THE DESCRIPTION

PROTEIN TYROSINE KINASE MODULATORS AND METHODS OF USE

Technical Field

This invention relates to heterocyclic pyrimidine compounds that modulate mutant-selective epidermal growth factor receptor (EGFR) kinase activity for modulating cellular activities such as proliferation, differentiation, programmed cell death, migration and chemoinvasion. More specifically, the invention provides pyrimidines which selectively inhibit, regulate and/or modulate kinase receptor, particularly in modulation of various EGFR mutant activity related to the changes in cellular activities as mentioned above, pharmaceutical compositions comprising the pyrimidine derivative, and methods of treatment for diseases associated with protein kinase enzymatic activity, particularly EGFR kinase activity including non-small cell lung cancer comprising administration of the pyrimidine derivative.

Background Art

The epidermal growth factor receptor (EGFR, Erb-Bl) belongs to a family of proteins, involved in the proliferation of normal and malignant cells (Artega, C. L., J. Clin Oncol 19, 2001, 32-40). Overexpression of Epidermal Growth Factor Receptor (EGFR) is present in at least 70% of human cancers (Seymour, L. K., Curr Drug Targets 2, 2001, 117- 133) such as, non-small cell lung carcinomas (NSCLC), breast cancers, gliomas, squamous cell carcinoma of the head and neck, and prostate cancer (Raymond et al., Drugs 60 Suppl 1, 2000, discussion 41-2; Salomon et al., Crit Rev Oncol Hematol 19, 1995, 183-232; Voldborg et al., Ann Oncol 8, 1997, 1197-1206). The EGFR-TK is therefore widely recognized as an attractive target for the design and development of compounds that can specifically bind and inhibit the tyrosine kinase activity and its signal transduction pathway in cancer cells, and thus can serve as either diagnostic or therapeutic agents. For example, the EGFR tyrosine kinase (EGFR-TK) reversible inhibitor, TARCEVA^{RTM}, is approved by the FDA for treatment of NSCLC and advanced pancreatic cancer. Other anti-EGFR targeted molecules have also been approved including LAPATINIB ^{RTM}, and IRESSA ^{RTM}.

The efficacy of erlotinib and gefitinib is limited when administered to all lung cancer patients. When erlotinib or gefitinib are used in the treatment of all lung cancer patients (not selected for presence/absence of activated (mutant) EGFR), the likelihood of tumor shrinkage (response rate) is 8-10% and the median time to tumor progression is approximately 2 months {Shepherd et al NEJM 2004, Thatcher et al. Lancet 2005}. In 2004 it was disovered that lung cancers with somatic mutations in EGFR were associated with dramatic clinical responses following treatment with geftinib and erlotinib{Paez et al. Science 2004; Lynch et al. NEJM 2004; Pao et al PNAS 2004}. Somatic mutations identified to date include point mutations in which a single aminoacid residue is altered in the expressed protein (e.g. L858R, G719S, G719C, G719A, L861Q), as well as small in frame deletions in Exonl9 or insetions in Exon20. Somatic mutations in EGFR are found in 10-15% of Caucasian and in 30-40% of Asian NSCLC patients. EGFR mutations are present more frequently in never-smokers, females, those with adenocarcinoma and in patients of East Asian ethnicity {Shigematsu et al JNCI 2005}. These are the same groups of patients previously clinically identified as most likely to benefit from gefltinib or erlotinib {Fukuoka et al. JCO 2003; Kris et al JAMA 2003 and Shepherd et al NEJM 2004}. Six prospective clinical trials treating chemotherapy na[iota]ve patients with EGFR mutations with gefltinib or erlotinib have been reported to date {Inoue et al JCO 2006, Tamura et al Br. J Cancer 2008; Asahina et al., Br. J. Cancer 2006; Sequist et al., JCO 2008}. Cumulatively, these studies have prospectively identified and treated over 200 patients with EGFR mutations. Together they demonstrate radiographic response rates ranging from 60-82% and median times to progression of 9.4 to 13.3 months in the patients treated with gefltinib and erlotinib. These outcomes are 3 to 4 folder greater than that observed with platin-based chemotherapy (20-30% and 3-4 months, respectively) for advanced NSCLC {Schiller, et al JCO 2002}. In a recently completed phase III clinical trial, EGFR mutant chemotherapy na[iota]ve NSCLC patients had a significantly longer (hazard ratio = 0.48 (95% CI; 0.36-0.64); $p < 0.0001$) progression free survival (PFS) and tumor response rate (71.3 vs. 47.2%; p=0.0001) when treated with gefltinib compared with conventional chemotherapy {Mok et al. ESMO meeting 2008}. Conversely, NSCLC patients that were EGFR wild type had a worse outcome when they received gefltinib compared to chemotherapy as their initial treatment for advanced NSCLC {Mok et al ESMO meeting 2008}. Thus EGFR mutations provide an important selection method for NSCLC patients for a therapy (EGFR TKIs) that is more effective than

conventional systemic chemotherapy. EGFR mutations are routinely being evaluated in NSCLC patients in many clinical centers.

Despite the initial clinical benefits of gefitinib/erlotinib in NSCLC patients harboring EGFR mutations, most if not all patients ultimately develop progressive cancer while receiving therapy on these agents. Initial studies of relapsed specimens identified a secondary EGFR mutation, T790M, that renders gefitinib and erlotinib ineffective inhibitors of EGFR kinase activity {Kobayashi et al NEJM 2005 and Pao et al PLOS Medicien 2005}. Subsequent studies have demonstrated that the EGFR T790M mutation is found in approximately 50% of tumors (24/48) from patients that have developed acquired resistance to gefitinib or erlotinib {Kosaka et al CCR 2006; Balak et al CCR 2006 and Engelman et al Science 2007}. This secondary genetic alteration occurs in the 'gatekeeper' residue and in an analogous position to other secondary resistance alleles in diseases treated with kinase inhibitors (for example T315I in ABL in imatinib resistant CML).

The initial identification of EGFR T790M also determined that an irreversible EGFR inhibitor, CL-387,785, could still inhibit EGFR even when it possessed the T790M mutation. Subsequent studies demonstrated that other irreversible EGFR inhibitors, EKB-569 and HKI- 272, could also inhibit phosphorylation of EGFR T790M and the growth of EGFR mutant NSCLC cell lines harboring the T790M mutation {Kwak et al PNAS 2005; Kobayashi et al NEJM 2005}. These irreversible EGFR inhibitors are structurally similar to reversible inhibitors gefitinib and erlotinib, but differ in that they contain a Michael-acceptor that allows them to covalently bind EGFR at Cys 797. The T790M mutation does not preclude binding of irreversible inhibitors; instead, it confers resistance to reversible inhibitors in part by increasing the affinity of the enzyme for ATP, at least in the L858R/T790M mutant EGFR {Yun et al., PNAS 2008}. Irreversible inhibitors overcome this mechanism of resistance because once they are covalently bound, they are no longer in competition with ATP. These observations have led to clinical development of irreversible EGFR inhibitors for patients developing acquired resistance to gefitinib or erlotinib. Three such agents (HKI-272, BIBW2992 and PF00299804) are currently under clinical development. However, the preclinical studies to date would suggest that these agents are not optimal at inhibiting EGFR variants bearing the T790M mutation.

