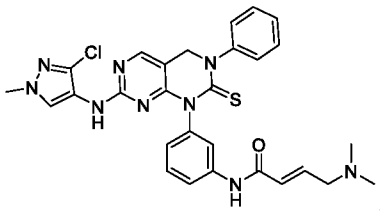
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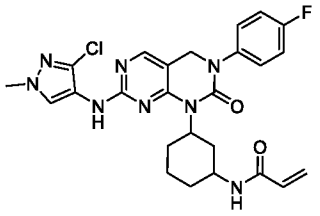
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[0130] In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0131] Particular embodiments of the present disclosure are compounds of Formula I or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, selected from the group consisting of,

N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 1),**

(E)-4-(dimethylamino)-N-(3-(3-(4-fluorobenzyl)-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 2),**

N-(3-(3-(4-fluorobenzyl)-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 3),**

N-(3-(3-benzyl-7-((1,5-dimethyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 4),**

N-(3-(3-benzyl-7-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 5),**

N-(3-(3-benzyl-7-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 6),**

(E)-N-(3-(3-benzyl-7-((1-cyclopropyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 7),**

(E)-N-(3-(3-benzyl-7-((3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 8),**

(E)-N-(3-(3-benzyl-7-((1-isopropyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 9),**

(E)-4-(dimethylamino)-N-(3-(7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-(1-phenylethyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 10),**

(E)-N-(3-(3-benzyl-7-((1,5-dimethyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 11),**

(E)-N-(3-(3-benzyl-2-oxo-7-((1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 12),**

N-(3-(3-benzyl-7-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 13),**

(E)-N-(3-(3-benzyl-7-((1-(2-hydroxyethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 14),**

N-(3-(3-benzyl-7-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 15),**

(E)-N-(3-(3-benzyl-7-((1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 16),**

N-(3-(3-(4-fluorophenyl)-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 17),**

(E)-4-(dimethylamino)-N-(3-(3-(4-fluorophenyl)-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 18),**

(E)-N-(3-(3-benzyl-7-((5-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 19),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 20),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)-N-methylbut-2-enamide **(Compound 21),**

(E)-N-(3-(3-benzyl-7-((3-methylisothiazol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 22),**

(E)-N-(3-(3-benzyl-7-((1,3-dimethyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 23),**

N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)acrylamide **(Compound 24),**

N-(3-(3-benzyl-7-((4-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 25),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-1,2,3-triazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 26),**

(E)-N-(3-(3-benzyl-7-((5-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide **(Compound 27),**

N-(3-(3-benzyl-7-((3-methylisothiazol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)acrylamide **(Compound 28),**

(E)-N-(3-(3-benzyl-7-((4-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide **(Compound 29),**

N-(3-(3-benzyl-7-((5-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)acrylamide **(Compound 30),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide **(Compound 31),**

(E)-N-(3-(3-benzyl-7-((3-methylisothiazol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide **(Compound 32),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)-4-(dimethylamino)but-2-enamide **(Compound 33),**

(E)-3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-1-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(Compound 34),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 35),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-(4-fluorophenyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)acrylamide **(Compound 36),**

1-(1-acryloylpyrrolidin-3-yl)-3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(Compound 37), (Racemic),**

(R)-1-(1-acryloylpyrrolidin-3-yl)-3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one**(Compound 38), (Enantiomer 1),**

(S)-1-(1-acryloylpyrrolidin-3-yl)-3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(Compound 39), (Enantiomer 2),**

N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)cyclohexyl)acrylamide **(Compound 40),**

(S)-1-(1-acryloylpyrrolidin-3-yl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(Compound 41),**

(S,E)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-1-(1-(4-(dimethylamino)but-2-enoyl)pyrrolidin-3-yl)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(Compound 42),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-indazol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 43),**

(E)-N-(3-(3-benzyl-7-((2-cyano-1-methyl-1H-indol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 44),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-indazol-6-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 45),**

N-(3-(3-benzyl-7-((6-morpholinopyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 46),**

N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)ethenesulfonamide **(Compound 47),**

(E)-N-(3-(3-benzyl-7-((4-methylthiazol-2-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 48),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 49),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-3-chloroacrylamide **(Compound 50),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 51),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 52),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 53),**

(E)-N-(3-(3-benzyl-7-((6-morpholinopyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 54),**

(E)-N-(3-(3-benzyl-7-((2-morpholinopyrimidin-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 55),**

(E)-N-(3-(3-benzyl-7-((3-methoxy-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 56),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-(4-fluorobenzyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 57),**

(E)-N-(3-(3-benzyl-7-(isoxazol-4-ylamino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 58),**

(E)-N-(3-(3-benzyl-7-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 59),**

(E)-N-(3-(3-benzyl-7-((3-methylisoxazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 60),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-(2,4-difluorobenzyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 61),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-((2-methoxypyridin-4-yl)methyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 62),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)-N-methylbut-2-enamide **(Compound 63),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrido[4,3-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 64),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide trifluoroacetate salt **(Compound 65),**

(E)-N-(3-(3-benzyl-7-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 66),**

N-(3-(3-benzyl-7-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 67),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-(2,4-dimethylbenzyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 68),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-(2,4-dimethylbenzyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 69),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(piperidin-1-yl)but-2-enamide **(Compound 70),**

N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 71),**

N-(3-(3-benzyl-7-((6-(4-(dimethylamino)piperidin-1-yl)pyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 72),**

N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 73),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-fluorobut-2-enamide **(Compound 74),**

(E)-N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 75),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-methoxybut-2-enamide **(Compound 76),**

N-(5-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-2-methoxyphenyl)acrylamide **(Compound 77),**

N-(5-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-2-(trifluoromethoxy)phenyl)acrylamide **(Compound 78),**

N-(3-(3-benzyl-7-((1-methylindolin-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 79),**

(E)-N-(3-(3-benzyl-7-((1-methylindolin-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 80),**

N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-4-fluorophenyl)acrylamide **(Compound 81),**

(E)-N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(piperidin-1-yl)but-2-enamide **(Compound 82),**

(E)-N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-methoxybut-2-enamide **(Compound 83),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-((6-fluoropyridin-3-yl)methyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 84),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-4-fluorophenyl)-4-(dimethylamino)but-2-enamide **(Compound 85),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-4-chlorophenyl)-4-(dimethylamino)but-2-enamide **(Compound 86),**

(E)-N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 87),**

(E)-N-(3-(3-benzyl-7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-fluorobut-2-enamide (**Compound 88**),

(E)-N-(3-(3-benzyl-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-4-fluorophenyl)-4-fluorobut-2-enamide (**Compound 89**),

(E)-N-(3-(3-benzyl-2-oxo-7-(pyrazolo[1,5-a]pyrimidin-3-ylamino)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 90),**

(E)-N-(3-(3-benzyl-2-oxo-7-(pyrazolo[1,5-a]pyridin-3-ylamino)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 91),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-(2-methoxyethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 92),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-(2-fluoroethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 93),**

(E)-N-(3-(3-benzyl-7-((3-(difluoromethyl)-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 94),**

(E)-N-(3-(3-benzyl-7-((1-methyl-3-(trifluoromethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 95),**

(E)-N-(3-(3-benzyl-2-oxo-7-(pyridin-4-ylamino)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 96),**

(E)-N-(3-(3-benzyl-7-((6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 97),**

(E)-N-(3-(3-benzyl-7-((1-(1-methylpiperidin-4-yl)indolin-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 98),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-indol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 99),**

(E)-N-(3-(3-benzyl-7-((2-methylimidazo[1,2-a]pyridin-6-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 100),**

(E)-N-(3-(3-benzyl-7-((3-chloro-1-(2,2-difluoroethyl)-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 101),**

(E)-N-(3-(3-benzyl-7-((1-methyl-1H-benzo[d]imidazol-5-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 102),**

(E)-N-(3-(3-benzyl-7-((2-methoxypyridin-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide trifluoroacetate salt **(Compound 103),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)-N-methylbut-2-enamide **(Compound 104),**

N-(3-(7-((3-chloro-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 105),**

(E)-N-(3-(7-((3-chloro-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **(Compound 106),**

(E)-4-(dimethylamino)-N-(3-(7-((1-(4-hydroxycyclohexyl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 107),**

N-(3-(7-((1-(4-hydroxycyclohexyl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 108),**

(E)-4-(dimethylamino)-N-(3-(7-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 109),**

N-(3-(7-((6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 110),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(piperidin-1-yl)but-2-enamide **(Compound 111),**

N-(3-(7-((6-(4-(dimethylamino)piperidin-1-yl)pyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 112),**

N-(3-(7-((3-fluoro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 113),**

(E)-4-(dimethylamino)-N-(3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 114),**

N-(3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 115),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 116),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-fluorobut-2-enamide **(Compound 117),**

N-(3-(7-((1-(1-methylpiperidin-4-yl)indolin-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 118),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-methoxybut-2-enamide **(Compound 119),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 120),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)methacrylamide **(Compound 121),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-morpholinobut-2-enamide **(Compound 122),**

N-(3-(7-((3-chloro-1-(2-cyanopropan-2-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide trifluoroacetate salt **(Compound 123),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(4-(dimethylamino)piperidin-1-yl)but-2-enamide **(Compound 124),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-ynamide **(Compound 125),**

(E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(4-methylpiperazin-1-yl)but-2-enamide **(Compound 126),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-2-methoxyacrylamide **(Compound 127),**

N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)-4-fluorophenyl)acrylamide trifluoroacetate salt **(Compound 128),**

N-(3-(7-((3-chloro-1-(4-hydroxycyclohexyl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide trifluoroacetate salt **(Compound 129),**

N-(2-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 130),**

N-(4-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 131),**

N-(3-(7-((3-chloro-1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide trifluoroacetate salt **(Compound 132),**

(R,E)-4-(dimethylamino)-N-(3-(7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-(1-phenylethyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 133),**

(S,E)-4-(dimethylamino)-N-(3-(7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-(1-phenylethyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 134),**

(E)-4-fluoro-N-(3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide **(Compound 135),**

N-(3-(7-((3-chloro-1-(oxetan-3-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide **(Compound 136)**.

[0132] An embodiment of the present disclosure relates to a compound of Formula I or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, for treating disease associated with epidermal growth factor receptor (EGFR) family kinases.

[0133] Another embodiment of the present disclosure relates to a compound of Formula I or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, for treating cancer.

[0134] Another embodiment of the present disclosure relates to a compound Formula I, or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof, for treating disease or condition associated with non-small cell or small cell lung cancer or prostate cancer or head and neck cancer or breast cancer or colorectal cancer.

[0135] The present disclosure relates to a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier, optionally in combination with one or more other pharmaceutical compositions.

[0136] The present disclosure further relates to the process of preparation of compounds of Formula I or its stereoisomers, tautomers, pharmaceutically acceptable salts, polymorphs, solvates and hydrates thereof.

Uses

[0137] Some embodiments provided herein describe a class of compounds that are useful as epidermal growth factor receptor (EGFR) family kinase inhibitors. Some embodiments provided herein describe a class of compounds that are useful as HER2 inhibitors. Some embodiments provided herein describe a class of compounds that are useful as EGFR inhibitors. Some embodiments provided herein describe a class of compounds that are useful as EGFR del19/T790M inhibitors. Some embodiments provided herein describe a class of compounds that are useful as EGFR L858R/T790M inhibitors. In some embodiments, the compounds described herein have improved potency and/or beneficial activity profiles and/or beneficial selectivity profiles and/or increased efficacy and/or improved safety profiles (such as reduced side effects) and/or improved pharmacokinetic properties. In some embodiments, the compounds described herein are selective inhibitors of EGFR del19/T790M over WT EGFR. In some embodiments, the compounds described herein are selective inhibitors of EGFR L858R/T790M over WT EGFR.

[0138] In some embodiments, the compounds described herein are useful to treat, prevent or ameliorate a disease or condition which displays drug resistance associated with EGFR del19/T790M activation. In some embodiments, the compounds described herein are useful to treat, prevent or ameliorate a disease or condition which displays drug resistance associated with EGFR L858R/T790M activation.

[0139] In some embodiments, EGFR family kinase mutants are detected with a commercially available test kit. In some embodiments, EGFR family kinase mutants are detected with a reverse transcription polymerase chain reaction (RT-PCR)-based method. In some embodiments, EGFR family kinase mutants are detected with a sequencing-based method. In some embodiments, EGFR family kinase mutants are detected with a mass spectrometry genotyping-based method. In some embodiments, EGFR family kinase mutants are detected with an immunohistochemistry-based method. In some embodiments, EGFR family kinase mutants are detected with a molecular diagnostics panel. In some embodiments, EGFR family kinase mutants are detected from a tumor sample. In some embodiments, EGFR family kinase mutants

are detected from circulating DNA. In some embodiments, EGFR family kinase mutants are detected from tumor cells.

[0140] In one aspect, provided herein is a method of inhibiting an epidermal growth factor receptor (EGFR) family kinase mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0141] In another aspect, provided herein is a method of inhibiting a human epidermal growth factor receptor 2 (HER2) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP. In some embodiments, the HER2 mutant is A775ins_G776insYVMA. In some embodiments, the HER2 mutant is A775_G776insSVMA. In some embodiments, the HER2 mutant is A775_G776insVVMA. In some embodiments, the HER2 mutant is G776del insVC. In some embodiments, the HER2 mutant is G776del insLC. In some embodiments, the HER2 mutant is G776del insAV. In some embodiments, the HER2 mutant is G776del insAVGC. In some embodiments, the HER2 mutant is S310F. In some embodiments, the HER2 mutant is S310Y. In some embodiments, the HER2 mutant is p95. In some embodiments, the HER2 mutant is V842I. In some embodiments, the HER2 mutant is P780_Y781insGSP.

[0142] In another aspect, provided herein is a method of inhibiting an epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0143] In another aspect, provided herein is a method of inhibiting a drug-resistant epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the drug-resistant EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR.

[0144] In another aspect, provided herein is a method of inhibiting human epidermal growth factor receptor 2 (HER2) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of a HER2 mutant relative to

wild-type EGFR. In some embodiments, the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP. In some embodiments, the HER2 mutant is A775ins_G776insYVMA. In some embodiments, the HER2 mutant is A775_G776insSVMA. In some embodiments, the HER2 mutant is A775_G776insVVMA. In some embodiments, the HER2 mutant is G776del insVC. In some embodiments, the HER2 mutant is G776del insLC. In some embodiments, the HER2 mutant is G776del insAV. In some embodiments, the HER2 mutant is G776del insAVGC. In some embodiments, the HER2 mutant is S310F. In some embodiments, the HER2 mutant is S310Y. In some embodiments, the HER2 mutant is p95. In some embodiments, the HER2 mutant is V842I. In some embodiments, the HER2 mutant is P780_Y781insGSP.

[0145] In another aspect, provided herein is a method of inhibiting epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of an EGFR mutant relative to wild-type EGFR.

[0146] In some embodiments, the EGFR mutant comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutant is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR. In some embodiments, the EGFR mutant is del19/T790M EGFR. In some embodiments, the EGFR mutant is L858R/T790M EGFR.

[0147] In another aspect, provided herein is a method of treating a disease or disorder associated with epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

[0148] In some embodiments, the disease or disorder in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame

deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP. In some embodiments, the HER2 mutation is A775ins_G776insYVMA. In some embodiments, the HER2 mutation is A775_G776insSVMA. In some embodiments, the HER2 mutation is A775_G776insVVMA. In some embodiments, the HER2 mutation is G776del insVC. In some embodiments, the HER2 mutation is G776del insLC. In some embodiments, the HER2 mutation is G776del insAV. In some embodiments, the HER2 mutation is G776del insAVGC. In some embodiments, the HER2 mutation is S310F. In some embodiments, the HER2 mutation is S310Y. In some embodiments, the HER2 mutation is p95. In some embodiments, the HER2 mutation is V842I. In some embodiments, the HER2 mutation is P780_Y781insGSP.

[0149] In some embodiments, the disease or disorder in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR. In some embodiments, the EGFR mutation is L858R/T790M EGFR.

[0150] In another aspect, provided herein is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer displays drug resistance associated with EGFR del19/T790M activation. In some embodiments, the cancer displays drug resistance associated with EGFR L858R/T790M activation. Other embodiments provided herein describe the use of the compounds described herein for treating cancer.

[0151] In some embodiments, the cancer is selected from bladder cancer, prostate cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, and non-small cell lung cancer. In some embodiments, the cancer

is selected from non-small cell lung cancer, prostate cancer, head and neck cancer, breast cancer, colorectal cancer, and glioblastoma. In some embodiments, the cancer is non-small cell lung cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is glioblastoma.

[0152] In some embodiments, the cancer in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP. In some embodiments, the HER2 mutation is A775ins_G776insYVMA. In some embodiments, the HER2 mutation is A775_G776insSVMA. In some embodiments, the HER2 mutation is A775_G776insVVMA. In some embodiments, the HER2 mutation is G776del insVC. In some embodiments, the HER2 mutation is G776del insLC. In some embodiments, the HER2 mutation is G776del insAV. In some embodiments, the HER2 mutation is G776del insAVGC. In some embodiments, the HER2 mutation is S310F. In some embodiments, the HER2 mutation is S310Y. In some embodiments, the HER2 mutation is p95. In some embodiments, the HER2 mutation is V842I. In some embodiments, the HER2 mutation is P780_Y781insGSP.

[0153] In some embodiments, the cancer in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR. In some embodiments, the EGFR mutation is L858R/T790M EGFR.

[0154] In another aspect, provided herein is a method of treating inflammatory disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Also described herein is the use of the compounds described herein for treating inflammatory diseases

associated with EGFR del19/T790M activation. Also described herein is the use of the compounds described herein for treating inflammatory diseases associated with EGFR L858R/T790M activation.

[0155] In some embodiments, the inflammatory disease is selected from psoriasis, eczema, and atherosclerosis. In some embodiments, the inflammatory disease is psoriasis. In some embodiments, the inflammatory disease is eczema. In some embodiments, the inflammatory disease is atherosclerosis.

[0156] In some embodiments, the inflammatory disease in the subject comprises a HER2 mutation. In some embodiments, the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30. In some embodiments, the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP. In some embodiments, the HER2 mutation is A775ins_G776insYVMA. In some embodiments, the HER2 mutation is A775_G776insSVMA. In some embodiments, the HER2 mutation is A775_G776insVVMA. In some embodiments, the HER2 mutation is G776del insVC. In some embodiments, the HER2 mutation is G776del insLC. In some embodiments, the HER2 mutation is G776del insAV. In some embodiments, the HER2 mutation is G776del insAVGC. In some embodiments, the HER2 mutation is S310F. In some embodiments, the HER2 mutation is S310Y. In some embodiments, the HER2 mutation is p95. In some embodiments, the HER2 mutation is V842I. In some embodiments, the HER2 mutation is P780_Y781insGSP.

[0157] In some embodiments, the inflammatory disease in the subject comprises an EGFR mutation. In some embodiments, the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21. In some embodiments, the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR. In some embodiments, the EGFR mutation is del19/T790M EGFR. In some embodiments, the EGFR mutation is L858R/T790M EGFR.

Administration and Pharmaceutical Composition

[0158] In certain embodiments, the EGFR inhibitory compound as described herein is administered as a pure chemical. In other embodiments, the EGFR inhibitory compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0159] Provided herein is a pharmaceutical composition comprising at least one EGFR inhibitory compound as described herein, or a stereoisomer, pharmaceutically acceptable salt, or N-oxide thereof, together with one or more pharmaceutically acceptable carriers. The carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (i.e., the subject or patient) of the composition.

[0160] One embodiment provides a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and a pharmaceutically acceptable excipient.

[0161] In certain embodiments, the EGFR inhibitory compound disclosed herein is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0162] Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (See, e.g., Remington: The Science and Practice of Pharmacy (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0163] The dose of the composition comprising at least one EGFR inhibitory compound as described herein differ, depending upon the patient's condition, that is, stage of the disease, general health status, age, and other factors.

[0164] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and

severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome), or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0165] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

EXAMPLES

Example 1: Synthetic procedures

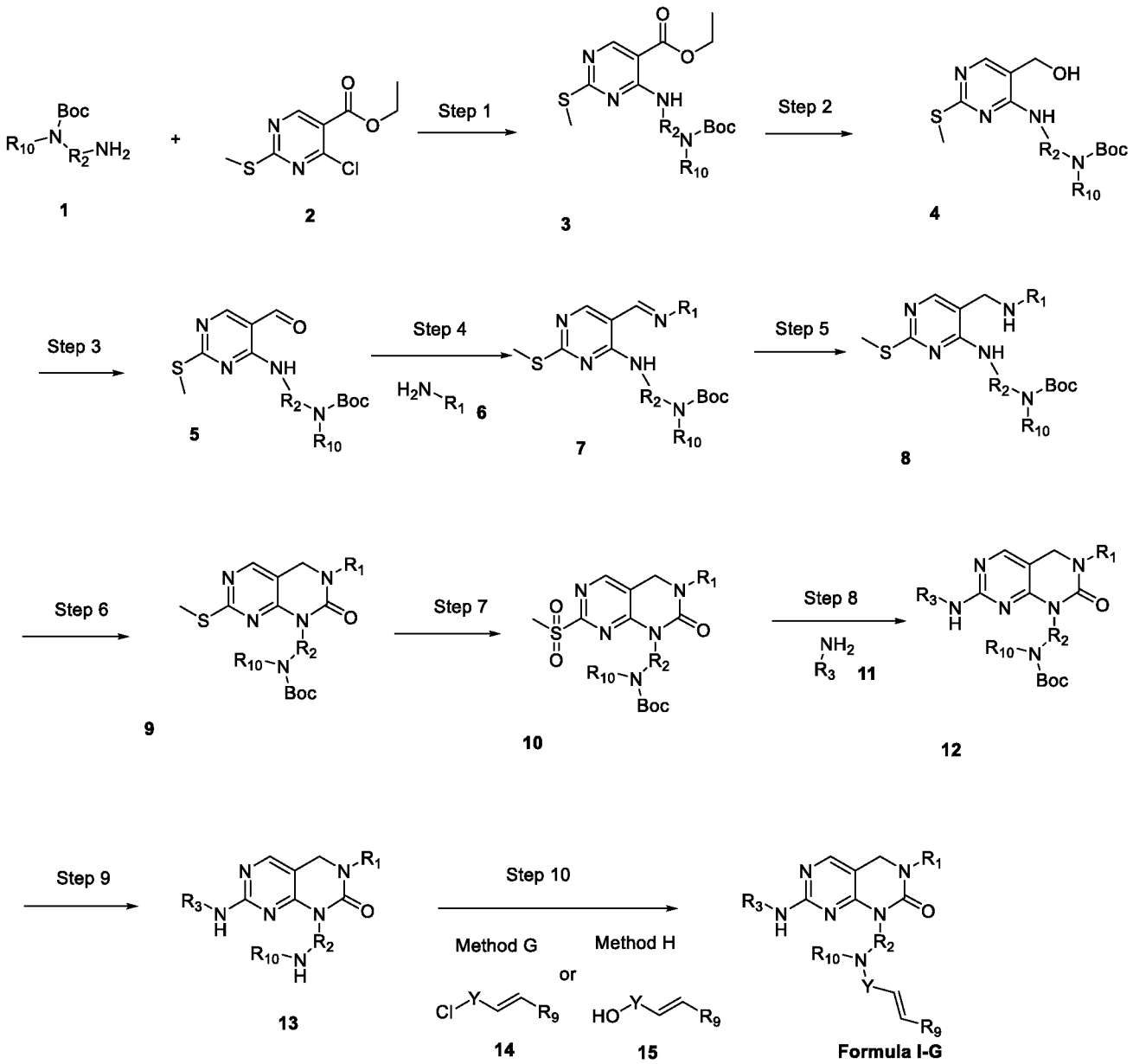
[0166] Yields reported herein refer to purified products (unless specified) and are not optimised. Analytical TLC was performed on Merck silica gel 60 F_{254} aluminum-backed plates. Compounds were visualised by UV light and/or stained either with iodine, potassium permanganate or ninhydrin solution. Flash column chromatography was performed on silica gel (100-200 M) or flash chromatography. ^{1}H-NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer with a BBO (Broad Band Observe) and BBFO (Broad Band Fluorine Observe) probe. Chemical shifts (δ) are expressed in parts per million (ppm) downfield by reference to tetramethylsilane (TMS) as the internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and bs (broad singlet). Coupling constants (*J*) are given in hertz (Hz). LC-MS analyses were performed on either an Acquity BEH C-18 column (2.10 × 100 mm, 1.70 μm) or on a Acquity HSS-T3 column (2.10 × 100 mm, 1.80 μm) using the Electrospray Ionisation (ESI) technique.

[0167] The following solvents, reagents or scientific terminology may be referred to by their abbreviations:

TLC	Thin Layer Chromatography
DCM	Dichloromethane
THF	Tetrahydrofuran
MeOH	Methanol
EtOH	Ethanol
IPA	Isopropyl alcohol
EtOAc	Ethyl acetate
Et_2O	Diethyl ether
DMA	N,N-Dimethylacetamide
DMF	N,N-Dimethylformamide
TEA/Et_3N	Triethylamine

DMSO	Dimethylsulfoxide
DIPEA	Diisopropylethylamine (Hunig's base)
MeI	Methyliodide
NBS	N-Bromosuccinimide
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
DIBAL-H	Diisobutylaluminum hydride
TFA	Trifluoroacetic acid
AcOH	Acetic acid
Boc	tert-butoxycarbonyl
Cat	Catalytic
mL	milliliters
mmol	millimoles
h	hour or hours
min	minute or minutes
g	grams
mg	milligrams
µl	Microlitres
eq	Equivalents
rt or RT	Room temperature, ambient, about 27°C
MS	Mass spectrometry
Boc	tert-Butyloxycarbonyl
m-CPBA	meta-Chloroperbenzoic acid
T3P	Propane phosphonic acid anhydride
BH_3-DMS	*Borane* dimethylsulfide complex
$LiBH_4$	Lithium aluminum hydride
$NaBH_4$	Sodium borohydride
H_2	Hydrogen
Pd/C	Palladium on charcoal
1,2-DCE	1,2-Dichloroethane

General synthetic scheme 1



[0168] The chloropyrimidine derivative **2** is reacted with primary or secondary amine **1** in presence of base and solvent as DMF, DMA, IPA, MeOH, EtOH, preferably, DMF at -20 °C to 150 °C, in order to produce compound **3**. The ester group of compound **3** can be reduced using variety of reducing agents including DIBAL-H, BH_3-DMS, $NaBH_4$, $LiALH_4$, preferably, $LiAlH_4$ in presence of organic solvent such as THF to obtain compound **4**. The alcohol group of compound **4** can be oxidized to aldehyde using activated manganese dioxide in presence of organic solvent such as dichloromethane, or ethylene dichloride to obtain aldehyde **5.** The aldehyde compound **5** is reacted with variety of primary amines **6** in presence of base such as sodium acetate in presence of organic solvent, preferably methanol or ethanol to obtain imine derivative **7**. Compound **7** can be reduced using variety of reducing agents including DIBAL-H, BH_3-DMS, $NaBH_4$, $LiALH_4$, H_2/Pd/C, preferably, $NaBH_4$ in presence of organic solvent,

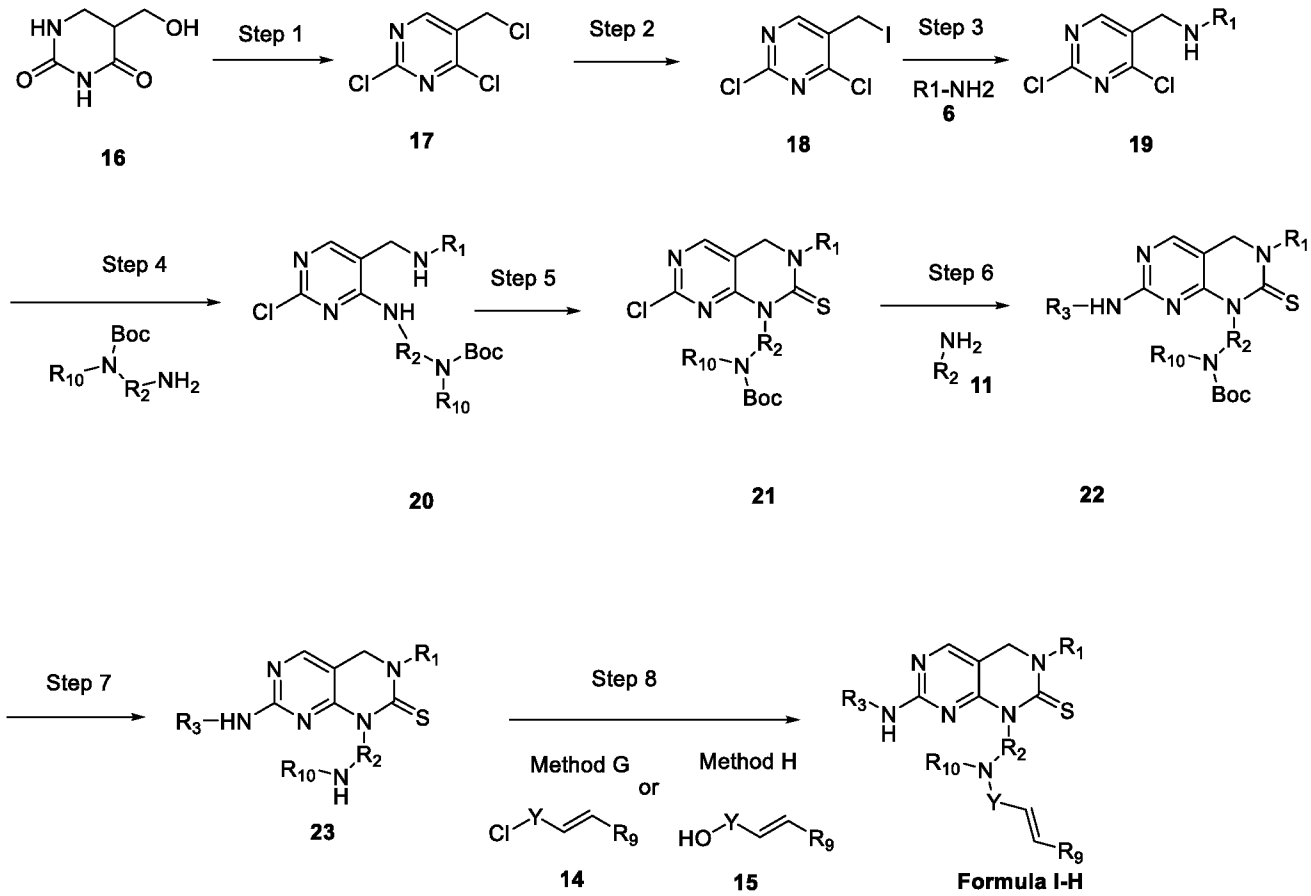
preferably, MeOH or EtOH or 1,2-dichloroethane in presence of acetic acid to yield compound **8**. The diamine compound **8** cyclized using triphosgene or carbonyldiimidazole (CDI) in presence of base preferably diisopropyl ethylamine and in presence of organic solvent such as THF to afford 3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one derivative **9**. The thiomethyl group in compound **9** can be oxidized using *m*-CPBA in presence of organic solvent such as DCM to obtain sulfone compound **10**. The sulfone **10** reacted with different primary amines **11** and trifluoroacetic acid and in presence of solvent such as 2-BuOH, IPA, EtOH, MeOH, *t*-BuOH, preferably 2-BuOH at elevated temperature to obtain compound **12**. In some cases of the invention, step 8 and 9 can happen as concerted reaction to yield compound **13** and mixture of compounds **12** and **13**. The Boc compound **12** can be deprotected using different acids such as HCl or TFA in presence of organic solvent such as DCM, THF, or dioxane or mixture of solvents to obtain amine compound **13**. Conversion of **13** to compound of Formula **I-G** was achieved either using compound **14**, wherein different acid chlorides, preferably substituted acryloyl chloride in presence of base such as DIPEA, TEA, DMAP and using solvents such as DCM, THF, DMF, preferably, TEA and THF or DCM. In another method of obtaining compound of Formula **I-G**, compound **13** was treated with different acids **15** such as *trans*-N,N-dimethylaminocrotonic acid in presence of different coupling reagents such as T_3P, and base such as TEA and solvent such as DCM, THF to obtain compound of Formula **I-G**. In few examples of the invention the final compounds were isolated as salts of formic acid or TFA through prep HPLC purification and in few examples the racemic compounds were separated by chiral HPLC chromatography separation to get pure enantiomers.

[0169] When R_2 and R_{10} forms a cyclic structure, similar procedure as described above was used for the synthesis of Formula **I-G**.

[0170] In another aspect of the invention, general procedures are provided, for the synthesis of **7**, **8, 9, 10, 12, 13** compounds for use in the synthesis of a compound of Formula **I-G**. Further, general procedure for the synthesis of compound of Formula **I-G** is also provided.

[0171] A resulting compound of the disclosure is converted into any other compound of the disclosure by methods analogous to known methods. For example: a resulting compound of Formula **I-G** is converted into a salt or solvate thereof; the oxidation state of an atom in a heterocyclic ring is increased or decreased by oxidation or reduction using known methods.

General synthetic scheme 2



[0172] The hydroxyl pyrimidone derivative **16** is treated with $POCl_3$ in presence of base and solvent preferably toluene at 0 °C to 120 °C to obtain compound **17**. The benzylic chloro compound **17** can be converted to corresponding iodo using sodium iodide in presence of organic solvent such as acetone to obtain compound **18**. The iodo group of compound **18** can be reacted with the corresponding amines in presence of base such as NaOH and organic solvent preferably toluene to obtain compound **19.** The compound **19** is reacted with variety of primary amines in presence of base such as diisopropylethyl amine and organic solvent preferably isopropyl alcohol to obtain diamine compound **20**. The diamine compound **20** can be cyclized using thiophosgene in presence of base preferably diisopropyl ethylamine and in presence of organic solvent such as tetrahydrofuran to afford 3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-thione derivative **21**. The compound **21** can be treated with different primary amines in presence of organic or inorganic bases or acids such as hydrochloric acid, trifluoroacetic acid preferably trifluoroacetic acid in presence of organic solvent such as 2-butanol, isopropyl alcohol, ethanol, methanol, *t*-butanol, preferably 2-butanol at elevated temperature to obtain compound **22**. In some cases of the invention, step 6 and 7 can happen as concerted reaction to yield compound **23** and mixture of compounds **22** and **23**. The Boc compound **22** can be deprotected using different acids such as hydrochloric acid or trifluoroacetic acid in presence of organic solvent

such as dichloromethane, tetrahydrofuran or dioxane or mixture of solvents to obtain amine compound **23**. Conversion of **23** to compound of Formula **I-G** was achieved either using compound **14**, wherein different acid chlorides, preferably, substituted acryloyl chloride in presence of base such as DIPEA, TEA, DMAP and using solvents such as DCM, THF, DMF, preferably TEA and THF or DCM. In another method of obtaining compound of Formula **I-G**, compound **23** was treated with different acids **15** such as *trans*-N,N-dimethylaminocrotonic acid in presence of different coupling reagents such as T_3P, and base such as TEA and solvent such as DCM, THF to obtain compound of Formula **I-G** and in few examples the racemic compounds were separated by chiral HPLC chromatography separation to get pure enantiomers.

[0173] When R_2 and R_{10} forms a cyclic structure, similar procedure as described above was used for the synthesis of Formula **I-G**.

[0174] In another aspect of the invention, general procedures are provided, for the synthesis of compounds **17**, 1**8, 19, 20, 21, 22** and **23** for use in the synthesis of a compound of Formula **I-G**. Further, general procedure for the synthesis of compound of Formula **I-G** is also provided.

[0175] A resulting compound of the disclosure is converted into any other compound of the disclosure by methods analogous to known methods. For example: a resulting compound of Formula **I-G** is converted into a salt or solvate thereof; the oxidation state of an atom in a heterocyclic ring is increased or decreased by oxidation or reduction using known methods.

General procedure A:

[0176] To a solution of aldehyde (**5**, 7.76 mmol) in MeOH or EtOH (30 mL) was added corresponding amine (**6**, 38.84 mmol) and sodium acetate (3.884 mmol) at RT and the reaction mixture was stirred for 4-20 h. The reaction was monitored by TLC. After the completion of reaction, the organic solvent was concentrated. The crude product was partitioned between DCM (3 x 200 mL) and water (50 mL). The organic layer was washed with brine (100 mL) and dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel chromatography to afford desired product **7.**

General procedure B:

[0177] A solution of imine compound (**7**, 6.88 mmol) in MeOH or 1,2-dichloroethane (50 mL) was cooled to 0 °C, then acetic acid (20 mL) was added and stirred for 10 min. Sodium borohydride (~20.6 mmol) was added portion wise until starting material was consumed. The reaction was monitored by TLC. After the completion of reaction, the reaction mixture was slowly quenched with sodium bicarbonate solution. The crude reaction mixture was partitioned between DCM (2 x 200 mL) and water (50 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain

crude product. The crude product was purified by silica gel chromatography to provide pure product **8**.

General procedure C:

[0178] To a solution of diamine compound (**8**, 5.98 mmol) in THF (35 mL) were added DIPEA (23.9 mmol,) and triphosgene (2.15 mmol) at 0 °C. The reaction mixture was stirred at RT for 2-12 h. The reaction was monitored by TLC. After completion of the reaction, sodium bicarbonate solution was added. The crude mixture was partitioned between DCM (2 x 100 mL) and water (50 mL). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel chromatography to get pure product **9**.

General procedure D:

[0179] To a solution of thiomethyl compound (**9**, 4.18 mmol) in DCM (30 mL) was added *m*-CPBA (12.56 mmol,) at RT. The reaction mixture was stirred at RT for 1-3 h. The reaction was monitored by TLC. After completion of the reaction, aqueous sodium bicarbonate solution was added. The crude mixture was partitioned between DCM (2 x 100 mL) and water (50 mL). The organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude product. The crude product was purified by recrystallization or by silica gel chromatography to afford desired sulfone derivative **10**.

General procedure E:

[0180] To a solution of sulfone (**10**, 0.982 mmol) in 2-butanol (10 mL) was added corresponding amine (R2-amine) (**11,** 0.982 mmol) and TFA (1.17 mmol). The reaction mixture was heated for 3-16 h at 100-110 °C. Reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated. Water (10 mL) and saturated sodium bicarbonate (20 mL) solution were added to the residue and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography to get pure product **12**. In some examples step 8 and 9 was concerted to give a mixture of compounds **12** and **13** and in some cases isolated compound **13**. In some examples, Chloro derivative (**21**) in place of sulfone derivative (**10**) was used to couple with R2-amine.

General procedure F:

[0181] To a solution of Boc compound (**12,** 0.507 mmol) in DCM (10 mL) and MeOH (3 mL) (some cases dioxane was used) cooled to 0 °C, 4N HCl in dioxane (5.48 mmol) (some cases TFA was used) was added. The reaction mixture was stirred for 2-6 h at RT. The reaction was monitored by TLC. After completion of the reaction, water (10 mL) and saturated sodium

bicarbonate (20 mL) solution were added and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography to get pure product **13**.

General procedure G:

[0182] A solution of amine (**13** or **23**, 0.175 mmol) in DCM (10 mL) (some cases THF or mixture of DCM and THF was used) was cooled to 0 °C to -60 °C, triethylamine (0.527 mmol) was added and stirred for 10 min. Then acryloyl chloride (0.527 mmol) was added and the reaction mixture was stirred for 0.5-6 h at 0 °C to -60 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was quenched with ice water at ~ -50 ^{0}C followed by sodium bicarbonate solution and extracted with DCM (100 mL). The organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude product. The crude product was purified to get pure product of Formula **I-G** or **I-H** and in few examples the racemic compounds were separated by chiral preparative HPLC using Chiral Cel-OJH (20x250) mm, 5µ or Chiralpak IC (20x250) mm, 5µ column and n-hexane:EtOH as a mobile phase to get pure enantiomers.

General procedure H:

[0183] Amine (**13** or **23**, 0.34 mmol) and *trans*-N,N-dimethylaminocrotonic acid hydrochloride (0.40 mmol) were suspended in dichloromethane (10 mL) (some cases mixture of DCM and THF or THF was used), triethyl amine (0.1 mL) was added and cooled to 0 °C. T_3P (0.68 mmol) was added drop-wise at 0 °C and the mixture was stirred at RT for 3-16 h. Completion of the reaction was monitored by TLC. The reaction mixture was partitioned between 5% methanol in dichloromethane and saturated bicarbonate solution. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude obtained was purified by silica gel chromatography to obtain pure product of Formula **I-G** or **I-H** and in few examples the racemic compounds were separated by chiral preparative HPLC to get pure enantiomers.

General Procedure I:

[0184] A solution of hydroxy compound (**16**, 83.7 mmol) in $POCl_3$ (103 mL) was cooled to 0 °C and N,N-diisopropylethylamine (75 mL, 419.4 mmol) was added dropwise. The reaction mixture was heated for 14 h at 110 °C. After the complete disappearance of starting material on TLC, the reaction mixture was quenched slowly with sodium bicarbonate solution. The resulting crude mixture was partitioned between ethyl acetate (200 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude product. The crude product was further purified by silica gel chromatography to provide pure product **17**.

General Procedure J:

[0185] Sodium iodide (14.06 mmol) was added to acetone (30 ml) and the mixture was stirred at RT until a clear solution was obtained. Then the chloro compound (**17**, 13.8 mmol) was added in single portion. The reaction mixture was stirred at RT for 30 min and heated to reflux for 20 min. The mixture was cooled to RT and the resulting white precipitate was filtered through sintered funnel and washed with acetone. The filtrate was concentrated at 30 °C. The crude iodo compound **18** obtained was diluted with toluene and used directly for the next step.

General Procedure K:

[0186] A solution of iodo compound (**18,** 0.35 mmol) in toluene (2 mL) was cooled to 0 °C and 4-fluoro aniline (0.35 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C. Then a solution of sodium hydroxide (0.45 mmol) in water (0.1 ml) was added and reaction mixture was stirred for 16 h at RT. The reaction was monitored by TLC. After completion of the reaction, water (3 mL) was added and extracted with ethyl acetate (2 x 10 mL). The organic layer was washed with brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude residue. The crude compound was purified by silica gel column chromatography to get the pure product **19**.

General Procedure L:

[0187] To a stirred solution of dichloropyrimidine derivative (**19**, 0.07 mmol) in IPA (1 mL), corresponding amine (A-NH_2, 0.07 mmol) and DIPEA (0.3 mmol) were added. The reaction mixture was heated at 100 °C for 16 h in a sealed tube. Solvent was then evaporated and the crude thus obtained was purified by flash chromatography to obtain the desired product **20**.

General Procedure M:

[0188] To a solution of diamine compound (**20**, 5.98 mmol) in THF (35 mL) were added DIPEA (23.9 mmol,) and thiophosgene (2.15 mmol) at 0 °C. The reaction mixture was stirred at RT for 2-12 h with TLC monitoring. After completion of the reaction, sodium bicarbonate solution was added. The crude mixture was partitioned between DCM (2 x 100 mL) and water (50 mL). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel chromatography to get desired product **21**.

General procedure N:

[0189] To a solution of compound of Formula **I-G** or **I-H** (0.087 mmol) in MeOH (15 ml) was added corresponding acid (0.087 mmol) at 10 °C. Then the temperature raised to RT and stirred for 4 h. The organic solvent was removed under vacuum to get solid. The solid obtained was washed with n-pentane and dried over vacuum to get pure product of corresponding salt.

General procedure O:

[0190] To an ice-cold solution of ethyl 4-chloro-2-(methylsulfanyl)pyrimidine-5-carboxylate (1.0 eq) in dimethylformamide (10 volume) was added potassium carbonate (2.0 eq) and *tert*-butyl(3-aminophenyl)carbamate or analogues (1.2 eq) under nitrogen atmosphere. The resultant reaction mixture was heated at 80 °C for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was cooled to room temperature and poured into an ice-cold water. The resulting solid precipitate was filtered and dried under vacuum to get desired products.

General procedure P:

[0191] To a solution of products (1.0 eq) obtained from **General procedure O** in tetrahydrofuran (10 volume) was cooled to -40 °C, followed by addition of lithium aluminum hydride (2.5 M in tetrahydrofuran, 3.0 eq) and the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was quenched with saturated ammonium chloride solution and stirred at room temperature for 30 minutes. The resulting reaction mixture was filtered and washed with dichloromethane. The filtrate was again washed with water and brine respectively. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afforded crude product. The crude product was triturated with dichloromethane afforded the desired products.

General procedure Q:

[0192] To a solution of products (1.0 eq) obtained from **General procedure P** in dichloromethane (10 volume) was added activated manganese dioxide (10.0 eq) at room temperature under nitrogen atmosphere. The resultant reaction mixture was stirred at same temperature for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was filtered through celite bed and washed with dichloromethane (3 times). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded the desired products.

General procedure R:

[0193] To a solution of products (1.0 eq) obtained from **General procedure Q** in methanol (10 volume) was added respective amines (3.0 eq) and sodium acetate (5.0 eq). The resultant reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (monitored by TLC), the reaction mixture was poured in ice-cold water and resultant solid was filtered. The solid was dried under vacuum afforded the desired products.

General procedure S:

[0194] To a solution of products (1.0 eq) obtained from **General procedure R** in methanol (2.5 vol) was added acetic acid (1.0 vol) and sodium borohydride (1.0 eq). The resulting reaction

mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was quenched with ice-cold water and resultant reaction mixture was filtered, washed with water. The solid was dried under vacuum afforded the desired products.

General procedure T:

[0195] To an ice-cold solution of products (1.0 eq) obtained from **General procedure S** in tetrahydrofuran (10 volume) was added N,N-diisopropylethylamine (4.0 eq) followed by the addition of triphosgene (0.4 eq) and the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring) saturated sodium bicarbonate solution was added and extracted with dichloromethane (3 times). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude was triturated with diethyl ether afforded the desired products.

General procedure U:

[0196] To an ice-cold solution of products (1.0 eq) obtained from **General procedure T** in dichloromethane (10 volume) was added *meta*-chloroperoxybenzoic acid (2.0 eq) and the reaction mixture was stirred at room temperature for 4 hours. After completion of reaction (TLC monitoring), saturated solution of sodium bicarbonates was added to the reaction mixture and extracted with dichloromethane (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude product was triturated with diethyl ether afforded the desired products.

General procedure V:

[0197] To an ice-cold solution of products (1.0 eq) obtained from **General procedure U** in isopropanol (10 volume) was added respective amines (1.2 eq) and trifluoroacetic acid (2.0 eq). The reaction mixture was heated at 110 °C for 16 hours. After completion of the reaction (TLC monitoring), the solvent was concentrated under reduced pressure, followed by saturated solution of sodium bicarbonate was added and extracted with dichloromethane (3 times). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure afforded the crude product. The crude was triturated with diethyl ether afforded the desired products which was used directly for the next step without any further purification.

General procedure W:

[0198] An ice-cold solution of products (1.0 eq) obtained from **General procedure V** in 20% trifluoroacetic acid in dichloromethane (10 volume) was stirred at room temperature for 3-16 hours. After completion of the reaction (TLC monitoring), the solvent was evaporated to dryness. The reaction mixture diluted with saturated solution of sodium bicarbonate and

extracted with 5% methanol in dichloromethane (3 times). The combined organic layers were washed with brine solution, dried over sodium sulfate and evaporated under reduced pressure. The crude was triturated with diethyl ether or purified over combiflash, eluted with 5-10% methanol in dichloromethane afforded the desired products.

General procedure X:

[0199] To an ice-cold solution of products (1.0 eq) obtained from **General procedure W** in dichloromethane (10 volume) was added triethylamine (5 eq), respective acids (1.1 eq), and propylphosphonic anhydride (T_3P, 50% in ethyl acetate, 2.5 eq). Then the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), reaction mixture was diluted with saturated solution of sodium bicarbonate and extracted with 5% methanol in dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afforded the crude product. The crude was purified over combiflash or Prep-TLC or Prep-HPLC afforded the final compounds.

General procedure Y:

[0200] A solution of products (1.0 eq) obtained from **General procedure W** in dichloromethane: tetrahydrofuran (1:1) (10 volume) was cooled to -70 °C followed by addition of triethylamine (5 eq) and acryloyl chloride (1.0 eq). The mixture was stirred at the same temperature for 2 hours. After completion of reaction (monitored by TLC), water was added and extracted with dichloromethane (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crudes were purified by Prep-HPLC afforded the final compounds.

General procedure Z:

[0201] To a solution of products (1.0 eq) obtained from **General procedure W** in tetrahydrofuran: water (3:1) (10 volume) at 0 °C was added triethylamine (3-5 eq) and acryloyl chloride (1.5 eq). The mixture was stirred at the same temperature for 2 hours. After completion of reaction (monitored by TLC), water was diluted with water and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crudes were purified by Prep-HPLC afforded the final compounds.

General procedure AA:

[0202] To an ice cold solution of nitro derivatives (1.0 eq) in methanol: tetrahydrofuran: water (2:2:1) (10 volume) was added zinc-dust or iron powder (5 eq) and ammonium chloride (5 eq). The resultant reaction mixture was stirred at room temperature for 2 hours. After completion of reaction (TLC monitoring), reaction mixture was passed through celite bed washed with 5%

methanol in dichloromethane, filtrates were washed with water, brine, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure afforded the amino derivatives.

General procedure BB (Suzuki coupling):

[0203] To a solution of halo derivatives (1.0 eq) in acetonitrile (10 volume) was added respective boronate ester derivatives (1.0 eq), followed by a solution of potassium carbonate (2.0 eq) in water (3 volume) under argon purging. The resulting reaction mixture degassed for 15 minutes, followed by addition of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (0.1 eq) and the reaction mixture was heated at 80 °C for 16 hours. After completion of reaction (TLC monitoring), diluted with ice water and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated to dryness under reduced pressure. The crude was purified over combiflash, elution with 40-60% ethyl acetate in hexane, desired fractions were concentrated under reduced pressure afforded the desired products.

General procedure CC:

[0204] To a solution of halo derivatives (1.0 eq) and respective boronic acids (1.1 eq) in toluene: ethanol (1:1) or dimethylformamide or dimethoxyethane (10 volume) was added a solution of potassium carbonate or sodium bicarbonate (2.0 eq) in water (3 volume) under argon degassing. The resulting reaction mixture was degassed for 15 minutes under argon atmosphere, followed by addition of [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.05 eq). The resulting reaction mixture was heated at 90 °C for 5-16 hours. After completion of reaction (TLC monitoring), the reaction mixture was cooled to room temperature, followed by water was added and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 30-50% ethyl acetate in hexane, and desired fractions were concentrated under reduced pressure afforded the desired products.

General procedure DD:

[0205] To a solution of halo derivatives (1.0 eq) and respective boronate ester derivatives (1.1 eq) in acetonitrile: water (1:1) was added cesium carbonate (2.0 eq) under argon degassing. The resulting reaction mixture was degassed under argon atmosphere for 15 minutes, followed by the addition of tetrakis(triphenylphosphine)palladium(0) (0.1 eq). The resulting reaction mixture was heated at 90 °C for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was cooled to room temperature, treated with water, and extracted with ethyl acetate (3 times). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified using

combiflash purifier, desired fractions were concentrated under reduced pressure afforded the desired products.

General procedure EE:

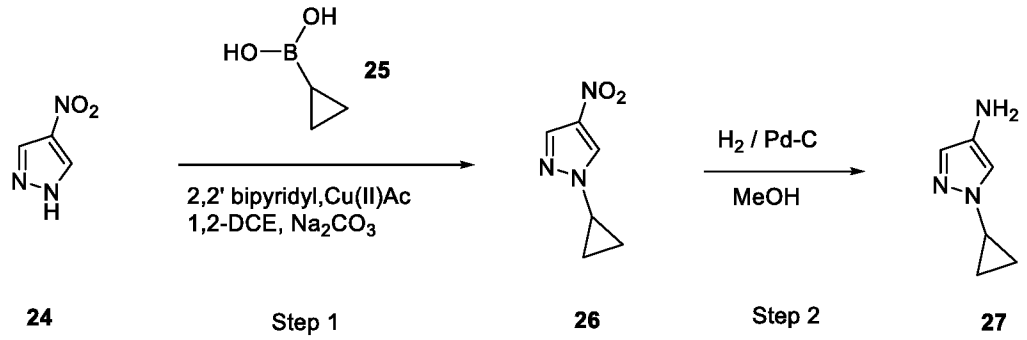
[0206] To an ice-cold solution of N-(3-(2-chloro-6-fluoroquinazolin-8-yl)phenyl)acrylamide (1.0 eq) in dimethylformamide was added sodium hydride (10.0 eq) portion-wise and stirred at the same temperature for 30 minutes, followed by addition of respective amines (1.2 eq). The resultant reaction mixture was stirred at room temperature for 16 hours. After completion of the reaction (as per TLC monitoring), reaction mixture was quenched with ice-cold water and extracted with 5% methanol/dichloromethane (3 times). The organic layers were combined and dried over anhydrous sulfate, filtered and concentrated under reduced pressure to obtain the crude product. The crude was purified over combiflash or Prep HPLC purification afforded the desired products.

General procedure FF:

[0207] To a solution of nitro derivatives (1.0 eq) in methanol (10 vol) was added 10% palladium on carbon (20% w/w). The reaction mixture was stirred under hydrogen atmosphere for 16 hours. After completion of reaction (TLC monitoring), reaction mixture was filtered through celite bed and washed with methanol. The filtrate was concentrated under reduced pressure afforded amino derivatives.

Synthesis of intermediate amines [A-NH_2 (1), R1-NH_2 (6) and R2-NH_2 (11)]:

Scheme 3: Synthesis of 1-cyclopropyl-1H-pyrazol-4-amine (27)



Step 1: 1-cyclopropyl-4-nitro-1H-pyrazole (26)

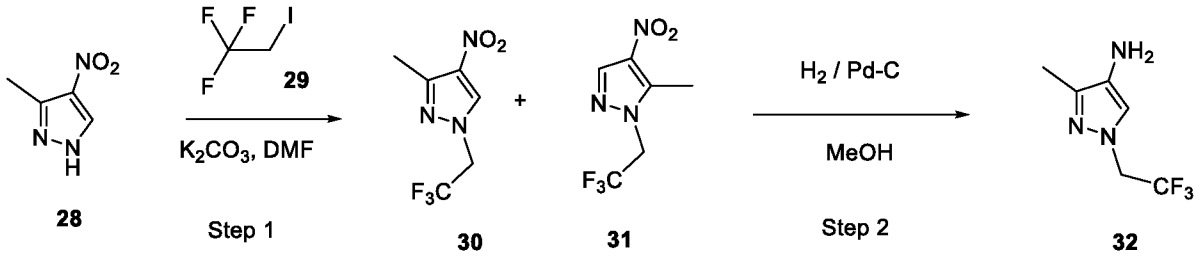
[0208] 4-nitro-1*H*-pyrrazole (**24**, 2.0 g, 18 mmol), cyclopropyl boronic acid (**25**, 3.0 g, 35 mmol), 2,2'-bipyridine (2.8 g, 18 mmol) and sodium carbonate (3.8 g, 35 mmol) were mixed in round bottom flask containing 1,2-dichloroethane (80 mL). The mixture was purged with oxygen gas for 10 min, copper (II) acetate (3.2 g, 18 mmol) was added, purged further for 15 min and heated at 80 °C for 6 h under oxygen atmosphere. The mixture was then passed through a celite pad, the filtrate was partitioned between dichloromethane and water. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtain a crude mass. The

crude mass was purified by flash column chromatography on silica gel (using 12 g SNAP column, and 8% ethyl acetate in hexane on a Biotage chromatography system) to give 1-cyclopropyl-4-nitro-1H-pyrazole (**26,** 41% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.97 (s, 1H), 3.70-3.64 (m, 1H), 1.03-1.02 (m, 2H), 0.88-0.86 (m, 2H).

Step 2: 1-cyclopropyl-1H-pyrazol-4-amine (27)

[0209] 1-cyclopropyl-4-nitro-1H-pyrazole (**26**, 1.10 g, 7.2 mmol) was dissolved in methanol (20 mL) under nitrogen atmosphere and 10% Pd on C (50% moisture, 0.4 g) was added to it. The mixture was subjected to hydrogenation under balloon pressure for 6 h. The catalyst was removed by filtering through celite and the filtrate was concentrated to obtain 1-cyclopropyl-1H-pyrazol-4-amine **(27,** 97% yield**)** as a brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.00-6.99 (d, 1H), 6.78-6.77 (d, 1H), 3.82 (s, 2H), 3.51-3.49 (m, 1H), 0.99-0.92 (m, 2H), 0.86-0.80 (m, 2H).