Recent studies in a mouse model of EGFR L858R/T790M mediated lung cancer demonstrate that a subset of cancers in these mice (bronchial tumors) were insensitive to HKI-272 alone {Li et

al Cancer Cell 2007}. Thus even in this solely EGFR-driven model, HKI-272 alone is unable to cause tumor regression. This is in sharp contrast to the dramatic effects of erlotinib alone in mouse lung cancer models that contain only EGFR activating mutations {Ji et al Cancer Cell 2006} and suggests that HKI-272 may also be ineffective in some NSCLC patients with EGFR T790M. Similar findings have been reported for BIBW 2992 (Li et al. Oncogene 2008) Furthermore, the IC50 of HKI-272 required to inhibit the growth of Ba/F3 cells harboring EGFR T790M in conjunction with different exon 19 deletion mutations ranges from 200-800 nM while the mean Cmax in the Phase I trial was only about 200 nM {Yuza et al Cancer Biol Ther 2007; Wong et al CCR 2009 in press}. Thus there continues to be a need to develop more effective EGFR targeted agents capable of inhibiting EGFR T790M.

A major limitation of all current EGFR inhibitors is the development of toxicity in normal tissues. Since ATP affinity of EGFR T790M is similar to WT EGFR, the concentration of an irreversible EGFR inhibitor required to inhibit EGFR T790M will also effectively inhibit WT EGFR. The class-specific toxicities of current EGFR kinase inhibitors, skin rash and diarrhea, are a result of inhibiting WT EGFR in non-cancer tissues. This toxicity, as a result of inhibiting WT EGFR, precludes dose escalation of current agents to plasma levels that would effectively inhibit EGFR T790M . A major advance would be the identification of a mutant specific EGFR inhibitor that was less effective against wild type EGFR. Such an agent would likely be clinically more effective and also potentially more tolerable as a therapeutic agent in patients with cancer.

Anaplastic lymphoma kinase (ALK) belongs to the receptor tyrosine kinase (RTK) superfamily of protein kinases. ALK expression in normal adult human tissues is restricted to endothelial cells, pericytes, and rare neural cells. Oncogenic, constitutively active ALK fusion proteins are expressed in anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumors (IMT). ALK has also recently been implicated as an oncogene in a small fraction of non-small-cell lung cancers and neuroblastomas (Choi et al, Cancer Res 2008; 68: (13); Webb et al, Expert Rev. Anticancer Ther. 9(3), 331-356, 2009).

Anaplastic large-cell lymphomas (ALCLs) are a subtype of the high-grade non-Hodgkin's family of lymphomas with distinct morphology, immunophenotype, and prognosis. ALCLs are postulated to arise from T cells and, in rare cases, can also exhibit a B cell phenotype. In addition, there are 40% of cases for which the cell of origin remains unknown and that are classified as

"null". First described as a histological entity by Stein et al. based on the expression of CD30 (Ki-1), ALCL presents as a systemic disease afflicting skin, bone, soft tissues, and other organs, with or without the involvement of lymph nodes. ALCL can be subdivided into at least two subtypes, characterized by the presence or absence of chromosomal rearrangements between the anaplastic lymphoma kinase (ALK) gene locus and various fusion partners such as nucleophosmin (NPM). Approximately 50-60% of cases of ALCL are associated with the t(2;5)(p23;q35) chromosomal translocation, which generates a hybrid gene consisting of the intracellular domain of the ALK tyrosine kinase receptor juxtaposed with NPM. The resulting fusion protein, NPM-ALK has constitutive tyrosine kinase activity and has been shown to transform various hematopoietic cell types in vitro and support tumor formation in vivo.

NPM-ALK, an oncogenic fusion protein variant of the Anaplastic Lymphoma Kinase, which results from a chromosomal translocation is implicated in the pathogenesis of human anaplastic large cell lymphoma (Pulford K, Morris SW, Turturro F. Anaplastic lymphoma kinase proteins in growth control and cancer. J Cell Physiol 2004; 199: 330-58). The roles of aberrant expression of constitutively active ALK chimeric proteins in the pathogenesis of ALCL have been well defined (Weihua Wan, et.al. Anaplastic lymphoma kinase activity is essential for the proliferation and survival of anaplastic large cell lymphoma cells. Blood First Edition Paper, prepublished online October 27, 2005; DOI 10.1182/blood-2005-08- 3254). NPM- ALK is implicated in the dysregulation of cell proliferation and apoptosis in ALCL lymphoma cells (Pulford et al, 2004).

Other less frequent ALK fusion partners, e.g., tropomyosin-3 and clathrin heavy chain, have also been identified in ALCL as well as in CD30-negative diffuse large-cell lymphoma. Despite subtle differences in signaling and some biological functions, all fusions appear to be transforming to fibroblasts and hematopoietic cells. Extensive analysis of the leukemogenic potential of NPM-ALK in animal models has further corroborated the importance of NPM-ALK and other ALK rearrangements in the development of ALK-positive ALCL and other diseases.

ALK fusion proteins have also been detected in cell lines and/or primary specimens representing a variety of other tumors including inflammatory myofibroblastic tumor (IMT), neuroectodermal tumors, glioblastomas, melanoma, rhabdomyosarcoma tumors, and esophageal squamous cell carcinomas (see review by Webb TR, Slavish J, et al. Anaplastic lymphoma kinase: role in cancer pathogenesis and small-molecule inhibitor development for therapy. Expert Rev

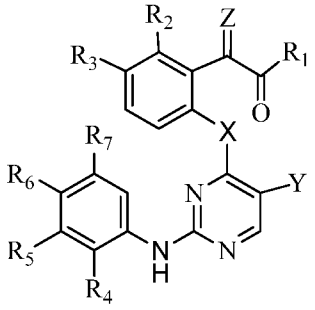
Anticancer Ther. 2009; 9(3): 331-356). Recently, ALK is also implicated in small percent of breast colorectal and non-small cell lung cancers (Lin E, Li L, et al. Exon Array Profiling Detects EML4-ALK Fusion in Breast, Colorectal, and Non-Small Cell Lung Cancers. Mol Cancer Res 2009; 7(9): 1466-76).

Approximately 3–7% of lung tumors harbor ALK fusions, and multiple different ALK rearrangements have been described in NSCLC. The majority of these ALK fusion variants are comprised of portions of the echinoderm microtubule-associated protein-like 4 (EML4) gene with the ALK gene. At least nine different EML4-ALK fusion variants have been identified in NSCLC (Takeuchi et al. Multiplex reverse transcription-PCR screening for EML4-ALK fusion transcripts.Clin Cancer Res.2008,15(9):3143-9).In addition, non-EML4 fusion partners have also been identified, including KIF5B-ALK (Takeuchi et al. KIF5B-ALK, a novel fusion oncokinase identified by an immunohistochemistry-based diagnostic system for ALK-positive lung cancer. 2009,15(9):3143-9) and TFG-ALK (Rikova et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007,131(6):1190-203).

The various N-terminal fusion partners promote dimerization and therefore constitutive kinase activity. Signaling downstream of ALK fusions results in activation of cellular pathways known to be involved in cell growth and cell proliferation (Mosse et al. Inhibition of ALK signaling for cancer therapy. Clin Cancer Res. 2009, 15(18):5609-14).

Summary of Invention

The present invention relates to heterocyclic pyrimidine compounds useful as EGFR or ALK inhibitors and for the treatment of conditions mediated by EGFR or ALK. The compounds of the invention have the general structure as Formula I or a pharmaceutically acceptable salt:



Formula I

and

X is absent, O, S, or NR_{16}; R_{16} is H or C_{1-6} alkyl;

Y is halogen, OH, NH_2, CN, N_3, NO_2, or substituted or unsubstituted C_{1-6} alkyl;

Z is O, S, NR_{20}, or $CR_{20}R_{21}$; and each R_{20} or R_{21} is independently H, halogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{1-6} alkoxy;

R_1 is hydroxy, $N(R_8)(R_9)$, $N(R_8)(CH_2)N(R_8)(R_9)$, $N(R_8)(R_9)CO(R_9)$, $N(R_8)CO(R_9)$, $C(O)R_8$, $C(O)OR_8$, $C(O)NH_2$, $C(O)NH(R_8)$, $C(O)N(R_8)(R_9)$, alkyl, haloalkyl, aryl, arylalkyl, alkoxy, heteroaryl, heterocyclic, or carbocyclic, each of which may be optionally substituted; each R_8 and R_9 is independently H, hydroxy, alkyl, alkenyl, vinyl, heterocyclic, cycloalkyl, or carbocyclic, each of which may be optionally substituted;

R_2 is H, F, or C_{1-4} alkyl; or

R_2 and R_1 together with the atoms to which they are attached form a 5- to 7-member heterocyclic ring comprising 1 - 3 hetero atoms independently selected from P, N, O or S, the heterocyclic ring being unsubstituted or substituted;

R_3 is H, halogen, or a 5 or 6 member heterocyclic ring comprising 1 or 2 N atoms, the heterocyclic ring being unsubstituted or substitute; or

R_2 and R_3 together form 5- to 12-membered substituted or unsubstituted heterocyclic ring comprising 1, 2, 3 or 4 hetero atoms independently selected from N, or O;

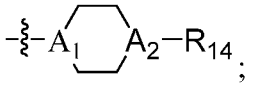
R_4 is H, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}cycloalkyloxy, halogen, -O-heterocyclic, heterocyclic, or $-NR_{24}(CH_2)_PNR_{24}R_{25}$, each of which may be optionally substituted; and P is 0, 1, 2, or 3, and each R_{24} or R_{25} is independently H, halogen, substituted or unsubstituted C_{1-6} alkyl, or substituted or unsubstituted C_{1-6} alkoxy;

R_5 is H, F, C_{1-6}alkyl, haloalkyl, C_{1-6}alkoxy, cycloalkyloxy, $-NR_{15}C(O)(CH_2)_nCR_{17}=CR_{18}R_{19}$, $-NR_{15}C(O)(CH_2)_nOCHR_{17}R_{18}$, $-NR_{15}C(O)(CH_2)_nCR_{17}(CH_2)_mCHR_{18}R_{19}$, $-NR_{15}C(O)(CH_2)_nCR_{17}=CH(CH_2)_mNR_{18}R_{19}$, $-NR_{15}C(O)CR_{17}(CH_2)_mNR_{18}(CH_2)_nNR_{18}R_{19}$, $-NR_{15}C(O)(CH_2)_nCHR_{17}R_{18}$, $-NR_{15}C(O)(CH_2)_nCR_{17}(CH_2)_mCHR_{18}R_{19}$, or $-NR_{15}C(O)(CH_2)_nC(=R_{17})(CH_2)_mCHR_{18}R_{19}$, each of which may be optionally substituted; or is a 5 or 6 member heterocyclic ring containing 1, 2 or 3 hetero atoms independently selected from N or O, the heterocyclic ring being unsubstituted or substituted; and each R_{15}, R_{17}, R_{18} or R_{19} is independently absent, -H, -OH, $-NH_2$, halogen, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl,

cycloalkynyl, aryl, heteroalkyl, heterocyclic, a bond, or heteroaryl, each of which may be optionally substituted; and each m or n is independently 0, 1, 2, or 3;

R_7 is H, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}cycloalkyloxy, $-OC(O)N(R_{10})(R_{11})$, $-NR_{10}C(O)OR_{11}$, $-NR_{22}C(O)CR_{23}=CR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sCHR_{10}R_{11}$, $NR_{15}C(O)(CH_2)_nC(R_{23})(CH_2)_mCHR_{18}R_{19}$, $-NR_{22}C(O)CR_{23}=CR_{10}(CH_2)_sR_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sNR_{10}(CH_2)_tNR_{10}R_{11}$, or $-NR_{22}C(O)(CH_2)_sCR_{23}=CH(CH_2)_tNR_{10}R_{11}$, each of which may be optionally substituted; or is a 5 or 6 member heterocyclic ring comprising 1, 2 or 3 hetero atoms independently selected from N or O, the heterocyclic ring being unsubstituted or substituted; and each R_{10}, R_{11}, R_{22} or R_{23} is independently H, alkyl, alkenyl, alkynyl, and heteroalkyl, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond, each of which may be optionally substituted; or R_{10} and R_{11}, together with the atoms to which they are attached, combine to form a 3-, 4-, 5- or 6-membered heterocyclic ring which is unsubstituted or substituted; and each s or t is independently 0, 1, 2, or 3;

R_6 combines with R_7 to form a 6 member heterocyclic ring, or is H, halogen, -CN, $-NO_2$, cycloalkyl, heteroalkyl, heterocyclic, heterocyclic-CO-alkyl, heterocyclic-CO-alkenyl, heteroaryl, $-R_{12}$, $-OR_{13}$, $-O\text{-}NR_{12}R_{13}$, $-NR_{12}R_{13}$, $-NR_{12}\text{-}NR_{12}R_{13}$, $-NR_{12}\text{-}OR_{13}$, $-C(O)GR_{13}$, $-OC(O)GR_{13}$, $-NR_{12}C(O)GR_{13}$, $-SC(O)GR_{13}$, $-NR_{12}C(=S)GR_{13}$, $-OC(=S)GR_{13}$, $-C(=S)GR_{13}$, $-YC(=NR_{12})GR_{13}$, $-GC(=N\text{-}OR_{12})GR_{13}$, $-GC(=N\text{-}NR_{12}R_{13})GR_{13}$, $-GP(=O)(GR_{12})(GR_{13})$, $-NR_{12}SO_2R_{13}$, $-S(O)_rR_{13}$, $-SO_2NR_{12}R_{13}$, $-NR^1SO_2NR_{12}R_{13}$, $-O(CH_2)_rR_{13}$, $-O(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rR_{13}$, $-(CH_2)_rNR_{12}R_{13}$, or $-CH_2O(CH_2)_rNR_{12}R_{13}$, each of which may be optionally substituted; or



each G is, independently, a bond, -O-, -S-, or $-NR_{15}$; and each R_{12}, R_{13}, or R_{15} is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl, each of which may be optionally substituted;

r is 0, 1, 2, or 3;

each A_1 or A_2 is, independently, CH or N; and R_{14} is alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroary, each of which

may be optionally substituted.

The present invention further provides some preferred technical solutions with regard to compound of Formula (I).

In some embodiments of Formula (I), Y is halogen, or substituted or unsubstituted C_{1-6} alkyl.

In some embodiments of Formula (I), Y is halogen, methyl, or methyl substituted with halogen.

In some embodiments of Formula (I), Y is Cl, or CF_3.

In some embodiments of Formula (I), Y is CH_3.

In some embodiments of Formula (I), X is NR_{16}.

In some embodiments of Formula (I), R_{16} is H.

In some embodiments of Formula (I), Z is O, or CH_2.

In some embodiments of Formula (I), Z is O.

In some embodiments of Formula (I), r is 0, 1, or 2.