Scheme 3a: Synthesis of Intermediate 32



Step 1: 3-methyl-4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (30) and 5-methyl-4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (31)

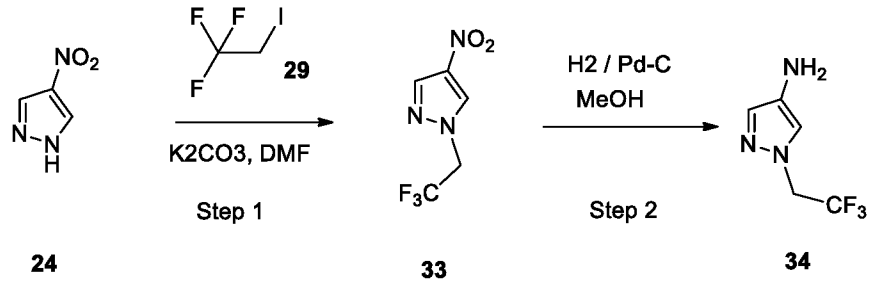
[0210] 3-methyl-4-nitro-1*H*-pyrrazole (**28**, 1.0 g, 7.8 mmol), trifluoroethyl iodide (**29**, 3.3 g, 15.7 mmol) and potassium carbonate (1.64 g, 11.9 mmol) were mixed in a vial containing DMF (5 mL). The vial was closed and the mixture was heated at 60 °C for 3 days. Water was added and extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered and solvents evaporated to obtain a sticky mass, purification of which by flash column chromatography on silica gel (using 12 g SNAP column and 0-10% ethyl acetate in hexane as eluent on a Biotage chromatography system) yielded 3-methyl-4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole **(30,** 29% yield**)** as major product and 5-methyl-4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole **(31)** as minor product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 4.69-4.63 (q, 2H), 2.56 (s, 3H).

Step 2: 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine (32)

[0211] 3-methyl-4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (**30**, 0.460 g, 2.2 mmol) was dissolved in methanol (20 mL) under nitrogen atmosphere and 10% Pd on C (50% moisture, 0.25 g) was added. The mixture was hydrogenated under balloon pressure for 5 h. The catalyst

was removed by filtering through celite and the filtrate was concentrated to obtain 3-methyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine **(32,** 91% yield**)** as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1H), 4.53-4.47 (q, 2H), 2.81 (s, 2H), 2.18 (s, 3H).

Scheme 4: Synthesis of 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine (34)



Step 1: 4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (33)

[0212] Title compound was prepared in a manner substantially similar to procedure mentioned in step 1 of Scheme 3a.

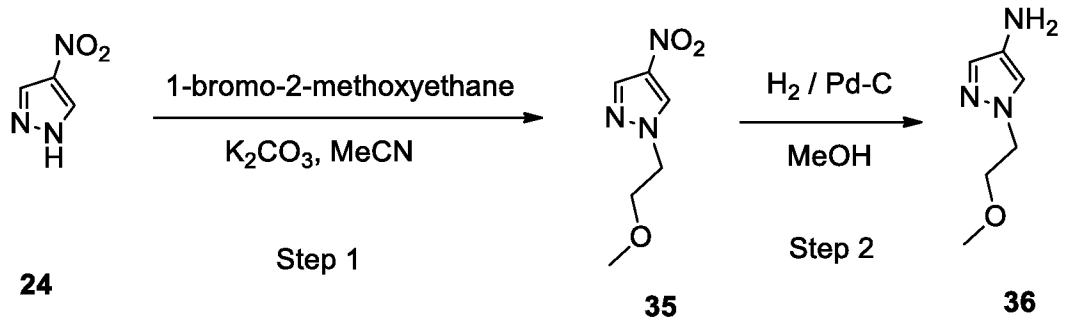
4-nitro-1*H*-pyrrazole (**24**) and trifluoroethyl iodide (**29**) gave 4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole **(33,** 42% yield**)** as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.15 (s, 1H), 4.79-4.73 (q, 2H).

Step 2: 1-(2,2,2-Trifluoroethyl)-1H-pyrazol-4-amine (34)

[0213] Title compound was prepared in a manner substantially similar to procedure mentioned in step 2 of scheme 3a.

4-Nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (**33**) gave 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine **(34)** as a light brown sticky mass. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.09 (s, 1H), 4.60-4.54 (q, 2H), 2.96 (bs, 2H).

Scheme 5: Synthesis of 1-(2-Methoxyethyl)-1H-pyrazol-4-amine (36)



Step 1: 1-(2-Methoxyethyl)-4-nitro-1H-pyrazole (35)

[0214] Title compound was prepared in a manner substantially similar to procedure mentioned in step 1 of Scheme 3a.

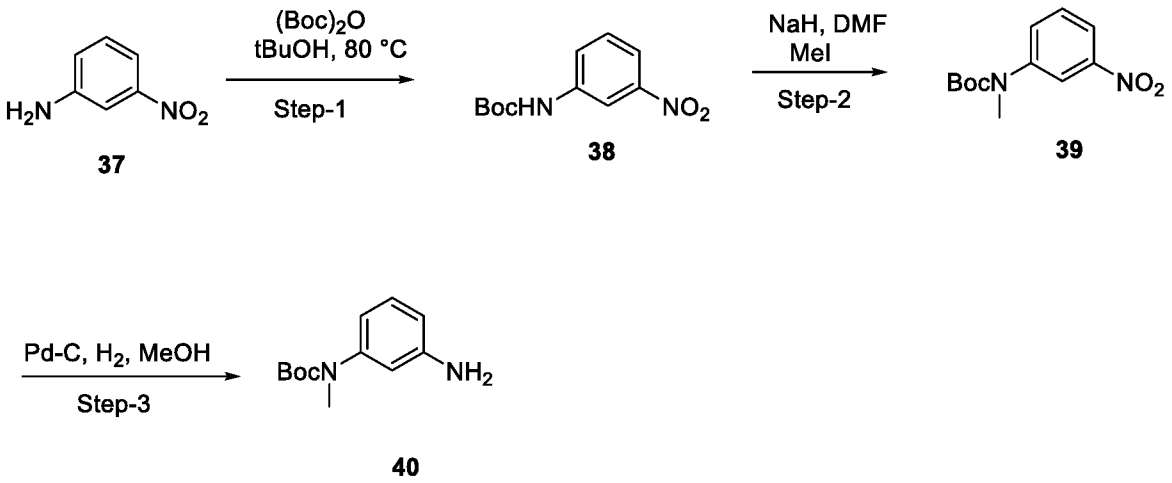
3-Methyl-4-nitro-1*H*-pyrrazole (**24**) and 1-bromo-2-methoxyethane gave 1-(2-methoxyethyl)-4-nitro-1H-pyrazole **(35,** 66% yield**)** as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.27 (s, 1H), 4.36-4.33 (t, 2H), 3.77-3.72 (t, 2H), 3.23 (s, 3H).

Step 2: 1-(2-Methoxyethyl)-1H-pyrazol-4-amine (36)

[0215] Title compound was prepared in a manner substantially similar to procedure mentioned in step 2 of Scheme 3a.

1-(2-Methoxyethyl)-4-nitro-1H-pyrazole (**35**) gave 1-(2-Methoxyethyl)-1H-pyrazol-4-amine **(36,** 91% yield**)** as a pink solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.03 (s, 1H), 6.89 (s, 1H), 4.19-4.17 (t, 2H), 3.78 (bs, 2H), 3.67-3.64 (t, 2H), 3.21 (s, 3H).

Scheme 6: Synthesis of *tert*-butyl (3-aminophenyl)(methyl)carbamate (40)



37 **38** **39** **40**

Step 1: *tert*-butyl (3-nitrophenyl)carbamate (38)

[0216] $(Boc)_2O$ (95 mL, 434.4 mmol) was added to 3-nitroaniline (**37**, 50.0 g, 362.0 mmol) in ^{t}BuOH (30 mL) at 0 °C. The reaction mixture was heated at 80 °C for 16 h and concentrated under reduced pressure. The crude was washed with pentane (5 x 30 mL) to afford the title compound as a light yellow solid (**38**, 85.0 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (t, 1H), 7.88 (dd, 1H), 7.68 (d, 1H), 7.42-7.46 (m, 1H), 6.73 (bs, 1H), 1.53 (s, 9H).

Step 2: *tert*-butyl methyl(3-nitrophenyl)carbamate (39)

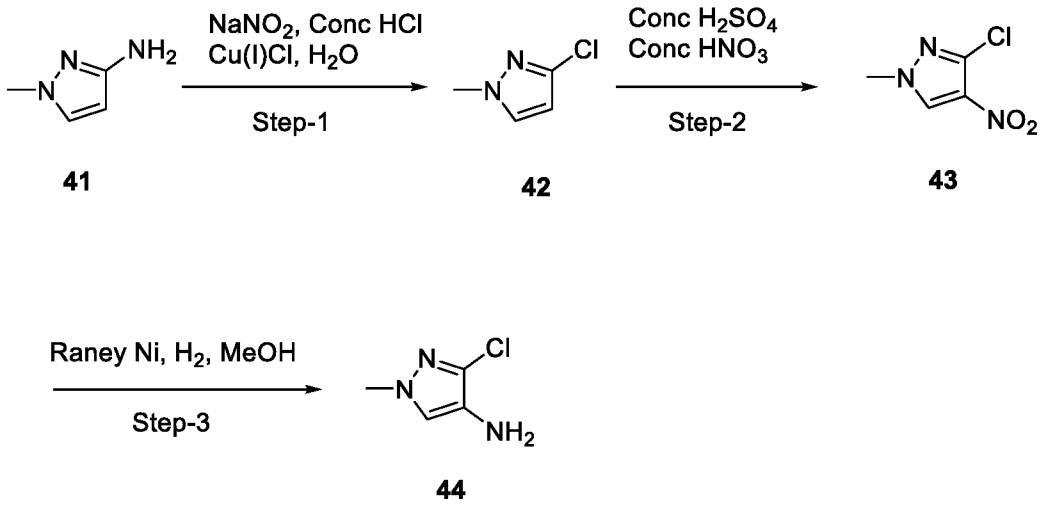
[0217] Sodium hydride (3.5 g, 83.9 mmol) was taken in a 500 mL round bottom flask under nitrogen atmosphere, DMF was added and cooled to 0 °C. To it was added *tert*-butyl (3-nitrophenyl)carbamate (**38**, 10.0 g, 42.0 mmol) and the reaction mixture was stirred for another 30 min at 0 °C. Iodomethane (4.0 mL, 63.0 mmol) was added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with ice-water (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was washed with Et_2O (3 x 50 mL) to afford the title compound as a light yellow solid (**39**, 8.0 g, 86% yield). ^{1}H NMR (400

MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.01-7.98 (m, 1H), 7.62 (d, 1H), 7.48 (t, 1H), 3.32 (s, 3H), 1.48 (s, 9H).

Step 3: *tert*-butyl (3-aminophenyl)(methyl)carbamate (40)

[0218] A par flask was charged with *tert*-butyl methyl(3-nitrophenyl)carbamate (**39**, 8.0 g, 1.9 mmol) and methanol (20 mL) followed by addition of Pd-C (10% w/w, 0.8 g). The flask was evacuated under vacuum and then purged with hydrogen. The reaction was stirred under hydrogen atmosphere (30 psi). The reaction was monitored by TLC. It was then filtered through sintered funnel with a pad of celite, washed with methanol and concentrated under reduced pressure to afford the title compound as a deep brown liquid (**40**, 0.35 g, 64% yield) that was used as such for the next step without any further purification. LCMS: 223.14 $(M+H)^+$

Scheme 7: Synthesis of 3-chloro-1-methyl-1H-pyrazol-4-amine (44)



Step 1: 3-chloro-1-methyl-1H-pyrazole (42)

[0219] 1-methyl-1H-pyrazol-3-amine (**41,** 5.0 g, 51.5 mmol) was taken in Conc. HCl (50 mL) in a 250 mL round bottom flask and cooled to 0 °C. A solution of sodium nitrite (5.3 g, 77.2 mmol) in H_2O (100 mL) was added slowly. The reaction mixture was stirred at room temperature for 30 min. Finally, Cu(I)Cl (10.2 g, 100.0 mmol) was added and the reaction mixture was heated at 60 °C for 1 h. The reaction was quenched with ice-cooled 50% sodium hydroxide solution (100 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to afford the title compound as a brown liquid (**42**, 6.2 g, 52% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, 1H), 6.15 (d, 1H), 3.85 (s, 3H).

Step 2: 3-chloro-1-methyl-4-nitro-1H-pyrazole (43)

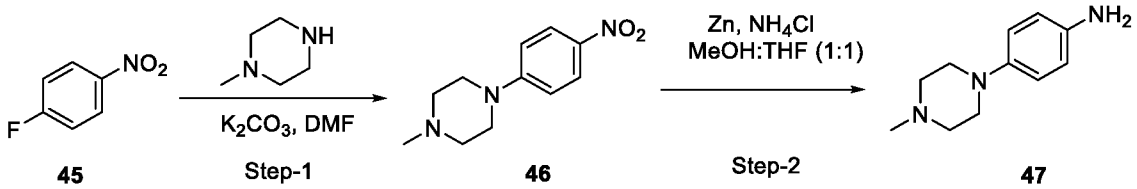
[0220] 3-chloro-1-methyl-1H-pyrazole (**42,** 6.2 g, 53.4 mmol) was taken in Conc. H_2SO_4 (10 mL) in a 100 mL round bottom flask under nitrogen atmosphere and cooled to 0 °C. Fuming HNO_3 (8.0 mL, 187.0 mmol) was added drop wise maintaining the internal bath temperature at 0

°C. After the addition was complete, the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with ice-water (40 g) and diluted with EtOAc (300 mL). The organic layer was washed with saturated $NaHCO_3$ solution (3 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was washed pentane (3 x 20 mL) to afford the title compound as a white solid (**43,** 5.2 g, 60% yield) that was used as such for the next step without any further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 3.88 (s, 3H).

Step 3: 3-chloro-1-methyl-1H-pyrazol-4-amine (44)

[0221] A par flask was charged with 3-chloro-1-methyl-4-nitro-1H-pyrazole **(43,** 5.2 g, 32.2 mmol) and methanol (100 mL) followed by addition of Raney Ni (10% w/w, 0.5 g). The flask was evacuated under vacuum and then purged with hydrogen. The reaction was stirred under hydrogen atmosphere (30 psi) for 2 days. The reaction was monitored by TLC. It was then filtered through sintered funnel with a pad of celite and washed with methanol and concentrated under reduced pressure to obtain the title compound as a brown colored liquid (**44**, 4.0 g, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.09 (s, 1H), 3.88 (bs, 2H), 3.64 (s, 3H).

Scheme 8: Synthesis of 4-(4-methylpiperazin-1-yl)aniline (47)



45 46 47

Step 1: 1-methyl-4-(4-nitrophenyl)piperazine (46)

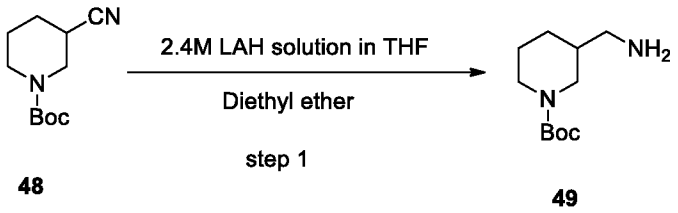
[0222] 1-fluoro-4-nitrobenzene (**45,** 25.0 g, 177.1 mmol) was taken in DMF (100 mL) in a 250 mL round bottom flask under nitrogen atmosphere and added 1-methylpiperazine **(**16.8 g, 168.0 mmol) and K_2CO_3 (36.7 g, 265.0 mmol). The reaction mixture was heated at 80 °C for 16 h. The reaction mixture was then poured onto ice water and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was purified by column chromatography on silica gel (100-200 mesh) using 50% EtOAc in hexane as eluent to afford the title compound as a yellow solid (**46**, 35.0 g, 89% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, 2H), 7.02 (d, 2H), 3.45-3.42 (m, 4H), 2.43-2.40 (m, 4H), 2.21 (s, 3H).

Step 2: 4-(4-methylpiperazin-1-yl)aniline (47)

[0223] 1-methyl-4-(4-nitrophenyl)piperazine (**46**, 5.1 g, 22.0 mmol) was taken in a 500 mL round bottom flask in a mixture of solvent MeOH and THF (100 mL, 1:1). NH_4Cl (12.0 g, 220.0 mmol) and Zn dust (14.7 g, 220.0 mmol) were added and the reaction mixture was stirred at

room temperature for 2 h. It was then filtered through sintered funnel with a pad of celite, washed with MeOH (50 mL) and concentrated under reduced pressure. The crude was further washed with *n*-pentane to afford **47** as a gummy residue (4.0 g, 93% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.34 (bs, 2H), 6.75-6.73 (m, 2H), 6.56-6.54 (m, 2H), 3.20 (m, 8H), 2.73 (s, 3H).

Scheme 9: Synthesis of *tert*-butyl 3-(aminomethyl) piperidine-1-carboxylate (49)

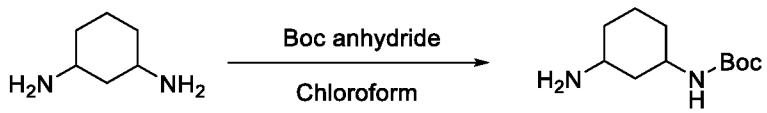


48 **49**

Step 1: *tert*-butyl 3-(aminomethyl) piperidine-1-carboxylate (49, Intermediate-6)

[0224] *tert*-butyl 3-cyanopiperidine-1-carboxylate (**48**, 5.0 g, 23.1 mmol) was taken in diethyl ether (50 mL) in a 250 mL round bottom flask under nitrogen atmosphere. The reaction mixture was cooled to -78 °C and 2.4M LAH solution in THF (19.8 mL, 47.0 mmol) was added drop wise. After the addition was complete, the reaction mixture was then stirred at room temperature for 2 h. The reaction was monitored by TLC. After the completion of reaction, the reaction mixture was quenched with 10% NaOH solution at 0 °C drop wise and organic layer was separated. The solvent was concentrated under reduced pressure to afford the title compound as a brown liquid (**49**, 4.6 g, 92% yield). LCMS Calcd for $[M+H]^+$ 215.3 found 215.12

Scheme 10: Synthesis of *tert*-butyl (3-aminocyclohexyl)carbamate (51)

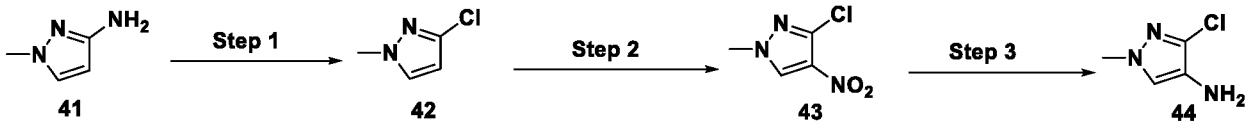


50 **51**

Step 1: *tert*-butyl (3-aminocyclohexyl)carbamate (51)

[0225] Cyclohexane-1,3-diamine (**51,** 4.0 g, 35.1 mmol) was taken in chloroform (160 mL) in a 250 mL round bottom flask under nitrogen atmosphere. The reaction mixture was cooled to -5 °C and a solution of Boc anhydride (3.3 mL, 14.0 mmol) in chloroform (60 mL) was added drop wise. After the addition was complete, the reaction mixture was then stirred at 0 °C for 6 h. The reaction was monitored by TLC (Ninhydrin active). The reaction mixture was then poured onto ice water and extracted with DCM (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford the title compound as a white sticky liquid (**51**, 4.5 g, 53% yield). Mass Calcd for $[M+H]^+$ 215.3 direct mass found 215.12

Scheme 11: Alternative Synthesis of 3-Chloro-1-methyl-1H-pyrazol-4-amine (44):



41 42 43 44

Step 1: Preparation of 3-Chloro-1-methyl-1H-pyrazole (42):

[0226] To an ice cold solution of 1-methyl-1H-pyrazol-3-amine (**41**) (50 g, 0.52 mol) in acetonitrile (400 mL) was added copper(I) chloride (154 g, 1.56 mol). The resulting mixture was stirred at room temperature for 30 minutes, followed by *tert*-butyl nitrite (268 g, 2.60 mol) was added and stirred at 60 °C for 30 minutes. After completion of the reaction (TLC monitoring), the reaction mixture was poured into water and extracted with ethyl acetate (3 x 300 mL). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded desired product (**42**) (32.0 g; Yield: 53%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.27 (d, J = 2.4 Hz, 1H), 6.15 (d, J = 2.4 Hz, 1H), 3.85 (s, 3H).

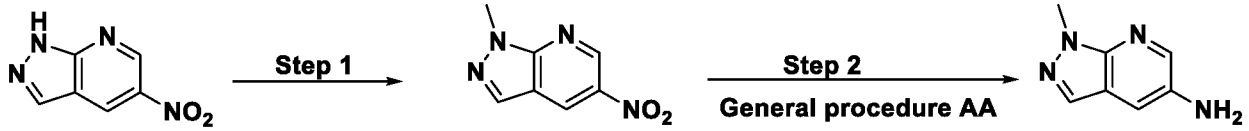
Step 2: Preparation of 3-Chloro-1-methyl-4-nitro-1H-pyrazole (43):

[0227] To an ice-cold solution of 3-chloro-1-methyl-1H-pyrazole (**42**) (30 g, 0.26 mol) in concentrated sulfuric acid (50 mL) was slowly added fuming nitric acid (40 mL, 0.91 mol) drop wise. The resulting mixture was stirred at room temperature for 6 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into ice-cold water, the resulting solid was filtered and washed with pentane afforded the desired product (**43**) as yellow solid (30 g; Yield: 73%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 3.94 (s, 3H).

Step 3: Preparation of 3-Chloro-1-methyl-1H-pyrazol-4-amine (44):

[0228] To a solution of 3-chloro-1-methyl-4-nitro-1H-pyrazole **(43)** (30 g, 0.186 mol) in methanol (300 mL) was added Raney nickel (10% w/w, 3 g). The reaction was stirred under hydrogen atmosphere for 16 hours. The reaction was monitored by TLC (after completion), the reaction mixture was filtered through celite bed and washed with methanol. The filtrate was concentrated under reduced pressure afforded **44** as viscous liquid (14.0 g; Yield: 57%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.09 (s, 1H), 3.88 (s, 2H), 3.64 (s, 3H).

Scheme 12: Synthesis of 1-methyl-1H-pyrazolo[3,4-b]pyridin-5-amine (54):



52 53 54

Step 1: Preparation of 1-Methyl-5-nitro-1H-pyrazolo[3,4-b]pyridine (53):

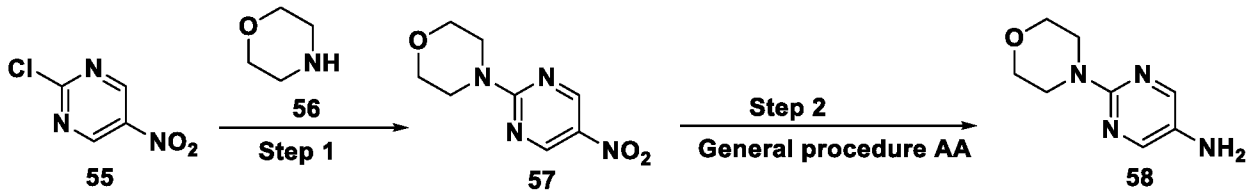
[0229] To an ice-cold solution of 5-nitro-1H-pyrazolo[3,4-b]pyridine (**52**) (3.0 g, 18.3 mmol) in dimethylformamide (50 mL) was added sodium hydride (60% dispersion in mineral oil, 0.88 g,

21.9 mmol) in portion wise. The resulting mixture was stirred at same temperature for 15 minutes, followed by the addition of methyl iodide (1.25 mL, 20.1 mmol) and stirred at 0 °C for 2 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into ice-cold water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded the crude product. The crude was purified by column chromatography on silica gel (100-200 mesh) eluted with 90% ethyl acetate-hexane as an eluent afforded **53** as white solid (2.0 g; Yield: 61%). LCMS: $[M+H]^+$ 179.18; 99.58%

Step 2: Preparation of 1-Methyl-1H-pyrazolo[3,4-b]pyridin-5-amine (54):

[0230] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure AA.** The crude was washed with *n*-pentane to afford **(54)** as light brown solid (1.0 g; Yield: 60%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.08 (d, J = 4.2 Hz, 1H), 7.79 (s, 1H), 7.17 (d, J = 4.2 Hz, 1H), 5.09 (s, 2H), 3.95 (s, 3H). LCMS: $[M+H]^+$ 149.15; 93.75%.

Scheme 13: Synthesis of 2-morpholinopyrimidin-5-amine (58):



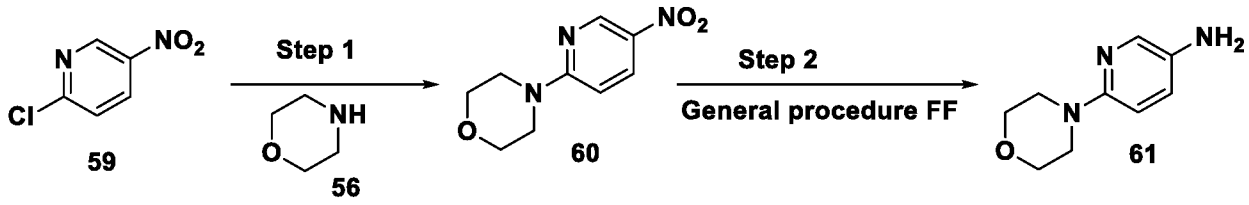
Step 1: Preparation of 4-(5-nitropyrimidin-2-yl)morpholine (57):

[0231] To an ice-cold solution of morpholine **(56)** (1.64 g, 18.8 mmol) in tetrahydrofuran (75 mL) was added triethylamine (5.24 mL, 37.6 mmol). The resulting mixture was stirred at same temperature for 15 minutes, followed by 2-chloro-5-nitropyrimidine **(55)** (3.0 g, 18.8 mmol) was added and stirred at room temperature for 12 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded **57** as yellow solid (3.4 g; Yield: 86%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.12 (s, 2H), 3.92-3.89 (m, 4H), 3.70 (m, 4H). LCMS: $[M+H]^+$ 211.21; 99.47%.

Step 2: Preparation of 2-morpholinopyrimidin-5-amine (58):

[0232] Title compound was prepared as pale yellow solid (2.0 g; Yield: 65%) in a manner substantially similar to procedure mentioned in **General procedure AA**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.90 (s, 2H), 4.64 (s, 2H), 3.64-3.62 (m, 4H), 3.45 (m, 4H). LCMS: $[M+H]^+$ 181.04, 96.0%

Scheme 14: Synthesis of 6-morpholinopyridin-3-amine (61):



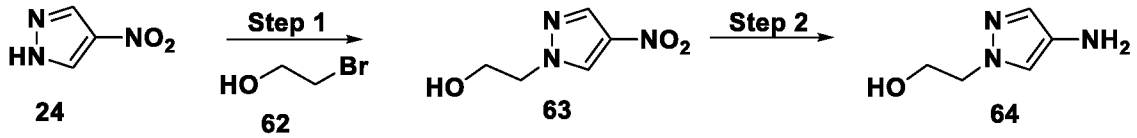
Step 1: Preparation of 4-(5-nitropyridin-2-yl)morpholine (60):

[0233] To an ice-cold solution of morpholine **(56)** (5.5 g, 63.1 mmol) in dichloromethane (50 mL) was added triethylamine (8.5 mL, 63.1 mmol). The resulting mixture was stirred at room temperature for 15 minutes, followed by addition of 2-chloro-5-nitropyridine **(59)** (10 g, 63.1 mmol) and stirred at room temperature for 3 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into water and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded **60** as yellow solid (6.0 g, Yield: 45%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.97 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 5.0 Hz, 1H), 6.95 (d, J = 5.0 Hz, 1H), 3.82-3.70 (m, 8H). LCMS: $[M+H]^+$ 210.14; 99.78%.

Step 2: Preparation of 6-morpholinopyridin-3-amine (61):

[0234] Title compound was prepared as a brown solid (2.7 g: Yield: 62%) in a manner substantially similar to procedure mentioned in **General procedure FF.** ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 1H), 7.05-7.02 (d, J = 5.02 Hz, 1H), 6.60 (d, J = 5.12 Hz 1H), 3.86-3.84 (m, 4H), 3.35 (m, 4H). LCMS: $[M+H]^+$ 180.12; 99.39%.

Scheme 15: Synthesis of 2-(4-amino-1H-pyrazol-1-yl) ethan-1-ol (64):



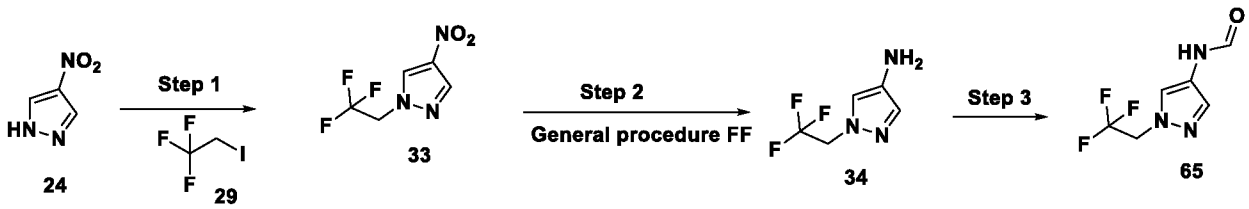
Step 1: Preparation of 2-(4-nitro-1H-pyrazol-1-yl) ethan-1-ol (63):

[0235] To an ice-cold solution of 4-nitro-1H-pyrazole (**24**) (10 g, 88.4 mmol) in dimethylformamide (130 mL) was added cesium carbonate (43.5 g, 133 mmol) and 2-bromoethan-1-ol **(62)** (12.2 g, 97.3 mmol) and the reaction mixture was heated at 100 °C for 8 hours. After completion of reaction (TLC monitoring), the reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded **63** as a brown solid (6.0 g; Yield: 41%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.81 (s, 1H), 8.26 (s, 1H), 4.99 (m, 1H), 4.22 (m, 2H), 3.76 (m, 2H).

Step 2: Preparation of 2-(4-amino-1H-pyrazol-1-yl) ethan-1-ol (64):

[0236] To a solution of 2-(4-nitro-1H-pyrazol-1-yl) ethan-1-ol (**63**) (6.0 g, 38.2 mmol) in ethanol (50 mL) was added 20% palladium hydroxide (10% w/w, 0.6 g) at room temperature and the reaction mixture was stirred under hydrogen atmosphere for 14 hours. After completion of reaction (TLC monitoring), the reaction mixture was filtered through celite and washed with methanol (100 mL), the filtrate was concentrated under reduced pressure to afford **(64)** as a brown solid (4.0 g; Yield: 81%). MS: $[M+H]^+$ 128.07.

Scheme 16: Synthesis of N-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl) formamide (65):



Step 1: Preparation of 4-nitro-1-(2,2,2-trifluoroethyl)-1H-pyrazole (33):

[0237] To a solution of 4-nitro-1H-pyrazole (**24**) (5.0 g, 44.21 mmol) in dimethylformamide (25 mL) was added cesium carbonate (17.3 g, 53.05 mmol) and 1,1,1-trifluoro-2-iodoethane (**29**) (14 g, 66.31 mmol). The resulting mixture was heated at 50 °C for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was cooled to room temperature, poured into water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude was purified over column chromatography over silica gel (100-200 mesh) using 10% ethyl acetate-hexane as eluent afforded **33** as an off white solid (2 g; Yield: 23%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 8.15 (s, 1H), 4.79 (m, 2H).

Step 2: Preparation of 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine (34):

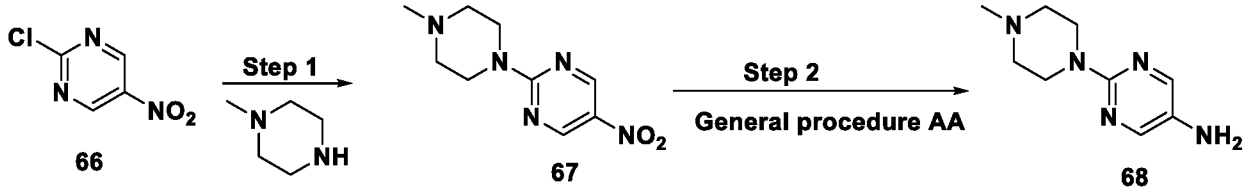
[0238] Title compound was prepared in a manner substantially similar to the procedure mentioned in **General procedure FF,** afforded **34** as a light brown sticky mass (1.5 g: Yield: 89%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.25 (s, 1H), 7.05 (s, 1H), 4.60 (m, 2H), 2.96 (bs, 2H).

Step 3: Preparation of N-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl) formamide (65):

[0239] A mixture of acetic anhydride (2.3 mL, 3.88 mmol) and formic acid (1.0 mL, 8.69 mmol) were heated at 70 °C for 1 hour to prepare the formylating mixture. This reaction mixture was then gradually cooled to 0 °C and 1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-amine (**34**) (400 mg, 2.42 mmol) in tetrahydrofuran (10 mL) was slowly added. The resulting mixture was stirred at room temperature for 2 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded **65** as a brown solid (400 mg; Yield: 86%). ^{1}H NMR (400 MHz,

DMSO-d_6): δ 10.24 (s, 1H), 8.17 (s, 1H), 8.09 (s, 1H), 7.55 (s, 1H), 5.12 (m, 2H). LCMS: $[M+H]^+$ 194.38, 87.09%.

Scheme 17: Synthesis of 2-(4-methylpiperazin-1-yl)pyrimidin-5-amine (68):



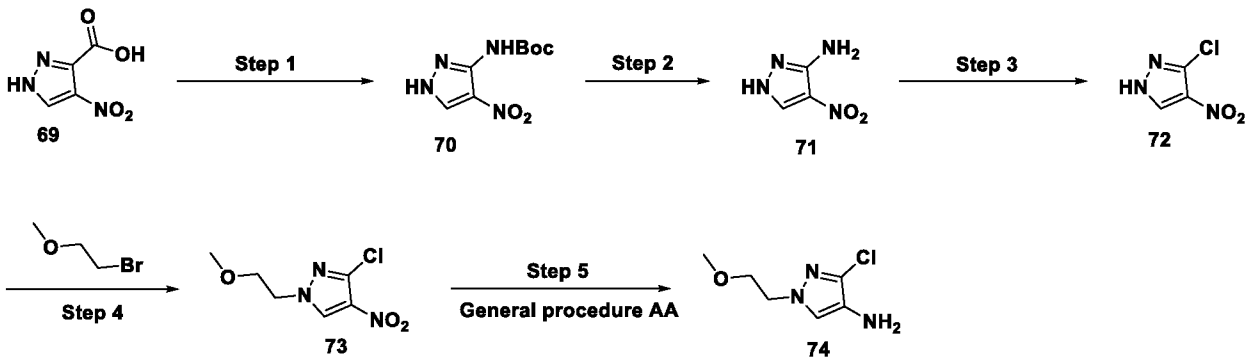
Step 1: Preparation of 2-(4-methylpiperazin-1-yl)-5-nitropyrimidine (67):

[0240] To an ice-cold solution of 1-methylpiperazine (1.88 g, 18.8 mmol) in tetrahydrofuran (75 mL) was added triethylamine (5.24 mL, 37.6 mmol). The resulting mixture was stirred at same temperature for 15 minutes, followed by the addition of 2-chloro-5-nitropyrimidine **(66)** (3.0 g, 18.8 mmol) and stirred at room temperature for 12 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated under reduced pressure afforded **67** as a yellow solid (3.6 g; Yield 83%). LCMS: $[M+H]^+$ 224.02; 96.28%.

Step 2: Preparation of 2-(4-methylpiperazin-1-yl)pyrimidin-5-amine (68):

[0241] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure AA**. The crude was washed with ether afforded **68** as a brown color solid (1.5 g; Yield: 46%). LCMS: $[M+H]^+$ 194.06; 99.6%

Scheme 18: Synthesis of 3-chloro-1-(2-methoxyethyl)-1H-pyrazol-4-amine (74)



Step 1: Preparation of *tert*-butyl (4-nitro-1H-pyrazol-3-yl)carbamate (70):

[0242] To an ice-cold solution of 4-nitro-1H-pyrazole-3-carboxylic acid **(69)** (2.5 g, 15.9 mmol) in toluene (50 mL) was added triethylamine (5.6 mL, 39.75 mmol) and diphenylphosphoryl azide (4.25 g, 17.5 mmol). The reaction mixture was stirred at room temperature for 6 hours. After completion of reaction (TLC monitoring), *tert*-butanol (25 mL) was added and heated at 130 °C for 16 hours. After completion of reaction, the reaction mixture was cooled to 0 °C, quenched with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined

organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 30% ethyl acetate in heptane afforded the desired product **(70)** (600 mg, Yield: 16%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.58 (bs, 1H), 9.33 (s, 1H), 8.44 (s, 1H), 1.44 (s, 9H).

Step 2: Preparation of 4-nitro-1H-pyrazol-3-amine (71):

[0243] An ice-cold solution of *tert*-butyl (4-nitro-1H-pyrazol-3-yl)carbamate **(70)** (500 mg, 21.9 mmol) in 4M hydrochloric acid in dioxane (5 mL) was stirred at room temperature 6 hours. After completion of reaction (TLC monitoring), solvent was evaporated under reduced pressure to get desired product **(71)** (287 mg, Yield: 80%) as off white solid. MS: $[M+H]^+$ 129.10

Step 3: Preparation of 3-chloro-4-nitro-1H-pyrazole (72):

[0244] To an ice-cold solution of 4-nitro-1H-pyrazol-3-amine **(71)** (500 mg, 3.9 mmol) in hydrochloric acid (5.0 mL) was added aqueous solution of sodium nitrite (547 mg, 7.8 mmol) in water (1.0 mL). The resulting reaction mixture stirred at same temperature for 1 hour, followed by addition of copper(I) chloride (773 mg, 7.8 mmol) and stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), reaction mixture was diluted with ice-cold water (50 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afforded the desired product **(72)** (250 mg, Yield: 43%). MS: $[M-H]^+$ 146.10

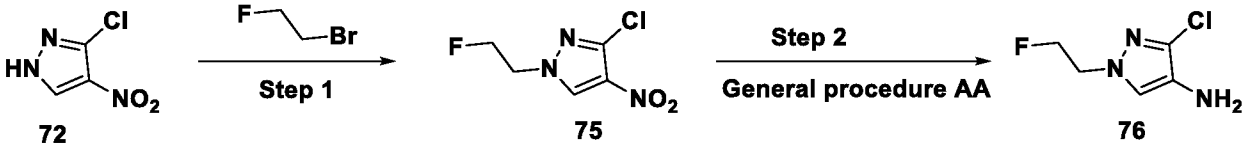
Step 4: Preparation of 3-chloro-1-(2-methoxyethyl)-4-nitro-1H-pyrazole (73):

[0245] To an ice-cold solution of 3-chloro-4-nitro-1H-pyrazole **(72)** (300 mg, 2.03 mmol) in dimethylformamide (5.0 mL) was added sodium hydride (60% dispersion in mineral oil, 73 mg, 3.05 mmol) in portion wise. The resulting reaction mixture was stirred at the same temperature for 15 minutes, and 1-bromo-2-methoxyethane (73 mg, 2.03 mmol) was added. The reaction mixture was heated at 100 °C for 16 hours. After completion of reaction (as per TLC monitoring), the reaction mixture was poured into ice-cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 35% ethyl acetate in heptane afforded the desired product **(73)** (250 mg, Yield: 60%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.08 (bs, 1H), 4.86 (m, 2H), 4.74 (m, 2H), 3.24 (s, 3H).

Step 5: Preparation of 3-chloro-1-(2-methoxyethyl)-1H-pyrazol-4-amine (74):

[0246] Title compound (**74**) was prepared (170 mg; Yield: 70%) as a viscous solid in a manner substantially similar to procedure mentioned in **General procedure AA.** MS: $[M+H]^+$ 176.09

Scheme 19: Synthesis of 3-chloro-1-(2-fluoroethyl)-1H-pyrazol-4-amine (76)



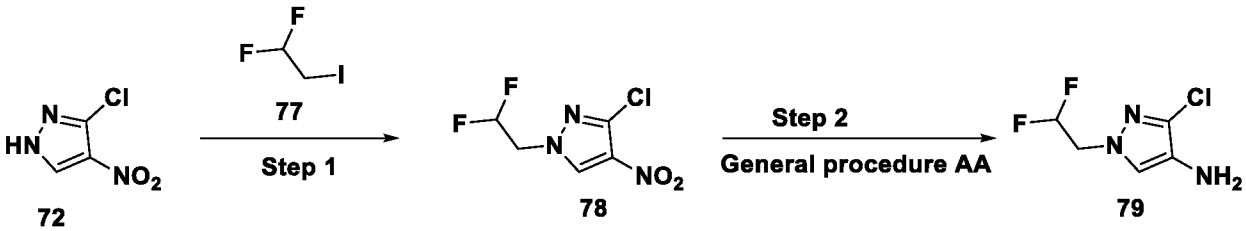
Step 1: Preparation of 3-chloro-1-(2-fluoroethyl)-4-nitro-1H-pyrazole (75):

[0247] To an ice-cold solution of 3-chloro-4-nitro-1H-pyrazole **(72)** (250 mg, 1.69 mmol) in dimethylformamide (5.0 mL) was added sodium hydride (60% dispersion in mineral oil, 122 mg, 2.54 mmol) in portion wise. The resulting reaction mixture was stirred at same temperature for 15 minutes, and 1-bromo-2-fluoroethane (258 mg, 2.03 mmol) was added. The reaction mixture was heated at 100 °C for 16 hours. After completion of reaction (as per TLC monitoring), the reaction mixture was poured in to ice-cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 15% ethyl acetate in heptane afforded the desired product **(75)** (250 mg, Yield: 76%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.99 (s, 1H), 4.31 (m, 2H), 3.70 (s, 2H).

Step 2: Preparation of 3-chloro-1-(2-fluoroethyl)-1H-pyrazol-4-amine (76):

[0248] Title compound (**76**) was prepared (200 mg; Yield: 95%) as viscous solid in a manner substantially similar to procedure mentioned in **General procedure AA.** MS: $[M+H]^+$ 164.10

Scheme 20: Synthesis of 3-chloro-1-(2,2-difluoroethyl)-1H-pyrazol-4-amine (79)



Step 1: Preparation of 3-chloro-1-(2,2-difluoroethyl)-4-nitro-1H-pyrazole (78):

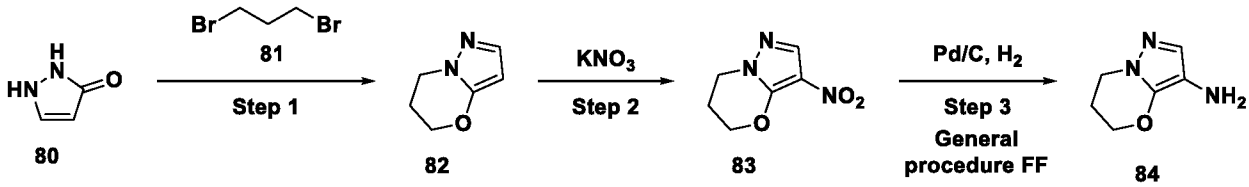
[0249] To an ice-cold solution of 3-chloro-4-nitro-1H-pyrazole **(72)** (300 mg, 2.04 mmol) in dimethylformamide (5.0 mL) was added sodium hydride (60% dispersion in mineral oil, 122 mg, 3.06 mmol) portion wise. The resulting reaction mixture was stirred at same temperature for 15 minutes, followed by the addition of 1-bromo-2-fluoroethane **(77)** (258 mg, 2.03 mmol). The resulting reaction mixture was heated at 100 °C for 16 hours. After completion of reaction (as per TLC monitoring), the reaction mixture was poured in to ice-cold water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 15% ethyl acetate in heptane afforded the desired product

(78) (180 mg, Yield: 50%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.06 (s, 1H), 6.31 (m, 1H), 4.68 (s, 2H).

Step 2: Preparation of 3-chloro-1-(2,2-difluoroethyl)-1H-pyrazol-4-amine (79):

[0250] Title compound (**79**) was prepared (120 mg; Yield: 78%) as viscous solid in a manner substantially similar to procedure mentioned in **General procedure AA**. MS: $[M+H]^+$ 182.04

Scheme 21: Synthesis of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-amine (84)



Step 1: Preparation of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (82):

[0251] To a solution of 1,2-dihydro-3H-pyrazol-3-one **(80)** (2.0 g, 23.8 mmol) in dimethylformamide (10 mL) was added potassium carbonate (2.96 g, 21.4 mmol) and 1,3-dibromopropane **(81)** (1.44 g, 7.14 mmol). The resulting reaction mixture was heated at 130 °C for 2 hours. After completion of reaction (as per TLC monitoring), reaction mixture was cooled to room temperature, quenched with ice-cold water and extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash, eluted with 0.5% methanol in dichloromethane afforded the desired product **(82)** (900 mg; Yield: 30%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.19 (d, J = 1.6 Hz, 1H), 5.42 (t, J = 2.0 Hz, 1H), 4.24 (t, J = 5.2 Hz, 2H), 4.03 (t, J = 6.0 Hz, 2H), 2.13 (m, 2H). MS: $[M+H]^+$ 125.02.

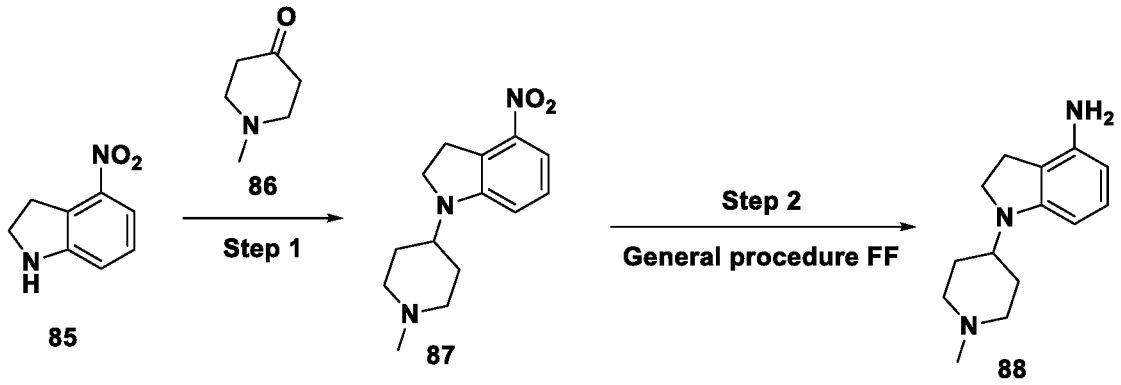
Step 2: Preparation of 3-nitro-6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine (83):

[0252] To an ice-cold solution of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazine **(82)** (900 mg, 7.25 mmol) in concentrated sulfuric acid (11 mL) was added potassium nitrate (1.46 g, 14.4 mmol) portion wise and stirred the reaction mixture at the same temperature for 1 hour. After completion of reaction (TLC monitoring), reaction mixture poured into crushed ice and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afforded the desired product **(83)** (630 mg; Yield: 52%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.07 (s, 1H), 4.54 (t, J = 5.2 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 2.24 (m, 2H). LCMS: $[M+H]^+$ 170.19, 97.58% purity.

Step 3: Preparation of 6,7-dihydro-5H-pyrazolo[5,1-b][1,3]oxazin-3-amine (84):

[0253] Title compound (**84**) was prepared (500 mg; Yield: 96%) in a manner substantially similar to procedure mentioned in **General procedure FF.** MS $[M+H]^+$ 140.02

Scheme 22: Synthesis of 1-(1-methylpiperidin-4-yl)indolin-4-amine (88)



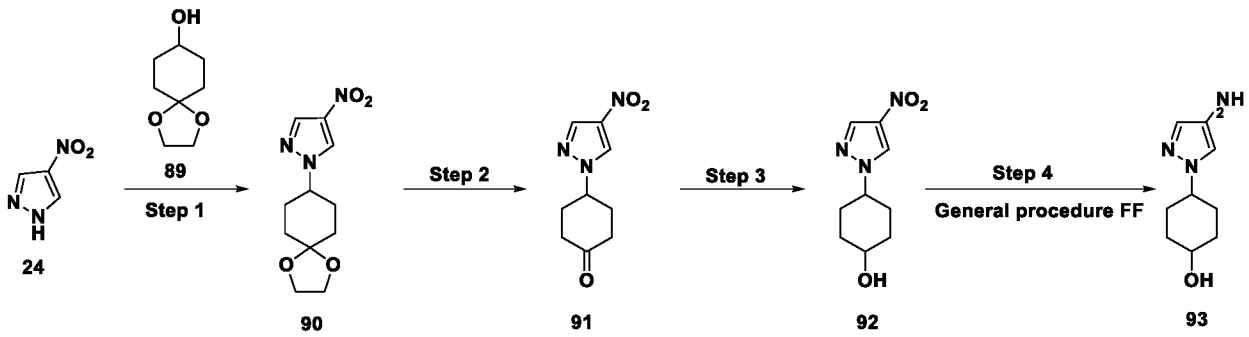
Step 1: Preparation of 1-(1-methylpiperidin-4-yl)-4-nitroindoline (87):

[0254] To an ice-cold solution of 4- nitro-2,3-dihydro-1H-indole **(85)** (1.0 g, 6.09 mmol) in dichloroethane (20 mL) was added 1- methylpiperidine-4-one **(86)** (1.0 g, 8.83 mmol), catalytic amount of acetic acid and the reaction mixture was stirred for 10 minutes. Then the sodium triacetoxyborohydride (2.45 g, 11.6 mmol) was added to the above reaction mixture at 0 °C and reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was quenched with saturated solution of sodium bicarbonate and extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude residue was purified by combiflash chromatography, eluted with 10% ethyl acetate in hexane afforded the desired product **(87)** (600 mg; Yield: 44%) as viscous liquid. MS $[M+H]^+$ 262.25

Step 2: Preparation of 1-(1-methylpiperidin-4-yl)indolin-4-amine (88):

[0255] Title compound (**88**) was prepared (400 mg; Yield: 82%) in a manner substantially similar to procedure mentioned in s **General procedure FF**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 6.64 (t, J = 8.0 Hz, 1H), 5.86 (d, J = 7.6 Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 4.62 (bs, 2H), 3.17 (m, 3H), 2.79 (m, 2H), 2.59 (m, 2H), 2.15 (s, 3H), 1.89 (m, 2H), 1.57 (m, 4H). LCMS $[M+H]^+$ 232.24, 98.71%.

Scheme 23: Synthesis of 4-(4-amino-1H-pyrazol-1-yl)cyclohexan-1-ol (52)



Step 1: Preparation of 4-nitro-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole (90):

[0256] To an ice-cold solution of 4-nitro-1H-pyrazole **(24)** (5.0 g, 44.21 mmol) in tetrahydrofuran (75 mL) was added 1,4-dioxaspiro[4.5]decan-8-ol **(89)** (8.40 g, 53.05 mmol), triphenylphosphine (23.19 g, 88.42 mmol) and diisopropyl azodicarboxylate (17.87 g, 88.42 mmol). Then the reaction mixture was stirred at room temperature for 16 hours. After completion of reaction (TLC monitoring), the reaction mixture was poured into water and extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified over combiflash chromatography using 20% ethyl acetate in hexane as an eluent, afforded the 4-nitro-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole **(90)** as off white solid (6.0 g; Yield: 54%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.24 (s, 1H), 4.40-4.33 (m, 1H), 3.89 (s, 4H), 2.08-1.95 (m, 4H), 1.83-1.62 (m, 4H).

Step 2: Preparation of 4-(4-nitro-1H-pyrazol-1-yl)cyclohexan-1-one (91):

[0257] To a solution of 4-nitro-1-(1,4-dioxaspiro[4.5]decan-8-yl)-1H-pyrazole **(90)** (6.0 g, 23.69 mmol) in acetone: water (1:1, 100 mL) was added pyridinium *p*-toluenesulfonate (17.86 g, 71.07 mmol). Then the reaction mixture was heated at 60 °C for 16 hours. After completion of reaction (TLC monitoring), solvent was evaporated, diluted with saturated solution of sodium bicarbonate and extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified using combiflash chromatography using (10-20%) ethyl acetate in hexane as an eluent, desired fractions were concentrated under reduced pressure afforded 4-(4-nitro-1H-pyrazol-1-yl)cyclohexan-1-one **(91)** as off white solid (4.0 g; Yield: 81%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 8.27 (s, 1H), 4.40-4.33 (m, 1H), 2.35-2.27 (m, 4H), 1.83-1.62 (m, 4H).

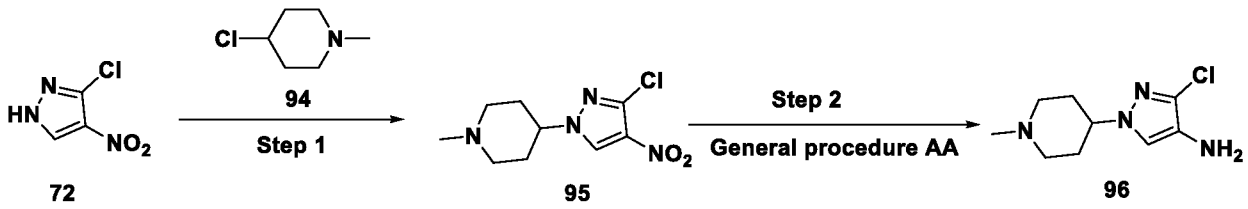
Step 3: Preparation of 4-(4-nitro-1H-pyrazol-1-yl)cyclohexan-1-ol (92):

[0258] To an ice cold solution of 4-(4-nitro-1H-pyrazol-1-yl) cyclohexan-1-one **(91)** (1.0 g, 19.11 mmol) in methanol (50 mL) was added sodium borohydride (1.45 g, 38.23 mmol) portion-wise and the reaction mixture was stirred at room temperature for 4 hours. After completion of reaction (TLC monitoring), reaction mixture was quenched with ice-cold water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure afforded 4-(4-nitro-1H-pyrazol-1-yl)cyclohexan-1-ol **(92)** as an off white solid (3.5 g; Yield: 86%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.90 (s, 1H), 8.25 (s, 1H), 4.30-4.19 (m, 1H), 3.50-3.44 (m, 1H), 2.28-1.95 (m, 4H), 1.85-1.70 (m, 5H).

Step 4: Preparation of 4-(4-amino-1H-pyrazol-1-yl)cyclohexan-1-ol (93):

[0259] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure FF,** afforded of 4-(4-amino-1H-pyrazol-1-yl)cyclohexan-1-ol **(93)** as a brown solid (2.5 g, Yield: 84%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.05 (s, 1H), 6.86 (s, 1H), 4.62-4.61 (m, 1H), 3.93-3.84 (m, 1H), 3.72 (s, 2H), 3.50-3.42 (m, 1H), 1.89-1.80 (m, 4H), 1.78-1.59 (m, 4H).

Scheme 24: Synthesis of 3-chloro-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-amine (96)



Step 1: Preparation of 4-(3-chloro-4-nitro-1H-pyrazol-1-yl)-1-methylpiperidine (95):

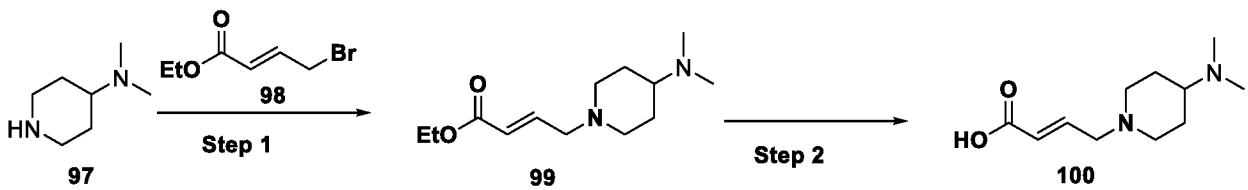
[0260] To a solution of 3-chloro-4-nitro-1H-pyrazole **(72)** (8.0 g, 0.054 mol) in dimethylformamide (100 mL) was added cesium carbonate (35.44 g, 0.108 mol) and 4-chloro-1-methylpiperidine **(94)** (10.90 g, 0.081 mol) and the reaction mixture was heated at 120 °C for 16 hours. After completion of reaction (TLC monitoring), reaction mixture was diluted with ice-cold water and extracted with 10% methanol in dichloromethane (3 x 100 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by combiflash chromatography using 5-10% methanol in dichloromethane as eluent, desired fractions were concentrated to dryness under reduced pressure afforded 4-(3-chloro-4-nitro-1H-pyrazol-1-yl)-1-methylpiperidine **(95)** as a brown solid (5.0 g, Yield: 38%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.05 (s, 1H), 4.25-4.18 (m, 1H), 2.90-2.80 (m, 2H), 2.21 (s, 3H), 2.10-1.85 (m, 6H).