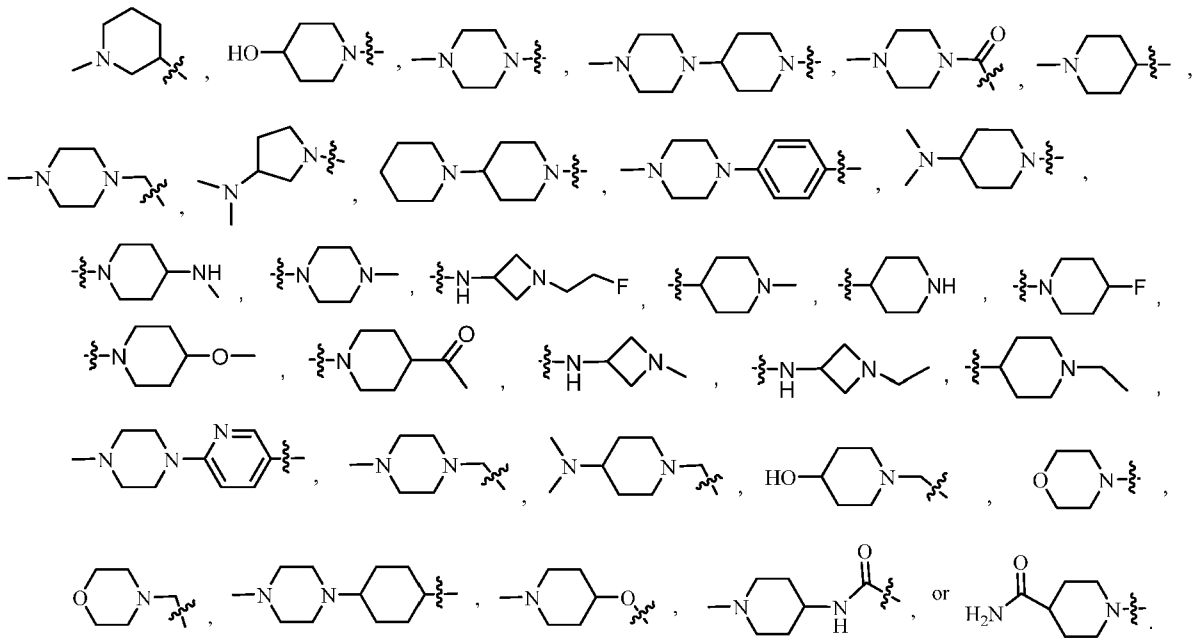
In some embodiments of Formula (I), r is 3.

In some embodiments of Formula (I), each R_6 is independently H, halo, $-R_{12}$, $-OR_{13}$, or $-NR_{12}R_{13}$, each of which may be optionally substituted.

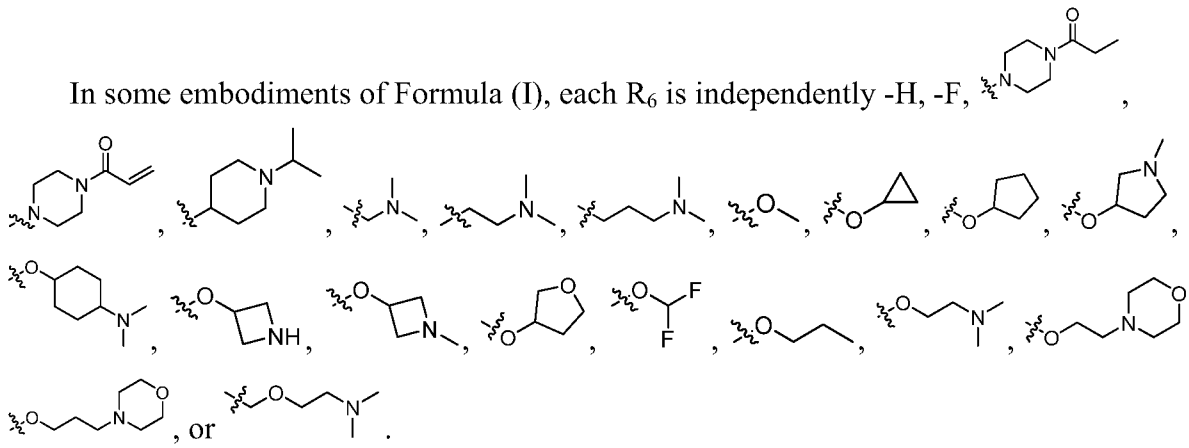
In some embodiments of Formula (I), each R_6 combines with R_7 to form a 6 member heterocyclic ring optionally substituted with H, hydroxy, alkyl, alkenyl, heterocyclic, cycloalkyl, $-OR_{13}$, $-C(O)R_{12}$, $-NR_{12}R_{13}$, or carbocyclic; or R_6 is $-O(CH_2)_rR_{13}$, $-O(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rR_{13}$, $-(CH_2)_rNR_{12}R_{13}$, or $-CH_2O(CH_2)_rNR_{12}R_{13}$, each of which may be optionally substituted with substituted or unsubstituted C_{1-6}alkyl, substituted or unsubstituted C_{2-6}alkenyl, substituted or unsubstituted C_{2-6}alknyl, haloalkyl, halogen, substituted or unsubstituted alkoxy, $-NH_2$, $–NCH_3CH_3$, or $–NHCH_3$.

In some embodiments of Formula (I), each R_{12}, R_{13}, or R_{15} is independently H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, or (C_{3-6})heterocyclic, each of which may be optionally substituted.

In some embodiments of Formula (I), each R_6 is independently -OH, -OEt, $-NH_2$, $-NHCH_3$, ,$-NCH_3CH_3$,



In some embodiments of Formula (I), each R_6 is independently -H, -F,



In some embodiments of Formula (I), each R_2 and R_3 is independently hydrogen, or halogen.

In some embodiments of Formula (I), R_2 and R_3 are both hydrogen.

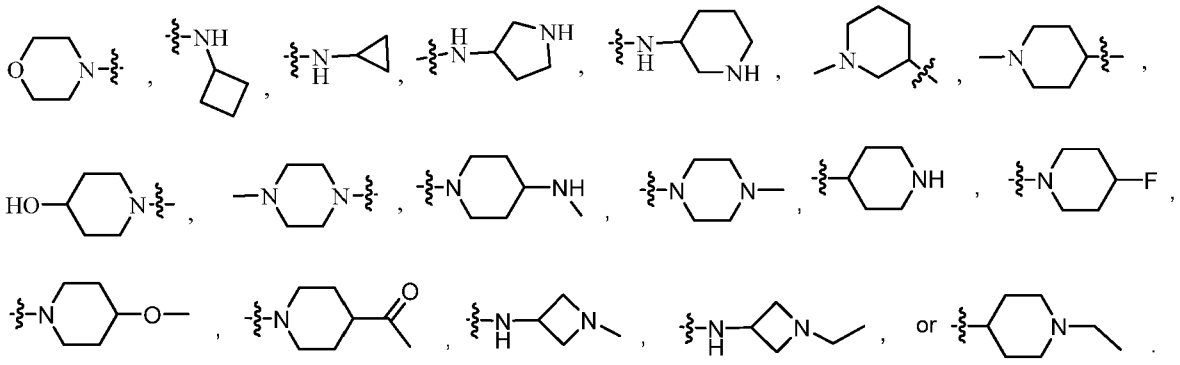
In some embodiments of Formula (I), R_1 is hydroxy, $N(R_8)(R_9)$, alkyl, alkoxy, or haloalkyl, each of which may be optionally substituted.

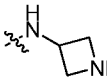
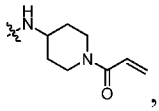
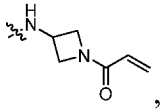
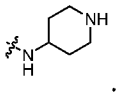
In some embodiments of Formula (I), each R_8 and R_9 is independently H, hydroxy, $C_{1\text{-}6}$alkyl, $C_{2\text{-}6}$alkenyl.

In some embodiments of Formula (I), each R_8 or R_9 is independently methyl, or vinyl.

In some embodiments of Formula (I), each R_8 and R_9 is independently heterocyclic, cycloalkyl, or carbocyclic, each of which may be optionally substituted.

In some embodiments of Formula (I), each R_1 is independently -OH, -OEt, -NHOH, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, $-NHCH_2CH_2NCH_3CH_3$, $-NHCH_2CH_2OH$,



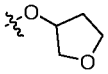
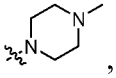
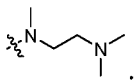
In some embodiments of Formula (I), each R_1 is independently $-CH_2CH_3$, , , , , , or .

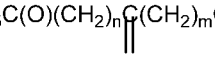
In some embodiments of Formula (I), R_2, R_3, and R_5 are all H.

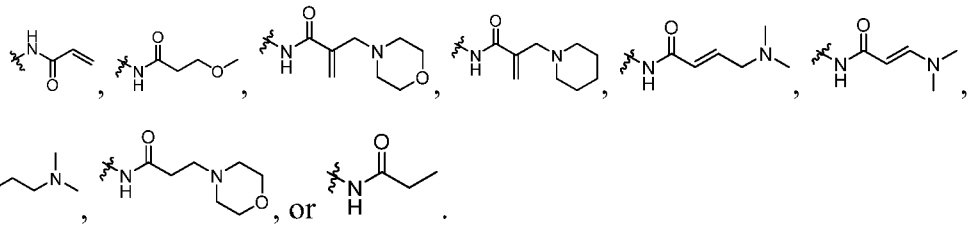
In some embodiments of Formula (I), R_4 is $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$ alkenyloxy, or $C_{3\text{-}6}$ cycloalkyloxy.

In some embodiments of Formula (I), R_4 is hydrogen, $-OCH_3$, -OEt, , or .

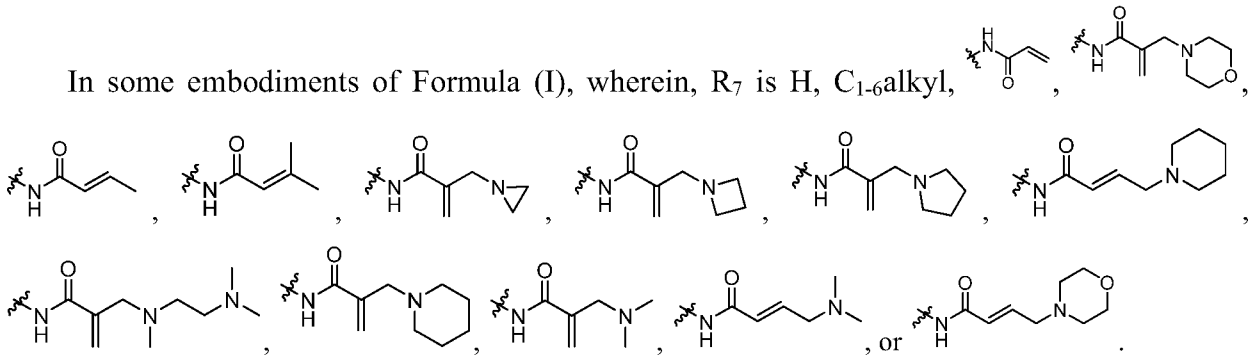
In some embodiments of Formula (I), R_4 is halogen, -O-heterocyclic, heterocyclic, or $-NR_{24}(CH_2)_PNR_{24}R_{25}$, each of which may be optionally substituted; and P is 1, or 2, each R_{24} or R_{25} is independently $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$alkoxy, -NHOH, $-NH_2$, $NHCH_3$, NCH_3CH_3, or halogen.

In some embodiments of Formula (I), R_4 is hydrogen, F, $-OCH_3$, , , , or .

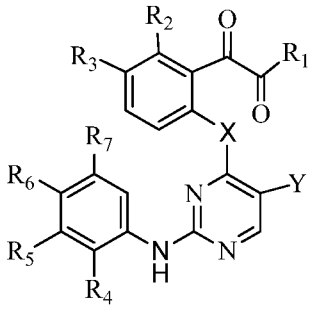
In some embodiments of Formula (I), R_5 is H, haloalkyl, $C_{1\text{-}6}$alkoxy, $-NR_{15}C(O)(CH_2)_nCR_{17}=CR_{18}R_{19}$, $-NR_{15}C(O)(CH_2)_nOCHR_{17}R_{18}$, , $-NR_{15}C(O)(CH_2)_nCR_{17}=CH(CH_2)_mNR_{18}R_{19}$, $-NR_{15}C(O)CR_{17}(CH_2)_mNR_{18}(CH_2)_nNR_{18}R_{19}$, or $-NR_{15}C(O)(CH_2)_nCHR_{17}R_{18}$, each of which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond; and each R_{15}, R_{17}, R_{18} or R_{19} is independently absent, -H, $C_{1\text{-}6}$alkyl, alkenyl, $C_{1\text{-}6}$alkoxy, -NHOH, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, a bond, or $C_{3\text{-}6}$heterocyclic; and each m or n is independently 0, 1, or 2.

In some embodiments of Formula (I), R_5 is H, methyl, methyl substituted by halogen, methoxy, , or .

In some embodiments of Formula (I), R_7 is H, $C_{1\text{-}6}$alkyl, $-NR_{22}C(O)CR_{23}=CR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sCHR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}=CR_{10}(CH_2)_sR_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sNR_{10}(CH_2)_tNR_{10}R_{11}$, or $-NR_{22}C(O)(CH_2)_sCR_{23}=CH(CH_2)_tNR_{10}R_{11}$, each of which may be optionally substituted; and each R_{10}, R_{11}, R_{22} or R_{23} is independently H, alkyl, alkenyl, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond, each of which may be optionally substituted with $C_{1\text{-}6}$alkyl, alkoxy, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond; and each s or t is independently 0, 1, or 2.

In some embodiments of Formula (I), wherein, R_7 is H, $C_{1\text{-}6}$alkyl, .

In some embodiments of Formula (I), the compound is of Formula II:



Formula II

The present invention further provides some preferred technical solutions with regard to compound of Formula (II).

In some embodiments of Formula (II), X is NH.

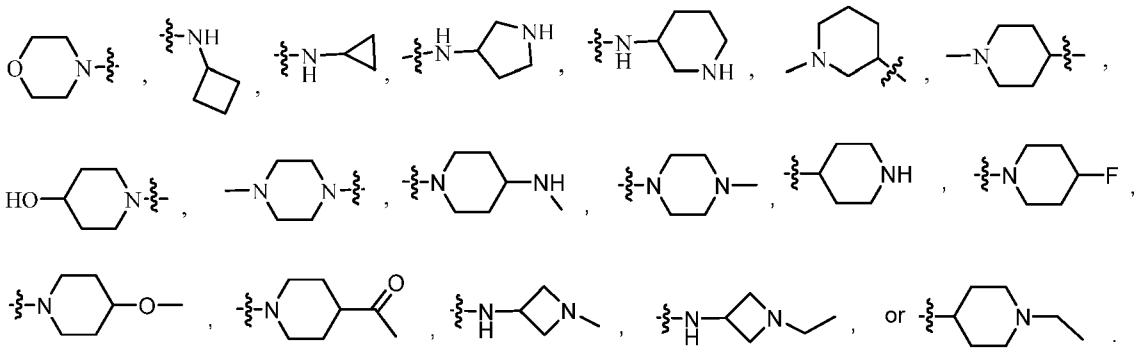
In some embodiments of Formula (II), Y is halogen, or haloalkyl.

In some embodiments of Formula (II), Y is Cl, or CF_3.

In some embodiments of Formula (II), Y is $C_{1\text{-}6}$alkyl.

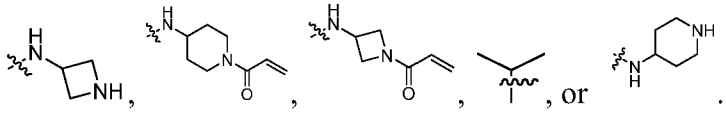
In some embodiments of Formula (II), Y is CH_3.