Step 2: Preparation of 3-chloro-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-amine (96):

[0261] Title compound (**96**) was prepared as a brown solid (3.5 g; Yield: 80%) in a manner substantially similar to procedure mentioned in **General procedure AA**. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.17 (s, 1H), 4.16 (m, 1H), 3.91-3.85 (m, 2H), 2.15 (s, 3H), 1.89-1.80 (m, 4H), 2.10-1.85 (m, 4H). MS: $[M+H]^+$ 215.21

Scheme 25: Synthesis of (E)-4-(4-(dimethylamino)piperidin-1-yl)but-2-enoic acid (100)



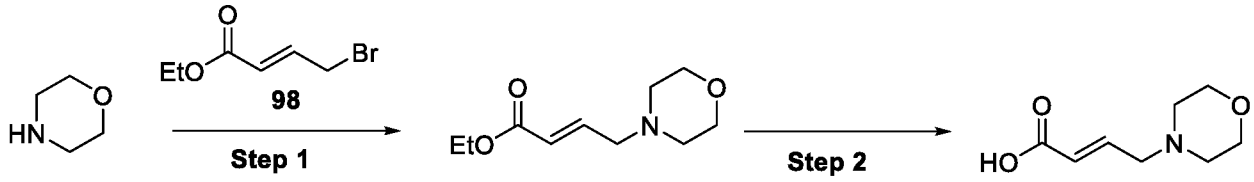
Step 1: Preparation of ethyl (E)-4-(4-(dimethyl amino) piperidin-1-yl)but-2-enoate (99):

[0262] To a stirred solution N,N-dimethylpiperidin-4-amine hydrochloride **(97)** (500 mg, 3.04 mmol) in dichloromethane (3.00 mL) were added N,N-diisopropylethylamine (2.65 mL, 15.2 mmol) and ethyl (2E)-4-bromobut-2-enoate **(98)** (0.461 mL, 3.34 mmol) and the reaction mixture was stirred at room temperature for 16 hours. Progress of the reaction was monitored by LCMS and TLC. After completion of reaction, the reaction mixture was diluted with water (5 mL) and extracted with dichloromethane (2 x 100 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography using combiflash purifier with 6% methanol in dichloromethane as eluent to obtain ethyl (2E)-4-[4-(dimethylamino)piperidin-1-yl]but-2-enoate (**99**) (270 mg, 37% yield) as brown color liquid. LCMS $[M+H]^+$ 241.2

Step 2: Preparation of (E)-4-(4-(dimethyl amino) piperidin-1-yl)but-2-enoicacid (100):

[0263] To a stirred solution of ethyl (2E)-4-[4-(dimethyl amino)piperidin-1-yl]but-2-enoate **(99)** (270 mg, 1.25 mmol) in 1,4-dioxane (3 mL), was added hydrochloric acid (3 mL, 2N) and refluxed for 5 h. The progress of the reaction was monitored by LCMS and TLC. After completion of the reaction, reaction mixture was concentrated. The residue was washed with ether and concentrated to obtain (E)-4-[4-(dimethyl amino)piperidin-1-yl]but-2-enoic acid (**100**) (250 mg, crude) as white solid. LCMS $[M+H]^+$ 213.2.

Scheme 26: Synthesis of (E)-4-morpholinobut-2-enoic acid (102)



56 **101** **102**

Step 1: Synthesis of ethyl (2E)-4-(morpholin-4-yl)but-2-enoate (101)

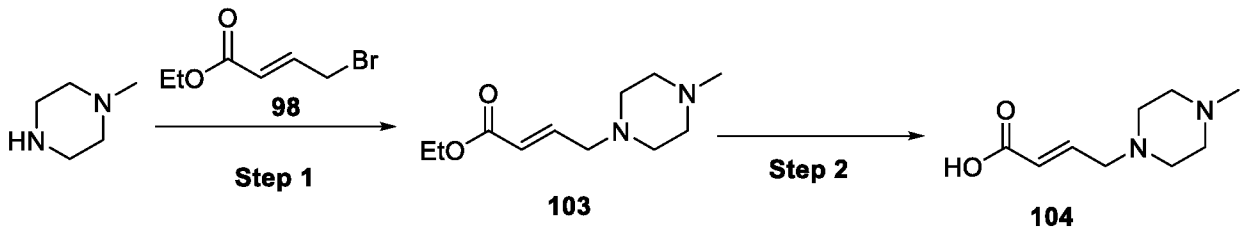
[0264] To a stirred solution of morpholine **(56)** (0.5 g, 5.74 mmol) in dichloromethane (10.0 mL) were added ethylbis(propan-2-yl)amine (1.50 mL, 8.61 mmol), ethyl (2E)-4-bromobut-2-enoate (**98**) (1.22 g, 6.31 mmol) and stirred at room temperature for 16 hours. The progress of the reaction was monitored by LCMS. After completion of the reaction, reaction mixture was diluted with water, extracted with dichloromethane (50 mL x 2). The combined organic layers were concentrated to afford title compound (**101**) (1.00 g, crude). LCMS $[M+H]^+$ 200.1

Step 2: Synthesis of (2E)-4-(morpholin-4-yl)but-2-enoic acid (102)

[0265] To a stirred solution of ethyl (2E)-4-(morpholin-4-yl)but-2-enoate **(101)** (1.00 g, 5.02 mmol) in 1,4-dioxane (10.0 mL), was added hydrochloric acid (10.0 mL, 2N) and refluxed for 3

hours. The progress of the reaction was monitored by LCMS. After completion of the reaction, reaction mixture was extracted with ethyl acetate (50 ml) and the organic layer was concentrated to obtain crude product. Residue was triturated ethyl acetate to afford title crude compound (**102**) (0.9 g, 90%) as light brown solid. LCMS $[M+H]^+$ 172.1.

Scheme 27: Synthesis of (E)-4-(4-methylpiperazin-1-yl)but-2-enoic acid (63)



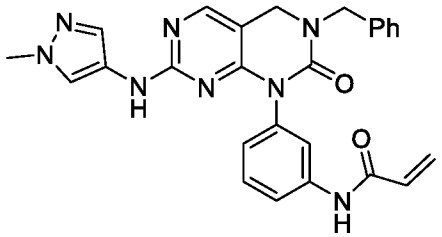
Step 1: Synthesis of ethyl (2E)-4-(4-methylpiperazin-1-yl)but-2-enoate (103)

[0266] To a stirred solution of 1-methylpiperazine (0.5 g, 4.99 mmol) in dichloromethane (10.0 mL) were added ethylbis(propan-2-yl)amine (1.30 mL, 7.49 mmol), ethyl (2E)-4-bromobut-2-enoate (**98**) (1.06 g, 5.49 mmol) and stirred at room temperature for 16 h. The progress of the reaction was monitored by LCMS. After completion of the reaction, reaction mixture was diluted with water (20 ml) and extracted with ethyl acetate (100 ml x 2). The combined organic layers were concentrated to obtain title compound (**103**) (0.66 g, crude). LCMS $[M+H]^+$ 213.2.

Step 2: Synthesis of (2E)-4-(4-methylpiperazin-1-yl)but-2-enoic acid (104)

[0267] To a stirred solution of ethyl (2E)-4-(4-methylpiperazin-1-yl)but-2-enoate **(103)** (0.66 g, 3.11 mmol) in 1,4-dioxane (10.0 mL), was added hydrochloric acid (10.0 mL, 2N) and refluxed for 3 hours. The progress of the reaction was monitored by LCMS. After completion of the reaction, reaction mixture was extracted with ethyl acetate (50 ml) and the organic layer was concentrated to obtain crude product. Residue was triturated with ether to obtain title compound (**104**) as light brown solid (0.6 g, crude). LCMS $[M+H]^+$ 185.1.

Compound 1: N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide



Step 1: Ethyl 4-((3-((tert-butoxycarbonyl)amino)phenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate

[0268] To a solution of 4-chloro-2-methylsulfanyl-pyrimidine-5-carboxylic acid ethyl ester (**2**, 10.84 g, 46.58 mmol) in DMF (100 mL) were added potassium carbonate (12.87 g, 93.16 mmol) and *tert*-butyl (3-aminophenyl)carbamate (9.69 g, 46.58 mmol). The reaction was heated to 80

°C and stirred for 16 h. The reaction was monitored by TLC, after the completion of reaction, the reaction mixture was cooled to room temperature and the reaction mixture was added to ice water. The precipitate was filtered and the filtered cake was rinsed with additional cold water and dried in vacuum to give ethyl 4-((3-((*tert*-butoxycarbonyl)amino)phenyl)amino)-2-(methylthio)pyrimidine-5-carboxylate (15.5 g, 82.4% yield). LCMS Calcd for $[M+H]^+$ 405.1, found 405.2

Step 2: *tert*-butyl (3-((5-(hydroxymethyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate

[0269] To a solution of the ethyl 4-((3-((*tert*-butoxycarbonyl) amino)phenyl)amino)-2-methylthio)pyrimidine-5-carboxylate (13 g, 32.17 mmol) in THF (200 mL) was added 1.0 M $LiAlH_4$ solution in THF (3.65 g, 96.5 mmol) at -40 °C. The temperature was raised to RT for a period of 3 h. The reaction mixture then treated with ammonium chloride solution (50 mL). After the mixture was stirred at RT for 30 min, the solid was filtered off. The filtrate was partitioned between DCM (5 x 200 mL) and water (200 mL). The organic layer was washed with brine (200 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by column chromatography using combiflash with 0-5% methanol in DCM as a solvent to get pure product *tert*-butyl (3-((5-(hydroxymethyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (4.3 g, 37% yield). LCMS Calcd for $[M+H]^+$ 363.1, LCMS found 363.2

Step 3: *tert*-butyl (3-((5-formyl-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate

[0270] To a solution of *tert*-butyl (3-((5-(hydroxymethyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (3.5 g, 9.66 mmol) in DCM (40 mL) was added activated manganese oxide (8.4 g, 96.6 mmol) at RT and the reaction mixture was stirred for 16 h. The reaction was monitored by TLC, after the completion of reaction, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure to obtain crude product *tert*-butyl (3-((5-formyl-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (2.8 g, 80.4% yield) and used as such for the next step. LCMS Calcd for $[M+H]^+$ 361.1, LCMS found 361.2

Step 4: (E)-*tert*-butyl (3-((5-((benzylimino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate

[0271] Title compound was prepared in a similar manner to general procedure A. *tert*-butyl (3-((5-formyl-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate and benzyl amine gave title compound (E)-*tert*-butyl (3-((5-((benzylimino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (3.1 g, 88.8% yield). LCMS Calcd for $[M+H]^+$ 450.1, LCMS found 450.2

Step 5: *tert*-butyl (3-((5-((benzylamino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate

[0272] Title compound was prepared in a similar manner to general procedure B. (E)-*tert*-butyl (3-((5-((benzylimino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate gave *tert*-butyl (3-((5-((benzylamino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate with 87% yield . LCMS Calcd for $[M+H]^+$ 452.2, LCMS found 452.3

Step 6: *tert*-butyl (3-(3-benzyl-7-(methylthio)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate

[0273] Title compound was prepared in a similar manner to general procedure C. *tert*-butyl (3-((5-((benzylamino) methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate gave *tert*-butyl (3-(3-benzyl-7-(methylthio)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate with 70% yield. LCMS Calcd for $[M+H]^+$ 478.1, LCMS found 478.2

Step 7: *tert*-butyl (3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate

[0274] Title compound was prepared in a similar manner to general procedure D. *tert*-butyl (3-(3-benzyl-7-(methylthio)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate gave *tert*-butyl (3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3, 4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate with 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.62 (s, 1H), 7.41-7.35 (m, 6H), 7.18-7.16 (d, 1H), 7.65 (s, 1H), 7.51-7.50 (t, 1H), 7.37-7.35 (m, 5H), 7.06-7.04 (d, 2H), 6.62 (s, 1H), 6.45-6.38 (m, 1H), 6.26-6.21 (m, 1H), 5.76-5.73 (d, 1H), 4.62 (s, 2H), 4.37 (s, 2H), 3.47(s, 3H);

Step 8: *tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate

[0275] Title compound was prepared in a similar manner to general procedure E. *tert*-butyl (3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate and 1-methyl-1H-pyrazol-4-amine gave *tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate as off white solid with 8% yield. LCMS Calcd for $[M+H]^+$ 527.2, found 527.5

Step 9: 1-(3-aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one

[0276] Title compound was prepared in a similar to general procedure F. *tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate and TFA and DCM as solvent gave 1-(3-aminophenyl)-3-benzyl-7-((1-

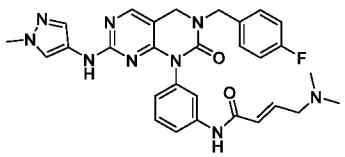
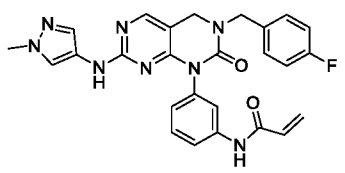
methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one as off white solid with 80% yield. LCMS Calcd for $[M+H]^+$ 427.1, found 427.5

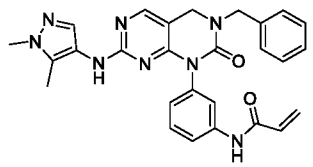
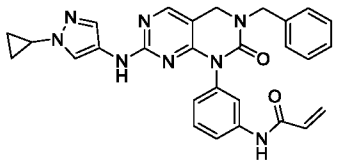
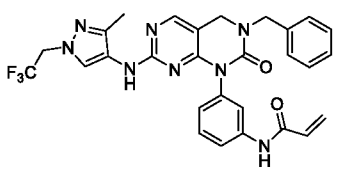
Step 10: N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide (Compound 1).

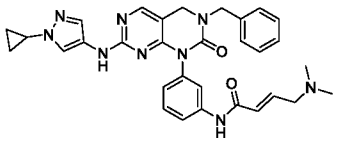
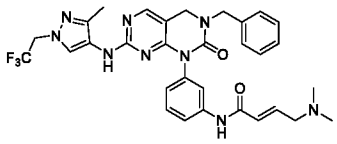
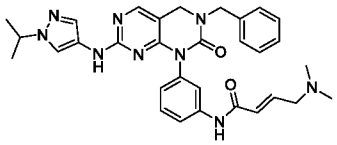
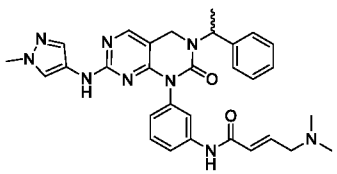
[0277] Title compound was prepared in a similar manner to general procedure G. 1-(3-aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one and acryloyl chloride gave N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide (**Compound 1**) as white solid with 29% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H), 9.33 (s, 1H), 8.06 (s, 1H), 7.79 (bs, 1H), 7.65 (s, 1H), 7.50 (bs, 1H), 7.37-7.35 (m, 5H), 7.05 (d, J = 8 Hz, 2H), 6.62 (s, 1H), 6.45-6.38 (m, 1H), 6.26-6.21 (m, 1H), 5.76-5.73 (m, 1H), 4.62 (s, 2H), 4.37 (s, 2H), 3.47 (s, 3H); LCMS Calcd for $[M+H]^+$ 481.2, found 481.5

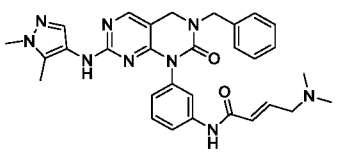
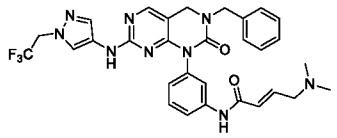
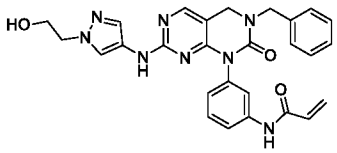
[0278] In some cases, for example compound 38 and compound 39, the racemic compounds (compound 37) were separated by chiral prep HPLC using Chiral Cel-OJH (20 x 250) mm, 5μ column (mobile phase:Hexane-EtOH) with a flow rate of 18 mL/min to get pure enantiomers.

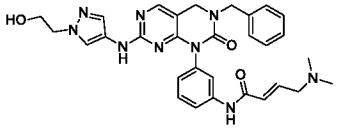
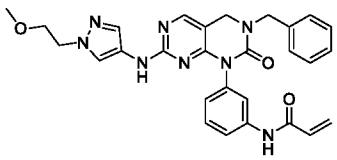
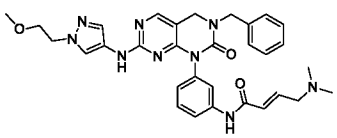
[0279] The following compounds were prepared using the methods described above

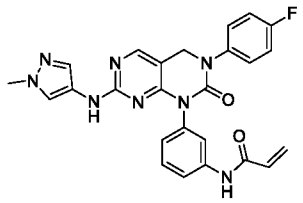
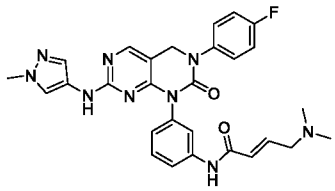
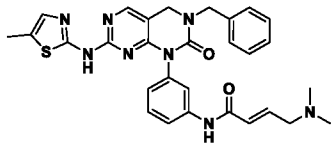
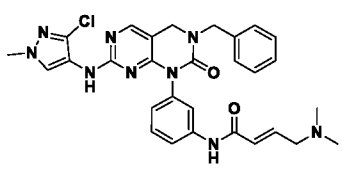
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
2		**H**	**556.25**	δ 10.26 (s, 1H), 9.38 (s, 1H), 8.09 (s, 1H), 7.78-7.70 (m, 1H), 7.68 (s, 1H), 7.51-7.49 (m, 1H), 7.44-7.40 (m, 2H), 7.21 (t, J = 8.8 Hz, 2H), 7.05-7.03 (m, 2H), 6.76-6.72 (m, 1H), 6.69 (s, 1H), 6.26 (d, J = 15.6 Hz, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.48 (s, 3H), 3.05 (d, J = 5.2 Hz, 2H), 2.16 (s, 6H).
3		**G**	**499.46**	δ 10.36 (s, 1H), 9.39 (s, 1H), 8.09 (s, 1H), 7.81-7.79 (m, 1H), 7.68 (s, 1H), 7.59-7.51 (m, 1H), 7.44-7.40 (m, 2H), 7.21 (t, J = 8.8 Hz, 2H), 7.08-7.03 (m, 2H), 6.62 (s, 1H), 6.47-6.40 (m, 1H), 6.25 (d, J = 17.2 Hz, 1H), 5.77

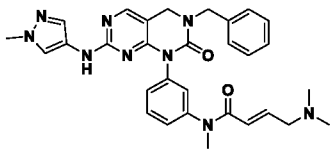
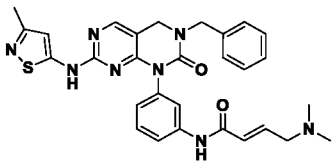
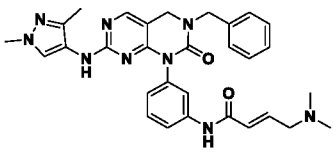
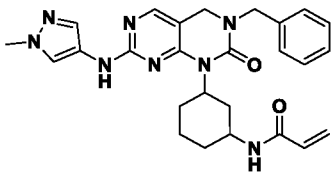
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				(d, J = 9.6 Hz, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.48 (s, 3H).
4		**G**	**493.44**	δ 10.25 (s, 1H), 8.62 (bs, 1H), 8.02 (s, 1H), 7.65-7.63 (m, 2H), 7.40-7.24 (m, 7H), 6.98 (d, J = 6.8 Hz, 1H), 6.47-6.40 (m, 1H), 6.25 (d, J = 16.8 Hz, 1H), 5.75 (d, J = 10.4 Hz, 1H), 4.62 (s, 2H), 4.36 (s, 2H), 3.55 (s, 3H), 2.00 (s, 3H).
5		**G**	**507.24**	δ 10.33 (s, 1H), 9.38 (s, 1H), 8.09 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.70 (s, 1H), 7.54-7.52 (m, 1H), 7.41-7.31 (m, 4H), 7.31-7.30 (m, 1H), 7.08-7.03 (m, 2H), 6.76 (s, 1H), 6.47-6.41 (m, 1H), 6.25 (d, J = 15.2 Hz, 1H), 5.76 (d, J = 10.4 Hz, 1H), 4.64 (s, 2H), 4.39 (s, 2H), 3.32-3.30 (m, 1H), 0.86-0.83 (m, 2H), 0.73-0.71 (m, 2H).
6		**G**	**563.48**	δ 10.34 (s, 1H), 8.97 (s, 1H), 8.13 (s, 1H), 7.79 (d, J = 7.6 Hz, 1H), 7.63 (s, 1H), 7.49-7.47 (m, 1H), 7.45-7.37 (m, 4H), 7.33-7.31 (m, 1H), 7.06-7.04 (m, 1H), 6.70 (s, 1H), 6.45-6.38 (m, 1H), 6.25 (d, J = 15.6 Hz, 1H), 5.78-5.75 (m, 1H), 4.6 (s, 2H), 4.41 (s, 2H), 4.43-4.41 (m, 2H), 2.09 (s, 3H).

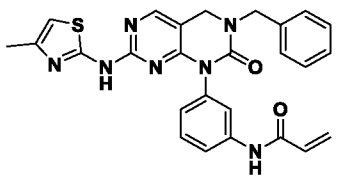
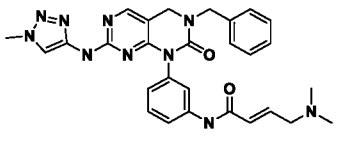
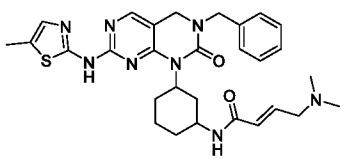
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
7		H	564.55	δ 10.25 (s, 1H), 9.55 (s, 1H), 9.38 (s, 1H), 8.09 (s, 1H), 7.83 (s, 1H), 7.78 (s, 1H), 7.50 (s, 1H), 7.37-7.32 (m, 5H), 7.03 (s, 1H), 6.75-6.70 (m, 2H), 6.27 (d, *J* = 14.4 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.05 (s, 2H), 2.16 (s, 6H), 1.17 (s, 1H), 0.85 (s, 2H), 0.73 (s, 2H).
8		H	620.54	δ 10.24 (s, 1H), 8.97 (bs, 1H), 8.13 (s, 1H), 7.76 (d, *J* = 5.2 Hz, 1H), 7.64 (s, 1H), 7.47-7.31 (m, 6H), 7.02 (d, *J* = 6.4 Hz, 1H), 6.75-6.70 (m, 2H), 6.24 (d, *J* = 17.2 Hz, 1H) 4.63 (s, 2H), 4.57-4.41 (m, 2H), 4.41 (s, 2H), 3.04 (d, *J* = 5.2 Hz, 2H), 2.16 (s, 6H), 2.09 (s, 3H).
9		H	566.29	δ 10.39 (s, 1H), 9.37 (s, 1H), 8.09 (s, 1H), 7.83-7.81 (m, 1H), 7.68 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.41-7.29 (m, 5H), 7.05-7.03 (m, 2H), 6.76-6.69 (m, 2H), 6.26 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 2H), 4.45 (s, 2H), 4.01-3.99 (m, 1H), 3.04 (d, *J* = 5.6 Hz, 2H), 2.15 (s, 6H), 1.21 (d, *J* = 20.8 Hz, 6H).
10		H	552.61	δ 10.27 (s, 1H), 9.37 (s, 1H), 8.06 (s, 1H), 7.78-7.76 (m, 1H), 7.69 (s, 1H), 7.49 (t, *J* = 6.8 Hz, 1H), 7.41-7.40 (m, 4H), 7.33-7.30 (m, 1H), 7.06-7.04 (m,

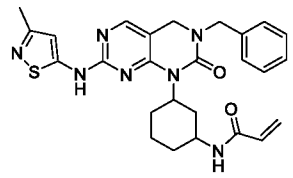
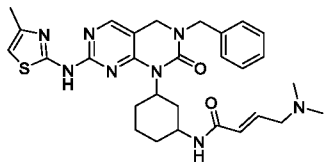
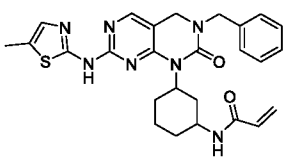
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				2H), 6.76-6.71 (m, 1H), 6.69 (s, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 5.77-5.72 (m, 1H), 4.43 (d, *J* = 14 Hz, 1H), 3.93 (d, *J* = 14 Hz, 1H), 3.48 (s, 3H), 3.07 (d, *J* = 5.6 Hz, 2H), 2.18 (s, 6H), 1.60 (d, *J* = 7.2 Hz, 3H).
11		**H**	**552.56**	δ 10.17 (s, 1H), 8.57 (bs, 1H), 8.02 (s, 1H), 7.64-7.62 (m, 2H), 7.39-7.31 (m, 7H), 6.95 (d, *J* = 8 Hz, 1H), 6.76-6.69 (m, 1H), 6.26 (d, *J* = 15.2 Hz, 1H), 4.61 (s, 2H), 4.36 (s, 2H), 3.55 (s, 3H), 3.05 (d, *J* = 4.2 Hz, 2H), 2.17 (s, 6H), 2.00 (s, 3H).
12		**H**	**606.52**	δ 10.29 (s, 1H), 9.51 (s, 1H), 8.12 (s, 1H), 7.89-7.77 (m, 1H), 7.66 (s, 1H), 7.49-7.41 (m, 1H), 7.41-7.37 (m, 4H), 7.35-7.31 (m, 1H), 7.20 (bs, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.77-6.69 (m, 2H), 6.28 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.62-4.55 (m, 2H), 4.40 (s, 2H), 3.18 (bs, 2H), 2.25 (s, 6H).
13		**G**	**511.49**	δ 10.39 (s, 1H), 9.38 (s, 1H), 8.09 (s, 1H), 7.78-7.76 (m, 1H), 7.72 (s, 1H), 7.50 (bs, 1H), 7.41-7.31 (m, 6H), 7.08-7.04 (m, 2H), 6.71 (bs, 1H), 6.49-6.42 (m, 1H), 6.27-6.22 (m, 1H), 5.77-5.74 (m, 1H), 4.71 (s, 1H), 4.64 (s, 1H), 4.39 (s, 2H),

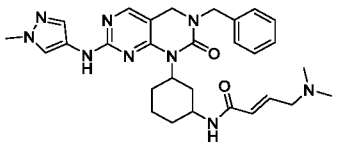
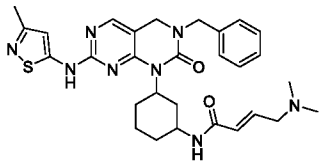
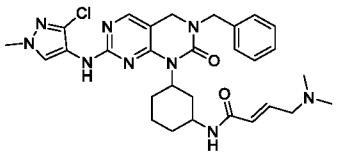
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				3.79-3.71 (m, 2H), 3.53-3.49 (m, 2H).
14		**H**	**568.51**	δ 10.31 (s, 1H), 9.38 (s, 1H), 8.09 (s, 1H), 7.75-7.71 (m, 2H), 7.52-7.48 (m, 1H), 7.42-7.29 (m, 5H), 7.06-7.04 (m, 2H), 6.76-6.70 (m, 2H), 6.30 (d, *J* = 15.2 Hz, 1H), 4.72 (bs, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.76 (bs, 2H), 3.52 (bs, 2H), 3.20 (bs, 2H), 2.29 (s, 6H).
15		**G**	**525.49**	δ 10.34 (s, 1H), 9.39 (s, 1H), 8.09 (s, 1H), 7.80-7.73 (m, 1H), 7.67 (s, 1H), 7.52-7.48 (m, 1H), 7.45-7.30 (m, 5H), 7.07-7.05 (m, 2H), 6.69 (s, 1H), 6.47-6.40 (m, 1H), 6.25 (d, *J* = 15.6 Hz, 1H), 5.76 (d, *J* = 11.6 Hz, 1H), 4.64 (s, 2H), 4.40 (s, 2H), 3.85 (bs, 2H), 3.44 (bs, 2H), 3.13 (s, 3H).
16		**H**	**582.55**	δ 10.25 (s, 1H), 9.39 (s, 1H), 8.09 (s, 1H), 7.84-7.78 (m, 1H), 7.68 (s, 1H), 7.54-7.45 (m, 1H), 7.45-7.31 (m, 5H), 7.08-7.03 (m, 2H), 6.76-6.69 (m, 2H), 6.26 (d, *J* = 15.6 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.85 (bs, 2H), 3.45 (bs, 2H), 3.13 (s, 3H), 3.04 (d, *J* = 6.0 Hz, 2H), 2.16 (s, 6H).

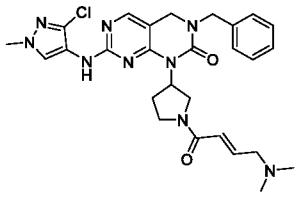
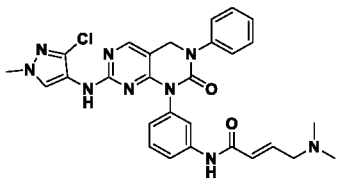
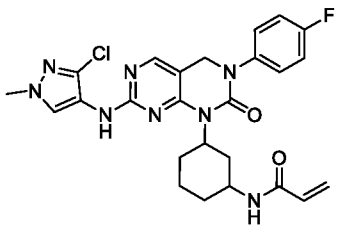
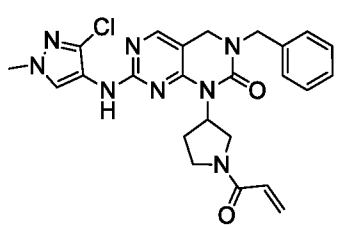
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
17		**G**	**483.44**	δ 10.41 (s, 1H), 9.46 (s, 1H), 8.17 (s, 1H), 7.79-7.77 (m, 1H), 7.76 (s, 1H), 7.52-7.49 (m, 3H), 7.26 (t, *J* = 8.8 Hz, 2H), 7.10 (d, *J* = 8 Hz, 1H), 7.05 (s, 1H), 6.66 (s, 1H), 6.49-6.42 (m, 1H), 6.28-6.23 (m, 1H), 5.78-5.75 (m, 1H), 4.85 (s, 2H), 3.49 (s, 3H).
18		**H**	**542.5**	δ 10.32 (s, 1H), 9.45 (s, 1H), 8.17 (s, 1H), 7.77-7.73 (m, 2H), 7.55-7.45 (m, 3H), 7.26 (t, *J* = 8.4 Hz, 2H), 7.10-7.04 (m, 2H), 6.75-6.66 (m, 2H), 6.29 (d, *J* = 15.6 Hz, 1H), 4.85 (s, 2H), 3.49 (s, 3H), 3.16 (bs, 2H), 2.24 (s, 6H).
19		**H**	**555.30**	δ 11.18 (s, 1H), 10.22 (s, 1H), 8.23 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.68 (s, 1H), 7.46-7.32 (m, 6H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.87 (s, 1H), 6.75-6.68 (m, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.45 (s, 2H), 3.05 (d, *J* = 4.8 Hz, 2H), 2.17 (s, 6H), 2.09 (s, 3H).
20		**H**	**572.52**	δ 10.26 (s, 1H), 8.77 (bs, 1H), 8.12 (s, 1H), 7.76-7.74 (m, 1H), 7.65 (s, 1H), 7.51-7.47 (m, 1H), 7.41 (s, 5H), 7.33-7.31 (m, 1H), 7.04 (d, *J* = 8 Hz, 1H), 6.77-6.70 (m, 1H), 6.26 (d, *J* = 15.6 Hz, 1H), 4.63 (s, 2H), 4.41 (s,

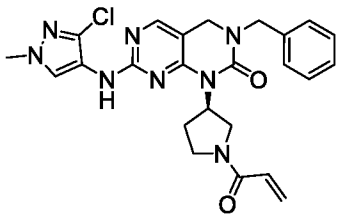
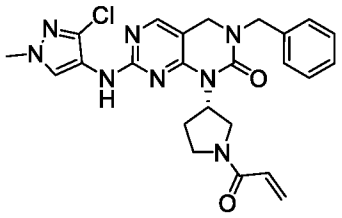
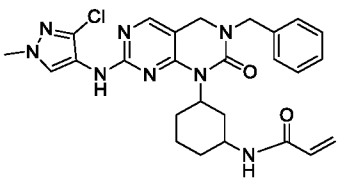
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				2H), 3.48 (bs, 3H), 3.04 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 6H).
21		**H**	**552.63**	δ 9.45 (bs, 1H), 8.27 (s, 1H), 7.72-7.65 (m, 1H), 7.54-7.47 (m, 1H), 7.37 (s, 5H), 7.32-7.27 (m, 2H), 7.02 (s, 1H), 6.74-6.68 (m, 1H), 6.64-6.56 (m, 1H), 6.00-5.90 (m, 1H), 4.64 (s, 2H), 4.37 (s, 2H), 3.51 (s, 3H), 3.27 (s, 3H), 2.43 (bs, 2H), 1.90 (s, 6H).
22		**H**	**555.57**	δ 11.13 (bs, 1H), 10.21 (s, 1H), 8.26 (bs, 1H), 7.80 (bs, 1H), 7.67-7.65 (m, 1H), 7.44-7.32 (m, 6H), 7.04 (bs, 1H), 6.74-6.63 (m, 1H), 6.56-6.46 (m, 1H), 6.27 (d, *J* = 14.8 Hz, 1H), 4.78 (s, 2H), 4.45 (s, 2H), 3.04 (bs, 2H), 2.16 (s, 9H).
23		**H**	**552.60**	δ 10.28 (s, 1H), 8.83 (bs, 1H), 8.10 (s, 1H), 7.79-7.77 (m, 1H), 7.65 (s, 1H), 7.51-7.43 (m, 1H), 7.37 (s, 4H), 7.33-7.31 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.76-6.70 (m, 1H), 6.58-6.55 (m, 1H), 6.28 (d, *J* = 16 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.39 (s, 3H), 3.10 (bs, 2H), 2.20 (s, 6H), 2.04 (s, 3H).
24		**G**	**487.58**	δ 9.41-9.29 (m, 1H), 8.15-8.13 (m, 1H), 8.05 (s, 1H), 7.84-7.82 (m, 1H), 7.49 (s, 1H), 7.36-7.22 (m, 5H), 6.23-6.16 (m, 1H),

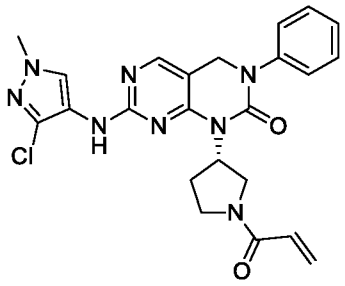
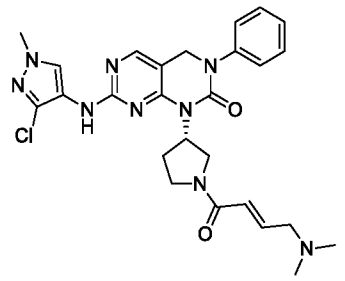
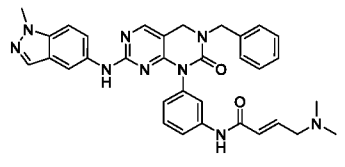
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				6.06 (d, *J* = 16.8 Hz, 1H), 5.57-5.54 (m, 1H), 4.75 (bs, 1H), 4.63-4.49 (m, 2H), 4.17 (s, 2H), 3.82 (bs, 4H), 2.40-2.33 (m, 2H), 1.90-1.82 (m, 3H), 1.62-1.58 (m, 1H), 1.40-1.28 (m, 1H), 1.16-1.09 (m, 1H).
25		**G**	**498.49**	δ 11.28 (bs, 1H), 10.26 (bs, 1H), 8.25 (s, 1H), 7.71-7.65 (m, 2H), 7.38-7.33 (m, 6H), 7.07 (bs, 1H), 6.42-6.40 (m, 1H), 6.26 (bs, 2H), 5.76 (bs, 1H), 4.64 (s, 2H), 4.46 (s, 2H), 2.12 (s, 3H).
26		**H**	**539.22**	δ 10.29 (s, 1H), 10.16 (s, 1H), 8.15 (s, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.66 (s, 1H), 7.54 (t, *J* = 8 Hz, 1H), 7.38 (s, 4H), 7.33-7.31 (m, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.77-6.70 (m, 1H), 6.44 (bs, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.43 (s, 2H), 3.71 (s, 3H), 3.07 (bs, 2H), 2.18 (s, 6H).
27		**H**	**561.25**	δ 11.37 (s, 1H), 8.15 (s, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.38-7.27 (m, 5H), 7.08 (s, 1H), 6.56-6.49 (m, 1H), 6.00 (d, *J* = 16 Hz, 1H), 4.89 (s, 1H), 4.64-4.51 (m, 2H), 4.23 (s, 2H), 3.83 (s, 1H), 3.01 (s, 2H), 2.46-2.37 (m, 2H), 2.33 (s, 3H), 2.16 (s, 6H), 1.99-1.76 (m, 3H), 1.76-1.71

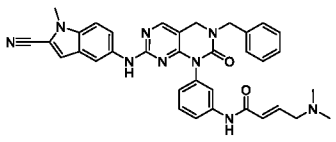
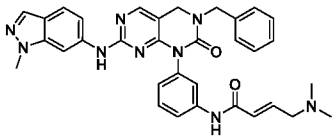
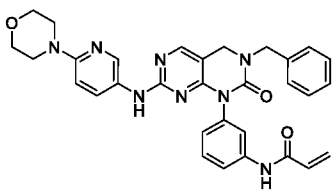
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				(m, 1H), 1.43-1.29 (m, 1H), 1.23-1.12 (m, 1H).
28		**G**	**504.21**	δ 11.35 (bs, 1H), 8.19-8.14 (m, 2H), 7.38-7.29 (m, 5H), 6.66 (s, 1H), 6.22-6.16 (m, 1H), 6.12-6.03 (m, 1H), 5.55 (d, *J* = 10 Hz, 1H), 5.0-4.9 (m, 1H), 4.66-4.49 (m, 2H), 4.24 (s, 2H), 3.33 (bs, 1H), 2.29 (s, 3H), 1.87-1.67 (m, 5H), 1.38-1.33 (m, 3H).
29		**H**	**561.25**	δ 11.47 (s, 1H), 8.17 (s, 1H), 8.11 (bs, 1H), 7.38-7.28 (m, 5H), 6.68 (s, 1H), 6.58-6.51 (m, 1H), 6.06 (d, *J* = 15.6 Hz, 1H), 4.86 (bs, 1H), 4.63-4.51 (m, 2H), 4.23 (s, 2H), 3.83 (bs, 1H), 3.24 (bs, 2H), 2.32 (s, 6H), 2.25 (s, 3H), 1.99-1.69 (m, 4H), 1.46-1.41 (m, 1H), 1.29-1.18 (m, 3H).
30		**G**	**504.18**	δ 11.36 (s, 1H), 8.16 (s, 1H), 8.12 (d, *J* = 7.6 Hz, 1H), 7.39-7.35 (m, 2H), 7.31-7.29 (m, 3H), 7.07 (s, 1H), 6.22-6.16 (m, 1H), 6.08-6.04 (m, 1H), 5.56-5.53 (m, 1H), 4.95-4.85 (m, 1H), 4.64-4.51 (m, 2H), 4.24 (s, 2H), 3.92-3.83 (m, 1H), 2.36 (s, 3H), 2.45-2.36 (m, 2H), 1.93-1.82 (m, 3H), 1.74-1.71 (m, 1H), 1.44-1.41 (m, 1H), 1.25-1.21 (m, 1H).

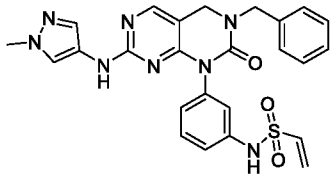
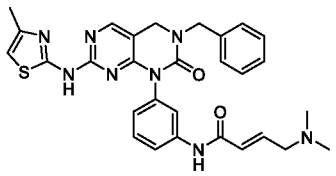
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
31		**H**	**544.31**	δ 9.31 (s, 1H), 8.05-8.00 (m, 2H), 7.81 (bs, 1H), 7.44 (s, 1H), 7.36-7.28 (m, 5H), 6.56-6.51 (m, 1H), 6.00 (d, *J* = 16 Hz, 1H), 4.74 (bs, 1H), 4.62-4.49 (m, 2H), 4.16 (s, 2H), 3.81 (s, 3H), 3.77 (bs, 1H), 2.95 (d, *J* = 6 Hz, 2H), 2.42-2.33 (m, 2H), 2.12 (s, 6H), 1.9-1.8 (m, 3H), 1.67-1.66 (m, 1H), 1.39-1.36 (m, 1H), 1.23-1.17 (m, 1H).
32		**H**	**561.25**	δ 11.25 (bs, 1H), 8.12 (s, 1H), 8.05 (d, *J* = 8 Hz, 1H), 7.38-7.29 (m, 5H), 6.66 (s, 1H), 6.56-6.50 (m, 1H), 6.00 (d, *J* = 15.2 Hz, 1H), 4.95-4.83 (m, 1H), 4.65-4.50 (m, 2H), 4.23 (s, 2H), 3.78 (bs, 1H), 2.97 (d, *J* = 4.8 Hz, 2H), 2,87 (s, 3H), 2.14 (s, 6H), 1.89-1.69 (m, 4H), 1.54-1.49 (m, 1H), 1.23-1.09 (m, 3H).
33		**H**	**580.22 [M+2 H]$^+$**	δ 8.61 (s, 1H), 7.97 (bs, 2H), 7.89 (s, 1H), 7.37-7.34 (m, 2H), 7.29-7.27 (m, 3H), 6.57-6.50 (m, 1H), 6.05-6.01 (m, 1H), 4.70-4.41 (m, 3H), 4.16 (s, 2H), 3.80 (s, 3H), 3.64 (bs, 1H), 3.03 (bs, 2H), 2.33-2.32 (m, 2H), 2.17 (s, 6H), 1.80-1.77 (m, 3H), 1.58-1.56 (m, 1H), 1.35-1.30 (m, 1H), 1.03 (bs, 1H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
34		**H**	**552.18 $[M+2H]^+$**	δ 8.59 (bs, 1H), 8.02-8.01 (m, 1H), 7.82-7.79 (m, 1H), 7.38-7.34 (m, 2H), 7.29 (d, *J* = 7.6 Hz, 3H), 6.66-6.61 (m, 1H), 6.39-6.28 (m, 1H), 5.37 (bs, 1H), 4.59-4.57 (m, 2H), 4.19 (bs, 2H), 3.73-3.72 (m, 5H), 3.58-3.55 (m, 1H), 3.06-3.00 (m, 2H), 2.73 (bs, 1H), 2.14 (s, 6H), 1.99-1.97 (m, 2H).
35		**H**	**560.17 $[M+2H]^+$**	δ 10.27 (bs, 1H), 8.86 (bs, 1H), 8.21 (s, 1H), 7.73 (s, 2H), 7.48-7.41 (m, 6H), 7.29-7.26 (m, 1H), 7.10-7.08 (m, 1H), 6.74-6.66 (m, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 4.89 (s, 2H), 3.50 (bs, 3H), 3.05 (d, *J* = 5.6 Hz, 2H), 2.17 (s, 6H).
36		**G**	**525.37**	δ 8.68 (bs, 1H), 8.06 (s, 1H), 8.04 (bs, 1H), 7.91 (s, 1H), 7.39-7.35 (m, 2H), 7.24-7.20 (m, 2H), 6.23-6.04 (m, 2H), 5.57-5.54 (m, 1H), 4.65-4.56 (m, 3H), 3.81 (s, 3H), 3.66 (bs, 1H), 2.32 (bs, 1H), 1.88-1.75 (m, 3H), 1.63 (bs, 1H), 1.30 (bs, 1H), 1.07 (bs, 2H).
37 (Racemic)		**G**	**493.12**	δ 8.58 (bs, 1H), 8.01 (s, 1H), 7.82-7.79 (m, 1H), 7.37-7.29 (m, 5H), 6.66-6.47 (m, 1H), 6.14 (d, *J* = 16.4 Hz, 1H), 5.63-5.40 (m, 1H), 5.38 (bs, 1H), 4.58 (s, 2H), 4.18 (s, 2H), 3.98-

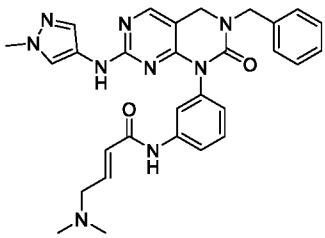
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				3.93 (m, 1H), 3.73-3.54 (m, 6H), 2.72-2.64 (m, 1H), 2.10-1.96 (m, 1H).
38 (Enantiomer 1)		**G**	**493.38**	δ 8.58 (bs, 1H), 8.01 (d, J = 3.60 Hz, 1H), 7.82-7.74 (m, 1H), 7.38-7.29 (m, 5H), 6.66-6.47 (m, 1H), 6.14 (d, J = 16.80 Hz, 1H), 5.67-5.62 (m, 1H), 5.42 (bs, 1H), 4.53 (s, 2H), 4.18 (s, 2H), 3.98-3.93 (m, 1H), 3.73-3.50 (m, 6H), 2.69-2.61 (m, 1H), 2.10-1.80 (m, 1H).
39 (Enantiomer 2)		**G**	**493.38**	δ 8.60 (bs, 1H), 8.01 (d, J = 3.60 Hz, 1H), 7.82-7.74 (m, 1H), 7.38-7.29 (m, 5H), 6.66-6.47 (m, 1H), 6.12 (d, J = 16.40 Hz, 1H), 5.70-5.63 (m, 1H), 5.38 (bs, 1H), 4.58 (s, 2H), 4.18 (s, 2H), 3.97-3.93 (m, 1H), 3.73-3.50 (m, 6H), 2.69-2.61 (m, 1H), 2.11-1.97 (m, 1H).
40		**G**	**521.38**	δ 8.61 (bs, 1H), 8.02 (bs, 1H), 7.97 (s, 1H), 7.88 (s, 1H), 7.37-7.27 (m, 5H), 6.23-6.16 (m, 1H), 6.09-6.04 (m, 1H), 5.55 (dd, J_1 = 2.0, J_2 = 10 Hz, 1H), 4.72-4.48 (m, 3H), 4.15 (s, 2H), 3.80 (s, 3H), 3.64 (bs, 1H), 3.38-3.32 (m, 2H), 1.81-1.75 (m, 3H), 1.56 (bs, 1H), 1.36-1.02 (m, 2H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
41		**G**	**479.33**	δ 8.68 (bs, 1H), 8.11 (d, *J* = 2.80 Hz, 1H), 7.90-7.80 (m, 1H), 7.42-7.35 (m, 4H), 7.27-7.23 (m, 1H), 6.64-6.47 (m, 1H), 6.13 (d, *J* = 17.20 Hz, 1H), 5.69-5.63 (m, 1H), 5.36 (bs, 1H), 4.66 (s, 2H), 3.97 (t, *J* = 9.2 Hz, 1H), 3.74-3.73 (m, 5H), 3.57-3.55 (m, 1H), 2.67-2.57 (m, 1H), 2.13-1.99 (m, 1H).
42		**H**	**536.40**	δ 8.68 (bs, 1H), 8.11-8.10 (m, 1H), 7.94-7.85 (m, 1H), 7.42-7.34 (m, 4H), 7.27-7.23 (m, 1H), 6.68-6.58 (m, 1H), 6.42-6.28 (m, 1H), 5.30 (bs, 1H), 4.66 (s, 2H), 3.99-3.94 (m, 1H), 3.80-3.65 (m, 5H), 3.60-3.50 (m, 1H), 3.05-3.02 (m, 2H), 2.72 (bs, 1H), 2.15 (s, 6H), 1.98-1.97 (m, 1H).
43		**H**	**588.50**	δ 10.35 (s, 1H), 9.46 (s, 1H), 8.16 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.75 (s, 1H), 7.62-7.59 (m, 2H), 7.53-7.49 (m, 1H), 7.38 (bs, 4H), 7.34-7.25 (m, 3H), 7.07 (d, *J* = 7.2 Hz, 1H), 6.73-6.68 (m, 1H), 6.29 (d, *J* = 12.8 Hz, 1H), 4.65 (s, 2H), 4.43 (s, 2H), 3.92 (s, 3H), 3.19 (bs, 2H), 2.25 (s, 6H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
44		**H**	**612.70**	δ 10.27 (s, 1H), 9.39 (s, 1H), 8.14 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.71 (bs, 1H), 7.57 (bs, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.36 (bs, 4H), 7.29-7.26 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 6.74-6.67 (m, 1H), 6.25 (d, *J* = 15.6 Hz, 1H), 4.63 (s, 2H), 4.41 (s, 2H), 3.76 (s, 3H), 3.09 (bs, 2H), 2.19 (s, 6H).
45		**H**	**588.59**	δ 10.26 (s, 1H), 9.58 (s, 1H), 8.21 (s, 1H), 7.79 (s, 1H), 7.72-7.69 (m, 2H), 7.50-7.31 (m, 8H), 7.15 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 1H), 6.76-6.69 (m, 1H), 6.28 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.43 (s, 2H), 3.65 (s, 3H), 3.17 (bs, 2H), 2.25 (s, 6H).
46		**G**	**563.8**	δ 10.26 (s, 1H), 9.15 (bs, 1H), 8.08 (s, 1H), 8.03 (bs, 1H), 7.78 (d, *J* = 8 Hz, 1H), 7.57 (s, 1H), 7.51 (bs, 1H), 7.44-7.29 (6H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.45-6.38 (m, 2H), 6.23 (d, *J* = 16.4 Hz, 1H), 5.74 (d, *J* = 10.8 Hz, 1H), 4.62 (s, 2H), 4.38 (s, 2H), 3.65 (s, 4H), 3.28 (s, 4H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
47		**G**	**517.2**	δ 10.19 (s, 1H), 9.37 (bs, 1H), 8.06 (s, 1H), 7.48 (bs, 1H), 7.37-7.35 (m, 4H), 7.29 (bs, 2H), 7.10-6.98 (m, 3H), 6.78-6.68 (m, 1H), 6.60-6.50 (m, 1H), 6.10-6.04 (m, 1H), 5.88-5.10 (m, 1H), 4.61 (s, 2H), 4.36 (s, 2H). 3H were merged with DMSO water peak.
48		**H**	**555.6**	δ 11.18 (bs, 1H), 10.12 (s, 1H), 8.21 (s, 1H), 7.67 (d, *J* = 8 Hz, 1H), 7.62 (s, 1H), 7.41-7.29 (m, 6H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.74-6.67 (m, 1H), 6.25 (s, 1H), 6.22 (s, 1H), 4.62 (s, 2H), 4.43 (s, 2H), 3.02 (d, *J* = 5.2 Hz, 2H), 2.14 (s, 6H), 2.10 (s, 3H).

Compound 49: (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide



Step 1: Synthesis of (E)-4-(dimethylamino)but-2-enoyl chloride

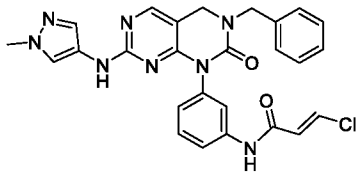
[0280] To a stirred mixture of acetonitrile (2 mL) and DMF (2 drop) under N_2 atmosphere was added N,N-dimethylamino crotonic acid hydrochloride (0.1 g, 0.77 mmol). After 10 min, this solution was cooled to 0-5 °C. Oxalyl chloride (0.122 g, 0.968 mmol) was added and the reaction mixture was maintained at 0-5 °C for 30 min. It was allowed to warm to RT and stirring was continued for 2 h. It was then heated to 40 °C for 5 min and again brought to RT and stirred

for 10 min. Formation of product was confirmed by TLC and the reaction mass was used as such to the next step without any workup.

Step-2: Synthesis of (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 49)

[0281] 1-(3-Aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (0.11g, 0.7 mmol) in DMP (2 mL) was cooled to -15 °C and then (E)-4-(dimethylamino)but-2-enoylchloride was added. The reaction mixture was stirred for 1 h at -15 °C to RT. After the completion of reaction, the reaction mass was quenched with ice water, sodium bicarbonate solution and extracted with DCM (100 mL x 2). The combined organic layer was washed with cold water (3 x 50 mL), brine solution (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by prep HPLC to get pure product (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (**Compound 49,** 0.022 g, 16 % yield) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.21 (s, 1H), 9.32 (s, 1H), 8.06 (s, 1H), 7.76 (bs, 1H) 7.65 (s, 1H), 7.48 (bs, 1H), 7.39-7.29 (m, 5H), 7.03 (d, J = 7.2 Hz, 2H), 6.74-6.68 (m, 1H), 6.62 (s, 1H), 6.25 (d, J = 15.2 Hz, 1H), 4.62 (s, 2H), 4.37 (s, 2H), 3.47 (s, 3H), 3.03 (d, J = 5.6 Hz, 2H), 2.15 (s, 6H); LCMS Calcd for $[M+H]^+$ 538.2, found 538.5

Compound 50: (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-3-chloroacrylamide



Step-1: Synthesis of (Z)-3-chloroacrylic acid

[0282] To a stirred solution propiolic acid (2 g, 28.5 mmol) in DMF (15 mL) under N_2 atmosphere was added thionyl chloride (4.07 g, 34.2 moles) slowly and the reaction mixture was maintained at 25 °C for 1 h. The reaction was monitored by TLC, after the completion of reaction, the residue was poured into ice and the resulting aqueous solution was extracted with ether (3 x100 mL). The organic layer was washed with brine (20 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified to get pure product (Z)-3-chloroacrylic acid (1.9 g, 62.9 % yield). LCMS Calcd for $[M-H]^+$, 104.98, found 105.1

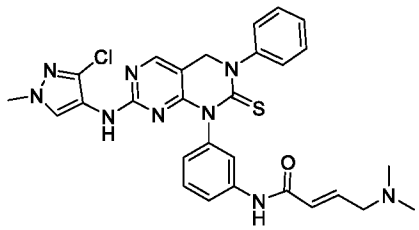
Step-2: Synthesis of (Z)-3-chloroacryloyl chloride

[0283] To a stirred solution of acetonitrile (3 mL) and DMF (3 drop) under N_2 atmosphere was added of (Z)-3-chloroacrylic acid (0.2 g, 1.87 mmol). After 10 min this solution was cooled 0-5 °C. Oxalyl chloride (0.122 g, 0.968 mmol) was added and the reaction mixture was maintained at 0-5 °C for 30 min. It was allowed to warm to RT and stirring was continued for 2 h to get (Z)-3-chloroacryloyl chloride. Formation of product was confirmed by TLC and the reaction mass was used as such to the next step without any workup.

Step-3: Synthesis of (E)-3-((3-(3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)amino)acryloyl chloride (Compound 50)

[0284] A solution of 1-(3-Aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-4-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (0.11 g, 0.7 mmol) in DMP (2 mL) was cooled to -15 °C and then (Z)-3-chloroacryloyl chloride was added. The reaction mixture was stirred for 1 h at -15 °C to RT. The reaction was monitored by TLC. After the completion of reaction, reaction mass was quenched with ice water and sodium bicarbonate solution. The aqueous layer was e 0.028 g, 22% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.35 (s, 1H), 9.32 (s, 1H), 8.06 (s, 1H), 7.74 (s, 1H), 7.59 (s, 1H), 7.51 (s, 1H), 7.41-7.35 (m, 5H), 7.30-7.29 (m, 1H), 7.08-7.02 (m, 2H), 6.62-6.58 (m, 2H), 4.62 (s, 2H), 4.37 (s, 2H), 3.47 (s, 3H); LCMS Calcd for $[M+H]^+$ 515.1, LCMS found 515.2

Compound 51: (E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide



Step-1: Synthesis of 2,4-dichloro-5-(chloromethyl)pyrimidine

[0285] Title compound was prepared in a similar manner to general procedure I. 5-(hydroxymethyl)pyrimidine-2,4-diol (15 g, 106 mmol) gave 2,4-dichloro-5-(chloromethyl)pyrimidine (11.50 g, 55% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 4.65 (s, 2H).

Step-2: Synthesis of 2,4-dichloro-5-(iodomethyl)pyrimidine

[0286] Title compound was prepared in a similar manner to general procedure J. 2,4-dichloro-5-(chloromethyl)pyrimidine (11.50 g, 58.20 mmol) on treatment with NaI (10.50 g, 69.0 mmol) in acetone (100 mL) resulted in 2,4-dichloro-5-(iodomethyl)pyrimidine (15.20 g, 91% yield). The

solid was immediately taken up in toluene and stored under refrigeration. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 4.39 (s, 2H).