In some embodiments of Formula (II), R_1 is -OH, -OEt, -NHOH, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, $-NHCH_2CH_2NCH_3CH_3$, $-NHCH_2CH_2OH$,



In some embodiments of Formula (II), each R_1 is independently $-CH_2CH_3$,

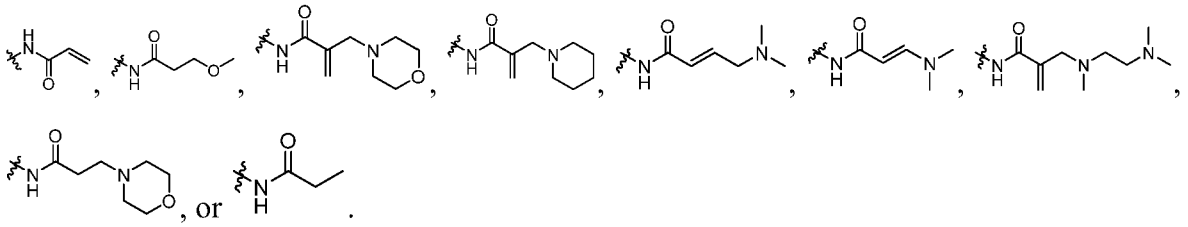




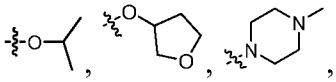
In some embodiments of Formula (II), R_2, R_3, R_5, and R_7 are all H.

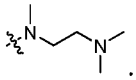
In some embodiments of Formula (II), R_2, R_3, and R_5 are all H.

In some embodiments of Formula (II), R_5 is H, methyl substituted by halogen, methoxy,

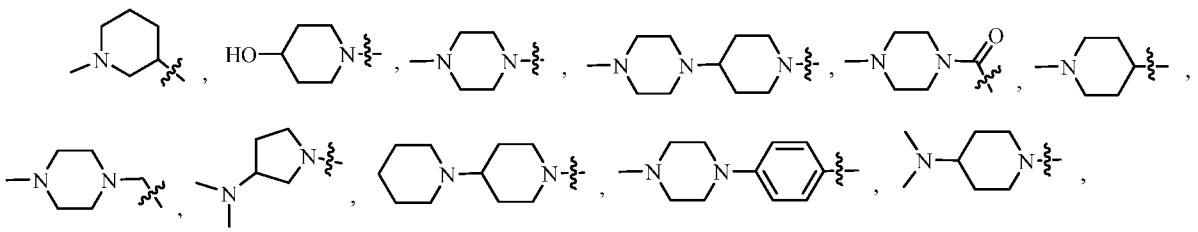


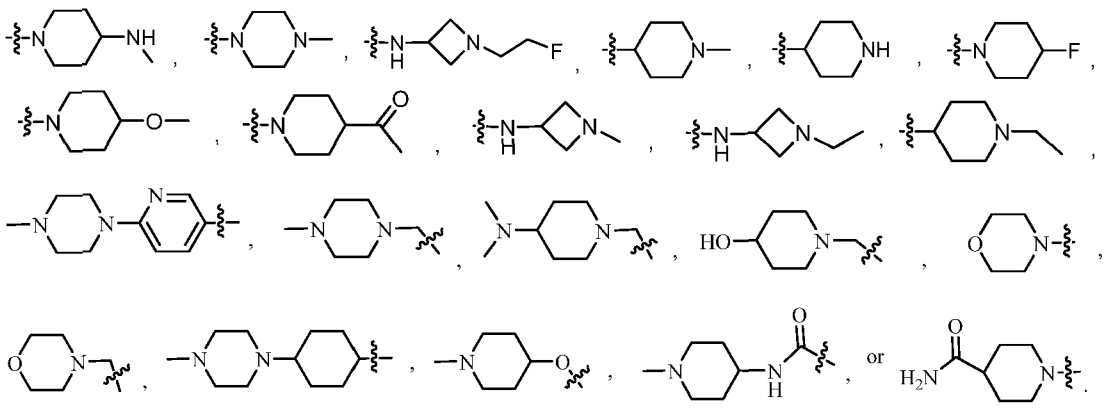
In some embodiments of Formula (II), R_4 is hydrogen, F, $-OCH_3$,

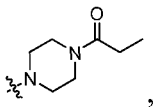


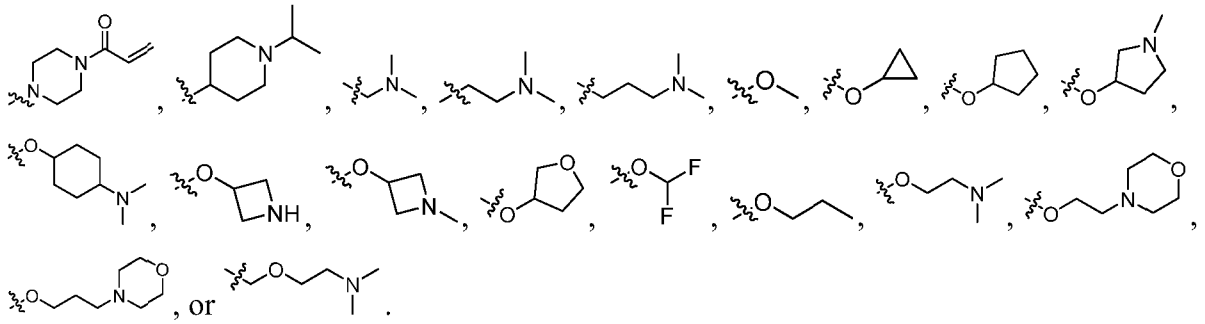


In some embodiments of Formula (II), each R_6 is independently -OH, -OEt, -NHOH, $-NH_2$, $-NHCH_3$, or $-NCH_3CH_3$,





In some embodiments of Formula (II), each R_6 is independently -H, -F, ,



The present invention further provides some preferred technical solutions with regard to compound of Formula (I) or Formula (II), compound is

1） ethyl 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino) pyrimidin-4-ylamino)phenyl)-2-oxoacetate;

2） 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyri midin-4-ylamino)phenyl)-2-oxoacetic acid;

3） 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyri midin-4-ylamino)phenyl)-N-hydroxy-2-oxoacetamide;

4） 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyri midin-4-ylamino)phenyl)-2-oxoacetamide;

5） ethyl 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino) pyrimidin-4-ylamino)phenyl)acrylate;

6） 2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4 -yl)amino)phenyl)-2-oxoacetamide;

7） 2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

8） 2-(2-((5-chloro-2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

9） 2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

10） 2-(2-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

11） 2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

12） 2-(2-((2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

13） 2-(2-((2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

14） 2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

15） 2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetic acid;

16） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-methyl-2-oxoacetamide;

17） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N,N-dimethyl-2-oxoacetamide;

18） 1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-morpholinoethane-1,2-dione;

19） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-(dimethylamino)ethyl)-2-oxoacetamide;

20） 2-(2-((5-chloro-2-((2-methoxy-4-(4-(methylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-hydroxyethyl)-2-oxoacetamide;

21） 1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-methylbutane-1,2-dione;

22） 1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)propane-1,2-dione;

23） 1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propane-1,2-dione;

24） N-(azetidin-3-yl)-2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

25） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-cyclopropyl-2-oxoacetamide;

26） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(pyrrolidin-3-yl)acetamide;

27） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(piperidin-4-yl)acetamide;

28） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

29） 2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

30） 2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

31） 2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

32） 2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

33） 2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

34） 2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

35） 2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

36） 2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

37） 2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

38） 2-(2-((5-chloro-2-((4-(4-fluoropiperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

39） 2-(2-((5-chloro-2-((2-methoxy-4-(4-methoxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

40） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

41） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(morpholinomethyl)acrylamide;

42） 1-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

43） 1-(2-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

44） 1-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

45） 1-(2-(2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

46） 2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

47） 2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

48） 2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

49） 2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

50） 2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

51） 2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

52） 2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

53） 2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

54） 2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

55） N-(1-acryloylazetidin-3-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

56） N-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

57） N-(3-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

58） N-(3-(4-(2-(2-amino-2-oxoacetyl)phenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)acrylamide;

59） *N*-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

60） 2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

61） 2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

62） 2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

63） 2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

64） N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

65） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

66） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluoro-4-methoxyphenyl)acrylamide;

67） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

68） N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide;

69） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide;

70） (*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)but-2-enamide;

71） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-3-methylbut-2-enamide;

72） (*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-(piperidin-1-yl)but-2-enamide;

73） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(piperidin-1-ylmethyl)acrylamide;

74） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

75） N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

76） N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

77） N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

78） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide;

79） (*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-morpholinobut-2-enamide;

80） (*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-(dimethylamino)but-2-enamide;

81） N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide;

82） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide;

83） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide;

84） N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide;

85） N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

86） N-(5-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

87） 2-(2-(2-(4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

88） 2-(2-(2-(4-(4-acryloylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

89） N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

90） N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

91） N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

92） N-(5-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

93） N-(5-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

94） 2-(2-(2-(4-(4-acetylpiperazin-1-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

95） 2-(aziridin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

96） 2-(azetidin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

97） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(pyrrolidin-1-ylmethyl)acrylamide;

98） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(2-morpholinoethoxy)phenyl)acrylamide;

99） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide;

100） N-(3-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide;

101） N-(5-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

102） N-(5-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

103） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)-3-methoxypropanamide;

104） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-cyclopropoxyphenyl)acrylamide;

105） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(cyclopentyloxy)phenyl)acrylamide;

106） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylpyrrolidin-3-yloxy)phenyl)acrylamide;

107） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-(dimethylamino)cyclohexyloxy)phenyl)acrylamide;

108） N-(2-(azetidin-3-yloxy)-5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

109） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylazetidin-3-yloxy)phenyl)acrylamide;

110） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide;

111） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

112） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(morpholinomethyl)acrylamide;

113） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(piperidin-1-ylmethyl)acrylamide;

114） (*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-4-(dimethylamino)but-2-enamide;

115） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide;

116） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(difluoromethoxy)phenyl)acrylamide;

117） 2-(2-(5-chloro-2-(3-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

118） 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

119） 2-(2-(5-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

120） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)propionamide;

121） (*E*)-N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-3-(dimethylamino)acrylamide;

122） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-propoxyphenyl)acrylamide;

123） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluorophenyl)-3-morpholinopropanamide;

124） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(tetrahydrofuran-3-yloxy)phenyl)acrylamide;

125） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide;

126） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide;

127） N-(3-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

128） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-2-(piperidin-1-ylmethyl)acrylamide;

129） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)-2-(piperidin-1-ylmethyl)acrylamide;

130） 2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-diethyl-2-oxoacetamide;

131） N-(3-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

132） N-(5-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

133） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-5-(trifluoromethyl)phenyl)acrylamide;

134） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide;

135） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-(4-methylpiperazin-1-yl)phenyl)acrylamide;

136） N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-(tetrahydrofuran-3-yloxy)phenyl)acrylamide;

137） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)phenyl)acrylamide;

138） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)-4-methoxyphenyl)acrylamide;

139） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)phenyl)acrylamide;

140） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)-4-methoxyphenyl)acrylamide;

141） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide;

142） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide;

143） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylpiperidin-4-yl)phenyl)acrylamide;

144） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(1-methylpiperidin-4-yl)phenyl)acrylamide;

145） 2-(2-(5-chloro-2-(3-methoxy-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

146） 2-(2-(2-(4-(1-acetylpiperidin-4-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

147） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethyl)phenyl)acrylamide;

148） N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(3-(dimethylamino)propyl)phenyl)acrylamide;

149） 2-(2-(5-chloro-2-(4-(1-isopropylpiperidin-4-yl)-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

150） 2-(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide.

The present invention also provides a pharmaceutical composition comprising a compound of any of claims 1-48 and a pharmaceutically acceptable excipient. such as hydroxypropyl methyl cellulose. In the composition,the said compound in a weight ratio to the said excipient within the range form about 0.0001 to about 10.

The present invention additionally provided a use of a pharmaceutical composition of Formula (I) or Formula (II) for the preparation of a medicament for treating a disease in a subject.

The present invention further provides some preferred technical solutions with regard to above-mentioned uses.

In some embodiments, a medicament thus prepared can be used for the treatment or prevention of, or for delaying or preventing onset or progression in, cancer, cancer metastasis, cardiovascular disease, an immunological disorder or an ocular disorder.

In some embodiments, a medicament thus prepared can be used for t inhibiting a kinase.

In some embodiments, the kinase comprises EGFR, ALK, ALK fusion proteins, Flt3, Jak3, Blk, Bmx, Btk, HER2 (ErbB2), HER4 (ErbB4), Itk, Tec, or Txk.

In some embodiments, the EGFR is a mutant EGFR; the cancer is EGFR-driven cancer, and the EGFR-driven cancer is characterized by the presence of one or more mutations selected from: (i) L858R, (ii) T790M, (iii) both L858R and T790M, (iv) delE746_A750, or (v) both delE746_A750 and T790M.

In some embodiments, the EGFR-driven cancer is a non-small cell lung cancer (NSCLS), glioblastoma, pancreatic cancer, head and neck cancer (e.g., squamous cell carcinoma), breast cancer, colorectal cancer, epithelial cancer, ovarian cancer, prostate cancer, or an adenocarcinoma.

In some embodiments, the ALK fusion proteins is MEL4-ALK or NPM-ALK kinases.

In some embodiments, the subject is a human.

The present invention also provides a method of inhibiting a kinase in a subject, comprising administering a compound of Formula (I) or Formula (II) or above-mentioned pharmaceutical composition.

The present invention further provides some preferred technical solutions with regard to above-mentioned methods.

In some embodiments, the kinase comprises EGFR, ALK, ALK fusion proteins, Flt3, Jak3, Blk, Bmx, Btk, HER2 (ErbB2), HER4 (ErbB4), Itk, Tec, or Txk.

In some embodiments, the EGFR is a mutant EGFR, the ALK fusion proteins is MEL4-ALK or NPM-ALK kinases.

The present invention also provides a method of treating a disease in a subject comprising administering to the subject a compound of Formula I or Formula II or above-mentioned pharmaceutical composition.

The present invention further provides some preferred technical solutions with regard to above-mentioned methods.

In some embodiments, the disease is caused by kinase regulation disorder, and the kinase comprises EGFR, ALK, ALK fusion proteins, Flt3, Jak3, Blk, Bmx, Btk, HER2 (ErbB2), HER4 (ErbB4), Itk, Tec, or Txk.

In some embodiments, the disease is EGFR-driven cancer, and the EGFR-driven cancer is characterized by the presence of one or more mutations selected from: (i) L858R, (ii) T790M, (iii) both L858R and T790M, (iv) delE746_A750, or (v) both delE746_A750 and T790M.

In some embodiments, the EGFR-driven cancer is a non-small cell lung cancer (NSCLS), glioblastoma, pancreatic cancer, head and neck cancer (e.g., squamous cell carcinoma), breast cancer, colorectal cancer, epithelial cancer, ovarian cancer, prostate cancer, or an adenocarcinoma.

In some embodiments, the ALK fusion proteins is MEL4-ALK or NPM-ALK kinases.

In some embodiments, the subject is a human.

By "EGFR-driven cancer" is meant a cancer characterized by a mutation in an EGFR gene that alters the biological activity of an EGFR nucleic acid molecule or polypeptide, including the specific mutations noted herein. EGFR-driven cancers can arise in any tissue, including brain, blood, connective tissue, liver, mouth, muscle, spleen, stomach, testis, and trachea. EGFR-driven cancers include non-small cell lung cancer (NSCLS), including one or more of squamous cell carcinoma, adenocarcinoma, adenocarcinoma, bronchioloalveolar carcinoma (BAC), BAC with focal invasion, adenocarcinoma with BAC features, and large cell carcinoma; neural tumors, such as glioblastomas; pancreatic cancer; head and neck cancers (e.g., squamous cell carcinoma); breast cancer; colorectal cancer; epithelial cancer, including squamous cell carcinoma; ovarian cancer; prostate cancer; adenocarcinomas; and including cancers which are EGFR mediated.