Step-3: Synthesis of N-((2,4-dichloropyrimidin-5-yl)methyl)aniline

[0287] A solution of iodo compound (**18,** 7.0 g, 24.20 mmol) in toluene (50 mL) was cooled to 0 °C and aniline (2.20 g, 24.20 mmol) was added. The reaction mixture was stirred for 30 min at 0 °C. Then a solution of sodium hydroxide (1.30 g, 32.50 mmol) in water (5 ml) was added and reaction mixture was stirred for 16 h at RT. The reaction was monitored by TLC. After completion of the reaction, water (25 mL) was added and extracted with ethyl acetate (2 x 100 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the crude residue. The crude compound was purified by silica gel column chromatography to afford the title compound as a white solid (10 g, 81% yield). LCMS Calcd for $[M+H]^+$ 254.11, found 254.09

Step-4: Synthesis of tert-butyl (3-((2-chloro-5-((phenylamino)methyl)pyrimidin-4-yl)amino)phenyl)carbamate

[0288] To a stirred solution of N-((2,4-dichloropyrimidin-5-yl)methyl)aniline (4.0 g, 15.08 mmol) in IPA (30 mL), tert-butyl (3-aminophenyl)carbamate (4.90 g, 23.0 mmol) and DIPEA (8.20 mL, 47 mmol) were added. The reaction mixture was heated at 100 °C for 16 h in a sealed tube. Solvent was then evaporated and the crude thus obtained was purified by flash column chromatography to afford the title compound as off white solid (2.50 g, 37% yield). LCMS Calcd for $[M+H]^+$ 425.92, found 426.35

Step-5: Synthesis of tert-butyl (3-(7-chloro-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate

[0289] To a solution of tert-butyl (3-((2-chloro-5-((phenylamino)methyl)pyrimidin-4-yl)amino)phenyl)carbamate (1.50 g, 3.50 mmol) in THF (35 mL) was added DIPEA (2.40 mL, 14.10 mmol) and thiophosgene (0.27 g, 3.50 mmol) at 0 °C. The reaction mixture was stirred at RT for 24 h with TLC monitoring. After completion of the reaction, sodium bicarbonate solution was added. The reaction mixture was partitioned between DCM (2 x 100 mL) and water (50 mL). The organic layer was washed with brine (10 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography to afford the title compound as a yellow solid (1.36 g, 82% yield). LCMS Calcd for $[M+H]^+$ 467.97, found 468.27

Step-6: Synthesis of tert-butyl (3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate

[0290] To a solution of tert-butyl (3-(7-chloro-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (1.30 g, 2.78 mmol) in IPA (15 mL) was added 3-

chloro-1-methyl-1H-pyrazol-4-amine (0.44 g, 3.34 mmol) and TFA (1 mL). The reaction mixture was heated for 16 h at 110 °C. Reaction was monitored by TLC. After the completion of reaction, the reaction mixture was concentrated, water (10 mL) and saturated sodium bicarbonate (20 mL) solution were added to the residue and extracted with DCM (3 x 200 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain the title compound (1.30 g) that was used as such for the next step without further purification. LCMS Calcd for $[M+H]^+$ 563.08, found 562.90

Step-7: Synthesis of 1-(3-aminophenyl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidine-2(1H)-thione

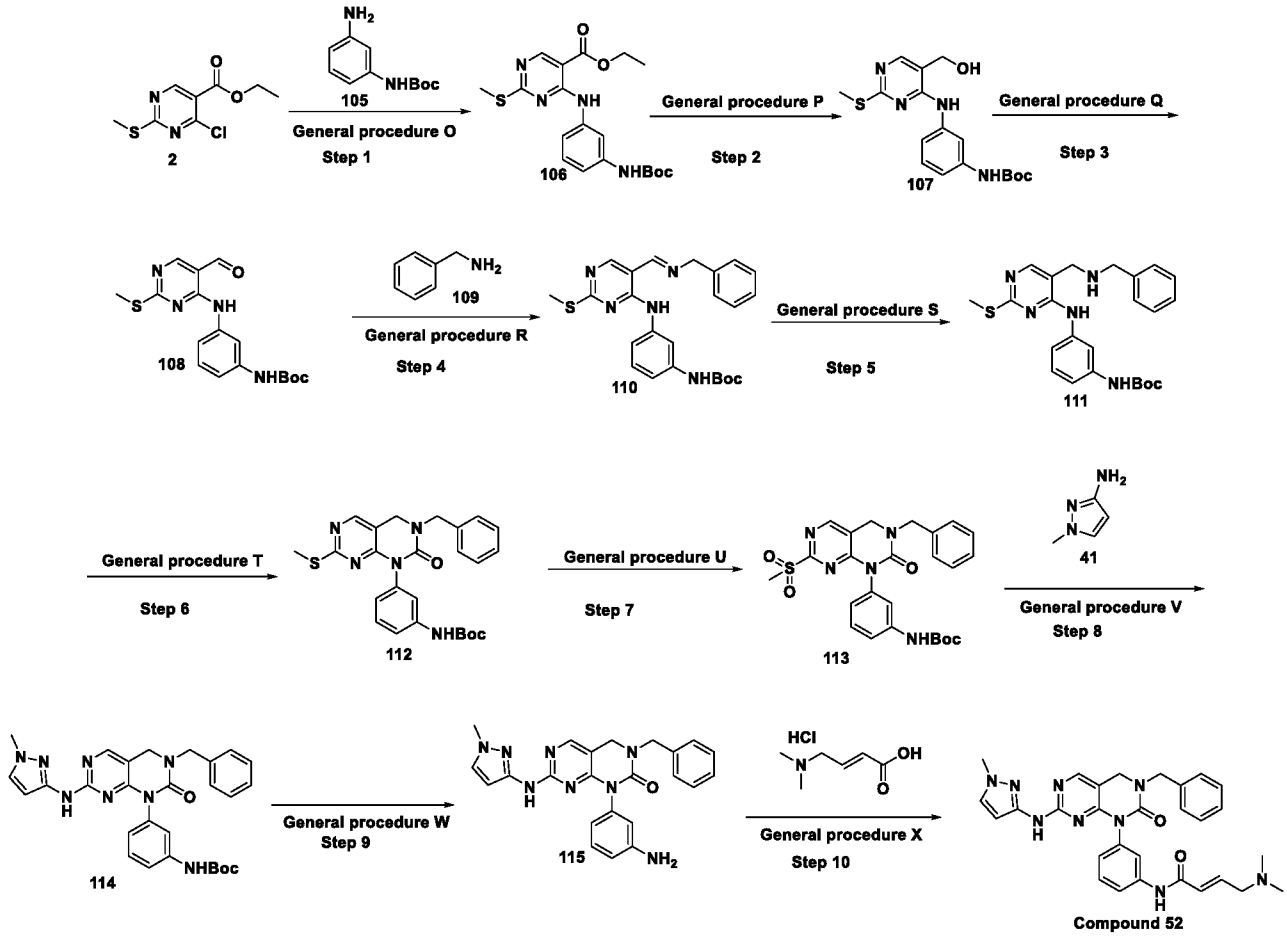
[0291] To an ice-cold solution of tert-butyl (3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (1.30 g, 2.30 mmol) in DCM (20 mL) and MeOH (10 mL) was added 4N HCl in dioxane (5 mL). The reaction mixture was stirred for 16 h at RT. The reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated followed by addition of water (10 mL) and saturated sodium bicarbonate (20 mL) solution and extraction with DCM (3 x 200 mL). The combined organic layer was washed with brine solution, dried over anhydrous sodium sulfate and evaporated under reduced pressure to obtain crude product. The crude product was purified by silica gel column chromatography to afford the title compound as a brown solid (0.20 g). LCMS Calcd for $[M+H]^+$ 462.96, found 463.0. Purity: 68%

Step-8: Synthesis of (E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-2-thioxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 51)

[0292] To an ice-cold solution of 1-(3-aminophenyl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidine-2(1H)-thione (0.18 g, 0.39 mmol) and *trans*-N,N-dimethylaminocrotonic acid hydrochloride (0.077 g, 0.47 mmol) in dichloromethane (10 mL) was added triethyl amine (1.2 mmol) followed by drop wise addition of propylphosphonic anhydride (T_3P) (0.26 g, 0.97 mmol). The mixture was stirred at RT for 6 h. Completion of the reaction was monitored by TLC. The reaction mixture was portioned between 5% methanol in dichloromethane and saturated bicarbonate solution. The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated. The crude obtained was purified by silica gel chromatography to afford the title compound as off white solid (**Compound 51,** 0.010 g, 5% yield). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (bs, 1H), 8.97 (bs, 1H), 8.25 (s, 1H), 7.72 (bs, 2H), 7.48-7.42 (m, 5H), 7.36-7.32 (m, 1H), 7.03 (d, J = 7.6 Hz, 1H),

6.76-6.60 (m, 2H), 6.30 (d, J = 14.8 Hz, 1H), 4.95 (s, 2H), 3.50 (s, 3H), 3.12 (bs, 2H), 2.21 (s, 6H); LCMS Calcd for $[M+H]^+$ 574.10, found 574.41

Scheme 28: Preparation of (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 52):



Step 1: Preparation of ethyl 4-((3-((*tert*-butoxycarbonyl) amino) phenyl) amino)-2-(methylthio) pyrimidine-5-carboxylate (106):

[0293] Title compound (**106**) was prepared as off-white solid (142 g; Yield: 74%) in a manner substantially similar to procedure mentioned in **General procedure O**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.36 (s, 1H), 8.77 (d, 1H), 7.89 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.25-7.22 (m, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.51 (s, 1H), 4.35 (q, J = 7.2 Hz, 2H), 2.54 (s, 3H), 1.51 (s, 9H), 1.42-1.38 (m, 3H). LCMS: $[M+H]^+$ 405.21, 89.28%.

Step 2: Preparation of *tert*-butyl (3-((5-(hydroxymethyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (107):

[0294] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure P.** The crude was triturated with dichloromethane afforded **107** as off white solid (40.0 g; Yield: 31%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.86 (m, 2H),

7.36 (d, J = 8.0 Hz, 1H), 7.25-7.15 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.55 (s, 1H), 4.59 (s, 2H), 2.50 (s, 3H), 1.51 (s, 9H). LCMS: $[M+H]^+$ 363.05, 91.24%.

Step 3: Preparation of *tert*-butyl (3-((5-formyl-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (108):

[0295] Title compound (**108**) was prepared as a pale yellow solid (31.0 g; Yield: 78%) in a manner substantially similar to procedure mentioned in **General procedure Q**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.59 (s, 1H), 9.75 (s, 1H), 8.42 (s, 1H), 7.97 (s, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 3.48 (s, 1H), 2.58 (s, 3H), 1.52 (s, 9H). LCMS: $[M+H]^+$ 361.30, 97.51%.

Step 4: Preparation of *tert*-butyl (E)-(3-((5-((benzylimino)methyl)-2(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (110):

[0296] Title compound (**110**) was prepared as a yellow solid (28 g; Yield: 72%) in a manner substantially similar to procedure mentioned in **General procedure R**. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 12.15 (s, 1H), 8.31 (s, 1H), 8.16 (s, 1H), 7.91 (s, 1H), 7.41 (m, 4H), 7.35-7.33 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.22 (m, 1H), 7.03 (d, J = 8.0 Hz, 1H), 6.46 (s, 1H), 4.84 (s, 2H), 2.59 (s, 3H), 1.52 (s, 9H). LCMS: $[M+H]^+$ 450.38; 99.66%.

Step 5: Preparation of *tert*-butyl (3-((5-((benzylamino)methyl)-2-(methylthio)pyrimidin-4-yl)amino)phenyl)carbamate (111):

[0297] Title compound (**111**) was prepared as a pale yellow solid (40 g; Yield: 80%) in a manner substantially similar to procedure mentioned in **General procedure S**. LCMS: $[M+H]^+$ 452.44; 83.57%

Step 6: Preparation of *tert*-butyl (3-(3-benzyl-7-(methylthio)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (112):

[0298] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure T.** The crude was triturated with diethyl ether afforded **112** as off white solid (12 g; Yield: 28%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.50 (s, 1H), 7.37 (m, 6H), 7.26 (m, 1H), 6.96 (m, 1H), 6.59 (s, 1H), 4.69 (s, 2H), 4.34 (s, 2H), 2.16 (s, 3H), 1.50 (s, 9H). LCMS: $[M+H]^+$ 478.16; 95.62%.

Step 7: Preparation of *tert*-butyl (3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido [4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (113):

[0299] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure U.** The crude was triturated with diethyl ether afforded **113** as an off white solid (8.0 g; Yield: 76%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.63 (s, 1H), 7.40 (m, 6H), 7.17 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.61 (s, 1H), 4.71 (s, 2H), 4.48 (s, 2H), 2.97 (s, 3H), 1.49 (s, 9H). LCMS: $[M+H]^+$ 510.31, 93.69%.

Step 8: Preparation of *tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (114):

[0300] Title compound was prepared in a manner substantially similar to **General procedure V,** *tert*-butyl (3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate **(113)** and 1-methyl-1H-pyrazol-3-amine **(41)** gave (*tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate **(114)** as a brown solid (Yield: 77%), which was used directly for the next step without any further purification. MS: $[M+H]^+$ 527.46.

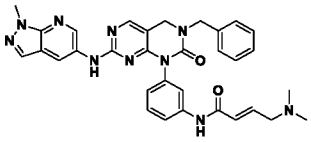
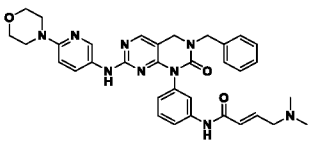
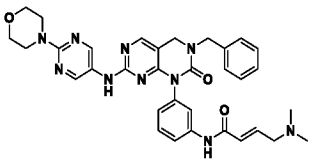
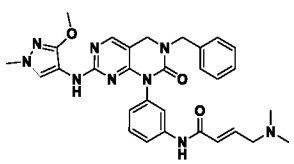
Step 9: Preparation of 1-(3-aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (115):

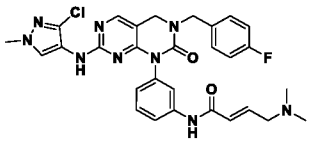
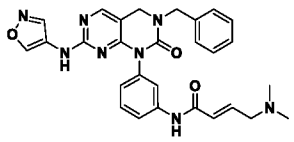
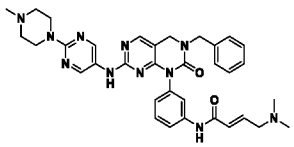
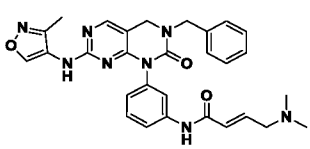
[0301] Title compound was prepared in a manner substantially similar to **General procedure W,** *tert*-butyl (3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate **(114)** gave 1-(3-aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(115)** as a brown solid (Yield: 93%), which was used directly for the next step. MS: $[M+H]^+$ 427.44.

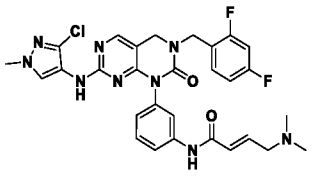
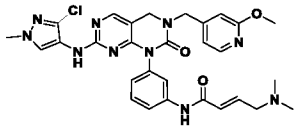
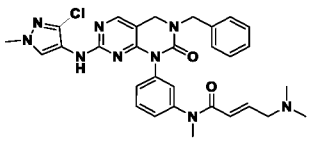
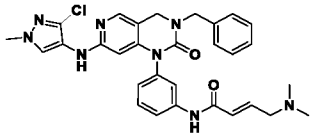
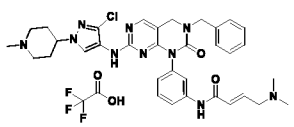
Step 10: Preparation of (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 52):

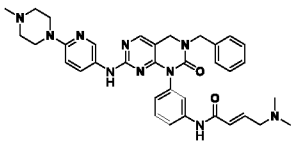
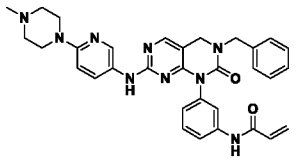
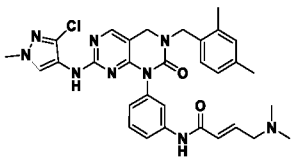
[0302] Title compound was prepared in a manner substantially similar **General procedure X,** 1-(3-aminophenyl)-3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(115)** and *trans*-N,N-dimethylaminocrotonic acid hydrochloride gave (E)-N-(3-(3-benzyl-7-((1-methyl-1H-pyrazol-3-yl)amino)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide **Compound 52**, as a white solid (48 mg; Yield: 13%), after prep-HPLC purification. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 10.17 (s, 1H), 9.51 (s, 1H), 8.08 (s, 1H), 7.72 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.43-7.35 (m, 5H), 7.33-7.29 (m, 1H), 7.10 (s, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.75-6.69 (m, 1H), 6.27 (d, J = 15.3 Hz, 1H), 5.51 (s, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.59 (s, 3H), 3.06 (d, J = 4.8 Hz, 2H), 2.17 (s, 6H). MS: $[M+H]^+$ 538.32.

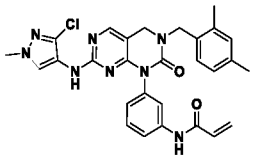
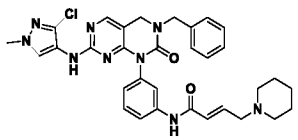
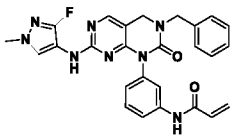
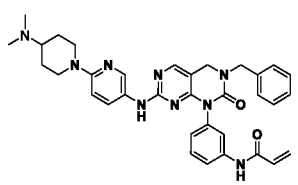
[0303] The following compounds were prepared using the methods described above

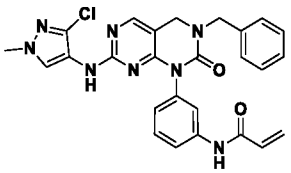
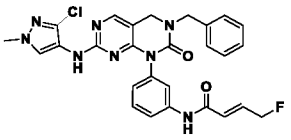
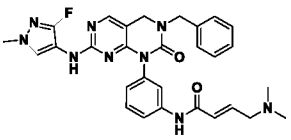
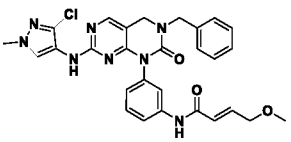
Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
53		**X**	**589.30**	δ 10.28 (s, 1H), 9.73 (s, 1H), 8.44 (d, *J* = 1.2 Hz, 1H), 8.19 (s, 1H), 7.97 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.78 (s, 1H), 7.70 (s, 1H), 7.50 -7.48 (t, *J* = 8.0 Hz, 1H), 7.41-7.37 (m, 4H), 7.33-7.30 (m, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.73-6.66 (m, 1H), 6.26 (d, *J* = 15.44 Hz, 1H), 4.65 (s, 2H), 4.44 (s, 2H), 3.94 (s, 3H), 3.03 (d, *J* = 5.6 Hz, 2H), 2.14 (s, 6H).
54		**X**	**620.33**	δ 10.2 (s, 1H), 9.20 (s, 1H), 8.10 (s, 1H), 8.04 (s, 1H), 7.78 (d, 1H), 7.58 (s, 1H), 7.52 (m, 1H), 7.45-7.37 (m, 5H), 7.32 (d, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.75-6.69 (m, 1H), 6.36 (s, 1H), 6.31 (d, *J* = 15.4 Hz, 1H), 4.4 (s, 2H), 4.39 (s, 2H), 3.66 (d, *J* = 4.4 Hz, 4H), 3.23 (s, 4H), 3.05 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 6H).
55		**X**	**621.34**	δ 10.15 (s, 1H), 9.09 (s, 1H), 8.30 (s, 2H), 8.10 (s, 1H), 7.68-7.64 (m, 2H), 7.40-7.29 (m, 6H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.74-6.67 (m, 1H), 6.28 (d, *J* = 15.4 Hz, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.62-3.60 (m, 4H), 3.54 (d, *J* = 4.4 Hz, 4H), 3.05 (d, *J* = 6.0 Hz, 2H), 2.16 (s, 6H).
56		**X**	**568.32**	δ 10.24 (s, 1H), 8.41 (bs, 1H), 8.06 (s, 1H), 7.67-7.78 (m, 1H), 7.63 (s, 1H), 7.46-7.50 (m, 1H), 7.28-7.41 (m, 5H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.70-6.77 (m, 1H), 6.45 (bs, 1H), 6.27 (d, *J* = 15.4 Hz, 1H), 4.63 (s, 2H), 4.38 (s, 2H),

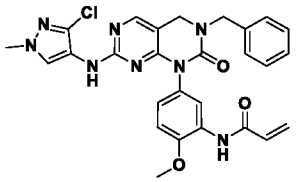
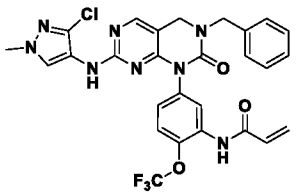
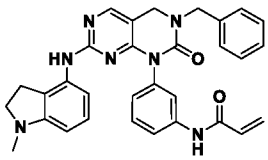
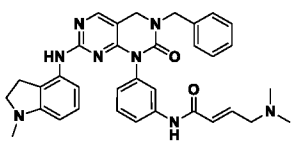
Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				3.71 (s, 3H), 3.32-3.65 (bs, 3H), 3.05 (d, J = 4.8 Hz, 2H), 2.17 (s, 6H).
57		**X**	**590.35**	δ 10.24 (s, 1H), 8.76 (bs, 1H), 8.12 (s, 1H), 7.75 (m, 1H), 7.65 (s, 1H), 7.50-7.46 (m, 1H), 7.43-7.40 (m, 2H), 7.23-7.18 (m, 2H), 7.04 (d, J = 7.8 Hz, 1H), 6.76-6.69 (m, 2H), 6.28 (d, J = 15.4 Hz, 1H), 4.61 (s, 2H), 4.40 (s, 2H), 3.48 (s, 3H), 3.05 (d, J = 5.8 Hz, 2H), 2.16 (s, 6H).
58		**X**	**525.28**	δ 10.25 (s, 1H), 9.62 (s, 1H), 8.25 (s, 1H), 8.17 (s, 1H), 7.77 (s, 1H), 7.69 (m, 1H), 7.50-7.46 (m, 2H), 7.41-7.37 (m, 4H), 7.33-7.29 (m, 1H), 7.06 (d, J = 7.2 Hz, 1H), 6.75-6.70 (m, 1H), 6.28 (d, J = 15.4 Hz, 1H), 4.64 (s, 2H), 4.42 (s, 2H), 3.06 (d, J = 5.2 Hz, 2H), 2.16 (s, 6H).
59		**X**	**634.28**	δ 10.15 (s, 1H), 9.05 (s, 1H), 8.27 (s, 2H), 8.09 (s, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.40-7.29 (m, 6H), 6.98 (d, 1H), 6.74-6.68 (m, 1H), 6.28 (d, J = 15.3 Hz, 1H), 4.62 (s, 2H), 4.38 (s, 2H), 3.57 (s, 4H), 3.05 (d, J = 5.6 Hz, 2H), 2.30-2.28 (m, 4H), 2.18 (m, 9H).
60		**X**	**539.33**	δ 10.24 (s, 1H), 9.19 (s, 1H), 8.19 (s, 1H), 7.76 (s, 1H), 7.67 (m, 1H), 7.49-7.45 (m, 1H), 7.41-7.29 (m, 6H), 7.05 (d, J = 8.0 Hz, 1H), 6.75-6.68 (m, 1H), 6.28 (d, J = 15.4 Hz, 1H), 4.64 (s, 2H), 4.43 (s, 2H), 3.05 (d, J = 5.2 Hz, 2H), 2.20 (s, 3H), 2.16 (s, 6H).

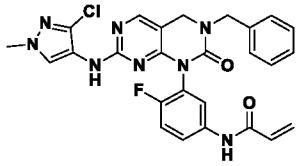
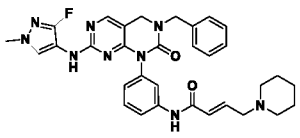
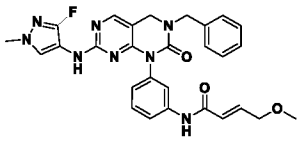
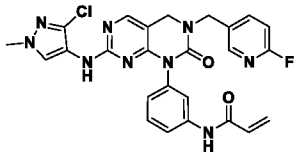
Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
61		**X**	**608.15**	δ 10.24 (s, 1H), 8.78 (s, 1H), 8.14 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.76 (m, 2H), 7.26 (m, 1H), 7.09 (m, 1H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.69 (m, 2H), 6.24 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.45 (s, 2H), 3.48 (s, 3H), 3.03 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 6H).
62		**X**	**603.21**	δ 10.25 (s, 1H), 8.80 (s, 1H), 8.13 (m, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 4.4 Hz, 1H), 6.78 (s, 1H), 6.69 (m, 2H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.61 (s, 2H), 4.45 (s, 2H), 3.84 (s, 3H), 3.48 (s, 3H), 3.04 (d, *J* = 5.5 Hz, 2H), 2.16 (s, 6H).
63		**X**	**586.17**	δ 8.78 (bs, 1H), 8.12 (s, 1H), 7.66 (m, 1H), 7.51 (m, 1H), 7.37 (m, 5H), 7.29 (m, 1H), 7.24 (s, 1H), 6.70 (m, 1H), 6.53 (m, 1H), 5.87 (m, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.49 (s, 3H), 3.26 (s, 3H), 2.50 (m, 2H), 1.90 (s, 6H).
64		**X**	**571.22**	δ 10.27 (s, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.81 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.46 (t, *J* = 8.4 Hz, 1H), 7.28 (m, 5H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.71 (m, 1H), 6.26 (d, *J* = 15.44 Hz, 1H), 5.70 (s, 1H), 4.60 (s, 2H), 4.39 (s, 2H), 3.72 (s, 3H), 3.05 (d, *J* = 5.32 Hz, 2H), 2.17 (s, 6H).
65		**X**	**655.39**	δ 10.69 (bs, 1H), 10.14 (bs, 1H), 9.76 (bs, 1H), 8.86 (bs, 1H), 8.14 (s, 1H), 7.98 (bs, 1H), 7.55 (bs, 1H), 7.41-7.35 (m, 2H), 7.33-7.30 (m, 1H), 7.26-7.24

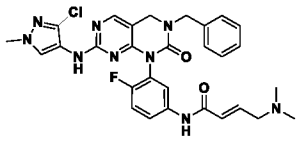
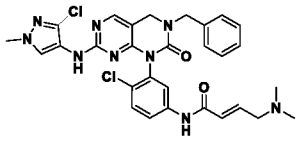
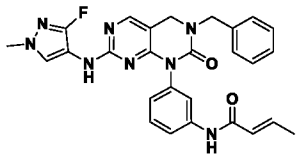
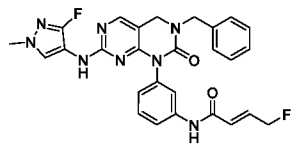
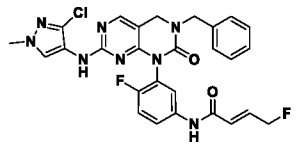
Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				(m, 2H), 7.01-6.98 (m, 2H), 6.79-6.72 (m, 1H), 6.50 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 2H), 4.42 (s, 2H), 3.94 (d, *J* = 5.6 Hz, 2H), 3.49 (bs, 1H), 3.29-3.25 (m, 4H), 2.84 (s, 3H), 2.79 (s, 6H), 2.09-2.00 (m, 4H).
66		**X**	**633.49**	δ 10.20 (bs, 1H), 8.09 (s, 1H), 8.09 (bs, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.29 (m, 8H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.71 (m, 2H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.61 (s, 2H), 4.39 (s, 2H), 3.28 (m, 4H), 3.04 (m, 2H), 2.34 (m, 4H), 2.19 (s, 3H), 2.16 (s, 6H).
67		**Y**	**576.39**	δ 10.21 (bs, 1H), 9.15 (bs, 1H), 8.09 (s, 1H), 8.01 (bs, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.30-7.47 (m, 7H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.35-6.46 (m, 2H), 6.22 (d, *J* = 16.8 Hz, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.27 (m, 4H), 2.34-2.36 (m, 4H), 2.19 (s, 3H).
68		**X**	**600.44**	δ 10.25 (bs, 1H), 8.75 (bs, 1H), 8.10 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.47-7.51 (m, 1H), 7.15-7.17 (m, 1H), 7.01-7.03 (m, 3H), 6.70-6.76 (m, 2H), 6.24 (d, *J* = 15.4 Hz, 1H), 4.60 (s, 2H), 4.32 (s, 2H), 3.48 (s, 3H), 3.04 (d, *J* = 5.6 Hz, 2H), 2.25 (s, 6H), 2.16 (s, 6H).

Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
69		**Y**	**543.33**	δ 10.34 (bs, 1H), 8.75 (bs, 1H), 8.10 (s, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.48-7.52 (m, 1H), 7.15-7.17 (m, 1H), 7.01-7.03 (m, 3H), 6.70 (s, 1H), 6.40-6.46 (m, 1H), 6.23-6.28 (m, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.60 (s, 2H), 4.32 (s, 2H), 3.48 (s, 3H), 2.25 (s, 6H).
70		**X**	**612.38**	δ 10.24 (bs, 1H), 8.76 (bs, 1H), 8.12 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.40-7.49 (m, 1H), 7.29-7.32 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.70-6.76 (m, 2H), 6.22 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.48 (s, 3H), 3.06 (d, *J* = 5.6 Hz, 2H), 2.33 (s, 4H), 1.49-1.50 (m, 4H), 1.37 (s, 2H).
71		**Y**	**499.36**	δ 10.33 (bs, 1H), 9.24 (bs, 1H), 8.10 (s, 1H), 7.78 (d, *J* = 6.4 Hz, 1H), 7.64 (s, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.29-7.33 (m, 5H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.40-6.52 (m, 2H), 6.23-6.28 (m, 1H), 5.75 (d, *J* = 11.6 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.38 (s, 3H).
72		**Y**	**604.47**	δ 10.29 (bs, 1H), 9.15 (bs, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.31-7.44 (m, 7H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.35-6.46 (m, 2H), 6.23-6.27 (m, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 4.04-4.07 (m, 2H), 2.60-2.63 (m, 2H), 2.15-2.21 (m, 7H), 1.73-1.76 (m, 2H), 1.23-1.32 (m, 2H).

Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
73		**Y**	**515.37**	δ 10.33 (bs, 1H), 8.74 (bs, 1H), 8.12 (s, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.64 (s, 1H), 7.49-7.52 (m, 1H), 7.31-7.37 (m, 5H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.70 (s, 1H), 6.40-6.46 (m, 1H), 6.23-6.28 (m, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.49 (s, 3H).
74		**X**	**547.30**	δ 10.37 (bs, 1H), 8.76 (bs, 1H), 8.12 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.46 (t, *J* = 8.0 Hz, 1H), 7.37-7.39 (m, 4H), 7.31-7.32 (m, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.69-6.89 (m, 2H), 6.34 (d, *J* = 15.6 Hz, 1H), 5.24 (s, 1H), 5.12 (s, 1H), 4.63 (s, 2H), 4.41 (s, 2H), 3.49 (s, 3H).
75		**X**	**556.42**	δ 10.33 (bs, 1H), 9.24 (bs, 1H), 8.10 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.64 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.33-7.40 (m, 4H), 7.31-7.32 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 1H), 6.70-6.75 (m, 1H), 6.51-6.54 (m, 1H), 6.31 (d, *J* = 15.4 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.31-3.38 (m, 5H), 2.40 (s, 6H).
76		**X**	**559.31**	δ 10.27 (bs, 1H), 8.72 (bs, 1H), 8.12 (s, 1H), 7.74 (d, *J* = 7.6 Hz, 1H), 7.65 (s, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.29-7.38 (m, 5H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.71-6.82 (m, 2H), 6.30 (d, *J* = 15.6 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 4.10 (s, 2H), 3.49 (s, 3H), 3.29 (s, 3H).

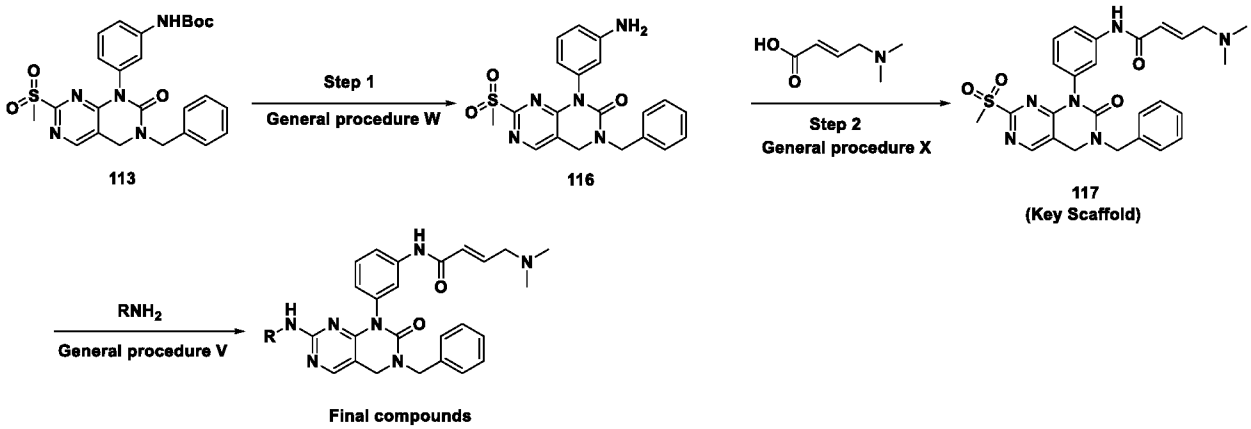
Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
77		X	546.0	δ 9.54 (s, 1H), 8.64 (s, 1H), 8.09-8.00 (m, 2H), 7.35-7.30 (m, 5H), 7.17 (s, 1 H), 7.05 (s, 1H), 6.72 (s, 2H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 8.4 Hz, 1H), 4.61 (s, 2H), 4.37 (s, 2H), 3.92 (s, 3H), 3.44 (s, 3H).
78		X	599.0	δ 10.06 (s, 1H), 8.68 (s, 1H), 8.1 (s, 1H), 7.96 (s, 1H), 7.55 (d, *J* = 18.4 Hz, 1H), 7.35-7.16 (m, 6H), 6.98 (s, 1H), 6.67-6.60 (m, 1H), 6.25 (d, *J* = 16.8 Hz, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 4.61 (s, 2H), 4.37 (s, 2H), 3.25 (s, 3H).
79		Y	532.25	δ 10.26 (bs, 1H), 8.41 (bs, 1H), 8.10 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.64 (s, 1H), 7.31-7.41 (m, 6H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.56 (t, *J* = 7.6 Hz, 1H), 6.40-6.46 (m, 1H), 6.22-6.27 (m, 1H), 6.05 (d, *J* = 8.0 Hz, 1H), 5.74 (d, *J* = 10.0 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.08 (t, *J* = 8.0 Hz, 2H), 2.71 (t, *J* = 8.0 Hz, 2H), 2.59 (s, 3H).
80		X	589.33	δ 10.16 (bs, 1H), 8.40 (bs, 1H), 8.10 (s, 1H), 7.64-6.67 (m, 2H), 7.31-7.40 (m, 6H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.66-6.75 (m, 2H), 6.54 (t, *J* = 8.0 Hz, 1H), 6.24 (d, *J* = 15.2 Hz, 1H), 6.05 (d, *J* = 7.6 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.04-3.13 (m, 4H), 2.71-2.76 (m, 2H), 2.59 (s, 3H), 2.16 (s, 6H).

Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
81		**Y**	**533.17**	δ 10.37 (bs, 1H), 8.85 (bs, 1H), 8.15 (s, 1H), 7.78 (d, *J* = 6.4 Hz, 2H), 7.29-7.43 (m, 6H), 6.76 (bs, 1H), 6.38-6.45 (m, 1H), 6.24 (dd, *J* = 2.0 & 16.8 Hz, 1H), 5.76 (d, *J* = 10.4 Hz, 1H), 4.64 (s, 2H), 4.38 (s, 2H), 3.52 (s, 3H).
82		**X**	**596.25**	δ 10.23 (bs, 1H), 9.26 (bs, 1H), 8.10 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.64 (s, 1H), 7.47-7.51 (m, 1H), 7.29-7.40 (m, 5H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.70-6.76 (m, 1H), 6.50 (bs, 1H), 6.22 (d, *J* = 15.4 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 3.38 (s, 3H), 3.06 (d, *J* = 5.2 Hz, 2H), 2.33 (s, 4H), 1.48-1.53 (m, 4H), 1.38-1.39 (m, 2H).
83		**X**	**543.21**	δ 10.27 (bs, 1H), 9.24 (bs, 1H), 8.10 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 1H), 7.47-7.50 (m, 1H), 7.29-7.40 (m, 5H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.77-6.82 (m, 1H), 6.52 (bs, 1H), 6.30 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 2H), 4.39 (s, 2H), 4.09-4.11 (m, 2H), 3.38 (s, 3H), 3.33 (s, 3H).
84		**Y**	**534.13**	δ 10.33 (bs, 1H), 8.77 (bs, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.97-8.02 (m, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.48-7.52 (m, 1H), 7.19-7.21 (m, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.68 (bs, 1H), 6.39-6.46 (m, 1H), 6.23 (dd, *J* = 2.0 & 17.2 Hz, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.65 (s, 2H), 4.46 (s, 2H), 3.48 (s, 3H).

Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
85		**X**	**590.23**	δ 10.29 (bs, 1H), 8.85 (bs, 1H), 8.15 (s, 1H), 7.74-7.79 (m, 2H), 7.29-7.42 (m, 6H), 6.70-6.77 (m, 2H), 6.23 (d, *J* = 15.2 Hz, 1H), 4.64 (s, 2H), 4.42 (s, 2H), 3.52 (s, 3H), 3.05 (d, *J* = 5.6 Hz, 2H), 2.17 (s, 6H).
86		**X**	**606.21**	δ 10.35 (bs, 1H), 8.82 (bs, 1H), 8.14 (s, 1H), 7.80-7.84 (m, 1H), 7.63-7.70 (m, 1H), 7.24-7.35 (m, 6H), 6.72-6.82 (m, 2H), 6.25 (d, *J* = 15.2 Hz, 1H), 4.71-4.75 (m, 1H), 4.55-4.59 (m, 1H), 4.37-4.44 (m, 2H), 3.52 (s, 3H), 3.08 (d, *J* = 4.8 Hz, 2H), 2.17 (s, 6H).
87		**X**	**513.23**	δ 10.15 (bs, 1H), 9.26 (bs, 1H), 8.10 (s, 1H), 7.69-7.76 (m, 1H), 7.56-7.63 (m, 1H), 7.47 (s, 1H), 7.31-7.40 (m, 5H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.49 (s, 1H), 5.91-5.98 (m, 1H), 5.11-5.19 (m, 1H), 4.62 (s, 2H), 4.39 (s, 2H), 3.38 (s, 3H), 3.12 (d, *J* = 6.8 Hz, 2H), 1.85 (d, *J* = 7.2 Hz, 1H) (Mixture of isomers)
88		**X**	**531.16**	δ 10.37 (s, 1H), 9.25 (bs, 1H), 8.10 (s, 1H), 7.73-7.71 (m, 1H), 7.63 (bs, 1H), 7.52-7.48 (m, 1H), 7.38-7.29 (m, 5H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.91-6.80 (m, 1H), 6.49 (bs, 1H), 6.34 (d, *J* = 14.8 Hz, 1H), 5.24-5.12 (m, 2H), 4.63 (s, 2H), 4.40 (s, 2H), 3.38 (bs, 3H).
89		**X**	**565.14**	δ 10.41 (s, 1H), 8.83 (bs, 1H), 8.15 (s, 1H), 7.80-7.75 (m, 2H), 7.43-7.30 (m, 6H), 6.94-6.71 (m, 2H), 6.35 (dd, *J* = 15.2 Hz, 1.6 Hz, 1H), 5.24-5.12 (m,

Cmpd No.	Structure	Synthesis Method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				2H), 4.64 (s, 2H), 4.47-4.39 (m, 2H), 3.53 (s, 3H).

Scheme 29: Preparation of (E)-N-(3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (117): Key scaffold:



Step 1: Preparation of 1-(3-aminophenyl)-3-benzyl-7-(methylsulfonyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (116):

[0304] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure W**, afforded **116** as off white solid (3.9 g; Yield: 79%). LCMS: $[M+H]^+$ 410.32 (81.02% purity).

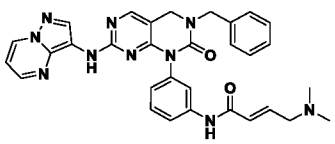
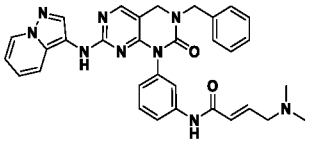
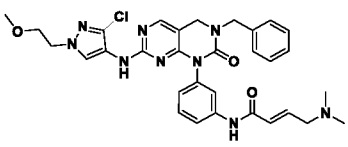
Step 2: Preparation of (E)-N-(3-(3-benzyl-7-(methylsulfonyl)-2-oxo-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (117):

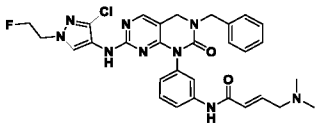
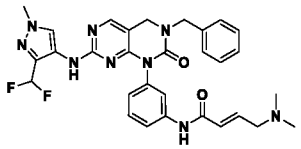
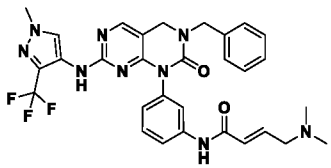
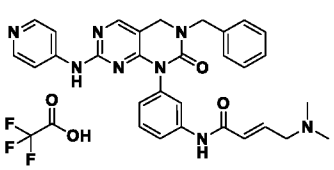
[0305] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure X.** The crude was triturated with diethyl ether afforded **117** as yellow solid (3.1 g; Yield: 36%). LCMS: $[M+H]^+$ 521.42 (91.75% purity).

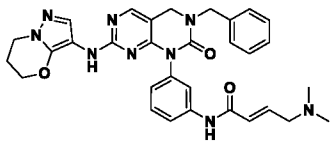
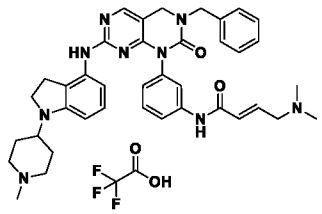
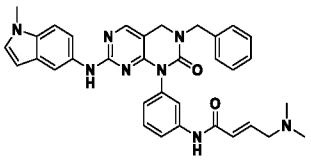
Step 3: Preparation of final compounds:

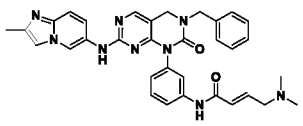
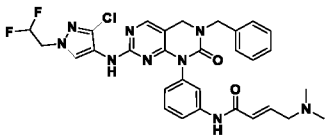
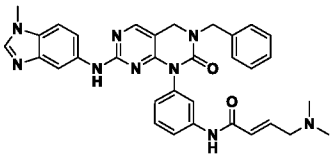
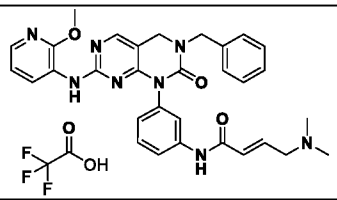
[0306] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure V.** The crude product was purified using combiflash chromatography or prep-HPLC purification to get final products.

[0307] The following compounds were prepared using the methods described above

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
90		**V**	**575.19**	δ 10.20 (s, 1H), 8.87 (m, 2H), 8.35 (d, *J* = 2.4 Hz, 1H), 8.10 (s, 1H), 7.69-7.65 (m, 3H), 7.41-7.32 (m, 5H), 7.32 (m, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.89-6.86 (m, 1H), 6.75-6.68 (m, 1H), 6.28 (d, *J* = 15.4 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.07 (d, *J* = 4.0 Hz, 2H), 2.17 (s, 6H).
91		**V**	**574.21**	δ 10.20 (s, 1H), 9.54 (s, 1H), 8.39 (d, *J* = 6.8 Hz, 1H), 8.12 (s, 1H), 7.82 (bs, 1H), 7.73 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.44-7.29 (m, 7H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.98-6.94 (t, *J* = 8.4 Hz, 1H), 6.75-6.68 (m, 2H), 6.28 (d, *J* = 16.5 Hz, 1H), 4.64 (s, 2H), 4.41 (s, 2H), 3.04 (d, *J* = 5.6 Hz, 2H), 2.15 (s, 6H).
92		**V**	**616.28**	δ 10.23 (s, 1H), 8.76 (bs, 1H), 8.12 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.64 (s, 1H), 7.44 (m, 1H), 7.35 (m, 4H), 7.28 (m, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.70 (m, 2H), 6.24 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 2H), 4.40 (s, 2H), 3.84 (s, 2H), 3.46 (s, 2H), 3.14 (s, 3H), 3.04 (d, *J* = 4.8 Hz, 2H), 2.16 (s, 6H).

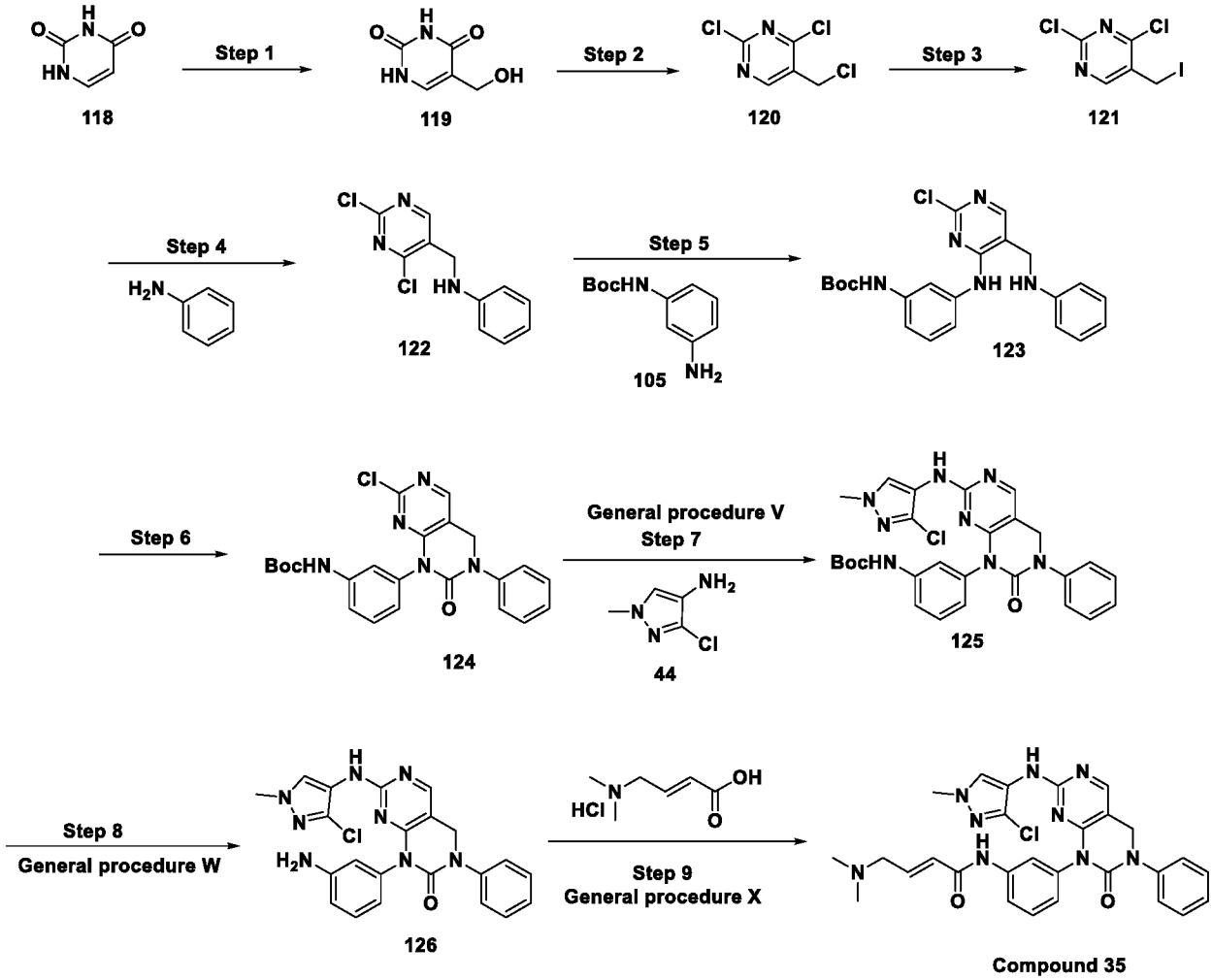
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
93		**V**	**604.21**	δ 10.21 (s, 1H), 8.67 (bs, 1H), 8.12 (s, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.62 (s, 1H), 7.40 (m, 1H), 7.31 (m, 4H), 7.29 (m, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.70 (m, 2H), 6.24 (d, *J* = 15.2 Hz, 1H), 4.63 (s, 3H), 4.49 (s, 1H), 4.40 (s, 2H), 4.00 (m, 2H), 3.08 (d, *J* = 4.8 Hz, 2H), 2.19 (s, 6H).
94		**V**	**588.26**	δ 10.26 (s, 1H), 9.03 (bs, 1H), 8.14 (s, 1H), 7.78 (m, 1H), 7.67 (s, 1H), 7.51 (m, 1H), 7.29 (m, 5H), 7.05 (m, 2H), 6.70 (m, 2H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.64 (s, 2H), 4.42 (s, 2H), 3.54 (s, 3H), 3.04 (d, *J* = 5.2 Hz, 2H), 2.16 (s, 6H).
95		**V**	**606.26**	δ 10.35 (s, 1H), 8.51 (bs, 1H), 8.13 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.65 (s, 1H), 7.48 (m, 1H), 7.35 (m, 4H), 7.29 (m, 1H), 6.92 (m, 2H), 6.71 (m, 1H), 6.32 (d, *J* = 15.6 Hz, 1H), 4.63 (s, 2H), 4.42 (s, 2H), 3.61 (s, 3H), 3.38 (s, 2H), 2.40 (s, 6H).
96		**V**	**535.26**	δ 10.52 (bs, 1H), 9.84 (bs, 1H), 8.91 (bs, 1H), 8.67 (d, *J* = 8.0 Hz, 2H), 8.61 (s, 1H), 7.77 (s, 1H), 7.66 (m, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.40 (m, 4H), 7.31 (m, 1H), 7.13 (m, 1H),

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				6.87 (m, 2H), 6.70 (m, 1H), 6.45 (d, J = 15.2 Hz, 1H), 4.67 (s, 2H), 4.63 (s, 2H), 3.93 (s, 2H), 2.79 (s, 6H).
97		**V**	**580.34**	δ 10.15 (s, 1H), 8.28 (bs, 1H), 7.97 (s, 1H), 7.60 (s, 2H), 7.28 (m, 6H), 6.93 (d, J = 7.6 Hz, 2H), 6.69 (m, 1H), 6.24 (d, J = 15.2 Hz, 1H), 4.60 (s, 2H), 4.33 (s, 2H), 4.13 (s, 2H), 3.94 (s, 2H), 3.04 (m, 2H), 2.17 (s, 6H), 2.06 (s, 2H).
98		**V**	**672.42**	δ 10.46 (bs, 1H), 9.85 (bs, 1H), 9.39 (s, 1H), 8.44 (s, 1H), 8.11 (s, 1H), 7.72 (m, 1H), 7.62 (s, 1H), 7.37 (m, 5H), 7.03 (d, J = 8.0 Hz, 1H), 6.69 (m, 1H), 6.63 (m, 1H), 6.55 (m, 1H), 6.43 (d, J = 15.2 Hz, 1H), 6.07 (d, J = 6.8 Hz, 1H), 4.63 (m, 2H), 4.40 (m, 2H), 3.94 (m, 2H), 3.46 (m, 3H), 3.17 (m, 2H), 3.03 (m, 2H), 2.77 (m, 11H), 1.72 (m, 4H).
99		**V**	**586.92**	δ 10.24 (bs, 1H), 9.21 (bs, 1H), 8.12 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.68 (s, 1H), 7.30 (m, 7H), 7.12 (m, 1H), 7.03 (m, 3H), 6.70 (m, 1H), 6.23 (d, J = 15.6 Hz, 1H), 6.07 (s, 1H), 4.64 (m, 2H), 4.40 (m, 2H), 3.66 (s, 3H), 3.02 (d, J = 5.2 Hz, 2H), 2.14 (s, 6H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
100		**V**	**588.27**	δ 10.33 (bs, 1H), 9.53 (bs, 1H), 8.20 (s, 2H), 7.98 (d, *J* = 7.6 Hz, 1H), 7.67 (m, 1H), 7.52 (s, 1H), 7.33 (m, 4H), 7.29 (m, 1H), 7.19 (d, *J* = 5.6 Hz, 1H), 7.16 (m, 2H), 7.08 (m, 1H), 6.70 (m, 1H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.64 (s, 2H), 4.44 (s, 2H), 3.05 (d, *J* = 5.6 Hz, 2H), 2.24 (s, 3H), 2.16 (s, 6H).
101		**V**	**622.28**	δ 10.22 (bs, 1H), 8.79 (bs, 1H), 8.13 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.47-7.29 (m, 7H), 7.03 (d, *J* = 7.92 Hz, 1H), 6.76-6.69 (m, 1H), 6.27-6.02 (m, 2H), 4.63 (s, 2H), 4.41 (s, 2H), 4.19 (m, 2H), 3.05-3.04 (m, 2H), 2.16 (s, 6H).
102		**V**	**588.34**	δ 10.21 (bs, 1H), 9.75 (m, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.77-7.75 (m, 1H), 7.67-7.61 (m, 3H), 7.49 (t, *J* = 8.04 Hz, 1H), 7.41-7.30 (m, 5H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.76-6.70 (m, 1H), 6.50-6.41 (m, 2H), 4.64 (s, 2H), 4.44 (s, 2H), 3.94-3.92 (m, 2H), 3.86 (s, 3H), 2.79 (s, 6H).
103		**V**	**565.39**	δ 10.49 (s, 1H), 9.75 (m, 1H), 8.20 (s, 1H), 7.81 (s, 1H), 7.77-7.75 (m, 1H), 7.67-7.61

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				(m, 3H), 7.49 (t, J = 8.0 Hz, 1H), 7.41-7.30 (m, 5H), 7.09 (d, J = 8.7 Hz, 1H), 6.76-6.70 (m, 1H), 6.50-6.41 (m, 2H), 4.64 (s, 2H), 4.44 (s, 2H), 3.94-3.92 (m, 2H), 3.86 (s, 3H), 2.79 (s, 6H).

Scheme 30: Alternative Preparation of (E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 35):



Step 1: Preparation of 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione (119):

[0308] An ice-cold solution of pyrimidine-2,4(1H,3H)-dione (**118**) (10 g, 89.21 mmol) and paraformaldehyde (9.63 g, 107.05 mmol) in aqueous potassium hydroxide (132 mL, 0.5 M, 66.74 mmol) was heated at 55 °C for 14 hours. After completion of starting material (TLC), the

reaction mixture was cooled to 0 °C and the pH was adjusted to 6 with 12N hydrochloric acid, the resulting white precipitate was filtered through sintered funnel and washed with diethyl ether afforded **119** as a white solid (6.3 g, Yield: 50%) which was used directly for the next step. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.98 (bs, 1H), 10.64 (bs, 1H), 7.24 (s, 1H), 4.78 (m, 1H), 4.12 (d, J = 12.8 Hz, 2H). LCMS: $[M+H]^+$ 143.04 (99.92% purity).

Step 2: Preparation of 2,4-dichloro-5-(chloromethyl)pyrimidine (120):

[0309] To an ice-cold solution of 5-(hydroxymethyl)pyrimidine-2,4(1H,3H)-dione (**119)** (10 g, 70.36 mmol) in toluene (25 mL) was added phosphoryl chloride (14 mL, 140.72 mmol) then N,N-diisopropylethylamine (37 mL, 211 mmol). The reaction mixture was heated at 120 °C for 16 hours. After the complete disappearance of starting material on TLC, the reaction mixture was quenched slowly with sodium bicarbonate solution and extracted with ethyl acetate (3 x 200 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure afforded **120** as a brown solid (12 g, Yield: 86%) which was used directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 4.64 (s, 2H). MS: $[M+H]^+$ 197.0

Step 3: Preparation of 2,4-dichloro-5-(iodomethyl)pyrimidine (121):

[0310] To a solution of 2,4-dichloro-5-(chloromethyl)pyrimidine (**120)** (8.0 g, 40.51 mmol in acetone (40 mL) was added sodium iodide (9.71 g, 64.82 mmol). The reaction mixture was stirred at room temperature for 30 min and heated to reflux for 2 hours. After completion of reaction (TLC monitoring), the reaction mixture cooled to room temperature. The resulting white precipitate was filtered through sintered funnel and washed with acetone. The filtrate was concentrated under reduced pressure afforded **121** as a brown solid (10 g, Yield: 85%) which was used directly for the next step. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1H), 4.39 (s, 2H).

Step 4: Preparation of N-((2,4-dichloropyrimidin-5-yl)methyl)aniline (122):

[0311] To an ice-cold solution of 2, 4-dichloro-5-(iodomethyl)pyrimidine (**121)** (5.0 g, 17.30 mmol) in acetone (50 mL) was added potassium carbonate (5.26 g, 38.06 mmol) and aniline (1.93 g, 20.76 mmol). The resulting reaction mixture was stirred at room temperature for 16 hours. After completion the reaction (as per TLC monitoring), the resulting white precipitate was filtered through sintered funnel and washed with acetone. The filtrate was concentrated under reduced pressure and crude was purified by column chromatography on silica gel (100-200 mesh) using 15% ethyl acetate-hexane as an eluent afforded **122** as a brown solid (2.5 g, Yield: 57%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.61 (s, 1H), 7.07 (t, J = 7.6 Hz, 2H), 6.58 (m, 3H), 6.30 (bs, 1H), 4.33 (m, 2H). LCMS: $[M+H]^+$ 254.03 (99.01% purity).

Step 5: Preparation of *tert*-butyl (3-(7-chloro-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (123):

[0312] To an ice-cold solution of N-((2,4-dichloropyrimidin-5-yl)methyl)aniline (**122**) (500 mg, 1.96 mmol), in isopropanol (5 mL) was added N,N-diisopropylethylamine (1.47 mL, 8.42 mmol) and *tert*-butyl (3-aminophenyl)carbamate (**105**) (409 mg, 1.96 mmol). The resulting reaction mixture was heated at 100 °C for 16 hours in a sealed tube. After completion of reaction (TLC monitoring), the solvent was then evaporated under reduced pressure and resulting crude was purified by column chromatography on silica gel (100-200 mesh) using 30% ethyl acetate-hexane as an eluent afforded **123** as a brown solid (500 mg, Yield: 60%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.96 (s, 1H), 8.10 (s, 1H), 7.73 (s, 1H), 7.25 (m, 2H), 7.12 (m, 3H), 6.61 (m, 3H), 6.14 (t, J = 7.2 Hz, 1H), 4.26 (m, 2H) and 1.53 (s, 9H). LCMS: $[M+H]^+$ 426.14 (93% purity).

Step 6: Preparation of *tert*-butyl (3-(7-chloro-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (124):

[0313] To an ice-cold solution of *tert*-butyl (3-(7-chloro-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**123**) (500 mg, 1.17 mmol) in tetrahydrofuran (6 mL) was added N,N-diisopropylethylamine (0.81 ml, 4.68 mmol) and triphosgene (139 mg, 0.46 mmol). The reaction mixture was stirred at room temperature for 3 hours. After completion of the reaction (TLC monitoring), aqueous triethylamine solution was added and extracted with dichloromethane (3 times). The combined organic layer was washed with brine and dried over sodium sulfate and evaporated under reduced pressure to obtain the crude residue. The crude was purified by column chromatography on silica gel (100-200 mesh) using 30% ethyl acetate-hexane as an eluent afforded **124** as a brown solid (450 mg, Yield: 85%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.43 (s, 1H), 7.58 (s, 1H), 7.44 (m, 4H), 7.29 (t, J = 7.2 Hz, 3H), 6.94 (s, 1H), 5.0 (s, 2H) and 1.47 (s, 9H). LCMS: $[M+H]^+$ 452.27 (99% purity).

Step 7: Preparation of *tert*-butyl (3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (125):

[0314] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure V**, (*tert*-butyl(3-(7-chloro-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**124**) and 3-chloro-1-methyl-1H-pyrazol-4-amine (**44**) gave *tert*-butyl (3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**125**) as a brown solid in 70% yield, which was used directly for the next step. MS: $[M+H]^+$ 547.17.

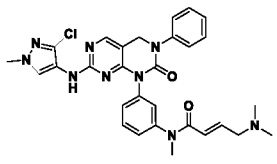
Step 8: Preparation of 1-(3-aminophenyl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (126):

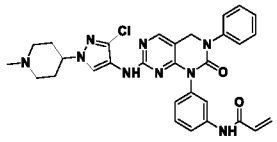
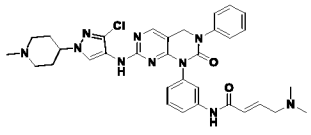
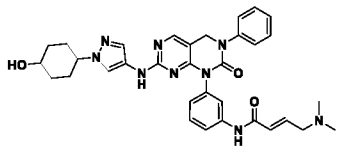
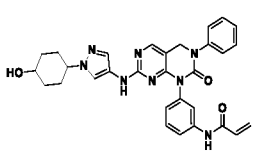
[0315] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure W**, *tert*-butyl (3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**125)** gave 1-(3-aminophenyl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one **(126)** as a brown solid (800 mg, Yield: 82%) which was used directly for the next step. MS: $[M+H]^+$ 447.08.

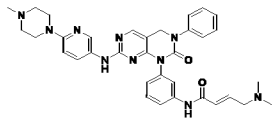
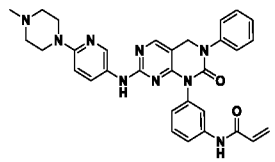
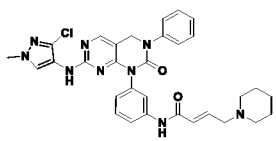
Step 9: Preparation of (E)-N-(3-(7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)-4-(dimethylamino)but-2-enamide (Compound 35):

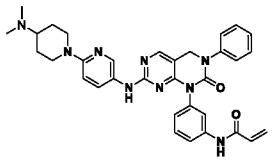
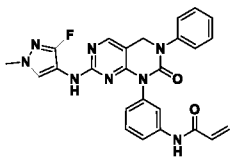
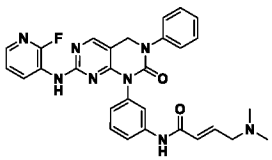
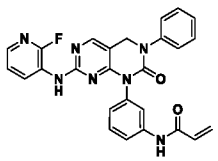
[0316] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure X**, 1-(3-aminophenyl)-7-((3-chloro-1-methyl-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (**126)** and *trans*-N,N-dimethylaminocrotonic acid hydrochloride gave the titled compound, which was purified by prep-HPLC purification to afforded the title compound **Compound 35** as a white solid (285 mg, Yield: 23%). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.27 (bs, 1H), 8.86 (s, 1H), 8.21 (s, 1H), 7.73 (s, 2H), 7.51-7.40 (m, 5H), 7.30-7.25 (m, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.76-6.70 (m, 2H), 6.29 (d, J = 15.4 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 3H), 3.05 (d, J = 4.8 Hz, 2H) and 2.16 (s, 6H). MS: $[M+H]^+$ 558.16.

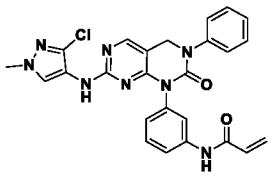
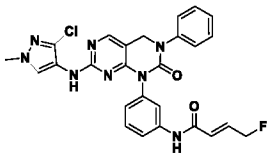
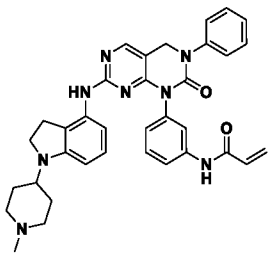
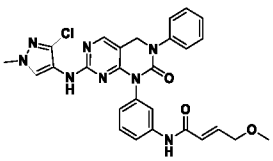
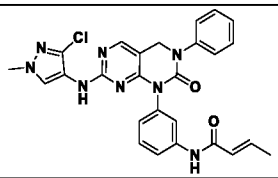
[0317] The following compounds were prepared using the methods described above

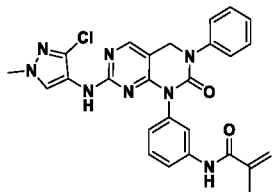
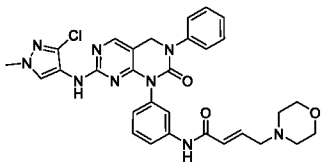
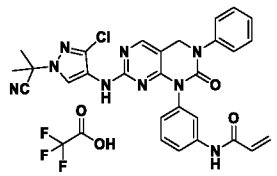
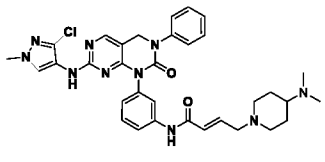
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
104		**X**	**572.26**	δ 8.31 (s, 1H), 8.20 (s, 1H), 7.64 (t, J = 7.2 Hz, 1H), 7.46-7.38 (m, 6H), 7.30-7.26 (m, 2H), 7.01 (s, 1H), 6.64-6.57 (m, 1H), 5.99 (d, J = 15.2 Hz, 1H), 4.87 (s, 2H), 3.56 (s, 3H), 3.27 (s, 3H), 2.73 (d, J = 4.8 Hz, 2H), 2.01 (s, 6H).

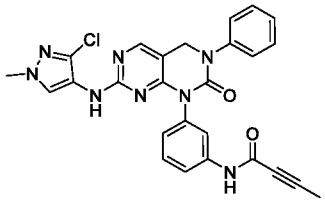
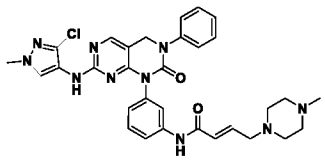
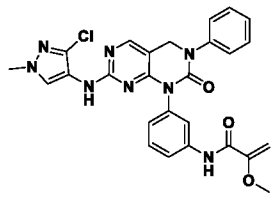
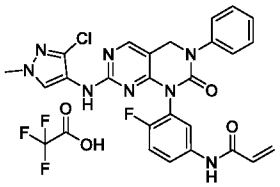
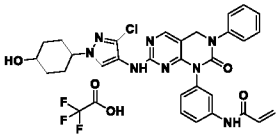
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
105		**Y**	**584.30**	δ 10.34 (bs, 1H), 8.80 (bs, 1H), 8.22 (s, 1H), 7.78 (d, *J* = 7.2 Hz, 1H), 7.69 (s, 1H), 7.40 (m, 5H), 7.26 (m, 1H), 7.08 (m, 1H), 6.91 (s, 1H), 6.40 (m, 1H), 6.24 (d, *J* = 16.4 Hz, 1H), 5.76 (d, *J* = 10.4 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 1H), 2.80 (m, 2H), 2.22 (s, 3H), 2.03 (m, 2H), 1.74 (m, 2H), 1.93 (m, 2H).
106		**X**	**641.37**	δ 10.27 (bs, 1H), 8.83 (bs, 1H), 8.22 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.50-7.40 (m, 5H), 7.30-7.20 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.91 (bs, 1H), 6.77-6.70 (m, 1H), 6.27 (d, *J* = 15.2 Hz, 1H), 4.88 (s, 2H), 3.50 (bs, 1H), 3.05 (d, *J* = 5.2 Hz, 2H), 2.81 (d, *J* = 11.2 Hz, 2H), 2.21 (s, 3H), 2.16 (s, 6H), 2.05-1.60 (m, 6H).
107		**X**	**608.42**	δ 10.30 (bs, 1H), 8.17 (s, 1H), 7.81-7.70 (m, 2H), 7.52-7.40 (m, 5H), 7.29-7.25 (m, 1H), 7.10-7.08 (m, 2H), 6.67-6.70 (m, 2H), 6.27 (d, *J* = 15.2 Hz, 1H), 4.86 (s, 2H), 4.60 (m, 1H), 3.57-3.42 (m, 2H), 3.05 (d, *J* = 5.6 Hz, 2H), 2.16 (s, 6H), 1.88-1.85 (m, 2H), 11.30 (s, 7H),
108		**Y**	**551.33**	δ 10.38 (bs, 1H), 9.54 (s, 1H), 8.17 (s, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.74 (s, 1H), 7.52 (t, *J* = 8.0 Hz, 1H), 7.40 (m, 4H), 7.28-7.25 (m, 1H), 7.12-7.08 (m, 2H), 6.74 (s, 1H), 6.47-6.40 (m, 1H), 6.26 (d, *J* = 18.4 Hz, 1H), 5.76 (d, *J* = 11.6 Hz, 1H), 4.86 (s, 2H), 4.66 (d, *J*

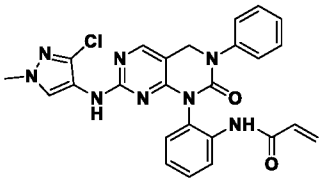
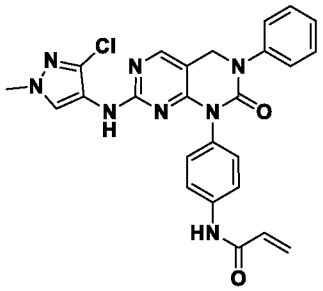
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				= 3.6 Hz, 1H), 3.60-358 (m, 1H), 3.49-3.42 (m, 1H), 1.87 (d, *J* = 10.4 Hz, 2H) 1.61-1.50 (m, 4H), 1.38-1.30 (m, 2H).
109		**X**	**619.45**	δ 10.20 (bs, 1H), 9.23 (bs, 1H), 8.18 (s, 1H), 8.03 (bs, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.41-7.46 (m, 6H), 7.26-7.29 (m, 1H), 7.03 (d, *J* = 7.2 Hz, 1H), 6.69-6.76 (m, 1H), 6.36 (m, 1H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.87 (s, 2H), 3.29 (m, 4H), 3.04 (d, *J* = 5.6 Hz, 2H), 2.34 (m, 4H), 2.20 (s, 3H), 2.16 (s, 6H).
110		**Y**	**562.34**	δ 10.30 (bs, 1H), 9.23 (bs, 1H), 8.18 (s, 1H), 8.04 (bs, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.66 (s, 1H), 7.40-7.51 (m, 6H), 7.26-7.29 (m, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.40-6.47 (m, 2H), 6.23 (d, *J* = 17.2 Hz, 1H), 5.74 (d, *J* = 11.6 Hz, 1H), 4.87 (s, 2H), 3.29 (m, 4H), 2.34-2.37 (m, 4H), 2.19 (s, 3H).
111		**X**	**598.36**	δ 10.25 (bs, 1H), 8.84 (bs, 1H), 8.21 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.40-7.51 (m, 5H), 7.26-7.29 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.70-6.77 (m, 2H), 6.23 (d, *J* = 15.2 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 3H), 3.06 (d, *J* = 5.2 Hz, 2H), 2.33 (s, 4H), 1.49-1.52 (m, 4H), 1.37 (s, 2H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
112		**Y**	**590.51**	δ 10.29 (bs, 1H), 9.15 (bs, 1H), 8.09 (s, 1H), 7.99 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.31-7.44 (m, 7H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.35-6.46 (m, 2H), 6.23-6.27 (m, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.87 (s, 2H), 4.06-4.09 (m, 2H), 2.61-2.67 (m, 2H), 2.17-2.24 (m, 7H), 1.74-1.77 (m, 2H), 1.25-1.33 (m, 2H).
113		**Y**	**485.20**	δ 10.35 (bs, 1H), 8.19 (s, 1H), 7.72-7.78 (m, 2H), 7.41-7.49 (m, 6H), 7.26-7.29 (m, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.40-6.53 (m, 2H), 6.23-6.28 (m, 1H), 5.75 (d, *J* = 10.4 Hz, 1H), 4.87 (s, 2H), 3.29 (s, 3H).
114		**X**	**539.49**	δ 10.21 (bs, 1H), 9.11 (bs, 1H), 8.27 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.74 (s, 1H), 7.65-7.68 (m, 2H), 7.41-7.45 (m, 5H), 7.28 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.69-6.74 (m, 1H), 6.24 (d, *J* = 15.6 Hz, 1H), 4.92 (s, 2H), 3.05 (d, *J* = 5.2 Hz, 2H), 2.17 (s, 6H).
115		**Y**	**482.30**	δ 10.29 (bs, 1H), 9.11 (bs, 1H), 8.27 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.68-7.74 (m, 3H), 7.41-7.47 (m, 5H), 7.28 (s, 1H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.40-6.46 (m, 1H), 6.23-6.27 (m, 1H), 5.74 (d, *J* = 10.4 Hz, 1H), 4.92 (s, 2H).

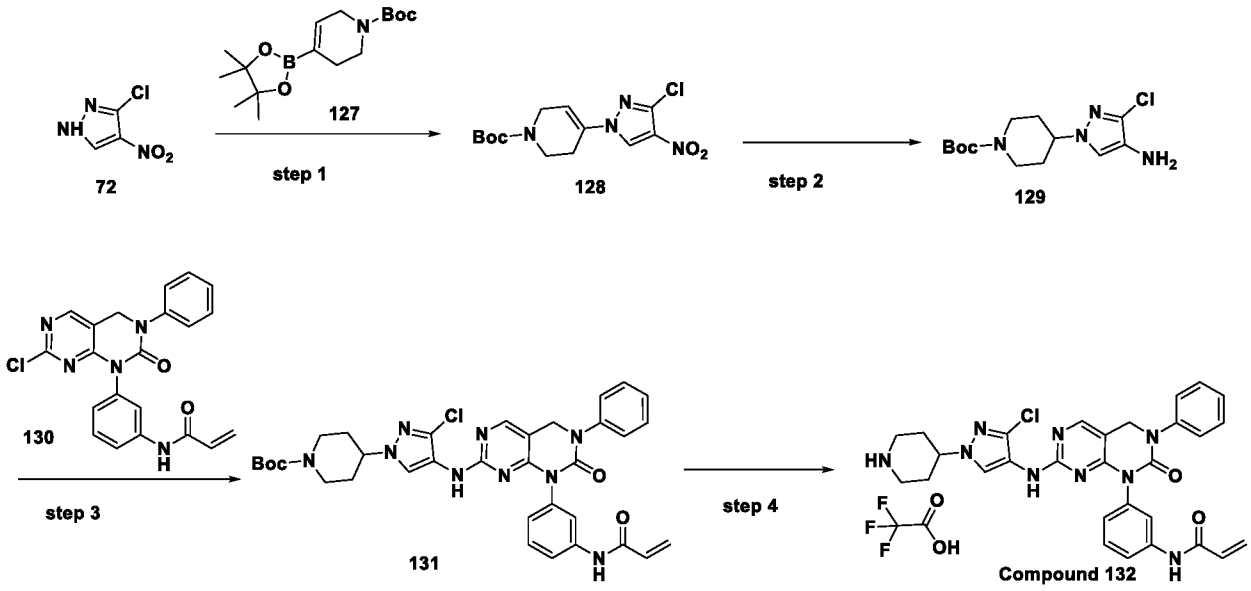
Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
116		**Y**	**501.35**	δ 10.34 (bs, 1H), 8.82 (bs, 1H), 8.21 (s, 1H), 7.72-7.77 (m, 2H), 7.43-7.53 (m, 5H), 7.28-7.30 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.74 (s, 1H), 6.40-6.47 (m, 1H), 6.23-6.28 (m, 1H), 5.75 (d, *J* = 10.0 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 3H).
117		**X**	**533.37**	δ 10.15 (bs, 1H), 8.28 (bs, 1H), 8.19 (s, 1H), 7.68-7.76 (m, 2H), 7.40-7.51 (m, 5H), 7.26-7.29 (m, 1H), 7.06-7.10 (m, 1H), 6.83-6.94 (m, 2H), 6.36-6.66 (m, 1H), 5.16-5.21 (m, 1H), 5.05-5.09 (m, 1H), 4.88 (s, 2H), 3.54 (s, 3H).
118		**Y**	**601.48**	δ 10.27 (bs, 1H), 8.42 (bs, 1H), 8.26 (s, 1H), 7.66-7.71 (m, 2H), 7.39-7.47 (m, 5H), 7.25-7.28 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.53-6.62 (m, 2H), 6.40-6.47 (m, 1H), 6.23-6.27 (m, 1H), 6.0 (d, *J* = 7.6 Hz, 1H), 5.74 (d, *J* = 11.6 Hz, 1H), 4.87 (s, 2H), 3.18-3.20 (m, 3H), 2.73-2.82 (m, 4H), 2.22 (s, 3H), 1.90-1.94 (m, 2H), 1.56-1.57 (m, 4H).
119		**X**	**545.36**	δ 10.26 (bs, 1H), 8.76 (bs, 1H), 8.20 (s, 1H), 7.73 (s, 2H), 7.30-7.44 (m, 5H), 7.25-7.30 (m, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.77-6.83 (m, 2H), 6.30 (d, *J* = 13.2 Hz, 1H), 4.88 (s, 2H), 4.09-4.11 (m, 2H), 3.51 (s, 3H), 3.29 (s, 3H).
120		**X**	**515.28**	δ 10.12 (bs, 1H), 8.74 (bs, 1H), 8.20 (s, 1H), 7.63 (s, 2H), 7.39-7.50 (m, 5H), 7.21-7.24 (m, 1H), 7.06 (d, *J* =

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				8.4 Hz, 1H), 6.75-6.84 (m, 2H), 6.14 (d, *J* = 15.2 Hz, 1H), 4.88 (s, 2H), 3.50 (s, 3H), 1.85 (d, *J* = 6.8 Hz, 3H).
121		**X**	**515.28**	δ 9.95 (bs, 1H), 8.74 (bs, 1H), 8.21 (s, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.73 (s, 1H), 7.41-7.51 (m, 5H), 7.25-7.29 (m, 1H), 7.09 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 5.81 (s, 1H), 5.52 (s, 1H) 4.88 (s, 2H), 3.52 (s, 3H), 1.94 (s, 3H).
122		**X**	**600.0**	δ 10.21 (s, 1H), 8.60-8.80 (bs, 2H), 8.19 (s, 1H), 7.90-7.80 (bs, 1H), 7.70 (s, 2H), 7.42 (s, 3H), 7.26 (s, 1H), 7.08 (s, 1H), 6.80-6.60 (m, 2H), 6.40-6.20 (m, 1H), 4.86 (s, 2H), 3.57 (s, 3H), 3.49 (s, 2H), 3.11 (s, 4H), 2.37 (s, 4H).
123		**Y**	**554.18**	δ 10.28 (bs, 1H), 8.80 (bs, 1H), 8.22 (s, 1H), 7.62-7.64 (m, 2H), 7.40-7.43 (m, 6H), 7.23-7.21 (m, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.39-6.46 (m, 1H), 6.22-6.27 (m, 1H), 5.77 (dd, *J* = 1.6 Hz & 10.0 Hz, 1H), 4.87 (s, 2H), 1.75 (s, 6H).
124		**X**	**641.0**	δ 10.19 (s, 1H), 8.75 (bs, 1H), 8.19 (d, *J* = 8.0 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.49-7.41 (m, 4H), 7.25 (s, 1H), 7.06 (d, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 16.0 Hz, 2H), 6.23 (d, *J* = 16.0 Hz, 1H), 4.86 (s, 2H), 3.48 (s, 3H), 3.06 (d, *J* = 4.0 Hz, 2H), 2.82 (d, *J* = 12.0 Hz, 2H), 2.14 (s, 6H), 1.90 (m, 5H), 1.67-1.68 (m, 2H).

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
125		**X**	**513.1**	10.77 (s, 1H), 8.18 (s, 1H), 7.63 (s, 2H), 7.48-7.38 (m, 4H), 7.27-7.25 (m, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.8-6.6 (m, 2H), 4.85 (s, 2H), 3.5-3.83 (m, 3H), 2.02 (s, 3H).
126		**X**	**613.2**	δ 10.23 (s, 1H), 8.9-8.7 (bs, 1H), 8.18 (s, 1H), 7.7 (s, 2H), 7.45-7.41 (m, 4H), 7.25 (s, 1H), 7.07 (s, 1H), 6.70 (d, *J* = 14.0 Hz, 3H), 6.23 (d, *J* = 15.2 Hz, 1H), 4.53 (s, 1H), 3.46 (s, 3H), 3.38 (s, 2H), 3.07 (s, 2H), 2.30 (m, 4H), 2.12 (s, 3H), 1.91 (s, 1H), 1.69 (s, 1H), 1.20 (s, 1H).
127		**X**	**531.13**	δ 10.02 (bs, 1H), 8.81 (bs, 1H), 8.21 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.81 (s, 1H), 7.41-7.50 (m, 5H), 7.26-7.29 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 6.53-6.67 (m, 1H), 5.20 (d, *J* = 2.0 Hz, 1H), 6.86 (s, 2H), 4.64 (d, *J* = 1.6 Hz, 1H), 3.69 (s, 3H), 3.50 (s, 3H).
128		**Y**	**519.3**	δ 10.34 (s, 1 H), 8.82 (bs, 1H), 8.21 (s, 1H), 7.85 (d, *J* = 4.8 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.37-7.43 (m, 5H), 7.26-7.29 (m, 1H), 6.85-7.19 (m, 2H), 6.37- 6.43 (m, 1H), 6.22-6.27 (m, 1H), 5.75 (d, *J* = 5.2 Hz, 1H), 4.48-4.95 (m, 2H), 3.53 (s, 3H).
129		**Y**	**585.28**	δ 10.30 (bs, 1H), 8.78 (bs, 1H), 8.22 (s, 1H), 7.72-7.74 (m, 2H), 7.40-7.50 (m, 6H), 7.20-7.27 (m, 1H), 7.09-7.11 (m, 1H), 6.87-6.95 (m, 1H), 6.40-6.47 (m, 1H), 6.24 (d, *J* = 15.2 Hz, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 4.88 (s, 2H),

Cmpd No.	Structure	Synthesis method	LCMS $[M+H]^+$	^{1}H-NMR (400 MHz, DMSO-d_6)
				3.45-3.46 (m, 2H), 1.86-1.88 (m, 2H), 1.56-1.62 (m, 4H), 1.33-1.38 (m 2H).
130		**Y**	**501.0**	δ 9.61 (s, 1H), 8.69 (bs, 1H), 8.17 (s, 2H), 7.35-7.47 (m, 6H), 7.25 (t, *J* = 7.6 Hz, 2H), 6.75 (bs, 1H), 6.49-6.56 (m, 1H), 6.16 (d, *J* = 16.8 Hz, 1H), 5.66 (d, *J* = 10.0 Hz, 1H). 4.77-4.93 (m, 2H), 3.52 (s, 3H).
131		**Z**	**501.0**	δ 10.33 (s, 1H), 8.73 (bs, 2H), 8.17 (bs, 1H), 6.52 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 2H), 7.42-7.25 (m, 6H), 6.48-6.42 (m, 1H), 6.30-6.26 (m, 1H), 5.78-5.75 (d, *J* = 12.0 Hz, 1H,), 4.85 (s, 2H), 3.45 (s, 3H).

Scheme 31: Preparation of N-(3-(7-((3-chloro-1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide (Compound 132):



Step 1: Preparation of tert-butyl 4-(3-chloro-4-nitro-1H-pyrazol-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (128)

[0318] To a stirred solution of 3-chloro-4-nitro-1H-pyrazole **(72)** (500 mg, 3.39 mmol) in methanol (15.0 mL) were added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate **(127)** (1.26 g, 4.07 mmol) and pyridine (0.54 mL, 6.78 mmol), and the resulting reaction mixture was stirred for 10 minutes. Copper(2+) diacetate (0.92 g, 5.08 mmol) was added and the reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was filtered through celite bed and the solvent was concentrated under reduced pressure. Crude compound was purified by column chromatography, eluted with 30% ethyl acetate in heptane to afford the title compound **(128)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.32 (s, 1H), 6.30 (s, 1H), 4.14 (s, 2H), 3.71 (s, 2H), 2.63 (s, 2H), 1.48 (s, 9H).

Step 2: Preparation of tert-butyl 4-(3-chloro-4-nitro-1H-pyrazol-1-yl)piperidine-1-carboxylate (129)

[0319] To a stirred solution of tert-butyl 4-(3-chloro-4-nitro-1H-pyrazol-1-yl)-1,2,3,6-tetrahydropyridine-1-carboxylate **(128)** (0.25 g, 0.76 mmol) in ethyl acetate (10.0 mL) was added platinum oxide (0.017 g, 0.076 mmol) and applied hydrogen gas (using bladder), stirred at room temperature for 5 hours. The reaction was monitored by TLC and LCMS. After completion of the reaction, the reaction mixture was filtered through celite bed and washed with ethyl acetate. The filtrate was concentrated afforded the crude product and it was purified by flash column chromatography (Combiflash) using a silica gel column and the product was eluted at 2 % methanol in dichloromethane. Desired fractions were concentrated under reduced pressure afforded tert-butyl 4-(4-amino-3-chloro-1H-pyrazol-1-yl)piperidine-1-carboxylate **(129)** (0.2 g, 87% yield) as brown solid. LCMS $[M+H]^+$ 245.1

Step 3: Preparation of tert-butyl 4-[3-chloro-4-({7-oxo-6-phenyl-8-[3-(prop-2-enamido)phenyl]-5H,6H,7H,8H-pyrimido[4,5-d][1,3]diazin-2-yl}amino)-1H-pyrazol-1-yl]piperidine-1-carboxylate (131)

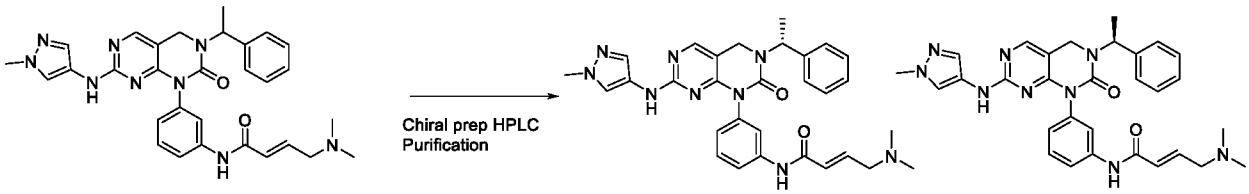
[0320] To a stirred solution of tert-butyl 4-(4-amino-3-chloro-1H-pyrazol-1-yl)piperidine-1-carboxylate **(129)** (70.0 mg, 0.233 mmol) in propan-2-ol (10.0 mL) were added N-(3-{7-chloro-2-oxo-3-phenyl-1H,2H,3H,4H-pyrimido[4,5-d][1,3]diazin-1-yl}phenyl)prop-2-enamide **(130)** (94.4 mg, 0.233 mmol) and trifluoroacetic acid (0.017 mL, 0.233 mmol). Then the reaction mixture was heated in a sealed tube at 100 °C for 4 hours. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. Then the obtained residue was dissolved in dichloromethane (10 mL) and washed with saturated sodium bicarbonate solution (5 mL), dried over sodium sulfate, filtered and concentrated. It was purified by combiflash chromatography, eluted with 2% methanol in dichloromethane to afford tert-butyl 4-[3-chloro-4-

({7-oxo-6-phenyl-8-[3-(prop-2-enamido)phenyl]-5H,6H,7H,8H-pyrimido[4,5-d][1,3]diazin-2-yl}amino)-1H-pyrazol-1-yl]piperidine-1-carboxylate **(131)** (0.12 g, crude) as semi solid. LCMS $[M+H]^+$ 670.3

Step 4: Preparation of N-[3-(7-{[3-chloro-1-(piperidin-4-yl)-1H-pyrazol-4-yl]amino}-2-oxo-3-phenyl-1H,2H,3H,4H-pyrimido[4,5-d][1,3]diazin-1-yl)phenyl]prop-2-enamide TFA salt (Compound 132)

[0321] To a stirred solution of tert-butyl 4-[3-chloro-4-({7-oxo-6-phenyl-8-[3-(prop-2-enamido)phenyl]-5H,6H,7H,8H-pyrimido[4,5-d][1,3]diazin-2-yl}amino)-1H-pyrazol-1-yl]piperidine-1-carboxylate **(131)** (100 mg, 0.149 mmol) in dichloromethane (5 mL) at 0 °C, trifluoroacetic acid (2 mL) was added dropwise and the reaction mixture was stirred at room temperature for 2 hours. After completion of the reaction, the solvent was evaporated under reduced pressure. The crude product was purified by preparative HPLC to give N-[3-(7-{[3-chloro-1-(piperidin-4-yl)-1H-pyrazol-4-yl]amino}-2-oxo-3-phenyl-1H,2H,3H,4H-pyrimido[4,5-d][1,3]diazin-1-yl)phenyl]prop-2-enamide TFA salt **(Compound 132)** as white solid (20.0 mg, 24%). ^{1}H NMR (400 MHz, DMSO d_6) δ 10.37 (s, 1H), 8.90 (s, 1H), 8.60 (s, 1H), 8.20 (s, 2H), 7.99 (s, 2H), 7.53-7.49 (m, 2H), 7.42 (s, 2H), 7.26 (s, 1H), 7.11 (d, J = 7.6 Hz, 1H), 6.76 (s, 1H), 6.45-6.41 (m, 1H), 6.28-6.23 (m, 1H), 5.78 (d, J = 10 Hz, 1H), 4.87 (s, 2H), 3.82 (s, 1H), 3.40-3.37 (m, 3H), 3.20-3.07 (m, 2H), 1.96-1.94 (m, 2H), 1.83-1.75 (m, 2H). LCMS $[M+H]^+$ 570.1.

Scheme 32: Preparation of (R,E)-4-(dimethylamino)-N-(3-(7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-(1-phenylethyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide (Compound 133) and (S,E)-4-(dimethylamino)-N-(3-(7-((1-methyl-1H-pyrazol-4-yl)amino)-2-oxo-3-(1-phenylethyl)-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide (Compound 134)



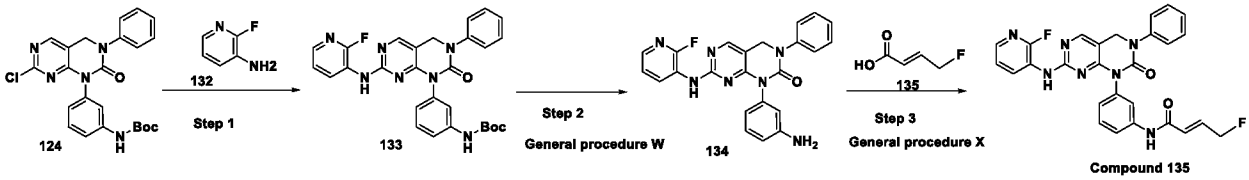
Compound 10 Compound 133 Compound 134

[0322] Compound 10 was separated by chiral preparative HPLC purification to afford the title compounds.

[0323] Compound 133 (Isomer 1): ^{1}H NMR (400 MHz, DMSO d_6) δ 10.25 (bs, 1H), 9.36 (bs, 1H), 8.01 (s, 1H), 7.73 (bs, 1H), 7.64 (s, 1H), 7.48 (bs, 1H), 7.37-7.36 (m, 4H), 7.29-7.28 (m, 1H), 7.02-7.01 (m, 2H), 6.74-6.67 (m, 1H), 6.62 (bs, 1H), 6.25-6.21 (m, 1H), 5.70-5.69 (m, 1H), 4.41 (d, J = 14.0 Hz, 1H), 3.91 (d, J = 14.0 Hz, 1H), 3.47 (s, 3H), 3.04 (d, J = 5.6 Hz, 2H), 2.14 (s, 6H), 1.57 (d, J = 6.8 Hz, 3H). LCMS $[M+H]^+$ 552.3.

[0324] Compound 134 (Isomer 2): ^{1}H NMR (400 MHz, DMSO d_6) δ 10.25 (bs, 1H), 9.36 (bs, 1H), 7.99 (s, 1H), 7.71 (bs, 1H), 7.63 (s, 1H), 7.48 (bs, 1H), 7.35-7.27 (m, 5H), 7.01-6.99 (m, 2H), 6.72-6.67 (m, 2H), 6.21 (d, *J* =15.6 Hz, 1H), 5.68-5.66 (m, 1H), 4.41 (d, *J* = 14.0 Hz, 1H), 3.91 (d, *J* = 14.0 Hz, 1H), 3.44 (s, 3H), 3.02-3.00 (m, 2H), 2.11 (s, 6H), 1.56 (d, *J* = 6.8 Hz, 3H). LCMS $[M+H]^+$ 552.3.

Scheme 33: Preparation of (E)-4-fluoro-N-(3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide (Compound 135)



Step 1: Preparation of tert-butyl (3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (133)

[0325] To a solution of tert-butyl (3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**124**) (0.2 g, 0.443 mmol) and 2-fluoropyridin-3-amine (**132**) (0.059 g, 0.531 mmol) in 1,4-dioxane (3.00 mL) were added potassium carbonate (0.183 g, 1.33 mmol), [2',6'-bis(propan-2-yloxy)-[1,1'-biphenyl]-2-yl]dicyclohexylphosphane (0.041 g, 0.088 mmol) and the reaction mixture was purged with nitrogen for 10 minutes. To this reaction mixture was added tris(dibenzylideneacetone)dipalladium(0) (0.04 g, 0.044 mmol) and the reaction mixture was heated in microwave at 130 °C for 2 hours. The progress of the reaction was monitored by LCMS. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layer was washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by combiflash purifier using 50 % ethyl acetate in hexane to afford tert-butyl (3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (**133**) (0.15 g) as yellow solid. LCMS: $[M+H]^+$ 528

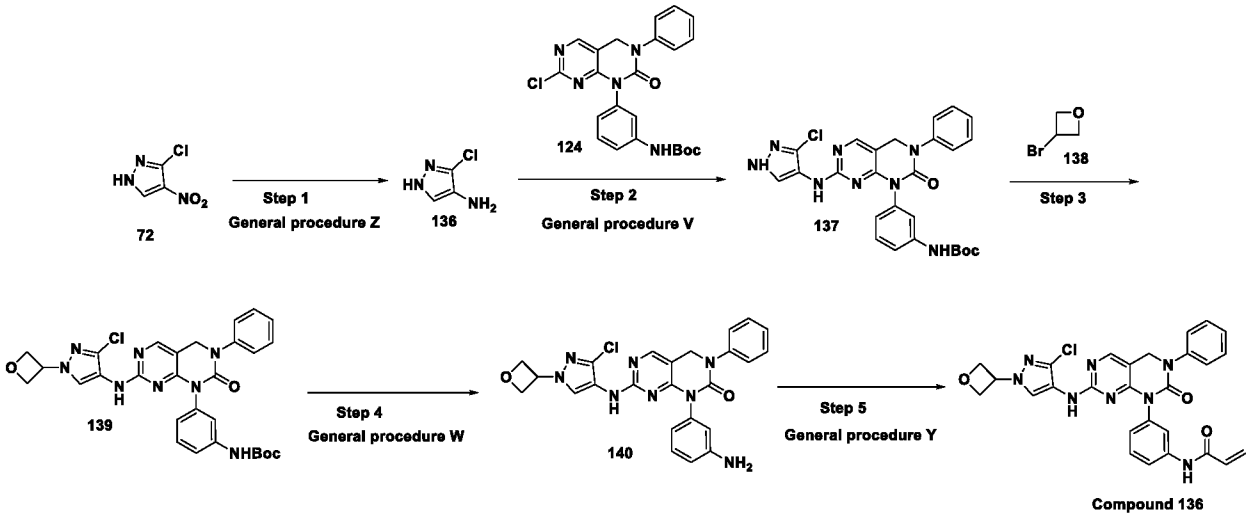
Step2: Preparation of 1-(3-aminophenyl)-7-((2-fluoropyridin-3-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (134)

[0326] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure W**, as a brown solid (0.13 g, crude) which was used directly for the next step. LCMS: $[M+H]^+$ 428.

Step3: Preparation of (E)-4-fluoro-N-(3-(7-((2-fluoropyridin-3-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)but-2-enamide (Compound 135)

[0327] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure X**, as off white solid (0.005 g, 4 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ10.31 (s, 1H), 9.06 (s, 1H), 8.26 (s, 1H), 7.87 (t, J = 10.6 Hz, 1H), 7.74 (s, 1H), 7.68-7.65 (m, 2H), 7.44 (s, 5H), 7.28 (bs, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.91-6.81 (m, 2H), 6.36 (d, J = 15.60 Hz, 1H), 5.17 (d, J = 46.4 Hz, 2H), 4.91 (s, 2H). LCMS: $[M+H]^+$ 514.

Scheme 34: Preparation of N-(3-(7-((3-chloro-1-(oxetan-3-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide (Compound 136)



Step 1: Preparation of 3-chloro-1H-pyrazol-4-amine (136)

[0328] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure Z**. LCMS: $[M+H]^+$ 117.78.

Step 2: Preparation of tert-butyl (3-(7-((3-chloro-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (137)

[0329] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure V**, as yellow solid (0.6 g, 51 %). LCMS: $[M+H]^+$ 533.41.

Step 3: Preparation of tert-butyl (3-(7-((3-chloro-1-(oxetan-3-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate (139)

[0330] To stirred a solution of tert-butyl (3-(7-((3-chloro-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)carbamate **(137)** (230 mg, 0.432 mmol) in N,N-dimethylformamide (5.00 mL) was added cesium carbonate (422 mg, 1.29 mmol), and the reaction mixture was stirred at room temperature for 5 minutes. 3-bromooxetane **(138)** (70.9 mg, 0.518 mmol) was added and the reaction mixture was heated at 140 °C for 2 hours in microwave. The progress of the reaction was monitored by TLC and LCMS analysis.

After completion of the reaction, the reaction mixture was poured into ice cold water (25 mL) and extracted with ethyl acetate (25 mL x 2). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by combiflash purifier and was eluted with 65 % ethyl acetate in hexane to afford the title compound as off white solid (0.09 g, 28 %). LCMS: $[M+H]^+$ 489.39 (deboc mass).

Step 4: Preparation of 1-(3-aminophenyl)-7-((3-chloro-1-(oxetan-3-yl)-1H-pyrazol-4-yl)amino)-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-2(1H)-one (140)

[0331] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure W**. LCMS: $[M+H]^+$ 489.39.

Step 5: Preparation of N-(3-(7-((3-chloro-1-(oxetan-3-yl)-1H-pyrazol-4-yl)amino)-2-oxo-3-phenyl-3,4-dihydropyrimido[4,5-d]pyrimidin-1(2H)-yl)phenyl)acrylamide (Compound 136)

[0332] Title compound was prepared in a manner substantially similar to procedure mentioned in **General procedure Y** as off white solid (20 mg, 19 %). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.36 (s, 1H), 8.89 (bs, 1H), 8.22 (s, 1H), 7.80-7.78 (m, 1H), 7.71 (bs, 1H), 7.52-7.48 (m, 1H), 7.44-7.40 (m, 4H), 7.29-7.26 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.85 (bs, 1H), 6.48-6.41 (m, 1H), 6.29-6.24 (m, 1H), 5.79-5.76 (m, 1H), 5.00 (bs, 1H), 4.88 (s, 2H), 4.81 (t, J = 7.2 Hz, 2H), 4.69 (bs, 2H). LCMS: $[M+H]^+$ 543.08.

Example 2: EGFR L858R & del19/T790M Assay protocol (To find the IC_{50} for the compounds using HTRF method)

Reagents for enzyme assay:

1. Enzyme Assay Buffer: 60 mM HEPES (pH 7.4), 50 mM NaCl, 20 mM $MgCl_2$, 5 mM $MnCl_2$, filtered using 0.2 μm pore size, stored at 4°C.
   Supplements (added fresh to the enzyme buffer): 1M DTT stock was made, 5% BSA stock and 0.1M Na_3OV_4 stored at 4°C. Enzyme assay buffer 50 mL, 1 M DTT 100 μL, 5% BSA 500 μL, 0.1M Na_3OV_4 50 μL.
2. GST-hEGFR (L858R), active: EGFR (T790M/L858R), active (Proqinase), 3.6 μM stock; 2.5 nM in final assay.
3. Gastrin Precusor-Biotinylated: Gastrin precursor (Tyr87) biotinylated peptide, EEAY*GWM, Cell Signaling Tech 1310, Lot-7, Want final 0.5 μM in assay.
4. ATP: 10 mM stock in 100 μL Enzyme assay buffer pH 7.4 prepared freshly, want 5 μM in final assay.

5. Test compounds: Powders were dissolved in 100% DMSO and made up to a final stock concentration of 10 mM (volume in µL to add for 10 mM = mg powder X 10^5/MW). Final compound concentration in the assay plate started at 10 µM.

Reagents for HTRF Assay:

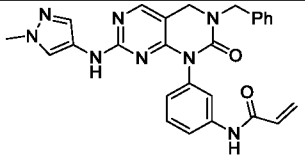
1. HTRF buffer: 50 mM Tris –HCl, pH-7.5, 100 mM NaCl, 0.1% BSA, 0.05% Tween20, 0.5mM EDTA, filtered using 0.2 µm pore size, stored at 4 °C.
   Phycolink® Streptavidin-Allophycocyanin (SA-APC) Prozyme, Cat. # PJ25S, Lot# 896 085, 2.06 mg/mL, APC concentration is 11.6 µM, streptavidin concentration is 15.5 µM. Want 12 nM final in assay (based on streptavidin concentration).
2. (Europium) Eu-W1024 Anti-phosphotyrosine (PT-66) Antibody: Perkin Elmer (Product Number: AD0068), monoclonal IgG1 that recognizes phosphotyrosine peptide 100 µg/ml stock. Want 0.1 nM final in assay.

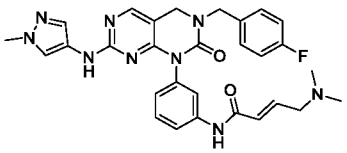
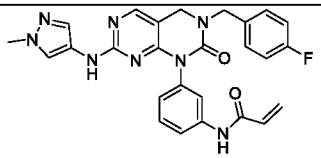
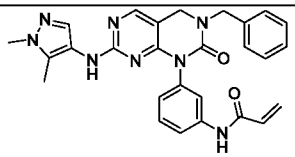
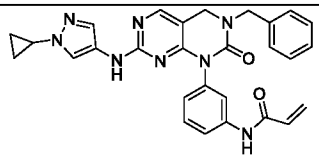
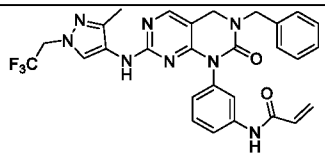
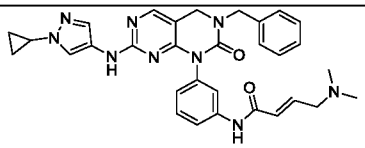
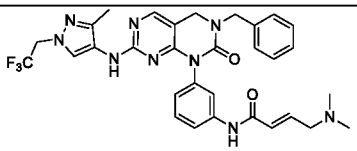
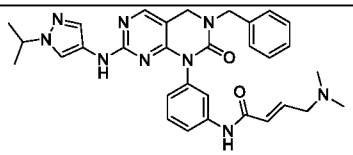
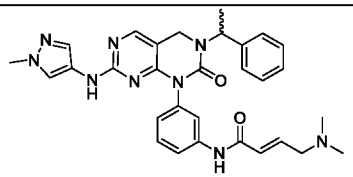
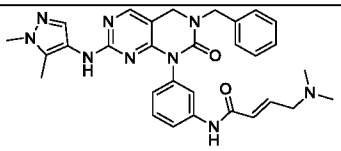
Assay Procedure

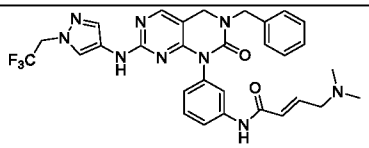
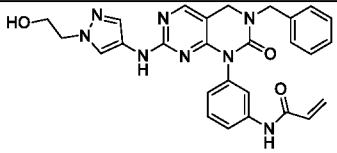
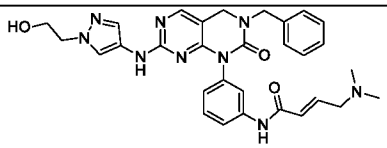
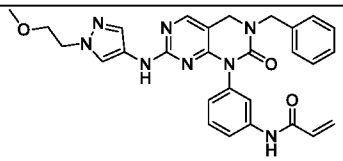
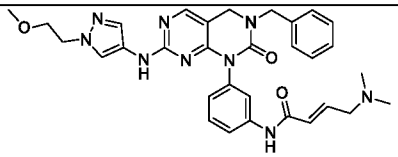
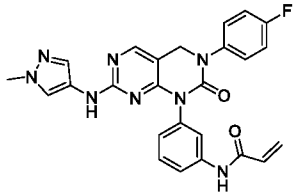
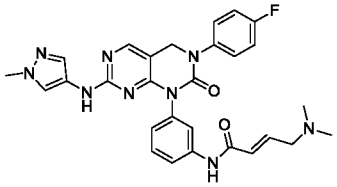
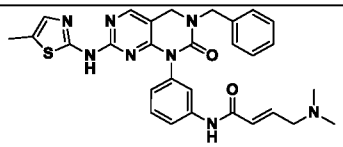
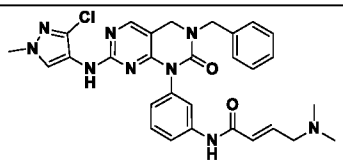
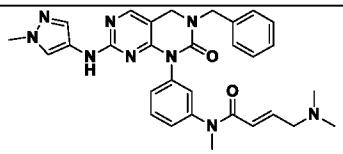
1. The compound dilution was made by TECAN as per the above scheme.
2. 16 µL of diluted compound was added to the assay plate by using TECAN.
3. 10 µL of enzyme mix was added to each well except mins.
4. 20 µL of substrate and ATP mix were added into each well of the assay plate, manually.
5. The plate was incubated on a laboratory shaker at room temperature for 60 min.
6. Meanwhile, the HTRF mix was prepared and 75 µL was added to the HTRF plate.
7. When the incubation was over, 10 µL of the reaction mixture was transferred to the HTRF assay plate and incubated on a laboratory shaker for 30 min at room temperature.
8. The reading was taken in Pherastar (ext 337 nm, Em 665 & 620 nm).
9. The results were analyzed using Graphpad prism after calculation of the z factor, signal window and % inhibition to get the IC_{50}.

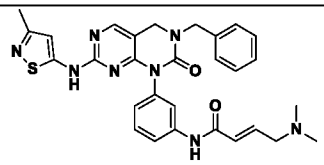
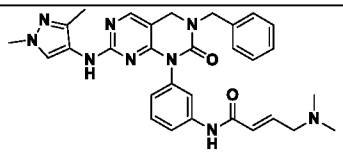
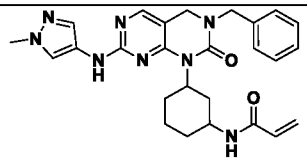
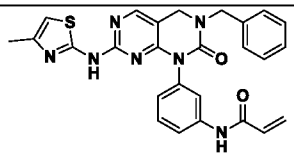
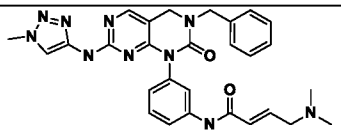
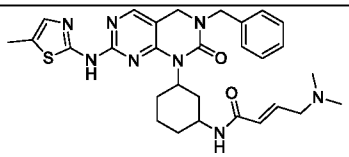
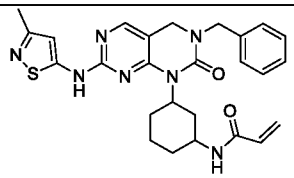
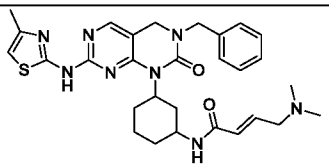
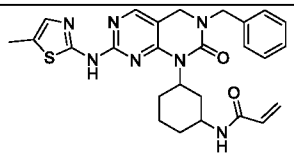
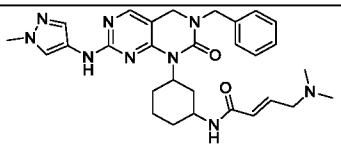
[0333] Table 1 shows the activity of compounds of this invention in the EGFR (L858R & del19/T790M) inhibition assay and (H1975) proliferation assay.

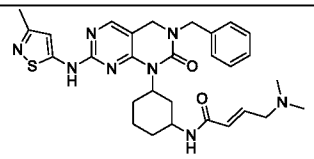
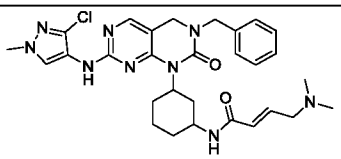
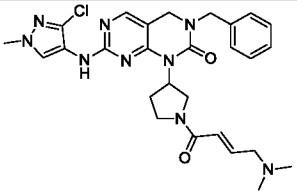
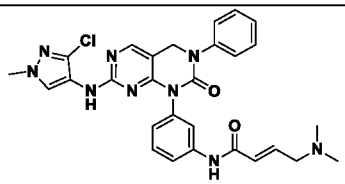
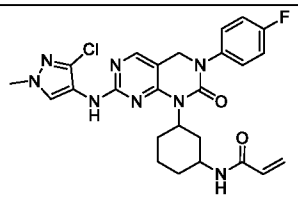
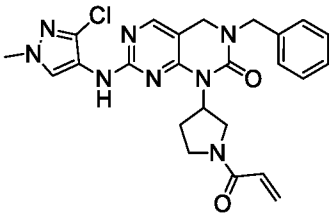
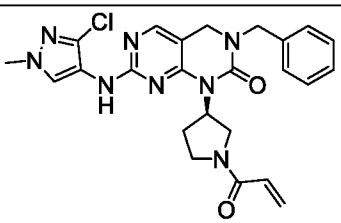
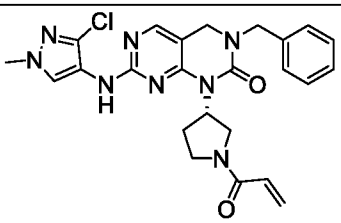
Table 1: Biochemical EGFR (L858R & del19/T790M) inhibition data and (H1975) proliferation data.

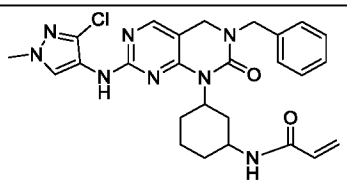
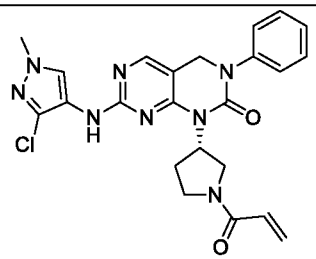
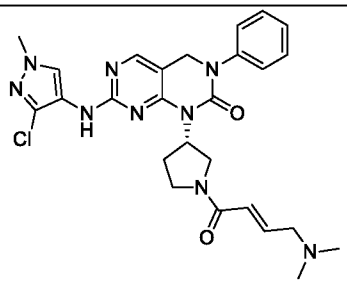
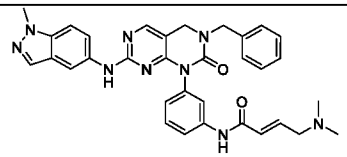
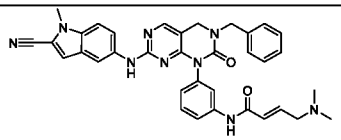
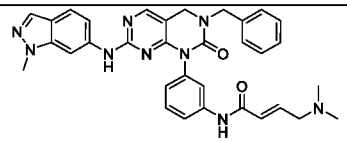
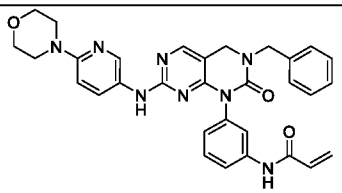
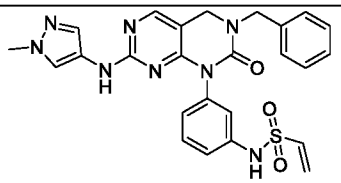
Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
1		0.4	6.8

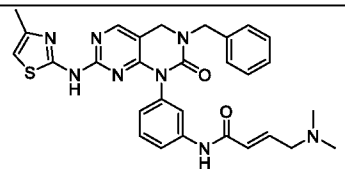
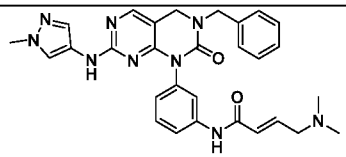
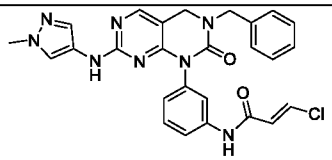
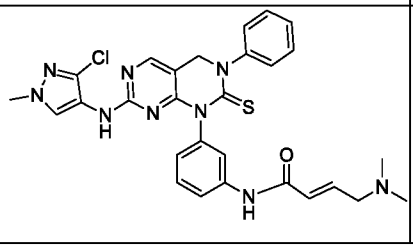
Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
2		2.0	19.7
3		13	40.9
4		2.4	4.9
5		1.0	5.7
6		1.0	8.1
7		6.0	9.3
8		9.0	9.2
9		4.0	17.6
10		4.0	4.5
11		2.0	9.6

Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
12		3.0	6.6
13		1.0	1.5
14		5.0	37.8
15		2.0	1.8
16		1.0	15.7
17		0.5	0.7
18		2.5	34.0
19		6.0	16.0
20		1.0	2.0
21		45	83.9

Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
22		7.0	10
23		3.0	6.4
24		53	71
25		3.0	29.0
26		5.0	221.5
27		303	10000
28		28	75.4
29		660	1079
30		164	413
31		281	299

Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
32		82	176
33		869	ND
34		6574	ND
35		7.8	79
36		2.97	ND
37 (racemic)		167	372
38 (Enantiomer 1)		446	ND
39 (Enantiomer 2)		112	637

Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
40		98	323
41		580	ND
42		10000	ND
43		3.8	6.3
44		9.0	37.6
45		11.0	46.7
46		2.6	3.7
47		0.9	819

Cmpd No.	Structure	EGFR_L858R T790M_IC_{50}_nM	Proliferation_Assay H1975 cells-EC_{50}_nM L858R_T790M_ mutant
48		**3.5**	**133**
49		**0.6**	**2.1**
50		**0.4**	**4198**
51		**8.0**	**9.8**

ND = Not done

Example 3: Cellular Proliferation (Alamar Blue) Assays

Cell line details:

1. EGFR(D770_N771insSVD) expressing Ba/F3 stable cell line
2. EGFR (A767_dupASV) expressing Ba/F3 stable cell line
3. A431 cells
4. HER2 (A775_G776insYVMA) expressing Ba/F3 stable cell line
5. HER2 (WT) expressing Ba/F3 stable cell line
6. BT-474 cells

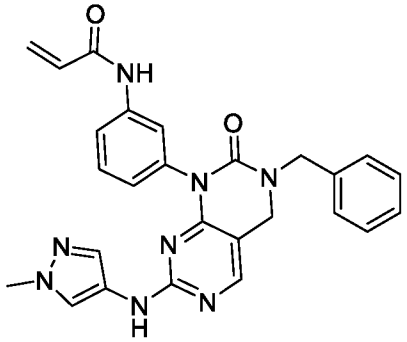
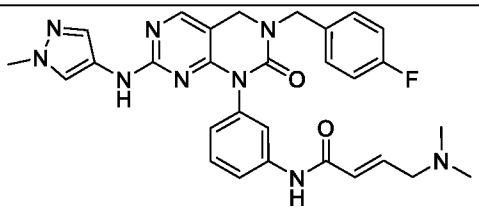
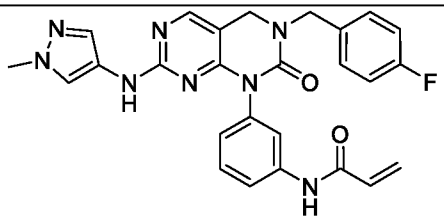
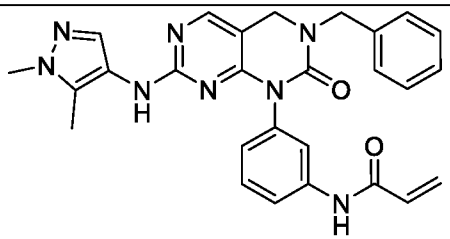
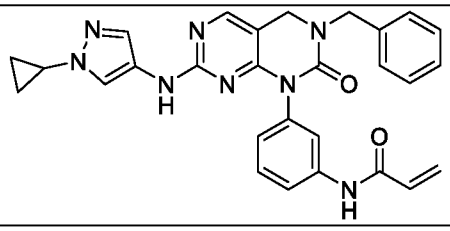
Assay Procedure:

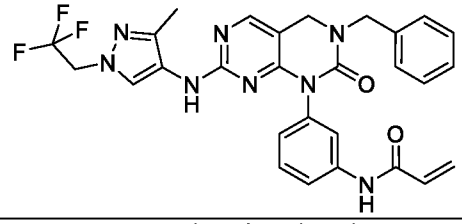
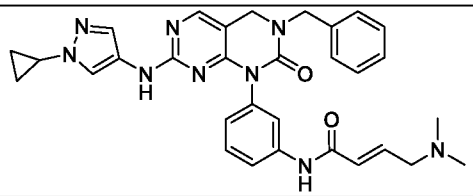
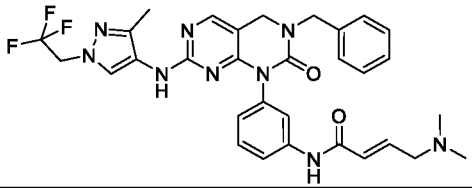
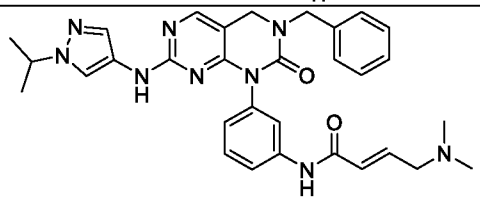
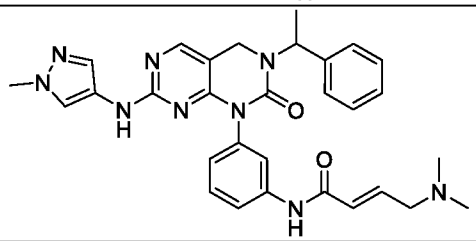
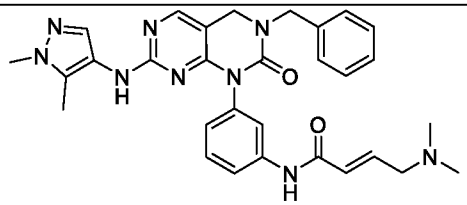
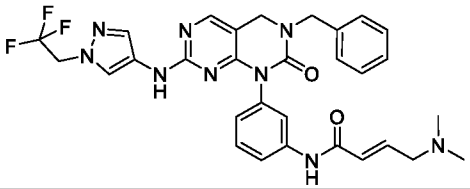
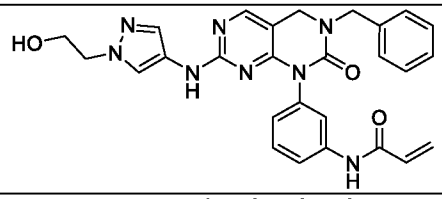
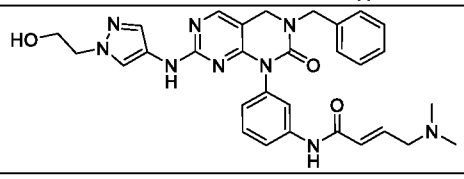
1. Seed cells at 5000 for A431 and 15,000 cells for Ba/F3 in 100µL /well in complete media (for A431: DMEM with 10%FBS and for Ba/F3 cells: RPMI with 10% FBS) in 96-well tissue culture plate. Leave outer wells without cells for background measurements. Incubate at 37 degree Celsius in 5% CO_2 humidified incubator for 16-18 hours.
2. Add 0.025 ml of 5X concentration compound dilution or DMSO control. Final compound concentration range is 10-0.0005 µM prepared in 3-fold serial dilutions. Incubate for 72 hr at 37 degree Celsius in 5% CO_2 humidified incubator.

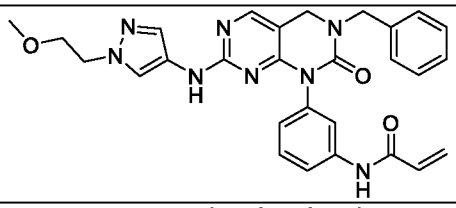
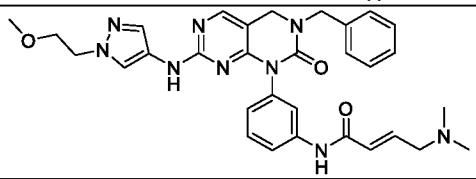
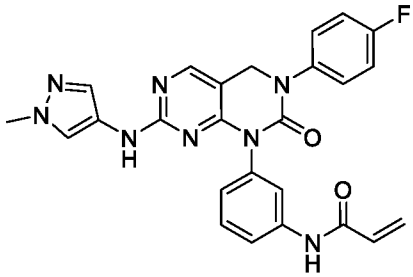
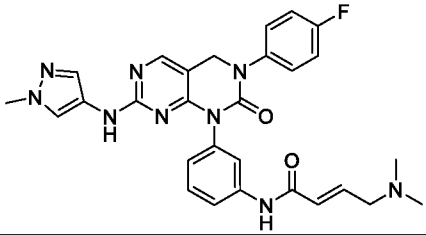
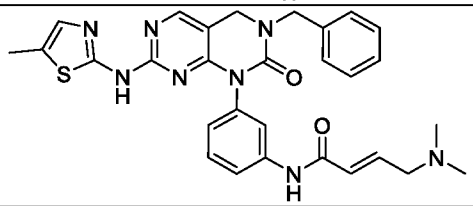
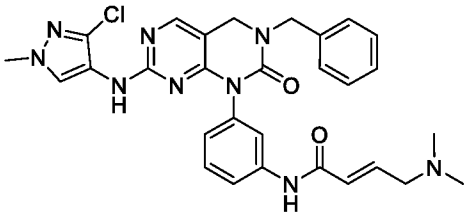
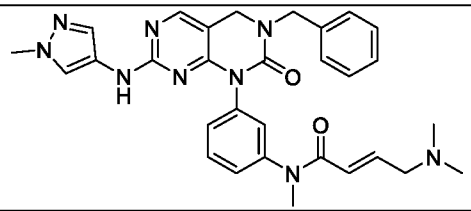
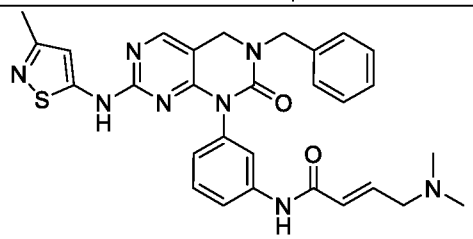
3. Add 0.0125 mL Alamar Blue™ reagent to each well with multi-channel pipette and tap gently on each side of the plate to mix. Incubate for 3 hours at 37 degree Celsius in 5% CO_2 humidified incubator.
4. Read plates on fluorescence reader (Tecan Spark Control, Device: Spark, Serial #: 1801006040) at 540 nm excitation, 590 nm emission wavelength.
5. Data analysis was performed using XLfit 5.5.0.5.

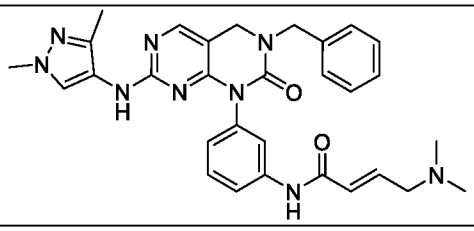
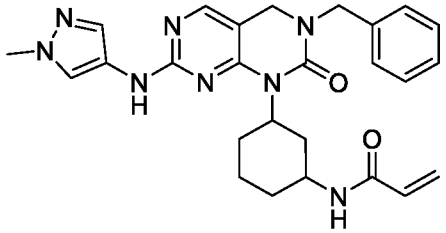
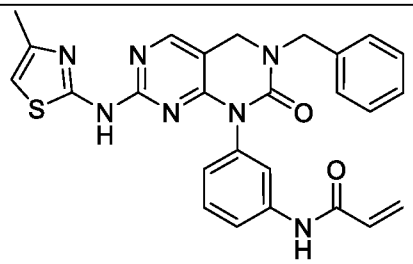
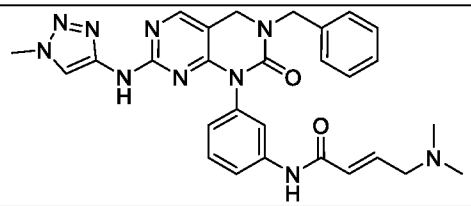
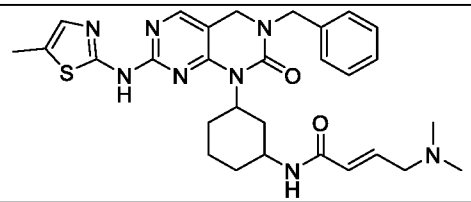
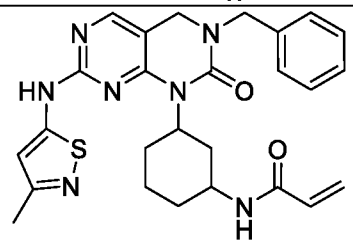
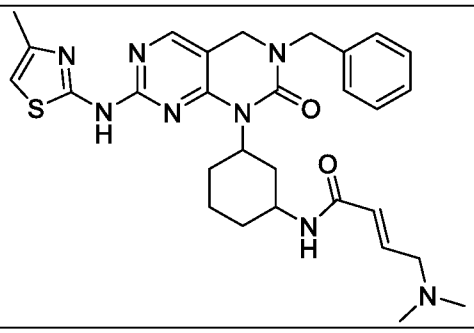
[0334] Table 2 shows the activity of compounds of this invention in the EGFR cellular proliferation assays.

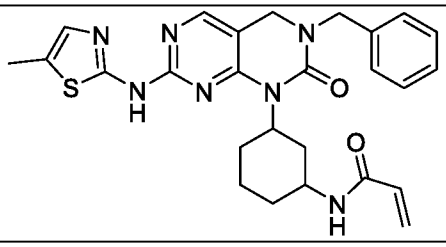
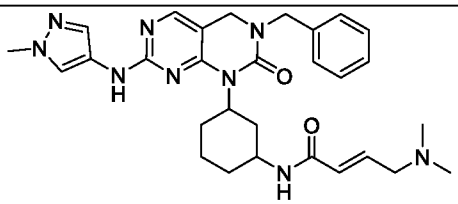
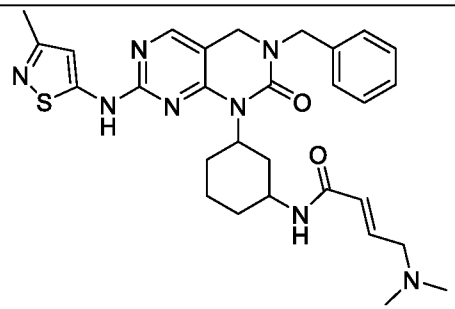
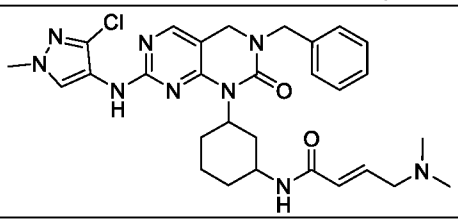
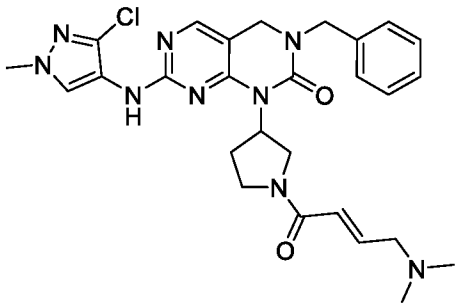
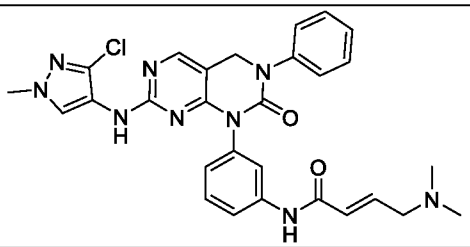
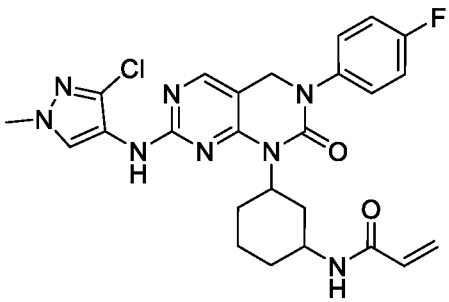
Table 2: Cellular proliferation data.

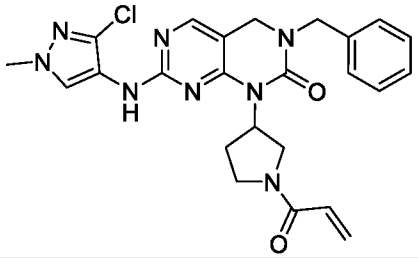
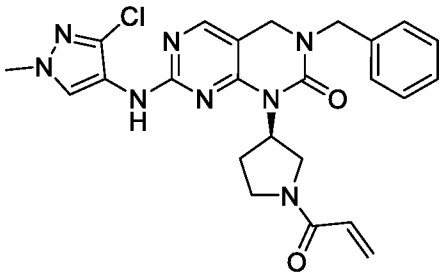
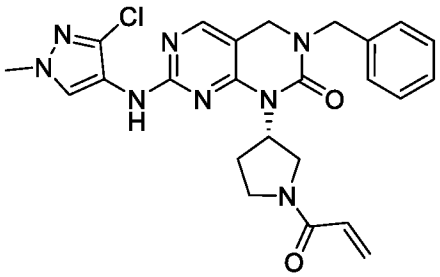
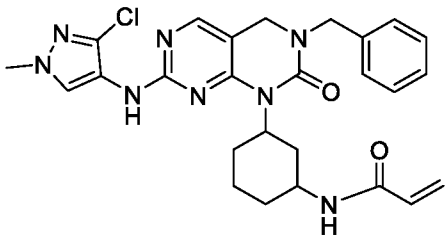
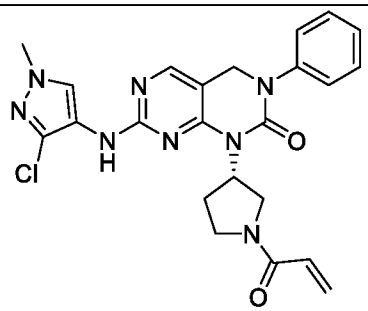
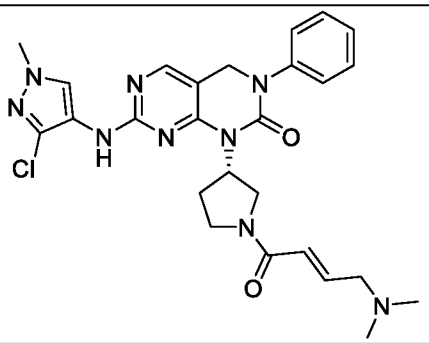
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
1		65	14	4
2		615	414	893
3		676	184	131
4		78	57	40
5		ND	ND	ND

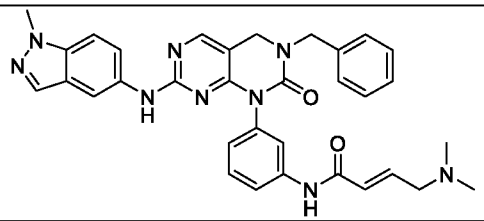
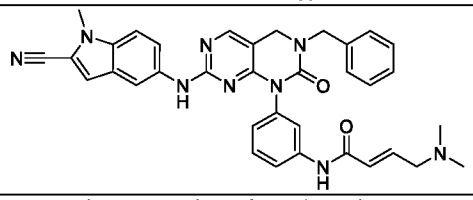
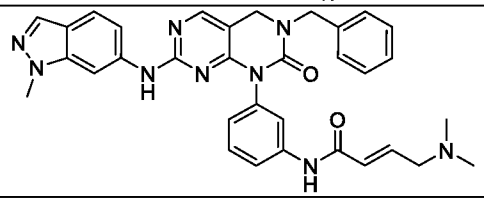
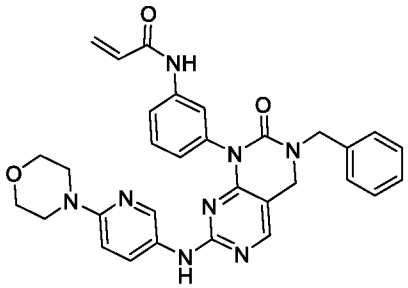
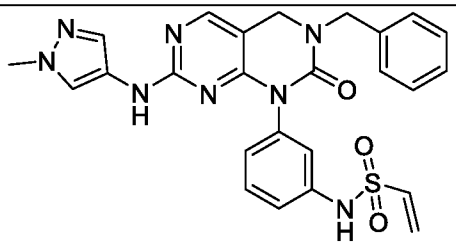
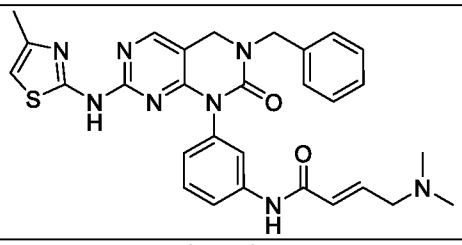
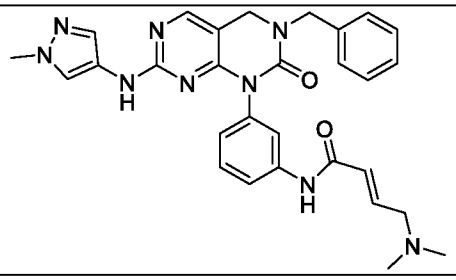
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
6		1890	9	9
7		ND	ND	ND
8		580	103	108
9		6870	103	114
10		638	105	108
11		1712	1154	2433
12		1243	106	134
13		59	45	42
14		6085	2568	2920

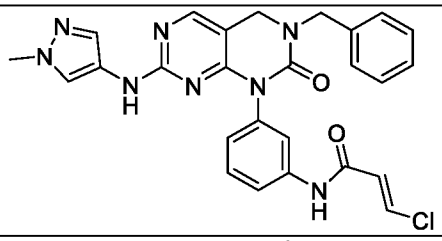
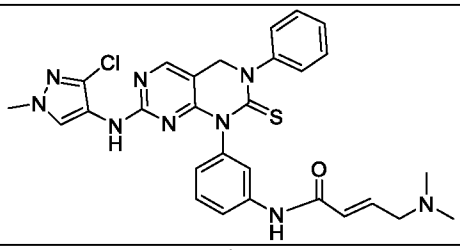
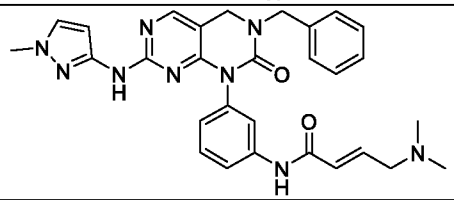
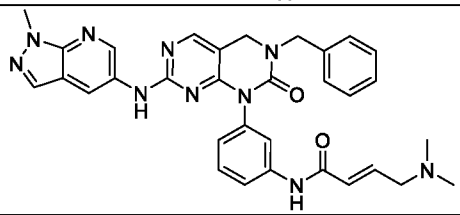
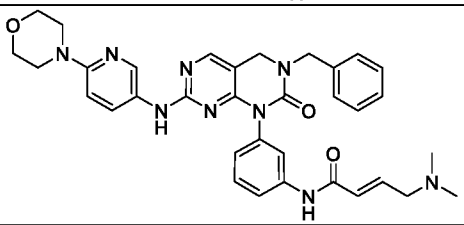
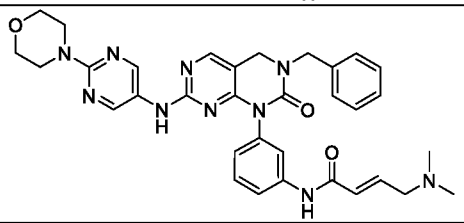
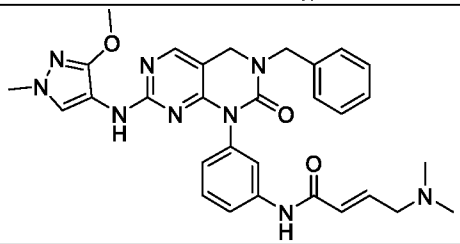
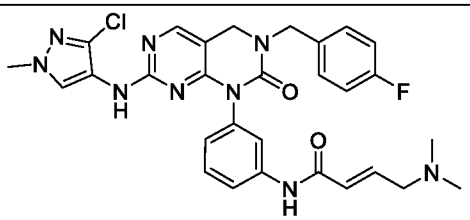
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
15		77	10	6
16		371	1168	2314
17		ND	ND	ND
18		332	421	1102
19		ND	ND	ND
20		595	34	35
21		2077	2814	3351
22		46	121	278

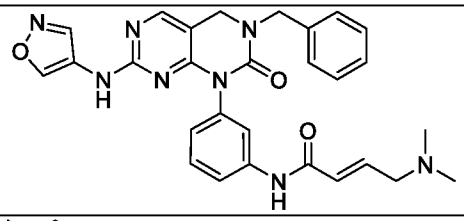
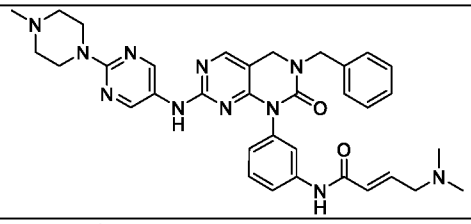
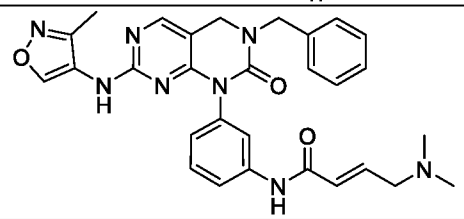
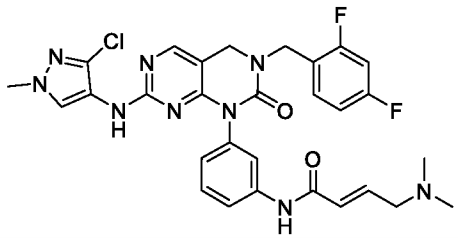
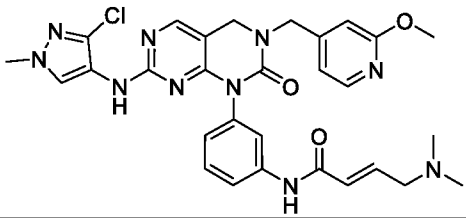
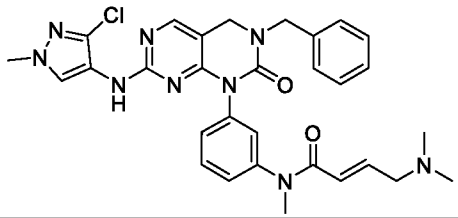
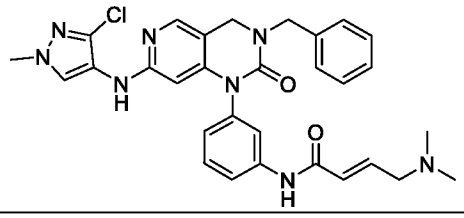
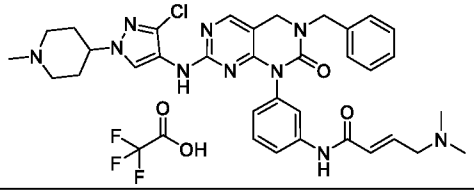
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
23		18	124	299
24		8336	356	340
25		83	320	69
26		3083	3326	3691
27		4403	9192	10000
28		150	417	149
29		4089	2600	431

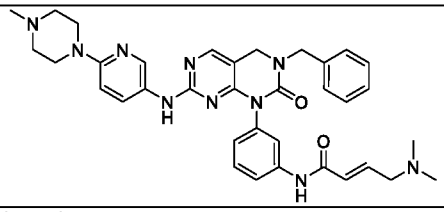
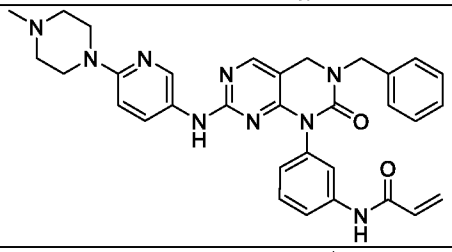
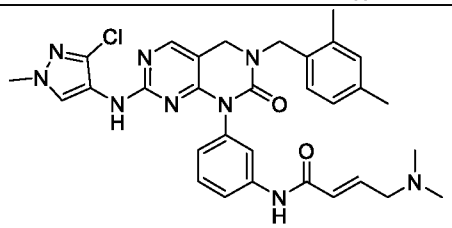
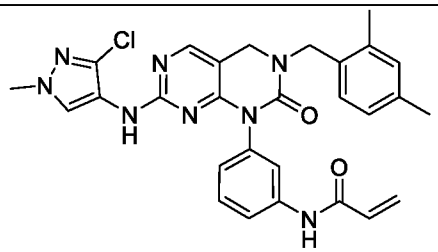
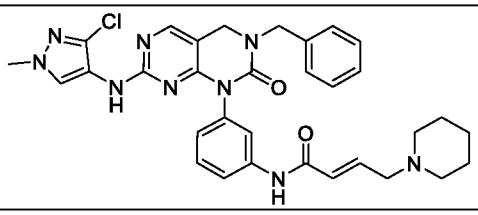
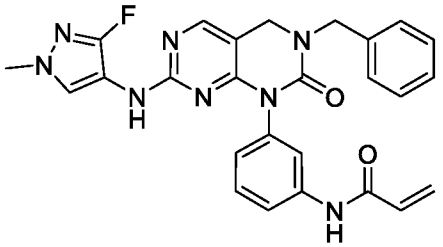
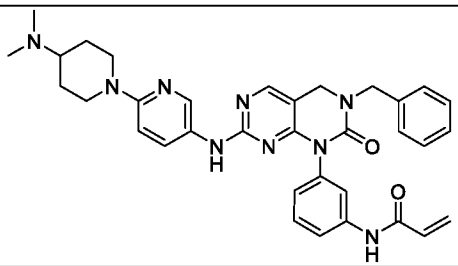
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
30		920	2805	2568
31		1974	3319	3480
32		1373	2906	2879
33		10000	4077	3876
34		ND	ND	ND
35		2166	12	55
36		10000	3923	10000

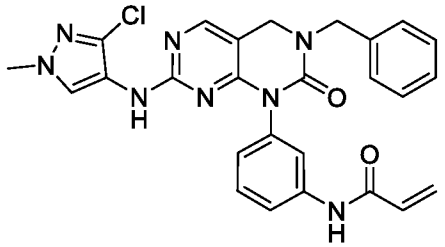
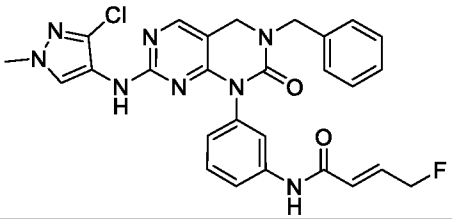
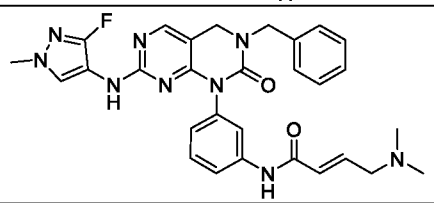
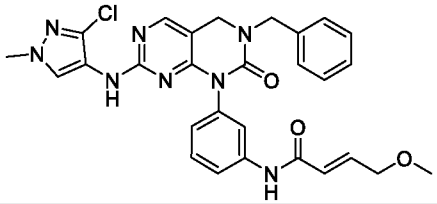
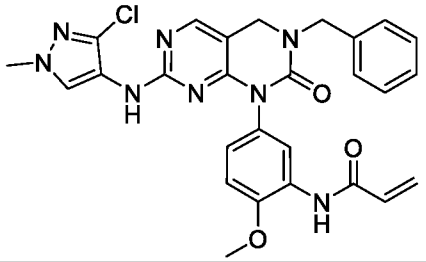
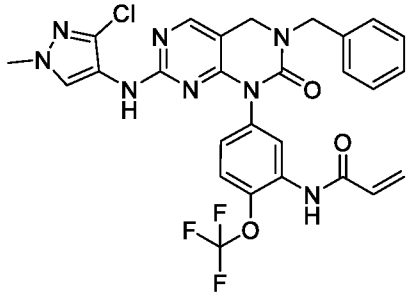
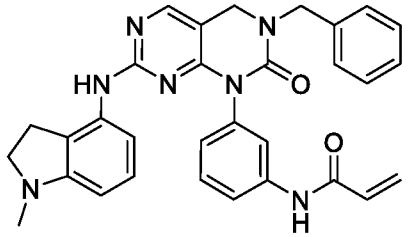
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
37		10000	10000	10000
38		7493	10000	10000
39		10000	10000	9346
40		10000	1697	1868
41		10000	504	759
42		10000	10000	10000

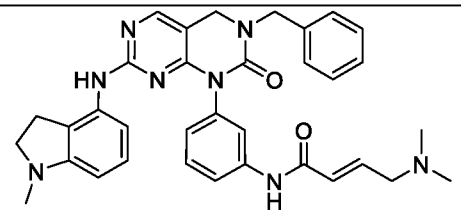
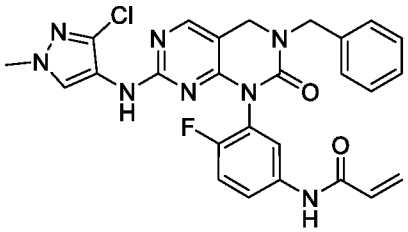
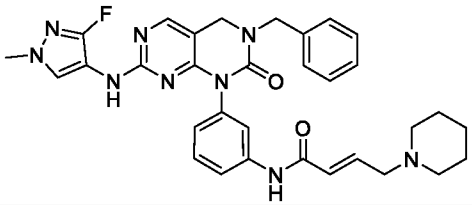
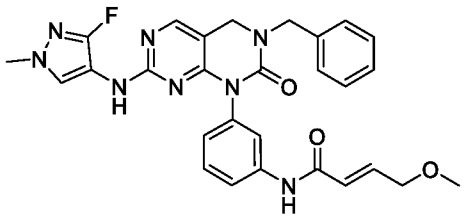
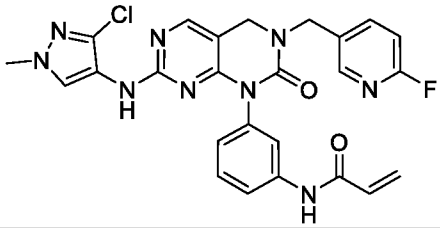
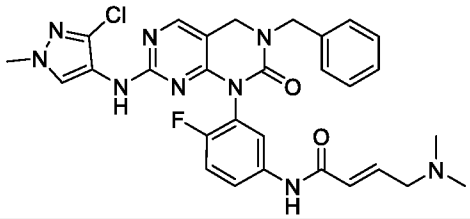
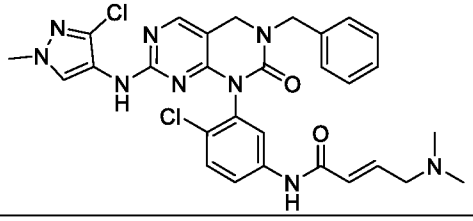
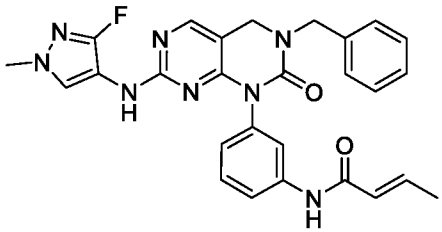
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
43		632	103	108
44		56	123	106
45		1129	352	350
46		1696	14	16
47		10000	2264	10000
48		148	456	361
49		10000	351	476

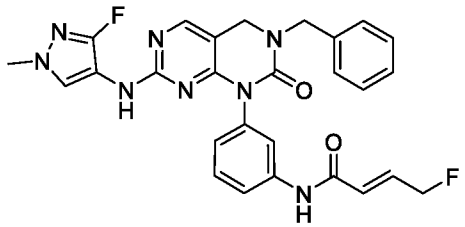
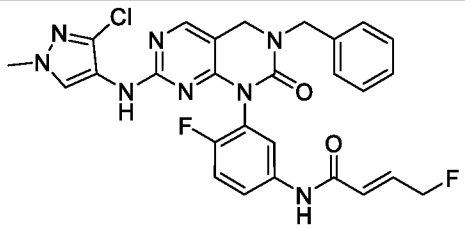
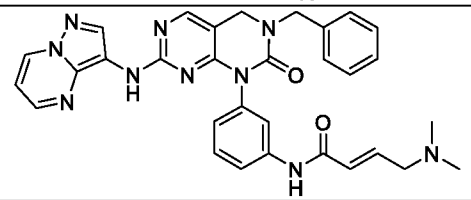
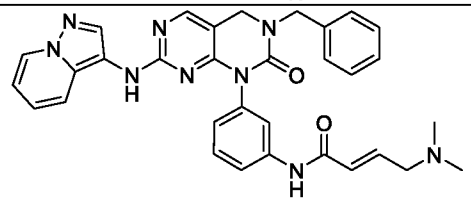
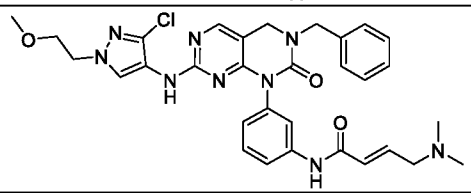
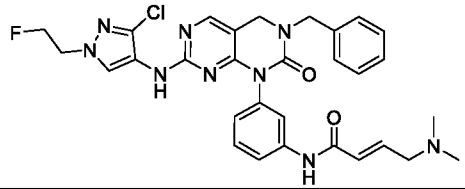
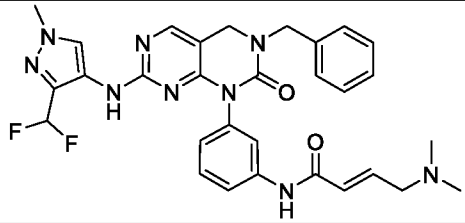
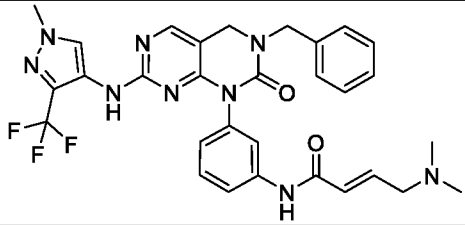
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
50		5383	1353	8722
51		ND	ND	ND
52		10000	244	341
53		10000	474	1052
54		10000	224	337
55		10000	1672	3856
56		10000	65	107
57		10000	115	476

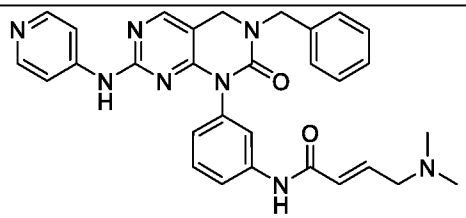
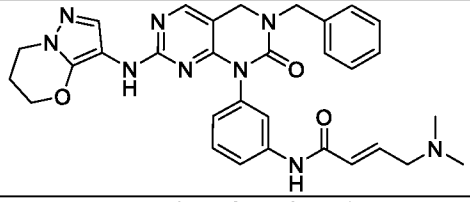
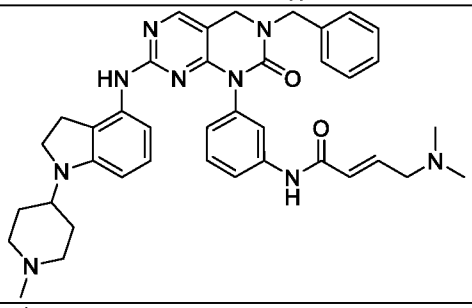
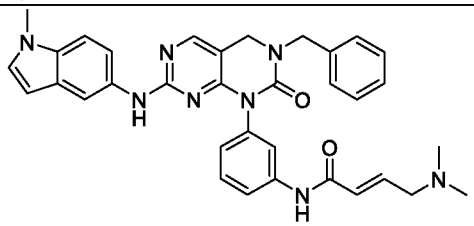
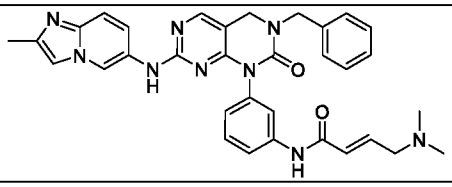
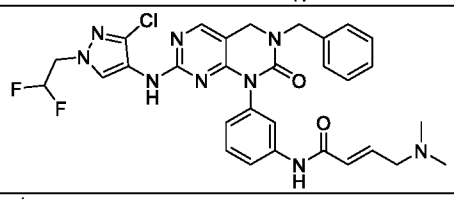
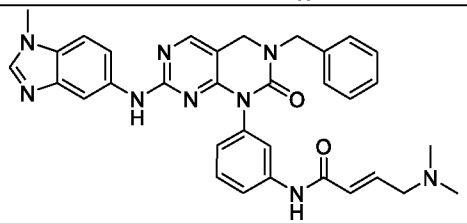
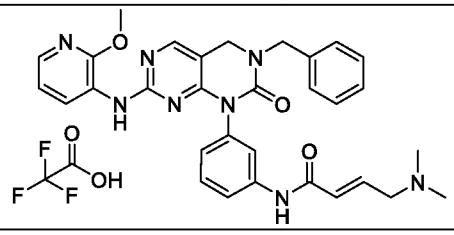
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
58		10000	801	2111
59		10000	8665	10000
60		10000	1698	2394
61		10000	58	105
62		10000	2255	5476
63		10000	532	1461
64		10000	809	1030
65		10000	964	1091

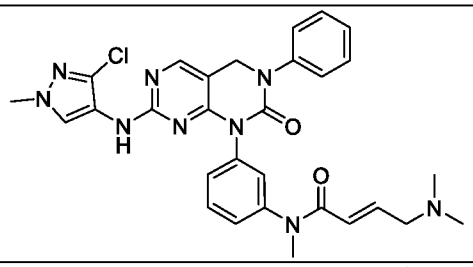
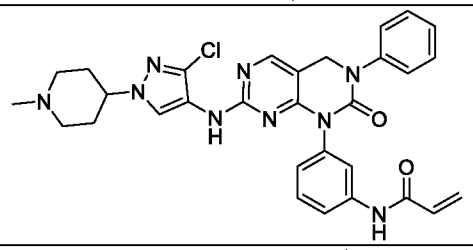
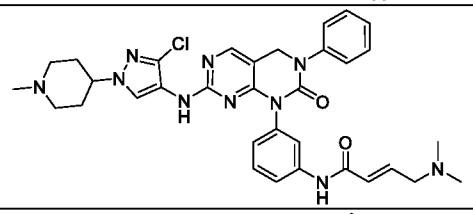
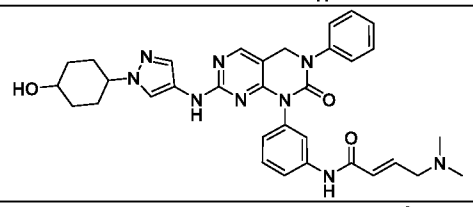
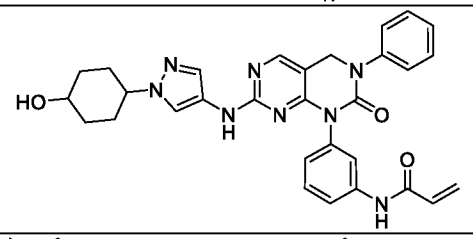
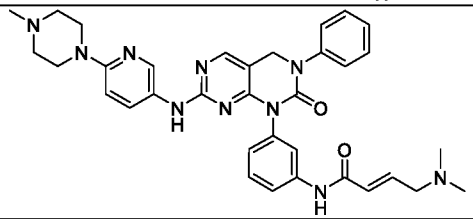
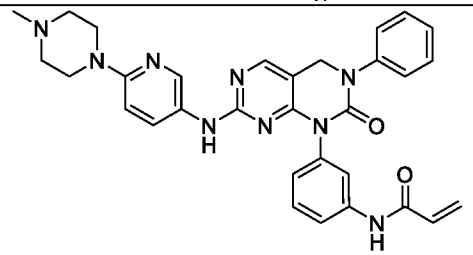
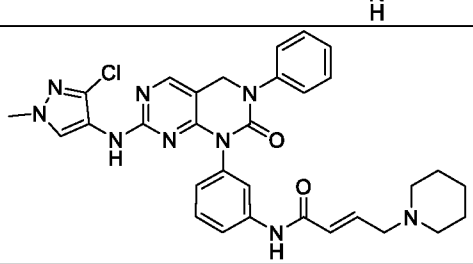
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
66		10000	3276	3186
67		10000	41	84
68		6024	356	798
69		10000	333	349
70		10000	42	72
71		10000	22	21
72		10000	100	296

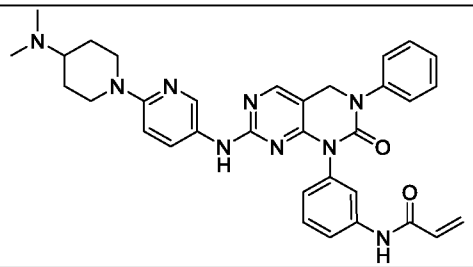
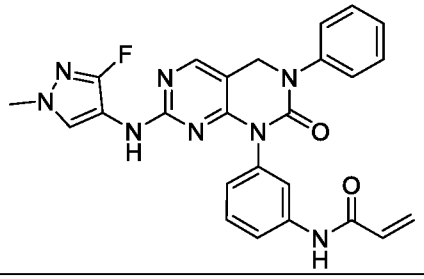
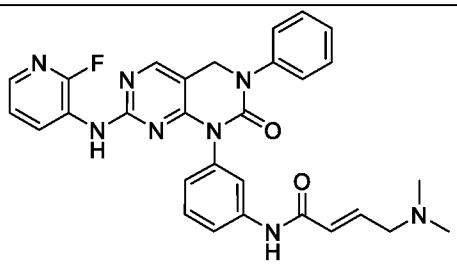
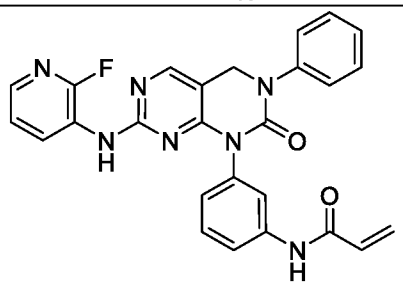
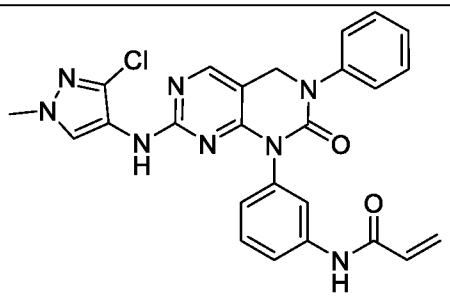
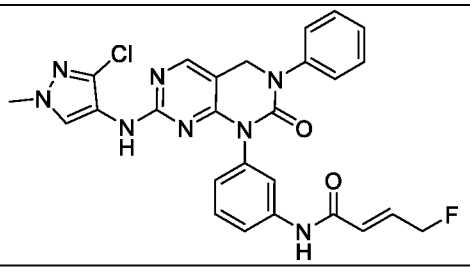
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
73		10000	4	20
74		10000	11	25
75		10000	394	980
76		10000	336	342
77		10000	10000	9132
78		4178	8367	8779
79		10000	89	107

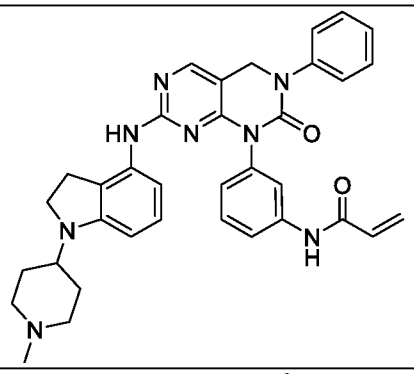
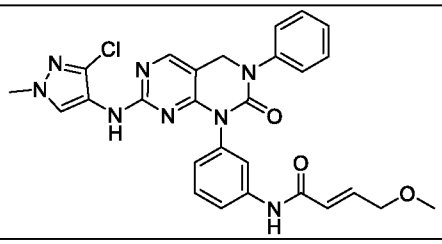
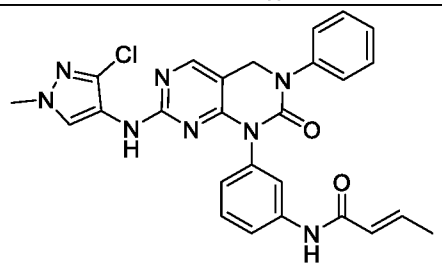
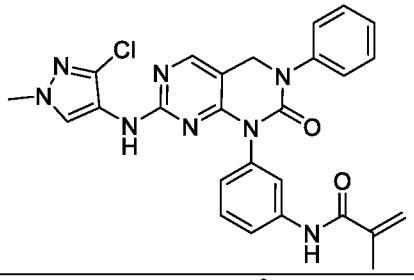
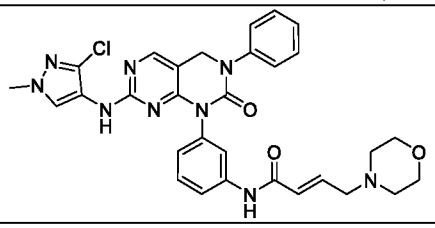
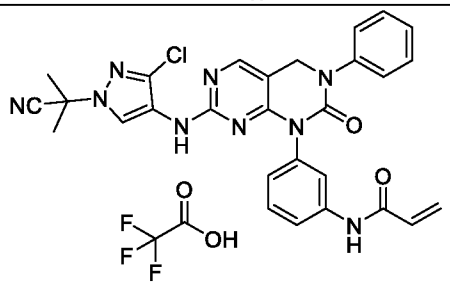
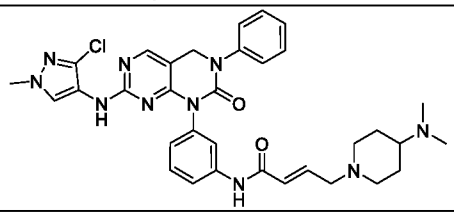
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
80		10000	343	806
81		10000	27	35
82		10000	123	280
83		10000	1013	992
84		>10000	347	374
85		1276	94	123
86		5441	694	900
87		>10000	2243	1978

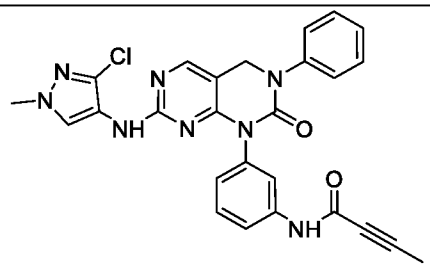
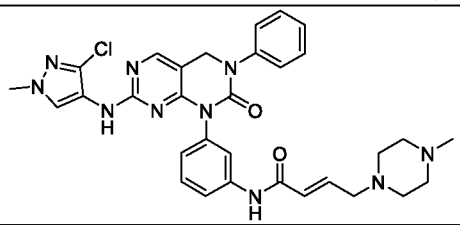
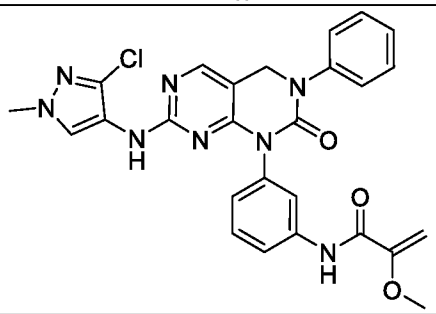
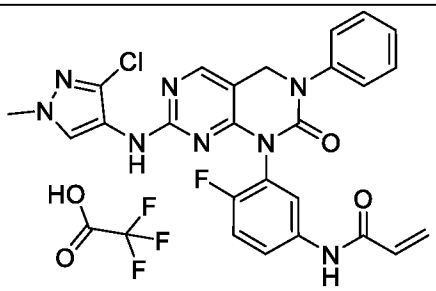
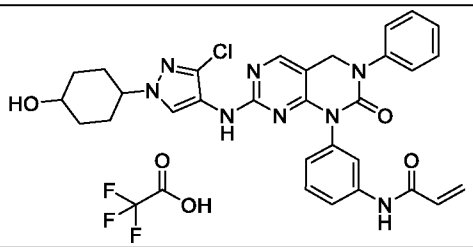
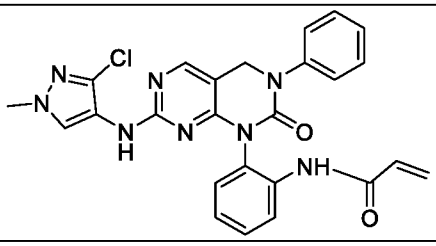
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
88		>10000	22	40
89		ND	ND	ND
90		10000	1148	1852
91		10000	329	645
92		10000	385	228
93		10000	108	91
94		10000	39	43
95		6500	106	97

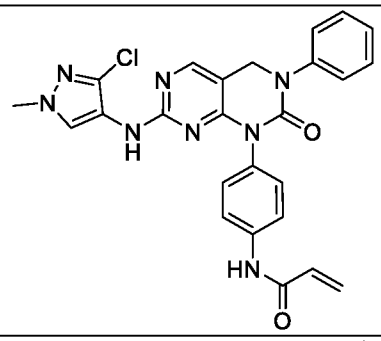
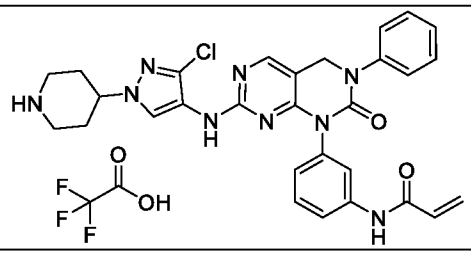
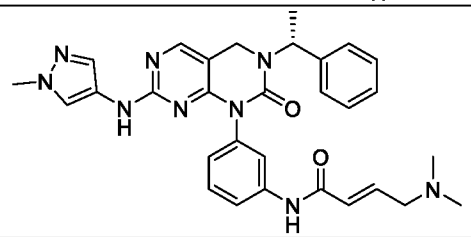
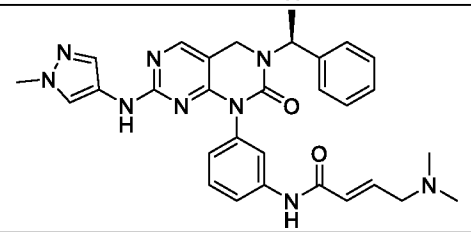
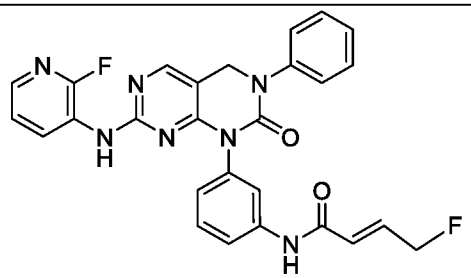
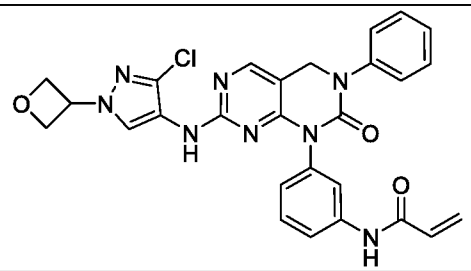
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
96		10000	>9351	4074
97		10000	2634	2542
98		10000	322	138
99		10000	115	145
100		10000	2972	4811
101		10000	100	176
102		10000	694	929
103		10000	269	224

Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
104		10000	255	885
105		3597	12	14
106		8927	926	1115
107		10000	10000	10000
108		10000	912	634
109		10000	2320	6027
110		3636	43	102
111		10000	39	128

Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
112		10000	229	295
113		10000	4	17
114		10000	164	1088
115		10000	8	28
116		10000	1	7
117		10000	35	50

Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
118		10000	32	110
119		10000	98	140
120		10000	107	183
121		10000	8596	10000
122		10000	101	284
123		10000	176	300
124		10000	2760	4977

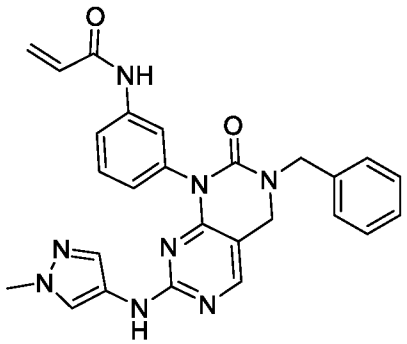
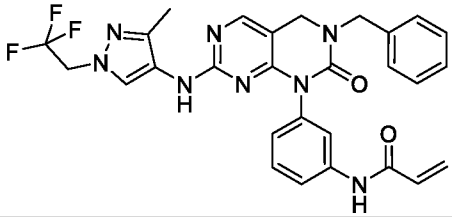
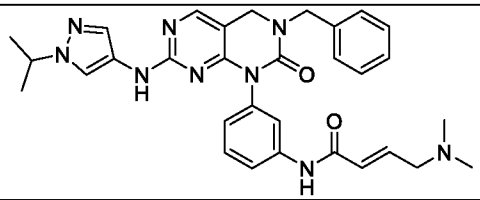
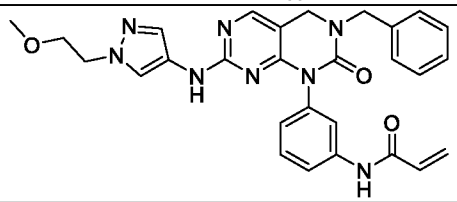
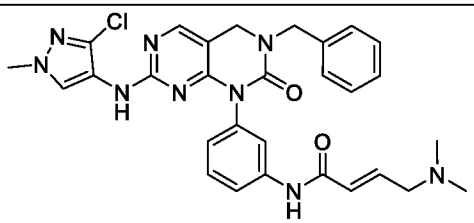
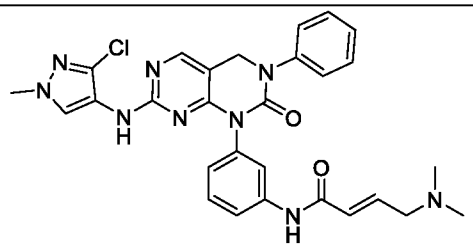
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
125		10000	269	338
126		10000	1086	2289
127		8170	10000	10000
128		10000	11	12
129		10000	157	333
130		10000	10000	9260

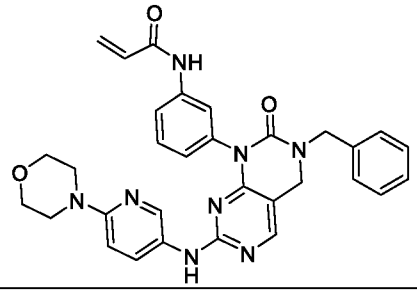
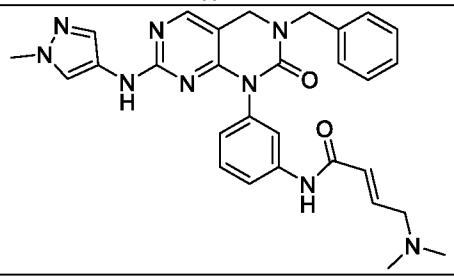
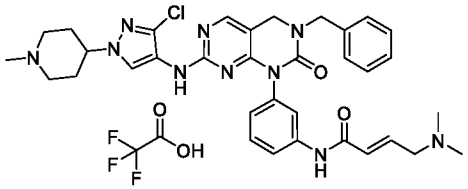
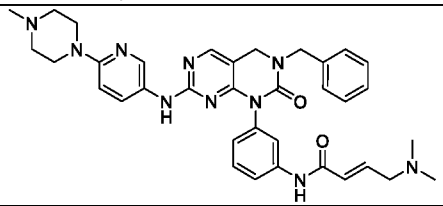
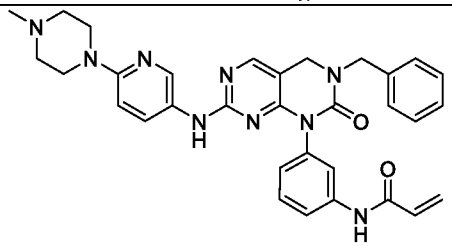
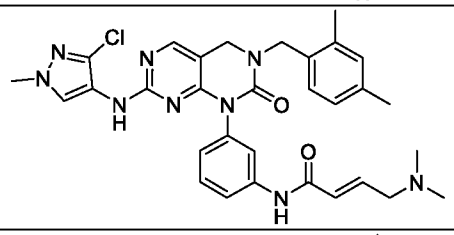
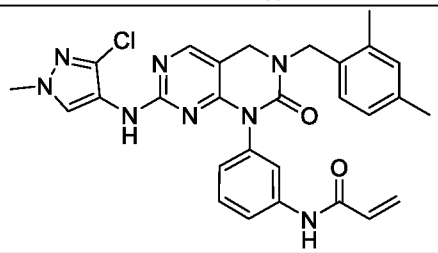
Cmpd No.	Structure	A431 IC_{50} (nM)	A767 IC_{50} (nM)	D770 IC_{50} (nM)
131		3511	373	765
132		10000	960	973
133 (Isomer 1)		10000	1124	2694
134 (Isomer 2)		10000	109	103
135		>10000	43	120
136		>10000	15	29

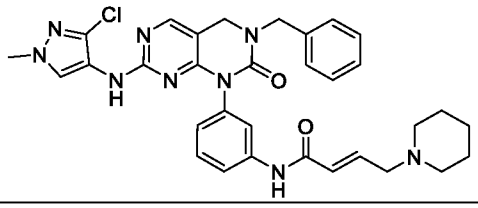
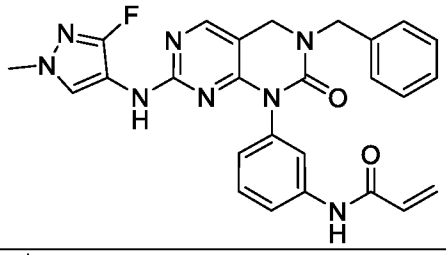
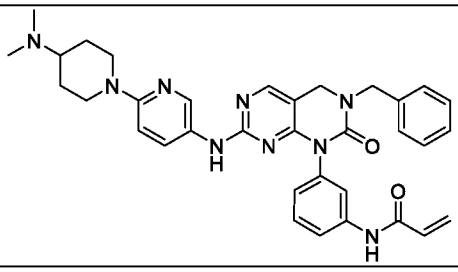
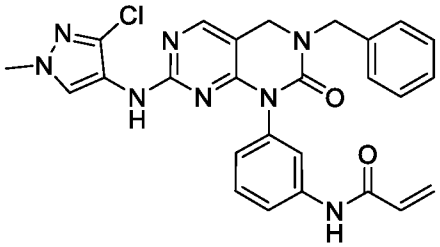
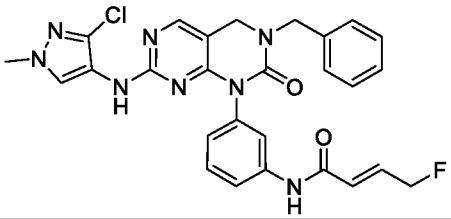
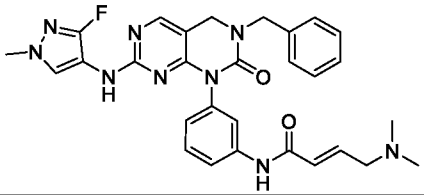
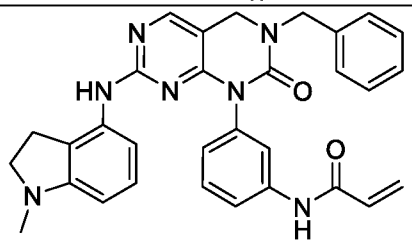
ND: Not determined

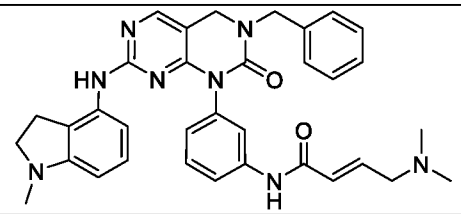
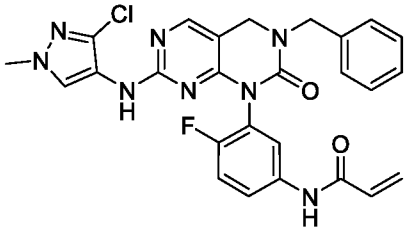
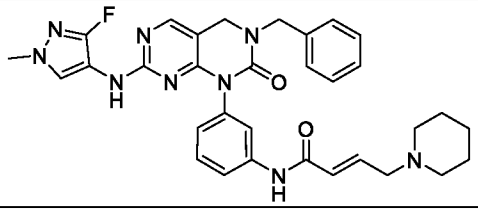
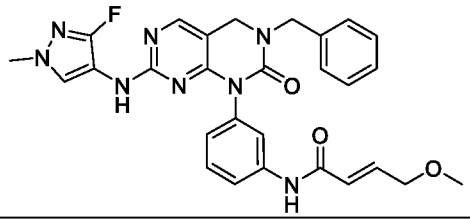
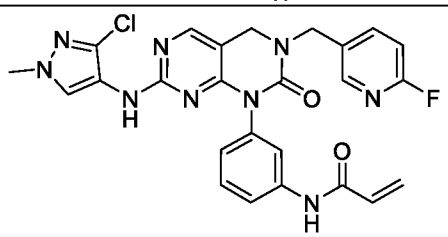
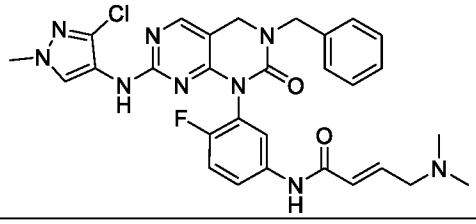
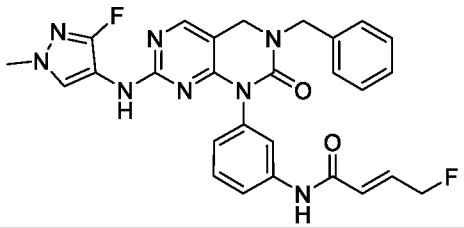
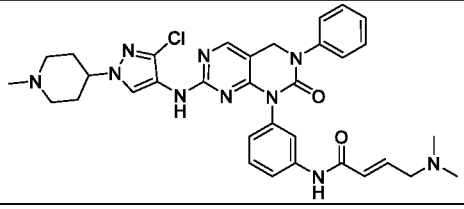
[0335] Table 3 shows the activity of compounds of this invention in the HER2 cellular proliferation assays.

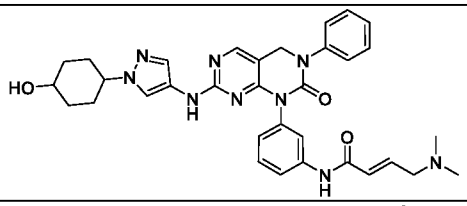
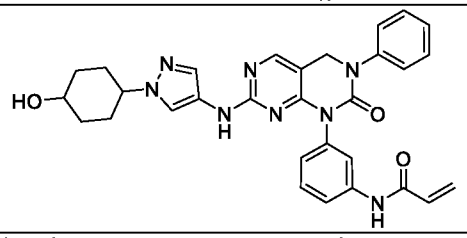
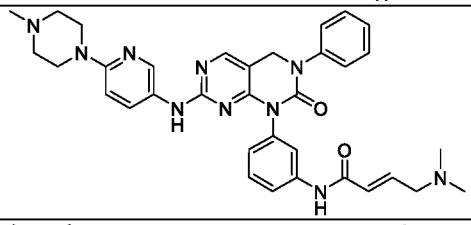
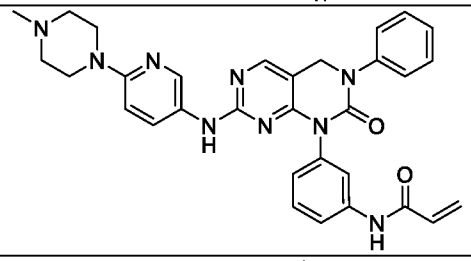
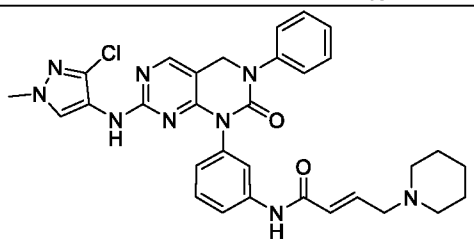
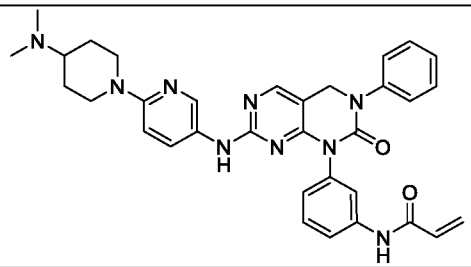
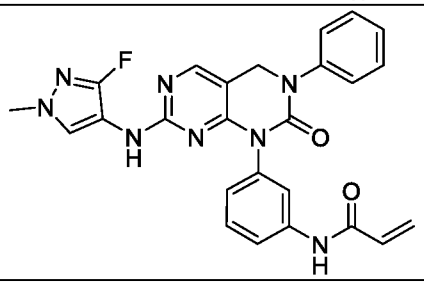
Table 3: Cellular proliferation data.

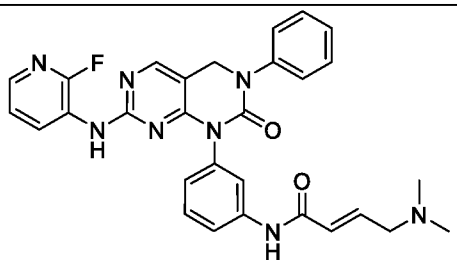
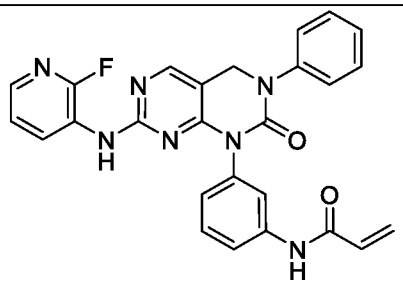
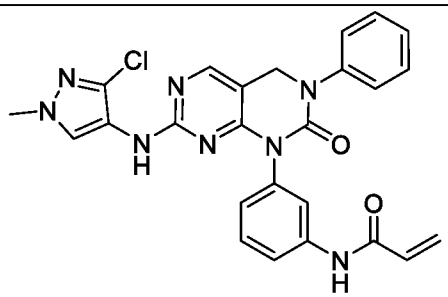
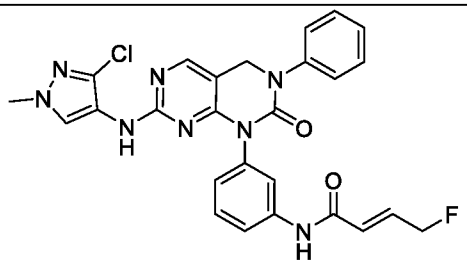
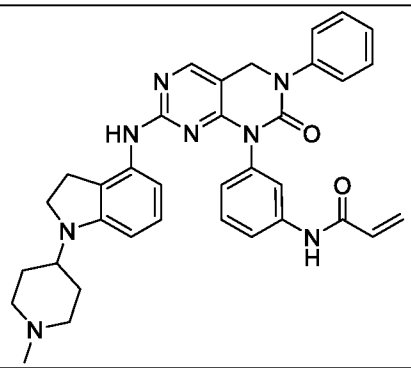
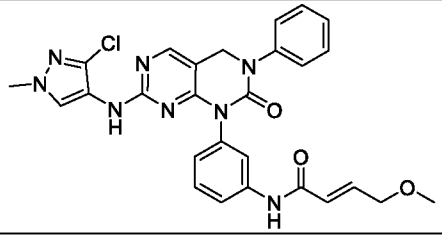
Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
1		9.9	7.7	<0.5
6		11	ND	ND
9		38	ND	ND
15		23	ND	ND
20		14.9	4.1	0.7
35		154	ND	ND

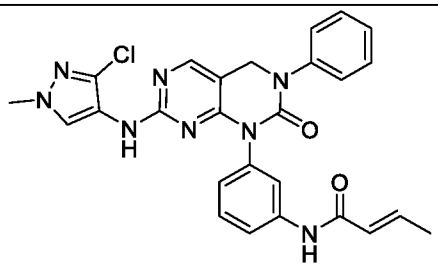
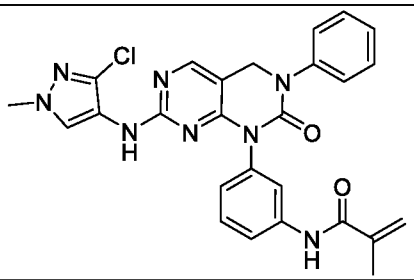
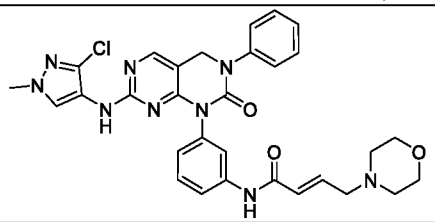
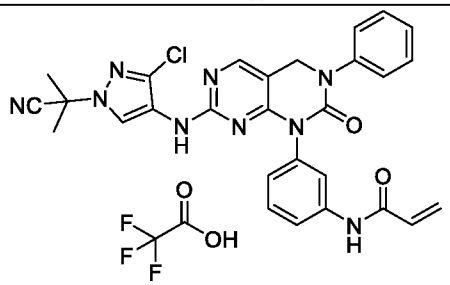
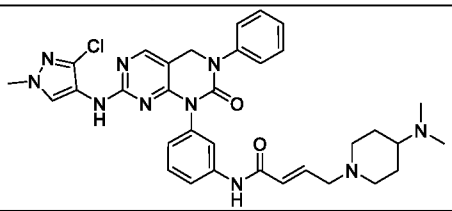
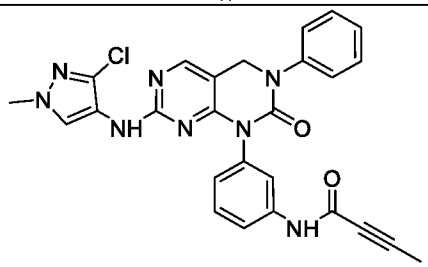
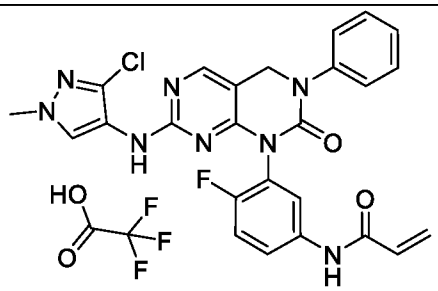
Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
46		67	ND	ND
49		178	ND	ND
65		732	ND	ND
66		1764	ND	ND
67		90	ND	ND
68		632	ND	ND
69		682	ND	ND

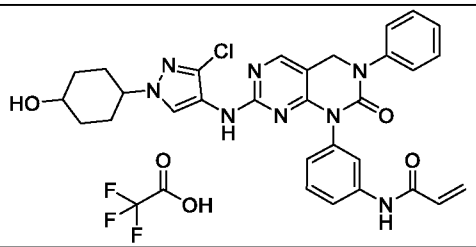
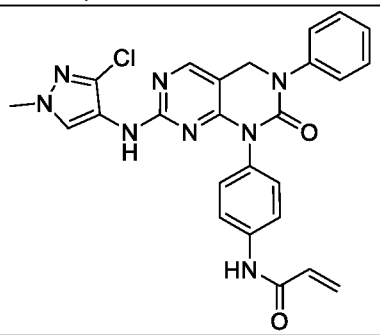
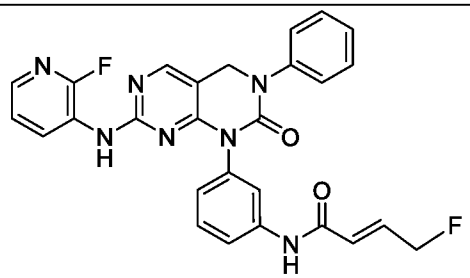
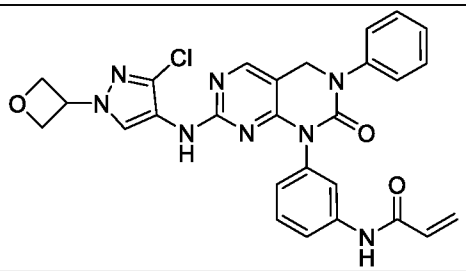
Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
70		38	ND	ND
71		137	ND	ND
72		575	ND	ND
73		49	ND	ND
74		80	ND	ND
75		125	ND	ND
79		338	ND	ND

Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
80		296	ND	ND
81		13	ND	ND
82		40	ND	ND
83		740	ND	ND
84		452	ND	ND
85		38	ND	ND
88		101	ND	ND
106		995	ND	ND

Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
107		10000	ND	ND
108		2021	ND	ND
109		3298	ND	ND
110		103	ND	ND
111		64	ND	ND
112		354	ND	ND
113		68	ND	ND

Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
114		1151	ND	ND
115		188	ND	ND
116		24	ND	ND
117		75	ND	ND
118		103	ND	ND
119		144	ND	ND

Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
120		158	ND	ND
121		883	ND	ND
122		132	ND	ND
123		319	ND	ND
124		1485	ND	ND
125		445	ND	ND
128		24	ND	ND

Cmpd No.	Structure	YVMA IC_{50} (nM)	BT-474 IC_{50} (nM)	HER2 WT Ba/F3 IC_{50} (nM)
129		312	ND	ND
131		1131	ND	ND
135		294	ND	ND
136		63	ND	ND

ND: Not determined

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula I:

Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

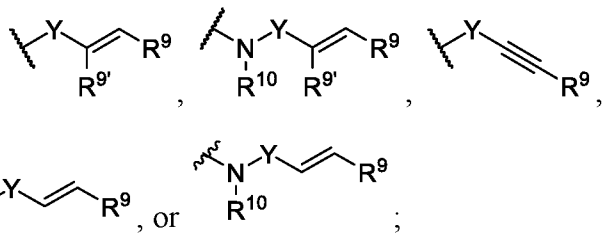
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, heteroaryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  ;

Y is $–C(=O)–$, $–S(=O)–$, or $–S(=O)_2–$;

R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, haloalkyl, cycloalkyl, heteroalkyl, or (alkyl)heterocycloalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{11})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

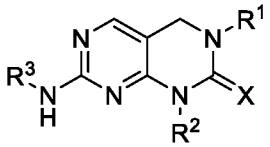
each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $–N(R^{13})_2$, $–S(=O)_2NH_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^{15})_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

2. A compound of Formula I:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

X is O or S;

R^1 is $–(C(R^4)_2)_nR^5$, wherein R^5 is substituted with 0, 1, or 2 $R^{5'}$;

n is 0, 1, 2, or 3;

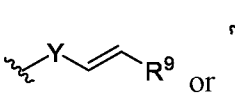
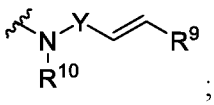
each R^4 is independently hydrogen, alkyl, halo, haloalkyl, hydroxy, alkoxy, or heteroalkyl;

R^5 is aryl or C-linked heteroaryl;

each $R^{5'}$ is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $–N(R^6)_2$, $–S(=O)_2$alkyl, $–S(=O)_2$aryl, $–S(=O)_2$heteroaryl, or alkoxy;

each R^6 is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^2 is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl, wherein the aryl, cycloalkyl, or heterocycloalkyl is substituted with at least one R^7 and 0, 1, or 2 R^8;

each R^7 is independently  or  ;

Y is –C(=O)–, –S(=O)–, or $–S(=O)_2–$;

R^9 is hydrogen, halo, alkyl, cycloalkyl, or heteroalkyl;

R^{10} is hydrogen, alkyl, haloalkyl, or cycloalkyl;

each R^8 is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy;

each R^{11} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

R^3 is heteroaryl substituted with 0, 1, 2, or 3 R^{12};

each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, alkoxy, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or cycloalkyl, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl are each independently substituted with 0, 1, or 2 R^{14};

each R^{13} is independently alkyl, cycloalkyl, aryl, or heteroaryl;

each R^{14} is independently aryl, heteroaryl, alkyl, cycloalkyl, heterocycloalkyl, halo, heteroalkyl, haloalkyl, cyano, hydroxy, amino, $-N(R^{15})_2$, $-S(=O)_2$alkyl, $-S(=O)_2$aryl, $-S(=O)_2$heteroaryl, or alkoxy; and

each R^{15} is independently alkyl, cycloalkyl, aryl, or heteroaryl.

3. The compound of claim 1 or claim 2, wherein n is 0 or 1.

4. The compound of any one of claims 1 to 3, wherein R^5 is phenyl, naphthyl, anthracenyl, phenanthrenyl, C-linked pyridyl, C-linked pyrimidinyl, C-linked pyrazolyl, or C-linked imidazolyl.

5. The compound of any one of claims 1 to 4, wherein R^5 is unsubstituted.

6. The compound of any one of claims 1 to 4, wherein R^5 is substituted with 1 or 2 $R^{5'}$.

7. The compound of any one of claims 1 to 6, wherein each R^4 is independently hydrogen, alkyl, halo, haloalkyl, or alkoxy.

8. The compound of any one of claims 1 to 7, wherein each R^4 is independently hydrogen, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, trifluoromethyl, trifluoroethyl, pentafluoroethyl, methoxy, ethoxy, or trifluoromethoxy.

9. The compound of any one of claims 1 to 8, wherein each R^4 is independently hydrogen, methyl, fluoro, trifluoromethyl, methoxy, or trifluoromethoxy.

10. The compound of any one of claims 1 to 4 or 6 to 9, wherein each $R^{5'}$ is independently aryl, heteroaryl, alkyl, heterocycloalkyl, halo, cyano, hydroxy, $-N(R^6)_2$, or alkoxy.

11. The compound of any one of claims 1 to 4 or 6 to 10, wherein each $R^{5'}$ is independently phenyl, pyrrolyl, imidazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, methyl, ethyl, *tert*-butyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, fluoro, chloro, cyano, hydroxy, $-N(R^6)_2$, methoxy, ethoxy, or trifluoromethoxy.

12. The compound of any one of claims 1 to 4 or 6 to 11, wherein each $R^{5'}$ is independently phenyl, imidazolyl, pyridinyl, methyl, *tert*-butyl, pyrrolidinyl, morpholinyl, fluoro, cyano, hydroxy, $-N(R^6)_2$, or methoxy.

13. The compound of any one of claims 1 to 4 or 6 to 12, wherein each R^6 is independently alkyl or aryl.

14. The compound of any one of claims 1 to 4 or 6 to 13, wherein each R^6 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl.

15. The compound of any one of claims 1 to 4 or 6 to 14, wherein each R^6 is independently methyl or phenyl.

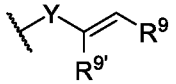
16. The compound of any one of claims 1 to 15, wherein X is S.

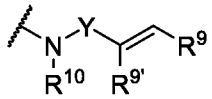
17. The compound of any one of claims 1 to 15, wherein X is O.

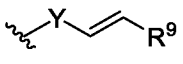
18. The compound of any one of claims 1 to 17, wherein R^2 is monocyclic.

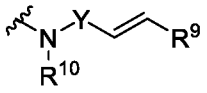
19. The compound of any one of claims 1 to 18, wherein R^2 is phenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, or triazinyl.

20. The compound of any one of claims 1 to 19, wherein R^2 is phenyl, cyclohexyl, or pyrrolyl.

21. The compound of any one of claims 1 or 3 to 20, wherein R^7 is  .

22. The compound of any one of claims 1 or 3 to 20, wherein R^7 is  .

23. The compound of any one of claims 1 to 20, wherein R^7 is  .

24. The compound of any one of claims 1 to 20, wherein R^7 is  .

25. The compound of any one of claims 1 to 24, wherein Y is –C(=O)–.

26. The compound of any one of claims 1 to 24, wherein Y is $–S(=O)_2–$.

27. The compound of any one of claims 1 or 3 to 26, wherein R^9 and $R^{9'}$ are independently hydrogen, halo, alkyl, heteroalkyl, haloalkyl, or (alkyl)heterocycloalkyl.

28. The compound of any one of claims 1 to 26, wherein R^9 is hydrogen, halo, or heteroalkyl.

29. The compound of any one of claims 1 or 3 to 27, wherein R^9 and $R^{9'}$ are independently hydrogen, fluoro, chloro, methyl, hydroxyethyl, methoxyethyl, methoxymethyl, dimethylaminomethyl, 1-piperidinylmethyl, 1-morpholinylmethyl, or fluoromethyl.

30. The compound of any one of claims 1 to 27, wherein R^9 is hydrogen, fluoro, chloro, hydroxyethyl, or methoxyethyl.

31. The compound of any one of claims 1 to 20, 22, or 24 to 29, wherein R^{10} is hydrogen, methyl, ethyl *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, trifluoromethyl, or cyclopropyl.

32. The compound of any one of claims 1 to 20, 22, or 24 to 31, wherein R^{10} is hydrogen or methyl.

33. The compound of any one of claims 1 to 32, wherein R^2 is substituted with 1 or 2 R^8.

34. The compound of any one of claims 1 to 33, wherein each R^8 is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, fluoro, chloro, heteroalkyl, cyano, hydroxy, amino, $-N(R^{11})_2$, methoxy, ethoxy, or trifluoromethoxy.

35. The compound of any one of claims 1 to 34, wherein each R^8 is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, fluoro, chloro, $-N(R^{11})_2$, hydroxyethyl, methoxyethyl, or cyano.

36. The compound of any one of claims 1 to 35, wherein each R^{11} is independently alkyl or aryl.

37. The compound of any one of claims 1 to 36, wherein each R^{11} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, phenyl, naphthyl, anthracenyl, or phenanthrenyl.

38. The compound of any one of claims 1 to 37, wherein each R^{11} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, phenyl, or naphthyl.

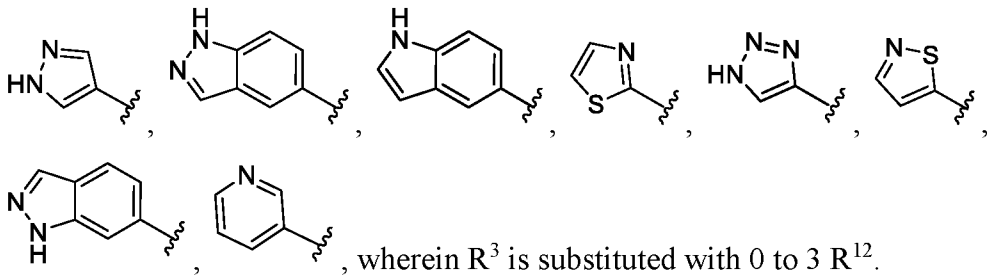
39. The compound of any one of claims 1 to 38, wherein each R^{11} is independently methyl or phenyl.

40. The compound of any one of claims 1 to 32, wherein R^2 is unsubstituted.

41. The compound of any one of claims 1 to 40, wherein R^3 is pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, indolyl, indazolyl, benzimidazolyl, azaindolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, or naphthyridinyl.

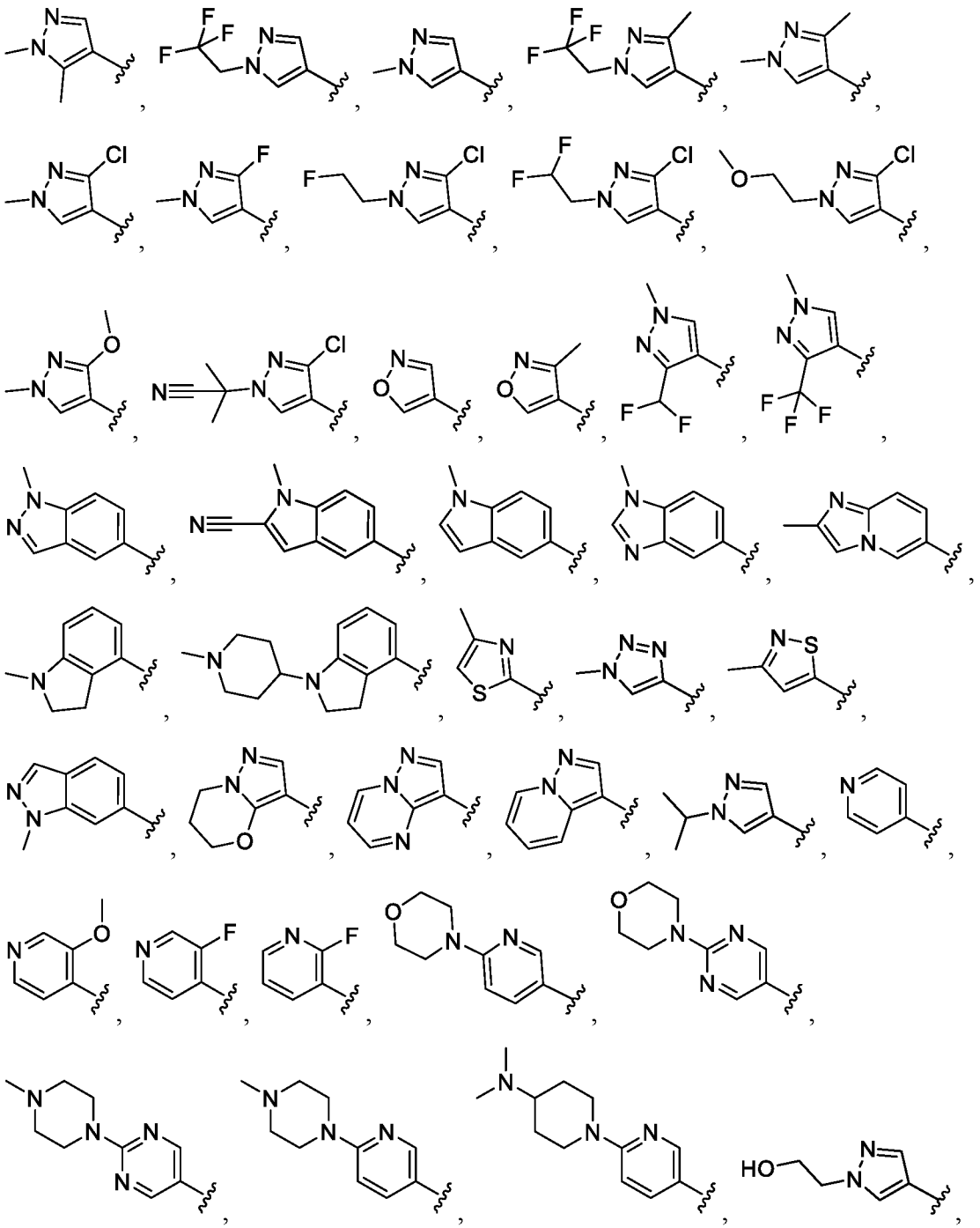
42. The compound of any one of claims 1 to 41, wherein R^3 is imidazolyl, triazolyl, indolyl, indazolyl, thiazolyl, isothiazolyl, or pyridinyl.

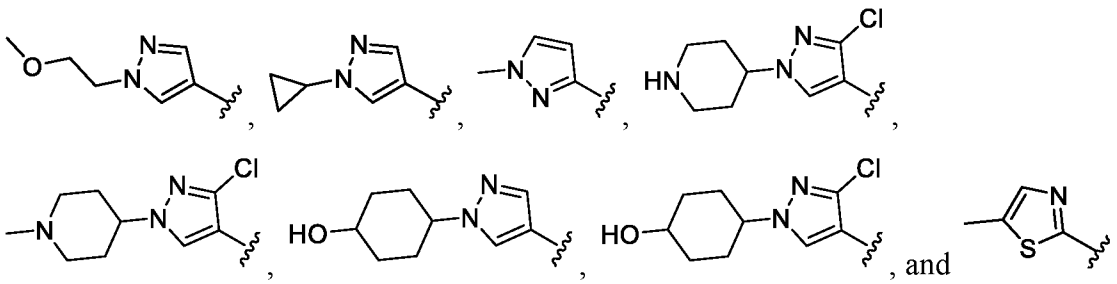
43. The compound of any one of claims 1 to 42, wherein R^3 is selected from:



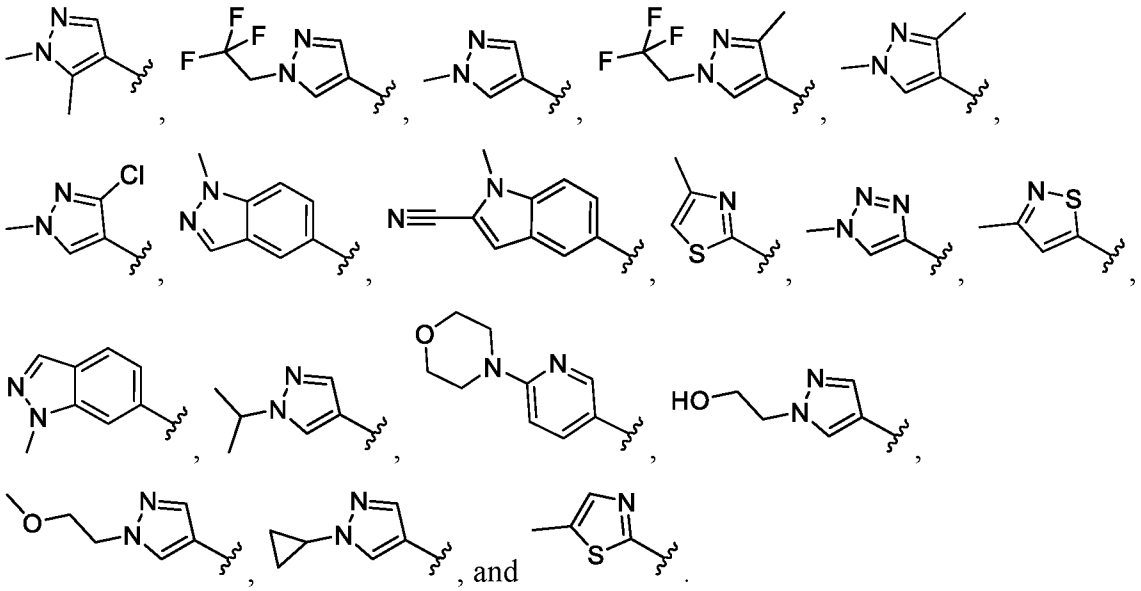
, wherein R^3 is substituted with 0 to 3 R^{12}.

44. The compound of any one of claims 1 to 40, wherein R^3 is selected from:





45. The compound of any one of claims 1 to 40 or 44, wherein R^3 is selected from:



46. The compound of any one of claims 1 to 43, wherein R^3 is unsubstituted.

47. The compound of any one of claims 1 to 43, wherein R^3 is substituted with at least 1 R^{12}.

48. The compound of any one of claims 1 to 43 or 47, wherein R^3 is substituted with at least 2 R^{12}.

49. The compound of any one of claims 1 to 43, 47, or 48, wherein each R^{12} is independently aryl, heteroaryl, alkyl, heteroalkyl, haloalkyl, halo, cyano, heterocycloalkyl, $-N(R^{13})_2$, $-S(=O)_2NH_2$, or cycloalkyl.

50. The compound of any one of claims 1 to 43 or 47 to 49, wherein each R^{12} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, pentafluoroethyl, fluoro, chloro, cyano, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl,

tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, $-N(R^{13})_2$, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

51. The compound of any one of claims 1 to 43 or 47 to 50, wherein each R^{12} is independently methyl, *iso*-propyl, *tert*-butyl, hydroxyethyl, methoxyethyl, trifluoromethyl, trifluoroethyl, chloro, cyano, morpholinyl, or cyclopropyl.

52. The compound of any one of claims 1 to 43 or 47 to 51, wherein each R^{12} is independently methyl, hydroxyethyl, methoxyethyl, trifluoroethyl, or chloro.

53. The compound of any one of claims 1 to 43 or 47 to 52, wherein each R^{12} is independently methyl or chloro.

54. The compound of any one of claims 1 to 43 or 47 to 50, wherein each R^{13} is independently alkyl or cycloalkyl.

55. The compound of any one of claims 1 to 43, 47 to 50, or 54, wherein each R^{13} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

56. The compound of any one of claims 1 to 43, 47 to 50, 54, or 55, wherein each R^{13} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, or cyclohexyl.

57. The compound of any one of claims 1 to 43, 47 to 50, or 54 to 56, wherein each R^{13} is independently methyl, cyclopropyl, or cyclohexyl.

58. The compound of any one of claims 1 to 49, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is unsubstituted.

59. The compound of any one of claims 1 to 49, wherein the aryl, heteroaryl, heterocycloalkyl, or cycloalkyl of R^{12} is substituted with 1 or 2 R^{14}.

60. The compound of any one of claims 1 to 49 or 59, wherein each R^{14} is independently alkyl, cycloalkyl, heterocycloalkyl, halo, cyano, $-N(R^{15})_2$, or alkoxy.

61. The compound of any one of claims 1 to 49, 59, or 60, wherein each R^{14} is independently methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, azetidinyl, oxetanyl, pyrrolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, piperazinyl, tetrahydropyranyl, morpholinyl, fluoro, chloro, cyano, $-N(R^{15})_2$, methoxy, ethoxy, or trifluoromethoxy.

62. The compound of any one of claims 1 to 49, or 59 to 61, wherein each R^{14} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, pyrrolidinyl, piperidinyl, morpholinyl, fluoro, chloro, $-N(R^{15})_2$, or methoxy.

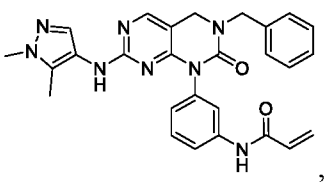
63. The compound of any one of claims 1 to 49 or 59 to 62, wherein each R^{15} is independently alkyl or cycloalkyl.

64. The compound of any one of claims 1 to 49 or 59 to 63, wherein each R^{15} is methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

65. The compound of any one of claims 1 to 49 or 59 to 64, wherein each R^{13} is independently methyl, ethyl, *iso*-propyl, *tert*-butyl, cyclopropyl, cyclopentyl, or cyclohexyl.

66. The compound of any one of claims 1 to 49 or 59 to 65, wherein each R^{13} is independently methyl, cyclopropyl, or cyclohexyl.

67. The compound of claim 1, wherein the compound is selected from: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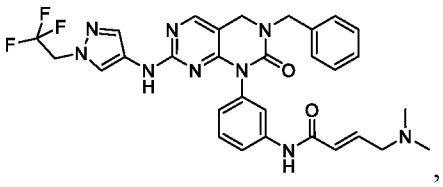
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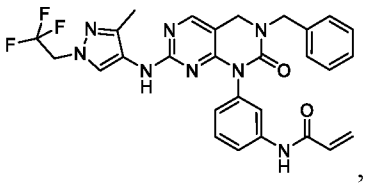
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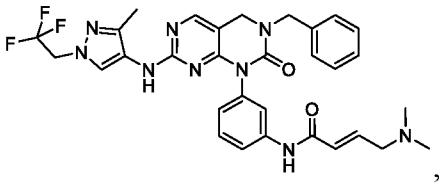
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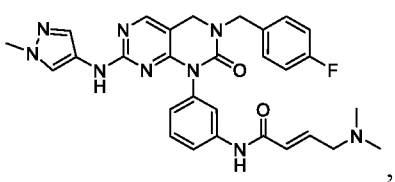
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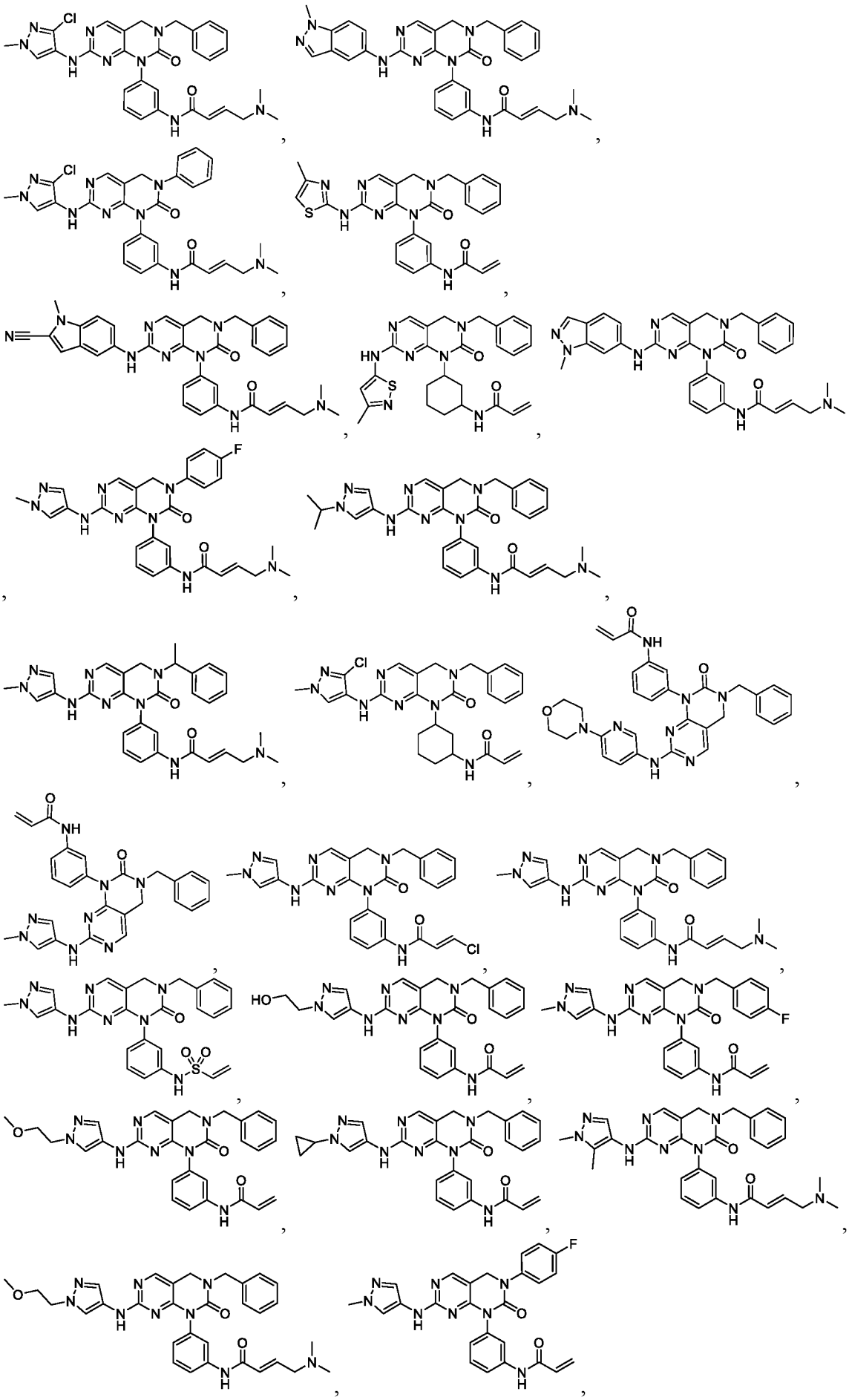

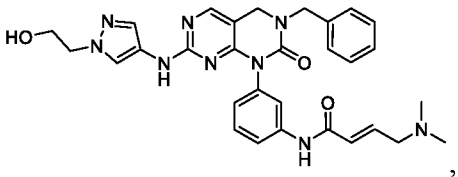
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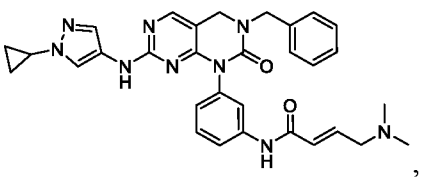
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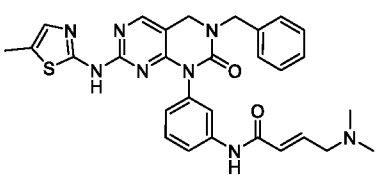
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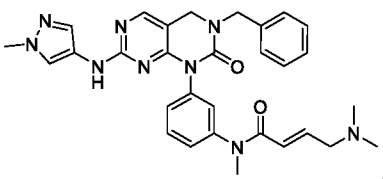
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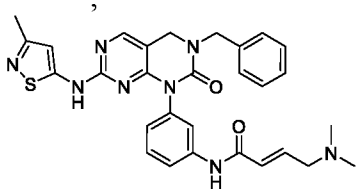
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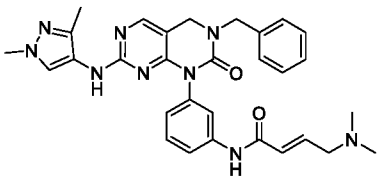
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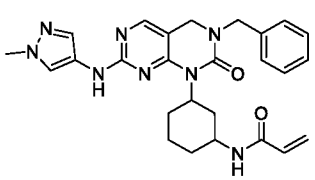
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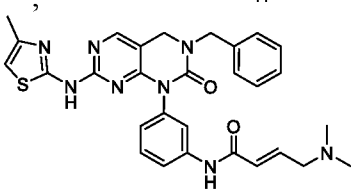
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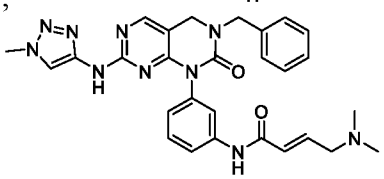
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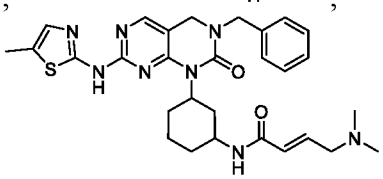
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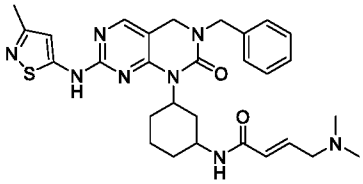
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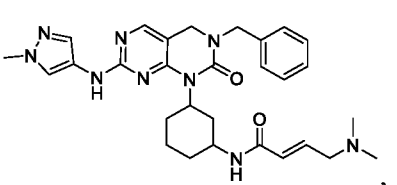
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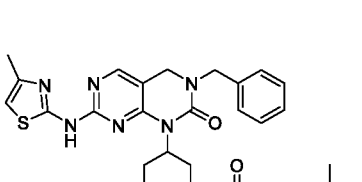
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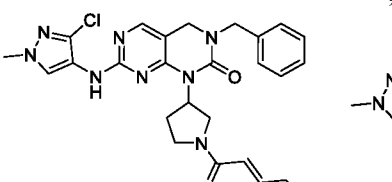
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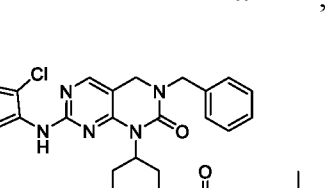
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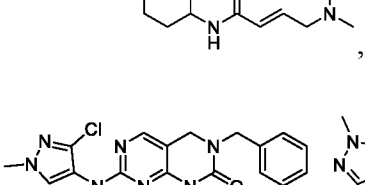
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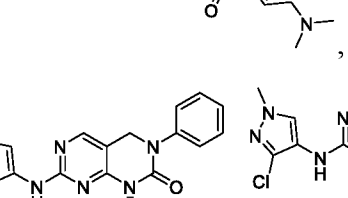
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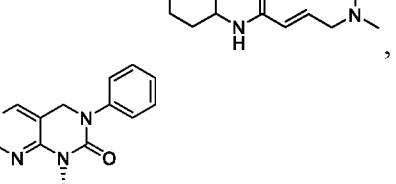
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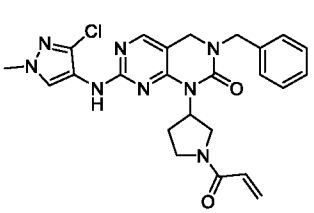
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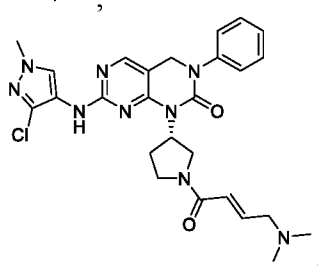
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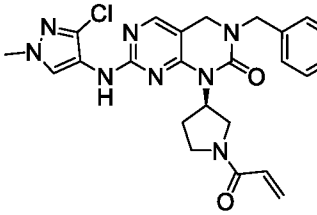
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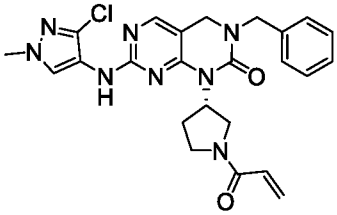
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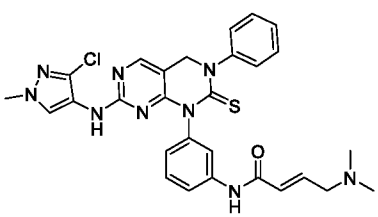
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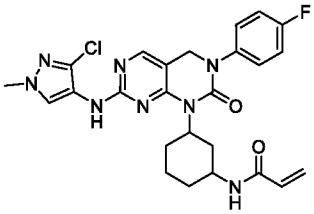
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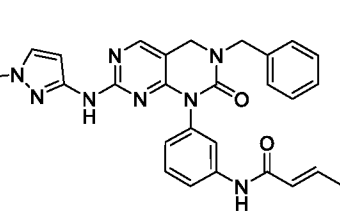
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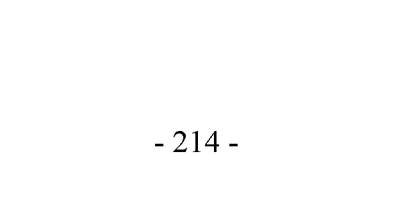
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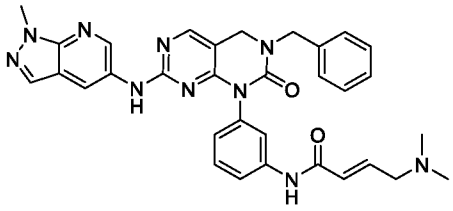
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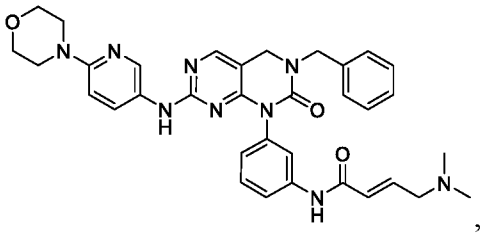
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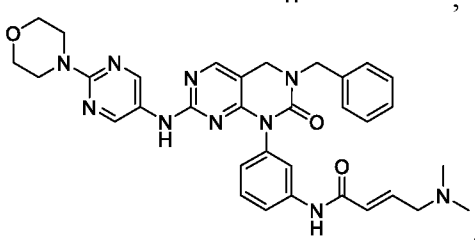
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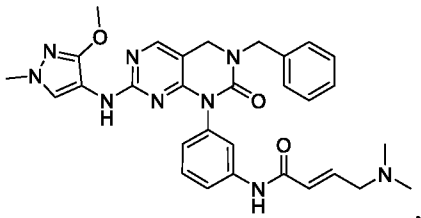
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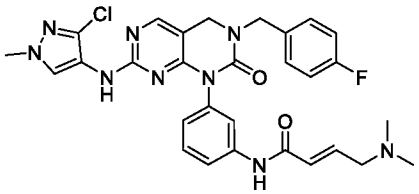
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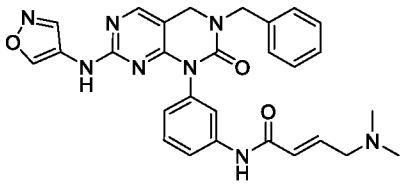
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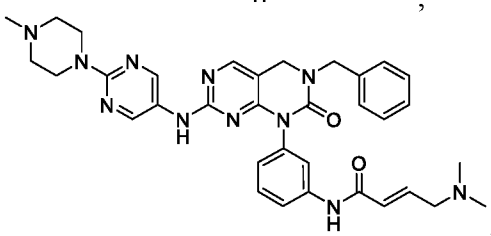
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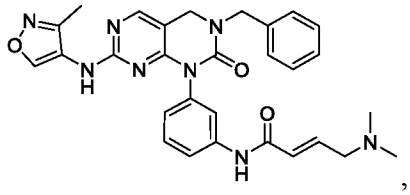
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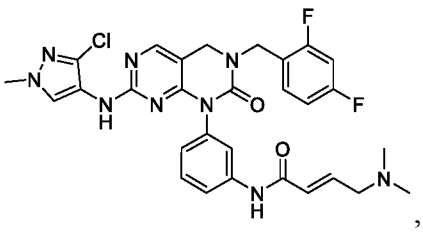
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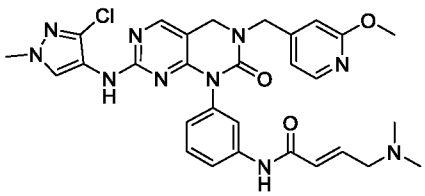
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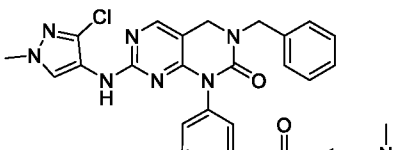
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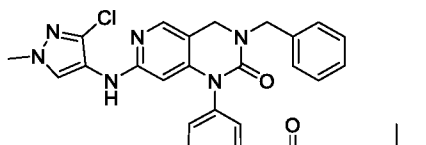
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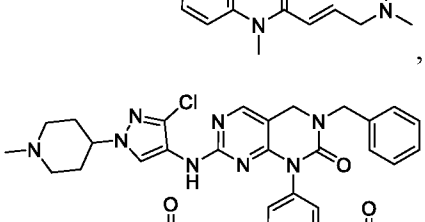
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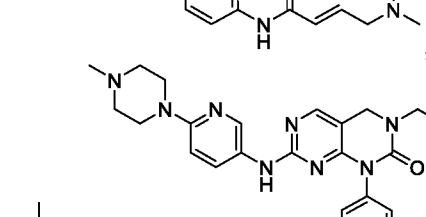
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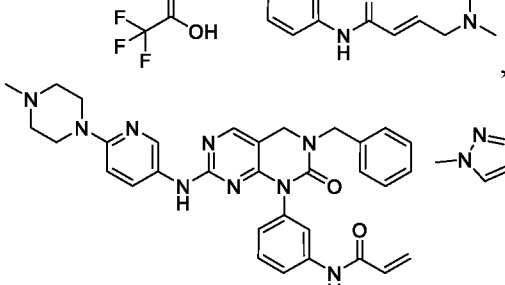
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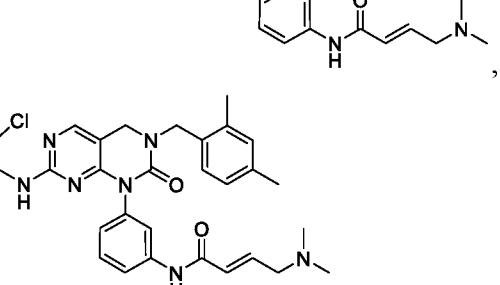
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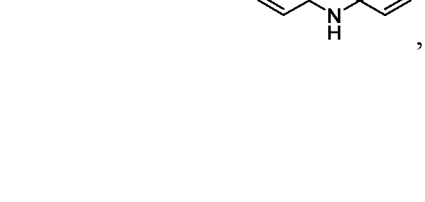
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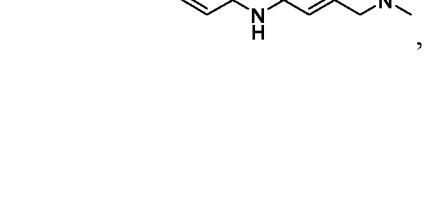
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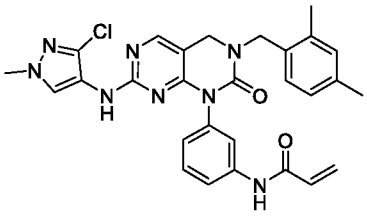
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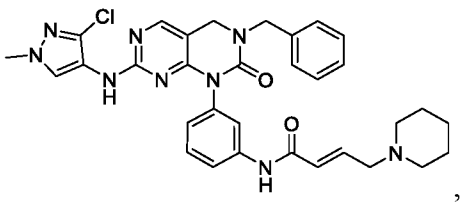
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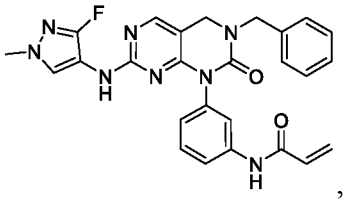
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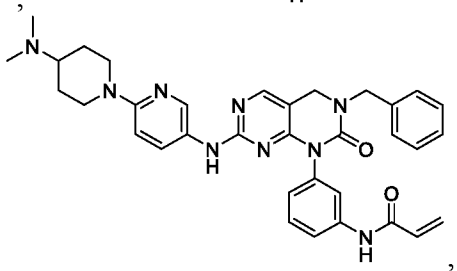
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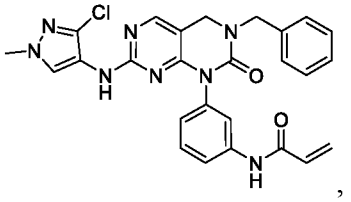
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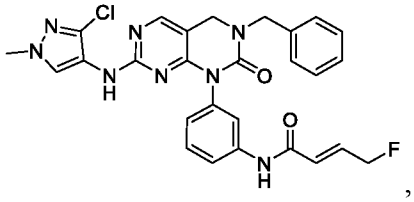
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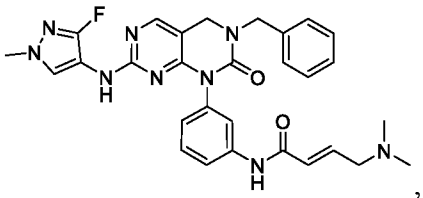
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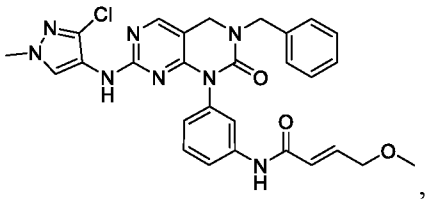
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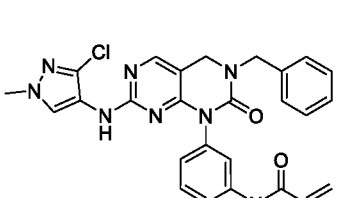
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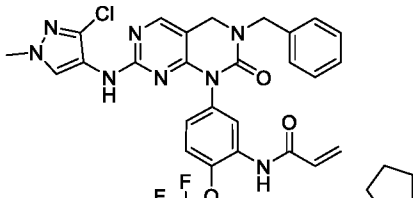
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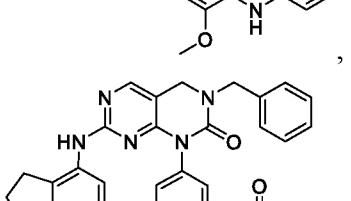
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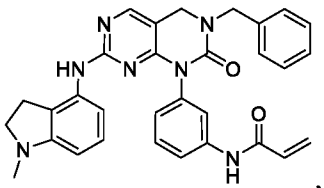
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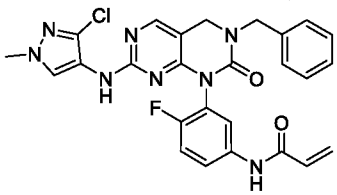
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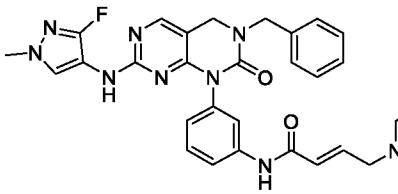
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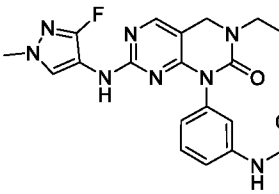
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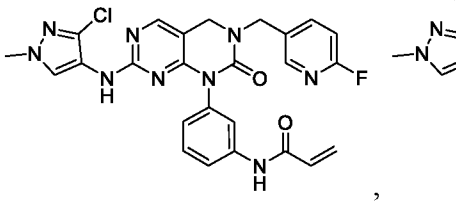
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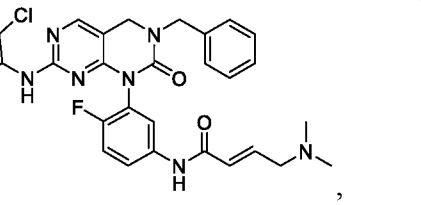
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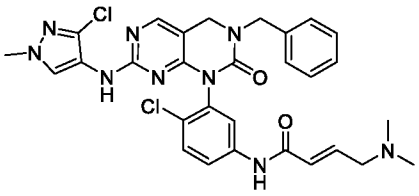
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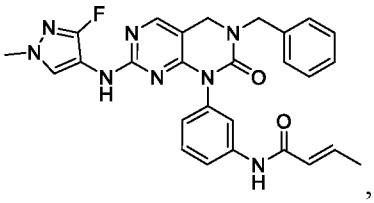
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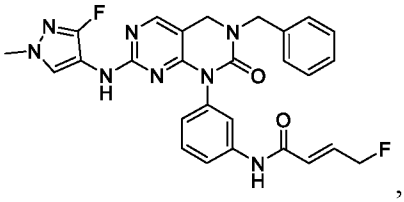
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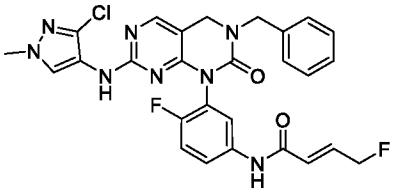
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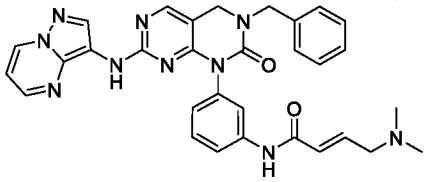
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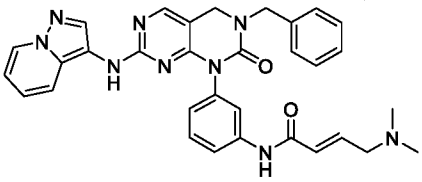
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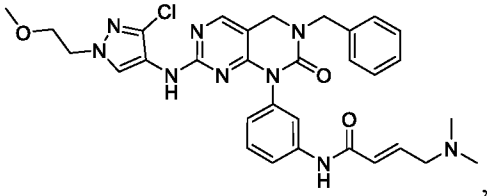
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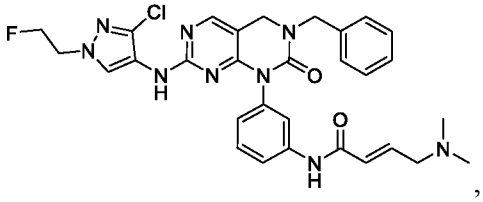
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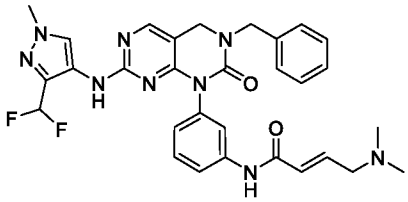
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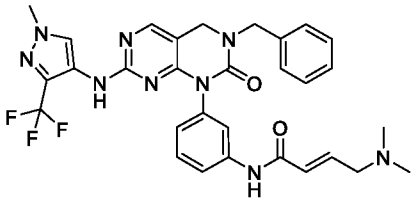
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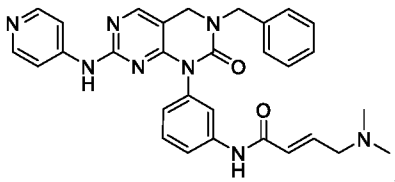
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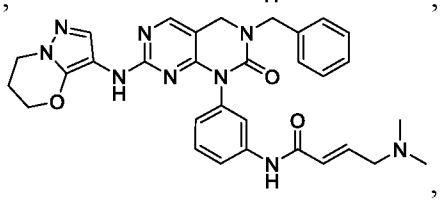
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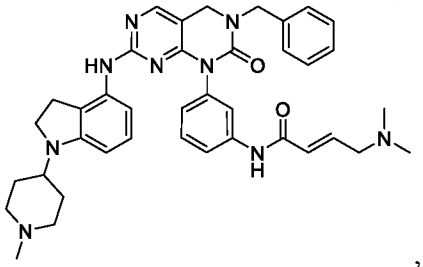
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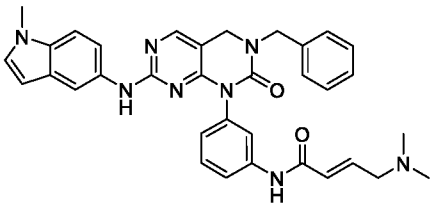
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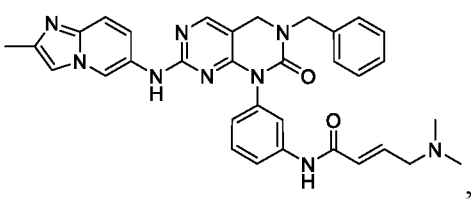
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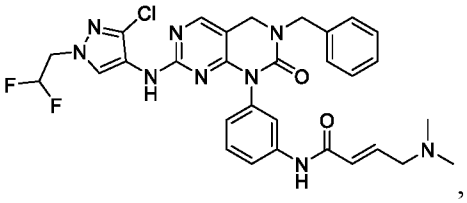
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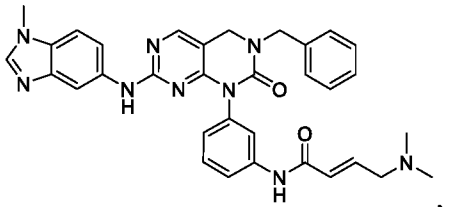
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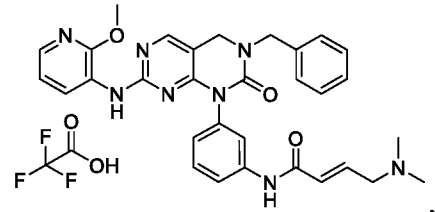
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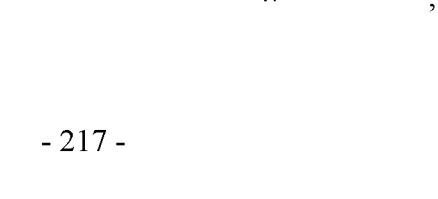
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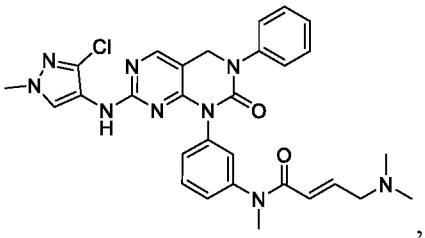
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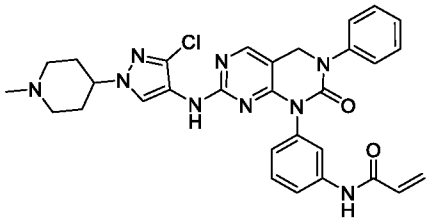
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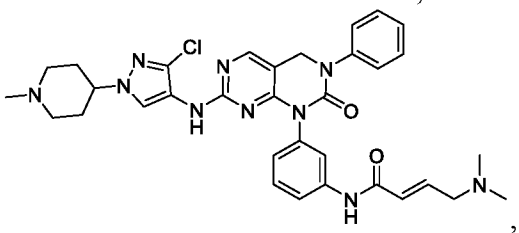
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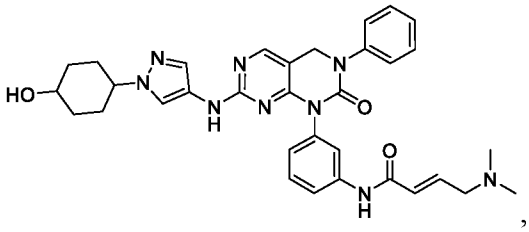
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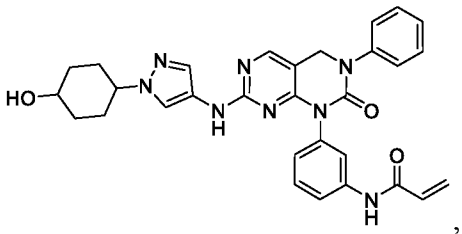
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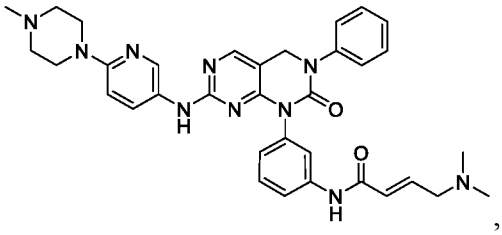
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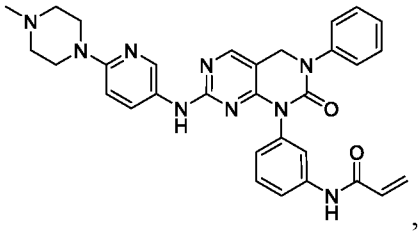
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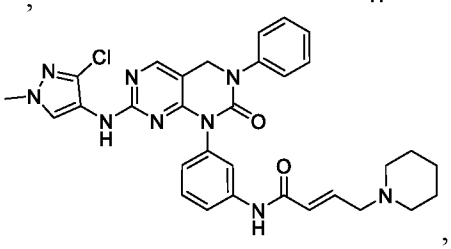
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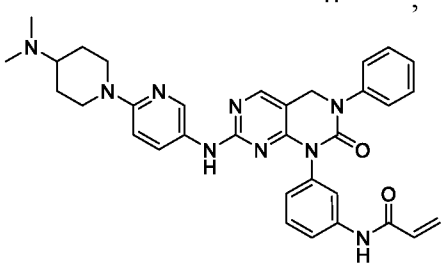
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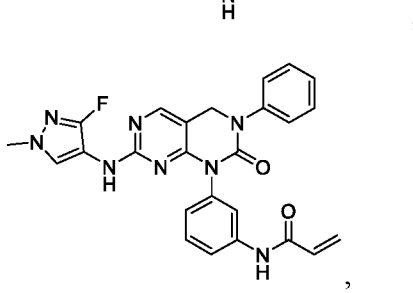
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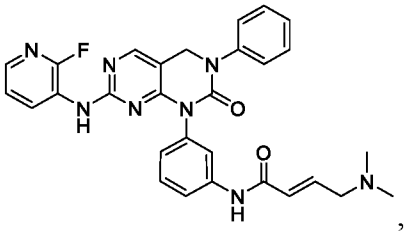
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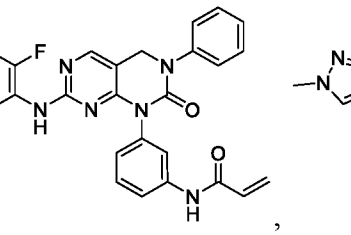
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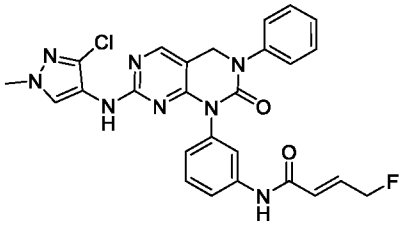
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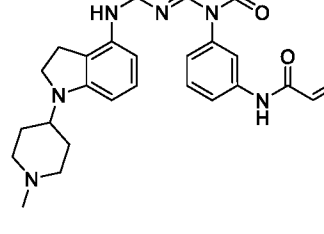
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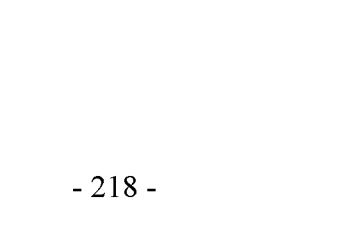
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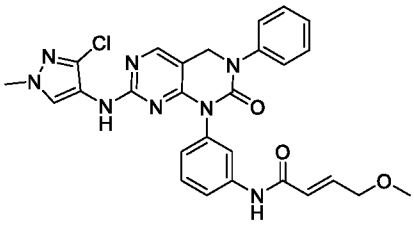
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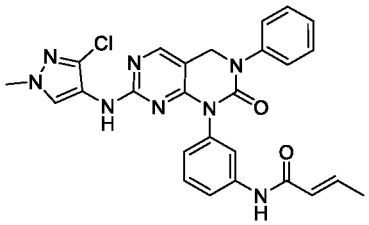
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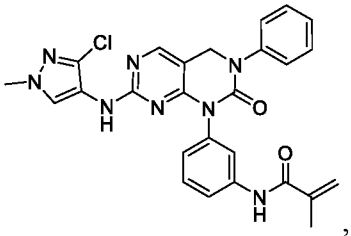
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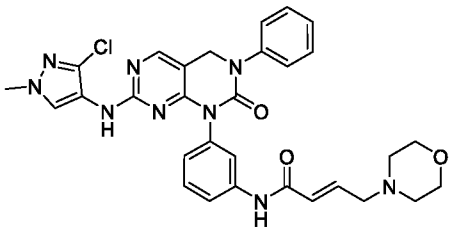
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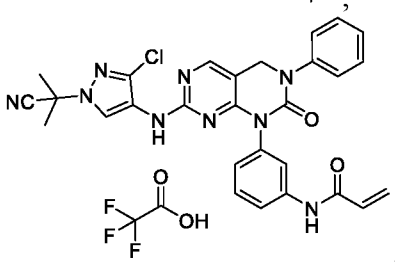
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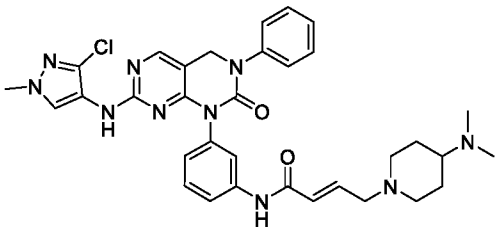
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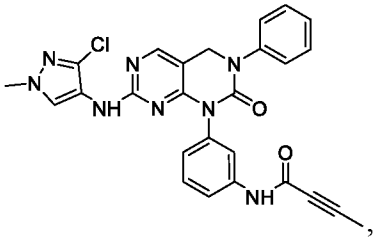
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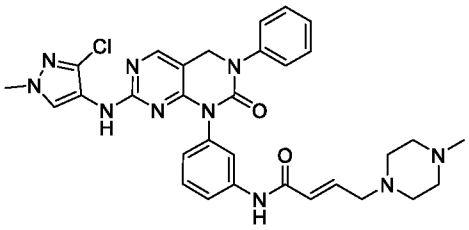
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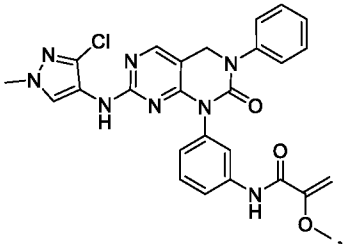
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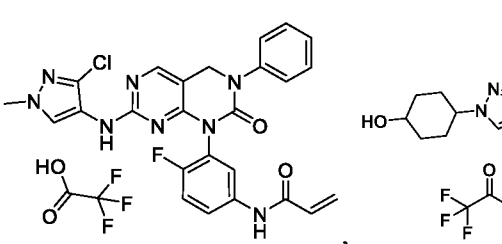
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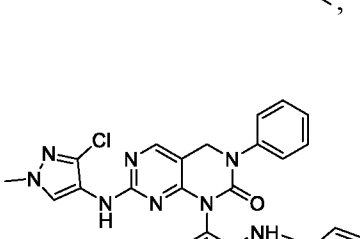
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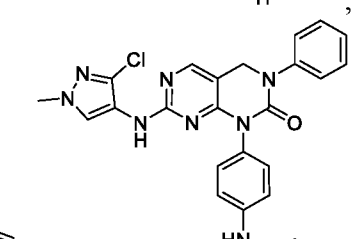
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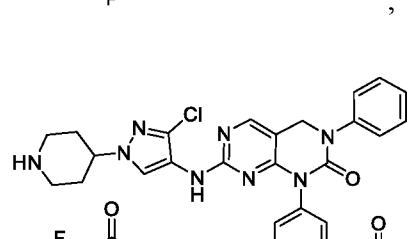
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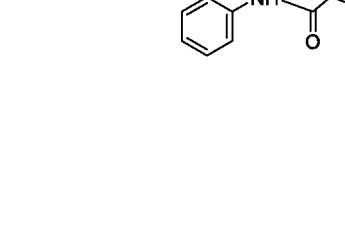
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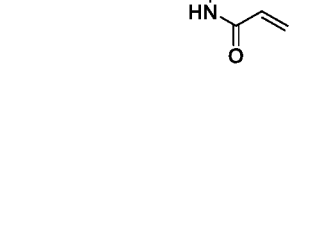
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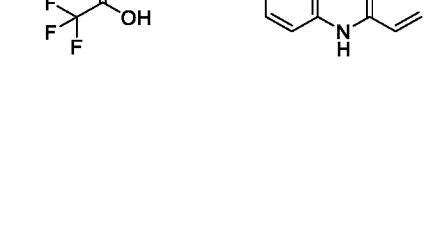

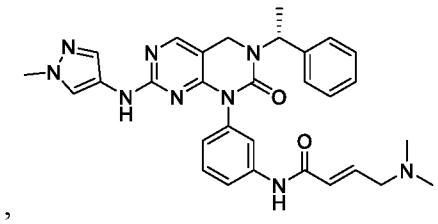
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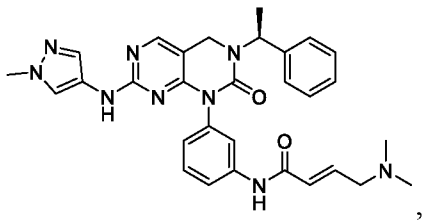
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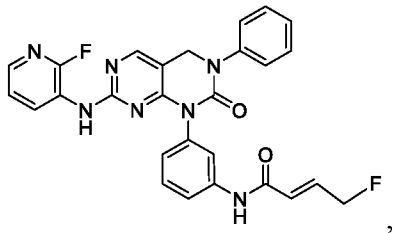
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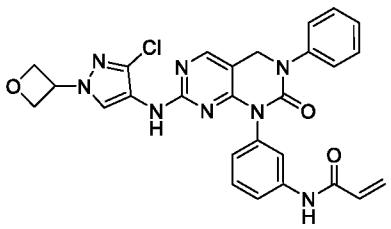
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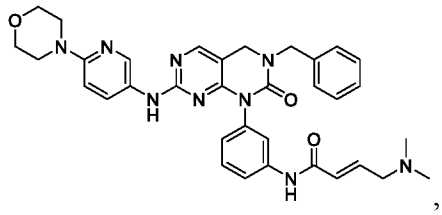
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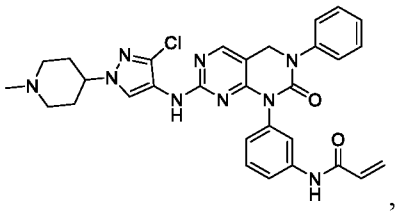
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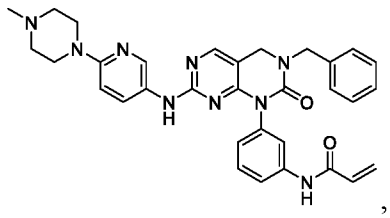
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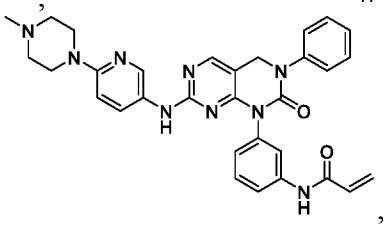
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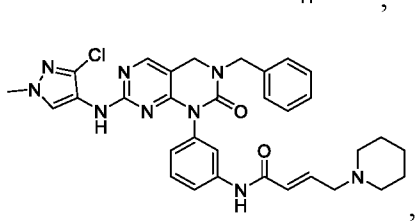
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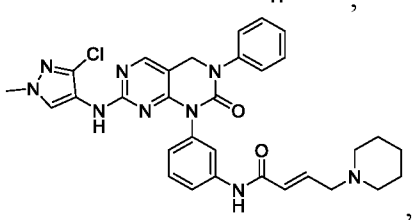
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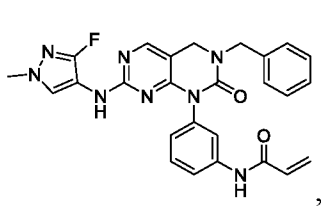
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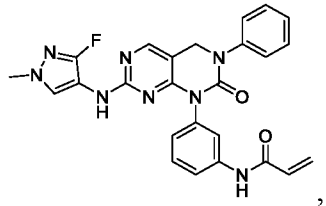
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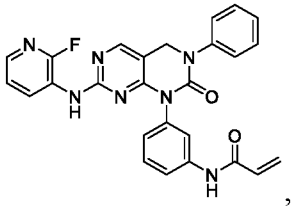
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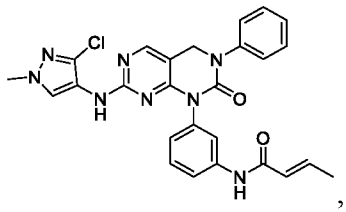
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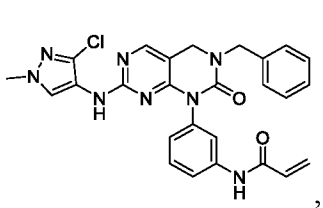
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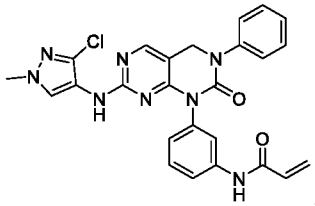
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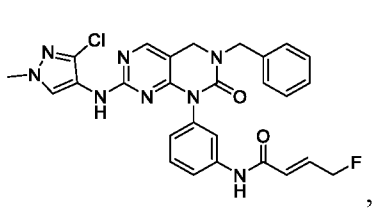
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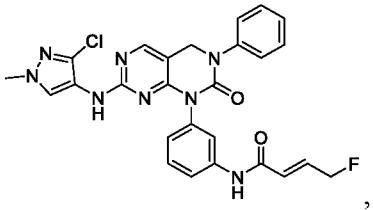
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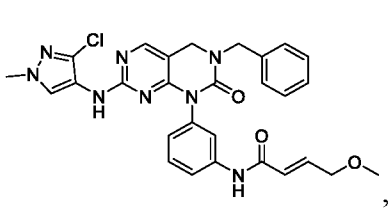
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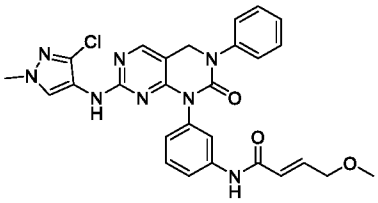
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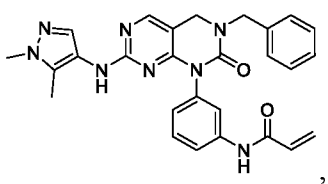
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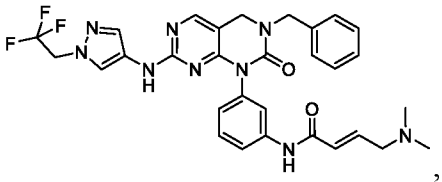
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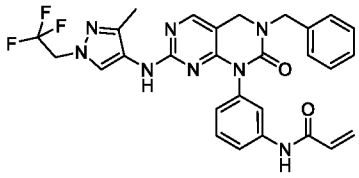
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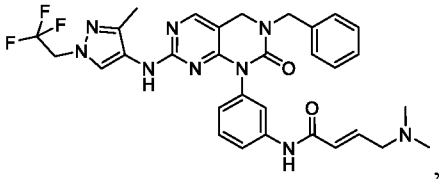
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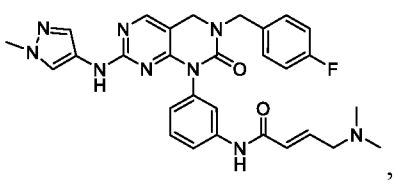
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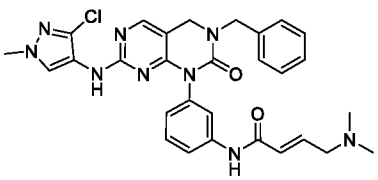
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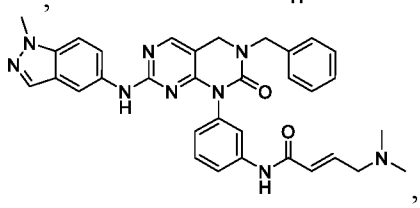
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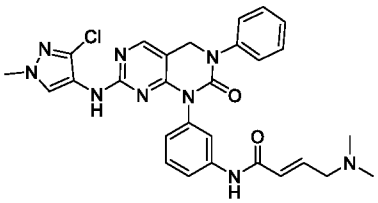
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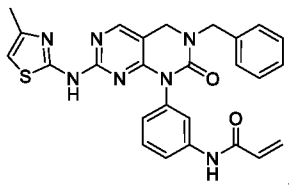
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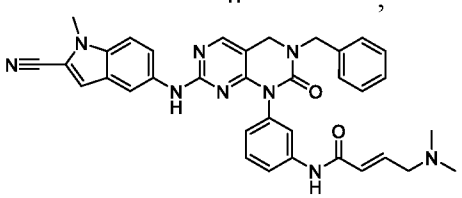
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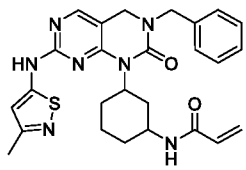
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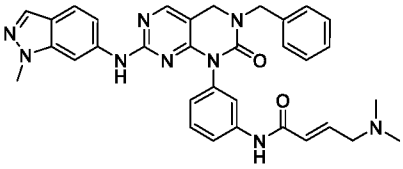
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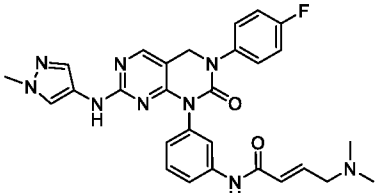
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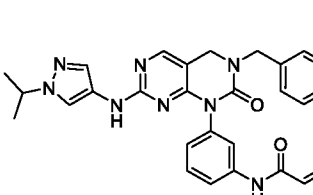
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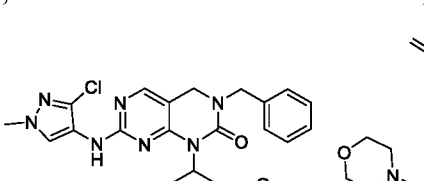
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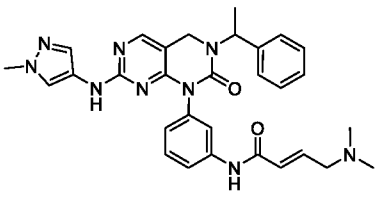
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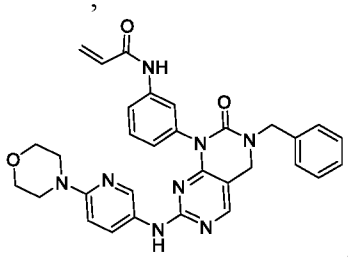
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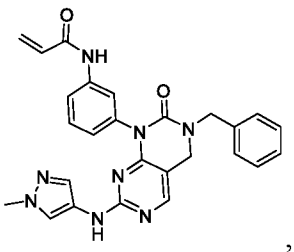
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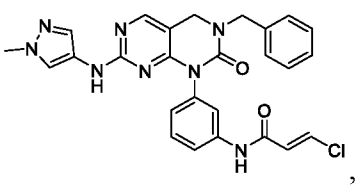
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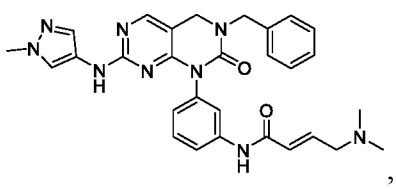
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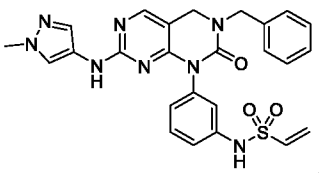
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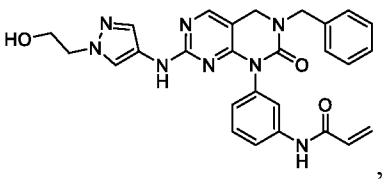
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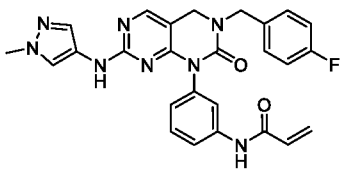
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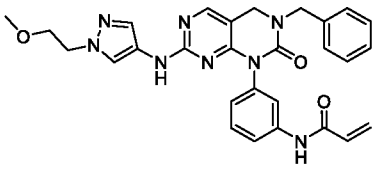
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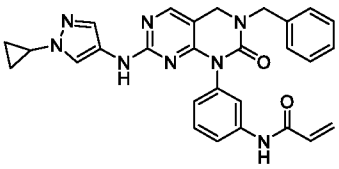
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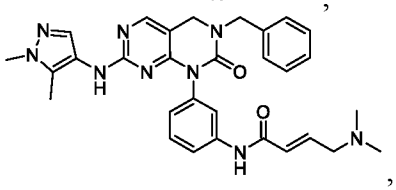
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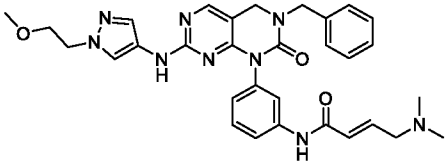
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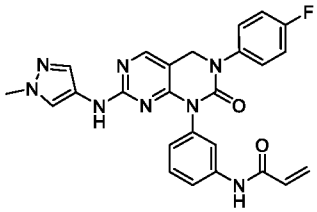
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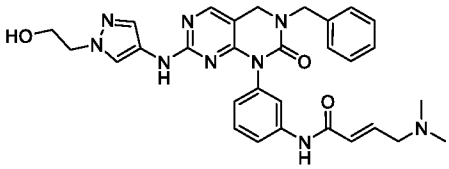
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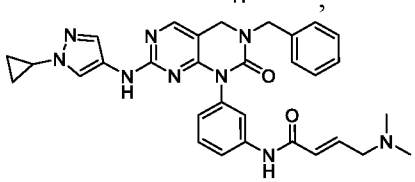
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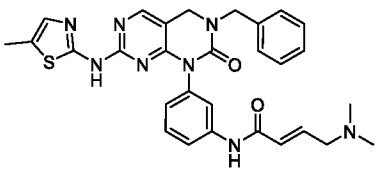
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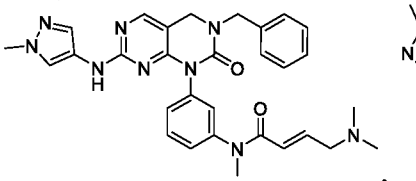
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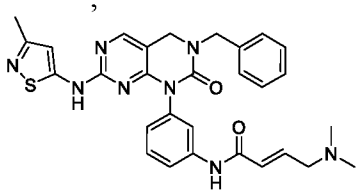
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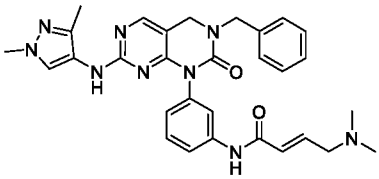
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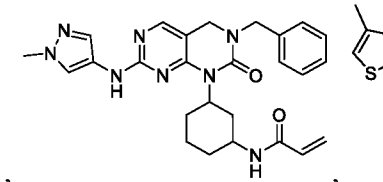
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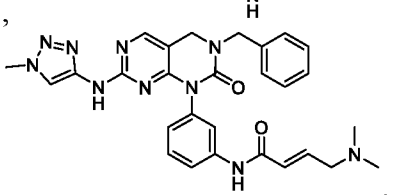
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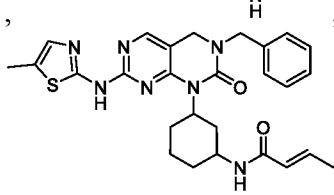
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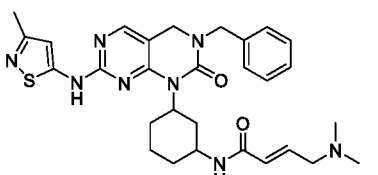
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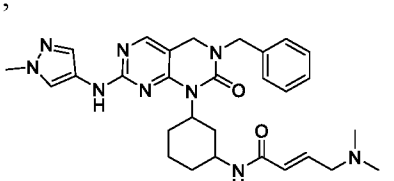
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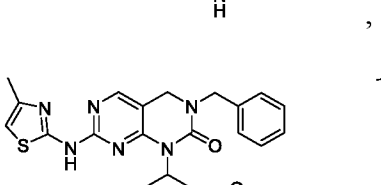
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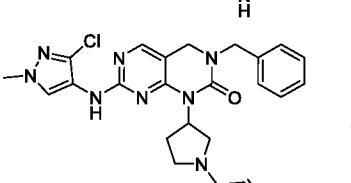
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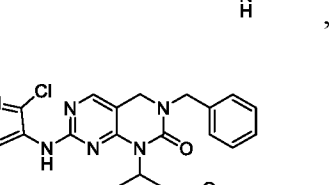
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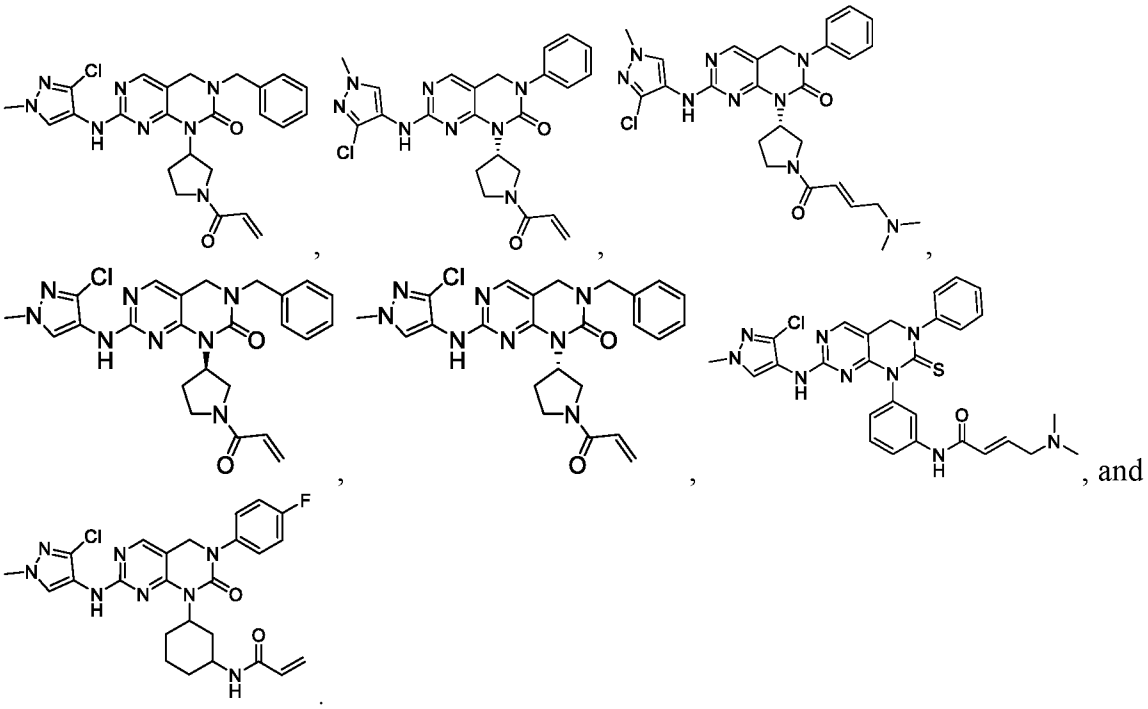

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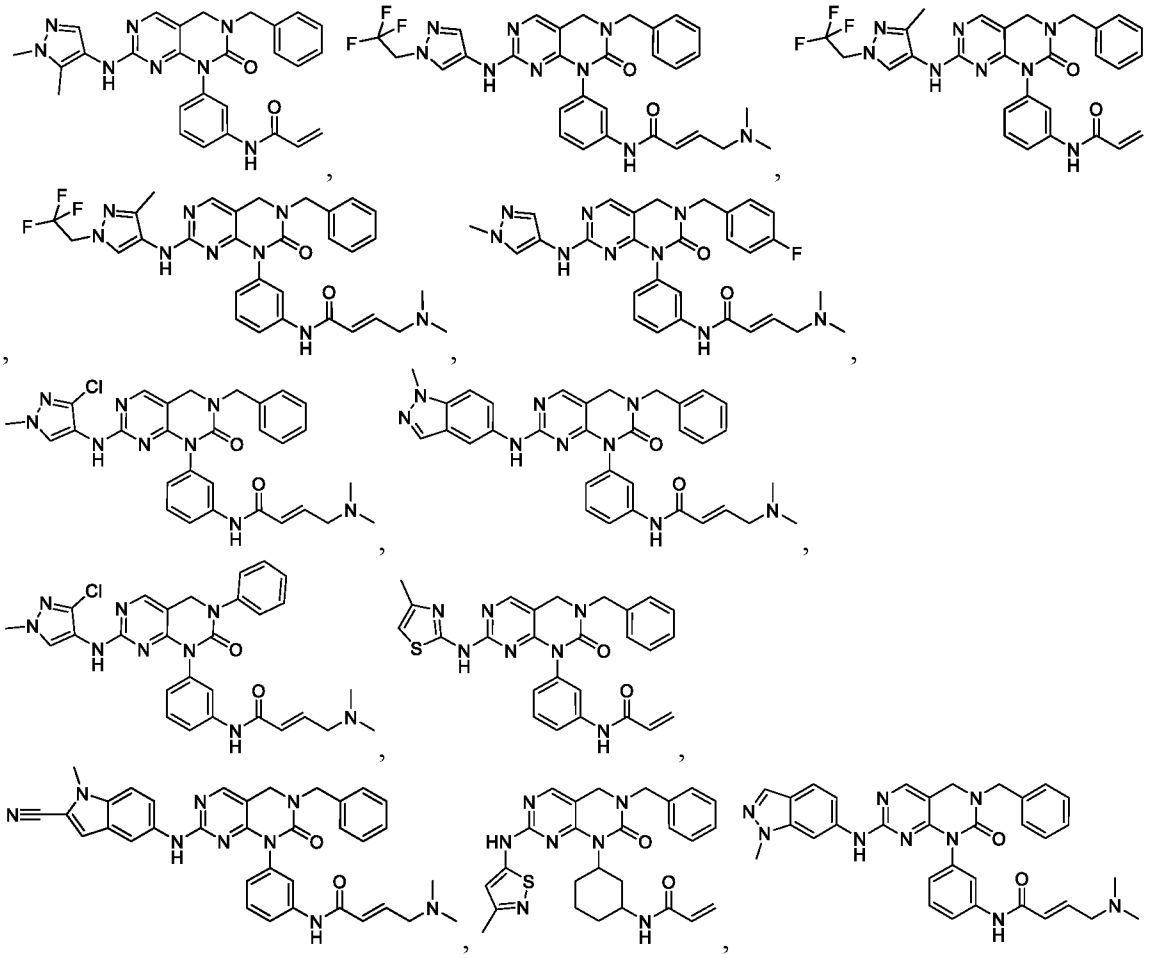

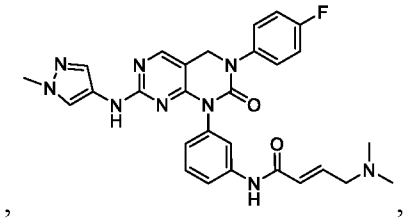
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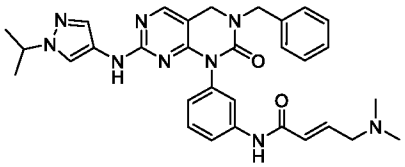
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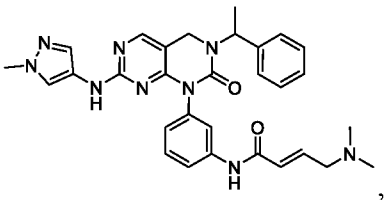
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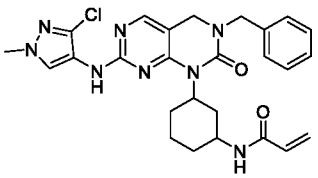
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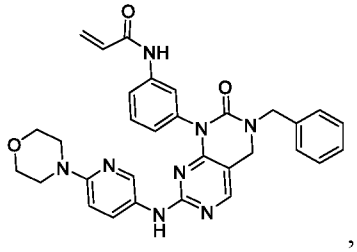
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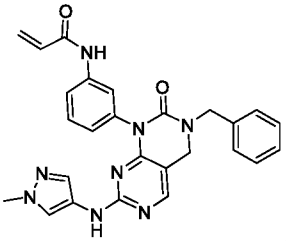
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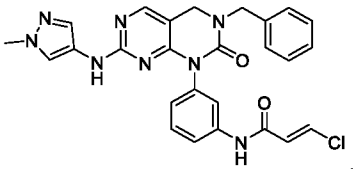
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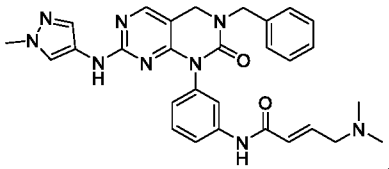
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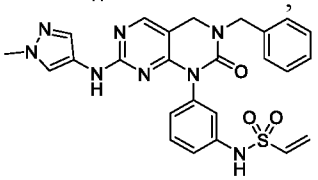
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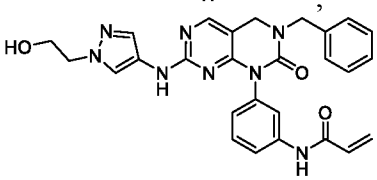
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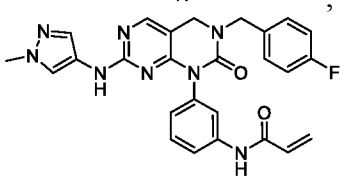
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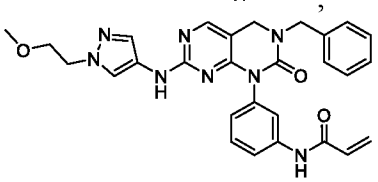
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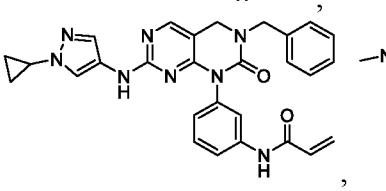
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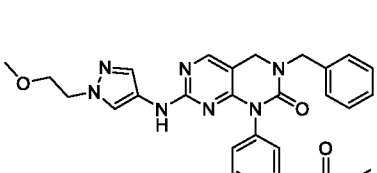
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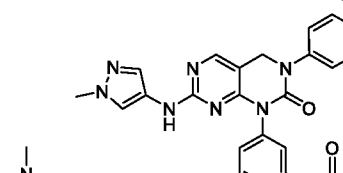
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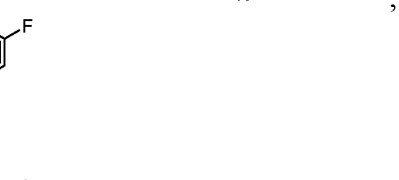
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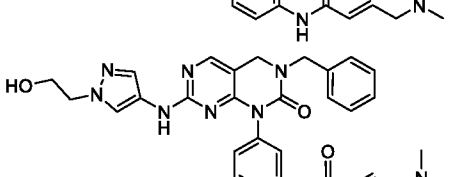
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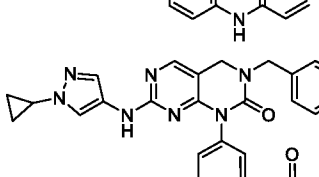
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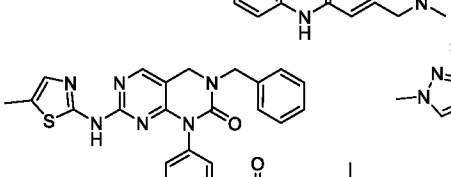
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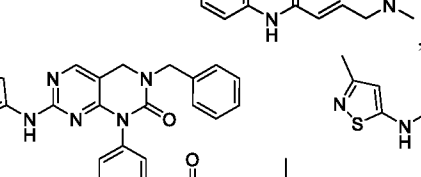
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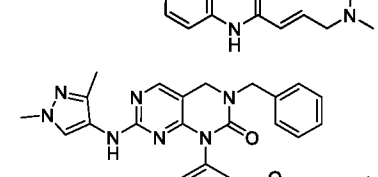
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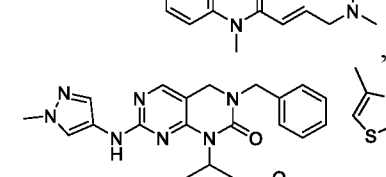
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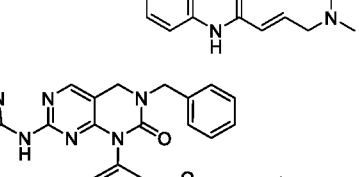
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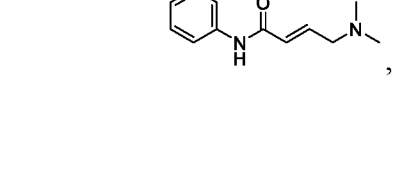
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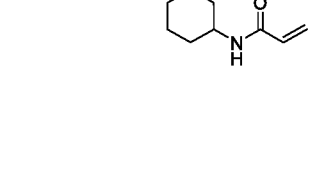
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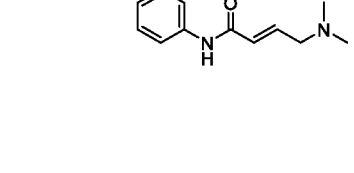
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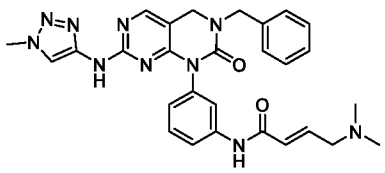
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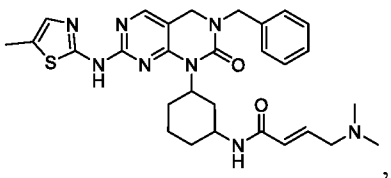
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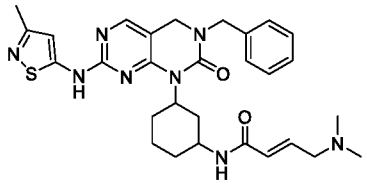
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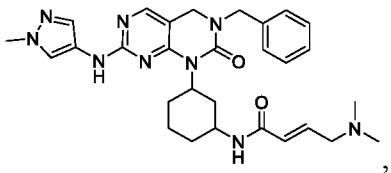
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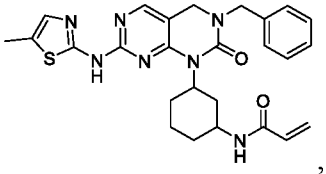
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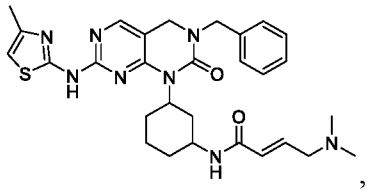
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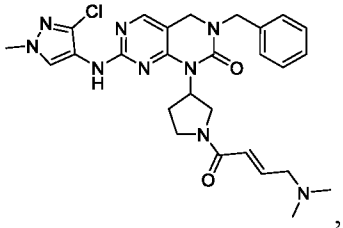
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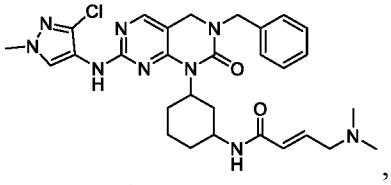
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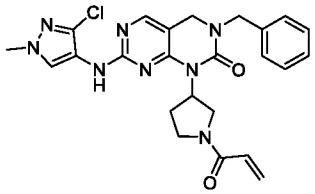
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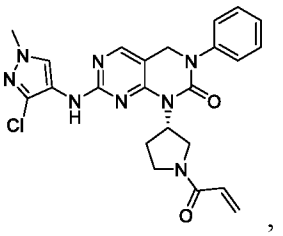
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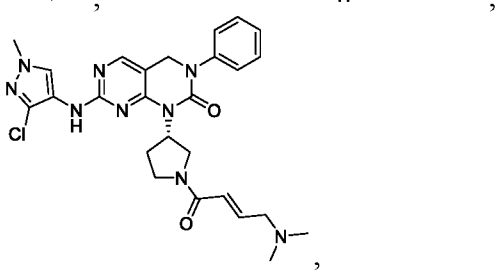
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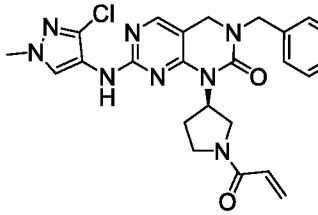
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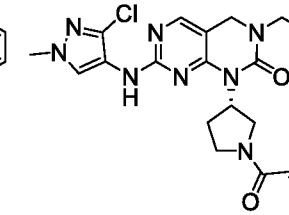
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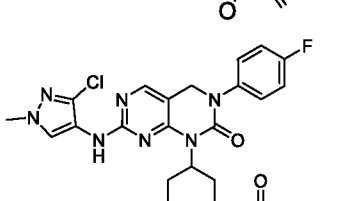
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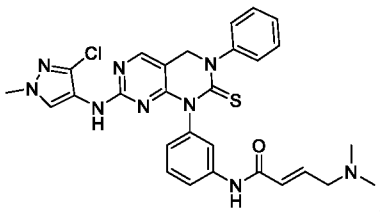
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70. A pharmaceutical composition comprising a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

71. A method of inhibiting an epidermal growth factor receptor (EGFR) family kinase mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

72. A method of inhibiting a human epidermal growth factor receptor 2 (HER2) mutant in a subject in need thereof, comprising administering to the subject a therapeutically

effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

73. The method of claim 72, wherein the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30.

74. The method of claim 73, wherein the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

75. A method of inhibiting an epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

76. A method of inhibiting a drug-resistant epidermal growth factor receptor (EGFR) mutant in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

77. The method of claim 76, wherein the drug-resistant EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR.

78. A method of inhibiting human epidermal growth factor receptor 2 (HER2) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of a HER2 mutant relative to wild-type EGFR.

79. The method of claim 78, wherein the HER2 mutant comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30.

80. The method of claim 79, wherein the HER2 mutant is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

81. A method of inhibiting epidermal growth factor receptor (EGFR) in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof, wherein the compound exhibits greater inhibition of an EGFR mutant relative to wild-type EGFR.

82. The method of claim 81, wherein the EGFR mutant comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21.

83. The method of claim 82, wherein the EGFR mutant is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR.

84. The method of claim 83, wherein the EGFR mutant is del19/T790M EGFR or L858R/T790M EGFR.

85. A method of treating a disease or disorder associated with an epidermal growth factor receptor (EGFR) family kinase in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

86. The method of claim 85, wherein the disease or disorder in the subject comprises a HER2 mutation.

87. The method of claim 86, wherein the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30.

88. The method of claim 87, wherein the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

89. The method of claim 85, wherein the disease or disorder in the subject comprises an EGFR mutation.

90. The method of claim 89, wherein the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21.

91. The method of claim 90, wherein the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR.

92. The method of claim 91, wherein the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

93. A method of treating one or more cancer cells in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

94. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

95. The method of claim 93 or 94, wherein the cancer is selected from bladder cancer, prostate cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, gastric cancer, glioblastoma, head and neck cancer, lung cancer, and non-small cell lung cancer.

96. The method of claim 95, wherein the cancer is selected from non-small cell lung cancer, prostate cancer, head and neck cancer, breast cancer, colorectal cancer, and glioblastoma.

97. The method of claim 93 or 94, wherein the cancer in the subject comprises a HER2 mutation.

98. The method of claim 97, wherein the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30.

99. The method of claim 98, wherein the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

100. The method of claim 93 or 94, wherein the cancer in the subject comprises an EGFR mutation.

101. The method of claim 100, wherein the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21.

102. The method of claim 101, wherein the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR.

103. The method of claim 102, wherein the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

104. A method of treating an inflammatory disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of any one of claims 1 to 69, or a pharmaceutically acceptable salt thereof.

105. The method of claim 104, wherein the inflammatory disease is selected from psoriasis, eczema, and atherosclerosis.

106. The method of claim 104, wherein the inflammatory disease in the subject comprises a HER2 mutation.

107. The method of claim 106, wherein the HER2 mutation comprises an insertion in exon 20, an in-frame deletion and insertion in exon 20, a substitution in the extracellular domain, an extracellular truncation, or a substitution in exon 30.

108. The method of claim 107, wherein the HER2 mutation is A775ins_G776insYVMA, A775_G776insSVMA, A775_G776insVVMA, G776del insVC, G776del insLC, G776del insAV, G776del insAVGC, S310F, S310Y, p95, V842I, or P780_Y781insGSP.

109. The method of claim 104, wherein the inflammatory disease in the subject comprises an EGFR mutation.

110. The method of claim 109, wherein the EGFR mutation comprises a substitution in exon 18, a deletion in exon 19, a substitution in exon 20, an insertion in exon 20, a mutation in the extracellular domain, or a substitution in exon 21.

111. The method of claim 110, wherein the EGFR mutation is del19/T790M EGFR, L858R/T790M EGFR, L858R EGFR, L861Q EGFR, G719X EGFR, 763insFQEA EGFR, 767insTLA EGFR, 769insASV EGFR, 769insGE EGFR, 770insSVD EGFR, 770insNPG EGFR, 770insGT EGFR, 770insGF EGFR, 770insG EGFR, 771insH EGFR, 771insN EGFR, 772insNP EGFR, 773insNPH EGFR, 773insH EGFR, 773insPH EGFR, EGFRvii, EGFRviii, D770_N771insSVD EGFR, H773insNPH EGFR, A767_dupASV EGFR, or 773insAH EGFR.

112. The method of claim 111, wherein the EGFR mutation is del19/T790M EGFR or L858R/T790M EGFR.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/052953

A. CLASSIFICATION OF SUBJECT MATTER

C07D 487/04(2006.01)i, A61K 31/519(2006.01)i, A61K 31/5377(2006.01)i, A61P 35/00(2006.01)i, A61P 29/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 487/04; A61K 31/519; C07D 213/75; C07D 401/12; C07D 471/04; A61K 31/5377; A61P 35/00; A61P 29/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal), STN(Registry, CAplus) & Keywords:fused pyrimidine, cancer, epidermal growth factor receptor(EGFR), human epidermal growth factor receptor 2 (HER2)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014-089913 A1 (KBP BIOSCIENCES CO., LTD.) 19 June 2014 claims 1, 6, 11	1-3,67-69
X	WO 2018-009544 A1 (THE BROAD INSTITUTE, INC. et al.) 11 January 2018 claims 1, 94, 99, 104	1-3,67-69
X	WO 2018-160076 A1 (AUCKLAND UNISERVICES LIMITED et al.) 07 September 2018 claims 1, 20-23	1-3,67-69
A	WO 2004-065378 A1 (WARNER-LAMBERT COMPANY LLC) 05 August 2004 the whole document	1-3,67-69
A	WO 2007-147109 A2 (GLAXO GROUP LIMITED) 21 December 2007 the whole document	1-3,67-69

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2021 (13.01.2021)	**13 January 2021 (13.01.2021)**

Name and mailing address of the ISA/KR
International Application Division
Korean Intellectual Property Office
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2020/052953

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 71-112
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 71-112 pertain to methods for treatment of the human body by surgery or therapy as well as diagnostic methods (PCT Article 17(2)(a)(i) and Rule 39.1(iv)).

2. ☒ Claims Nos.: 73, 74, 77, 79, 80, 82-84, 86-92, 96, 98, 99, 101-103, 105-112
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 73, 74, 77, 79, 80, 82-84, 86-92, 96, 98, 99, 101-103 and 105-112 are regarded to be unclear because they refer to claims which do not comply with PCT Rule 6.4(a).

3. ☒ Claims Nos.: 4-66, 70-72, 75, 76, 78, 81, 85, 93-95, 97, 100, 104
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2020/052953

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014-089913 A1	19/06/2014	CN 104968664 A	07/10/2015
WO 2018-009544 A1	11/01/2018	AU 2017-291812 A1	21/02/2019
		CA 3069016 A1	11/01/2018
		CN 110225914 A	10/09/2019
		EP 3481830 A1	15/05/2019
		JP 2019-527682 A	03/10/2019
		KR 10-2019-0075043 A	28/06/2019
		US 2019-0315752 A1	17/10/2019
		US 2020-0317675 A9	08/10/2020
WO 2018-160076 A1	07/09/2018	AU 2018-229148 A1	10/10/2019
		CN 110809576 A	18/02/2020
		EP 3589634 A1	08/01/2020
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