An "EGFR mutant" or "mutant" includes one or more deletions, substitutions, or additions in the amino acid or nucleotide sequences of EGFR protein, or EGFR coding sequence. The EGFR mutant can also include one or more deletions, substitutions, or additions, or a fragment thereof, as long as the mutant retains or increases tyrosine kinase activity, compared to wild type EGFR. In particular EGFR mutations, kinase or phosphorylation activity can be increased (e.g., by at least 5%, 10%, 15%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, or even 100%), as compared to wild type EGFR. Particular EGFR mutants are described herein, where mutations are provided relative to the position of an amino acid in human EGFR, as described in the sequence provided in NCBI GenBank Reference Sequence: NP_005219.2.

As used herein, the term "inhibiting the proliferation of a cell expressing an EGFR mutant" refers to measurably slowing, stopping, or reversing the growth rate of the EGFR-expressing cells in vitro or in vivo. Desirably, a slowing of the growth rate is by at least 10%, 20%, 30%, 50%, or even 70%, as determined using a suitable assay for determination of cell growth rates (e.g., a cell growth assay described herein). The EGFR mutant can be any EGFR mutant described herein.

In addition, the present invention provides at least one compound for use in the treatment of cancer, the prevention of cancer metastasis or the treatment of cardiovascular disease, an immunological disorder or an ocular disorder.

The present invention also provides a method of treating a patient having a condition which is mediated by protein kinase activity, said method comprising administering to the patient a therapeutically effective amount of at least one compound as described herein, or a pharmaceutically acceptable salt thereof. Examples of the protein kinase include mutant EGFR, KDR, Tie-2, Flt3, FGFR3, AbI, Aurora A, c-Src, IGF-IR, ALK, c-MET, RON, PAKl, PAK2, and TAKl.

In some embodiments, the condition mediated by protein kinase activity is cancer.

Examples of cancer include a solid tumor, a sarcoma, fibrosarcoma, osteoma, melanoma, retinoblastoma, a rhabdomyosarcoma, glioblastoma, neuroblastoma, teratocarcinoma, hematopoietic malignancy, and malignant ascites.

Also provided is at least one compound as described herein or a pharmaceutically acceptable salt thereof for use as a medicament.

Further provided is at least one compound as described herein or a pharmaceutically acceptable salt thereof for use in the treatment of cancer.

Additionally provided is a method of treating cancer selected from the group consisting of lung cancer, breast cancer, colorectal cancer, renal cancer, pancreatic cancer, head cancer, neck cancer, hereditary papillary renal cell carcinoma, childhood hepatocellular carcinoma, and gastric cancer in a mammal comprising administering to a mammal in need of such treatment an effective amount of at least one compound described herein or a pharmaceutically acceptable salt thereof.

The term "halogen", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. The preferred halogen groups include F, Cl and Br.

As used herein, unless otherwise indicated, alkyl includes saturated monovalent hydrocarbon radicals having straight, branched or cyclic moieties. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, cyclcopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, cyclcobutyl, n-pentyl, 3- (2-methyl) butyl, 2-pentyl, 2-methylbutyl, neopentyl, cyclcopentyl, n- hexyl, 2-hexyl, 2-methylpentyl and cyclohexyl. Similary, C_{1-8}, as in C_{1-8}alkyl is defined to identify the group as having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or branched arrangement.

Alkenyl and alkynyl groups include straight, branched chain or cyclic alkenes and alkynes. Likewise, "C_{2-8} alkenyl" and "C_{2-8} alkynyl"means an alkenyl or alkynyl radicals having 2, 3, 4, 5, 6, 7 or 8 carbon atoms in a linear or brached arrangement.

Alkoxy radicals are oxygen ethers formed from the previously described straight, branched chain or cyclic alkyl groups.

The term"aryl", as used herein, unless otherwise indicated, refers to an unsubstituted or substituted mono- or polycyclic ring system containing carbon ring atoms. The preferred aryls are mono cyclic or bicyclic 6-10 membered aromatic ring systems. Phenyl and naphthyl are preferred aryls. The most preferred aryl is phenyl.

The term"heterocyclyl", as used herein, unless otherwise indicated, represents an unsubstituted or substituted stable three to eight membered monocyclic saturated ring system which consists of carbon atoms and from one to three heteroatoms selected from N, O or S, and wherein the nitrogen or sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heterocyclyl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclyl groups include, but are not limited to azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxopiperazinyl, oxopiperidinyl, oxoazepinyl, azepinyl, tetrahydrofuranyl, dioxolanyl, tetrahydroimidazolyl, tetrahydrothiazolyl, tetrahydrooxazolyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone and oxadiazolyl.

The term"heteroaryl", as used herein, unless otherwise indicated, represents an unsubstituted or substituted stable five or six membered monocyclic aromatic ring system or an unsubstituted or substituted nine or ten membered benzo-fused heteroaromatic ring system or bicyclic heteroaromatic ring system which consists of carbon atoms and from one to four heteroatoms selected from N, O or S, and wherein the nitrogen or sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroaryl group may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of heteroaryl groups include, but are not limited to thienyl, furanyl, imidazolyl, isoxazolyl, oxazolyl, pyrazolyl, pyrrolyl, thiazolyl, thiadiazolyl, triazolyl, pyridyl, pyridazinyl, indolyl, azaindolyl, indazolyl, benzimidazolyl, benzofuranyl, benzothienyl, benzisoxazolyl,

benzoxazolyl, benzopyrazolyl, benzothiazolyl, benzothiadiazolyl, benzotriazolyl adeninyl, quinolinyl or isoquinolinyl.

The term"carbonyl"refers to the group C(O).

The term “alkoxycarbonyl”refers to straight or branched chain esters of a carboxylic acid derivative of the present invention of the number of carbon atoms specified (e.g., C_{1-6} alkoxycarbonyl), or any number within this range (e.g., methyloxycarbonyl(MeOCO-), ethyloxycarbonyl, or butyloxycarbonyl).

Whenever the term "alkyl" or "aryl" or either of their prefix roots appear in a name of a substituent (e.g., aralky or dialkylamino) it shall be interpreted as including those limitations given above for"alkyl"and"aryl."Designated numbers of carbon atoms (e.g., C_{1-6}) shall refer independently to the number of carbon atoms in an alkyl moiety or to the alkyl portion of a larger substituent in which alkyl appears as its prefix root.

The term "alkylsulphinyl"refers to straight or branched chain alkylsulfoxides of the number of carbon atoms specified (e.g., C_{1-6} alkylsulfinyl), or any number within this range (e.g., methylsulphinyl (MeSO-), ethylsulphinyl, isopropylsulphinyl).

The term"alkylsulphonyl"refers to straight or branched chain alkylsulfones of the number of carbon atoms specified (e. g., C_{1-6} alkylsulphonyl), or any number within this range [e. g , methylsulphonyl ($MeSO_2$-), ethylsulphonyl, isopropylsulphonyl, etc].

The term "alkylthio"refers to straignt or branched chain alkylsulfides of the number of carbon atoms specified (e. g., C_{1-6} alkylthio), or any number within this range [e. g.,.methylthio (MeS-), ethylthio, isopropylthio, etc].

The term "alkenyloxy" refers to the group –O-alkenyl, where alkenyl is defined as above.

The term "alknyloxy" refers to the group –O-alknyl, where alknyl is defined as above.

The term"composition", as used herein, is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts. Accordingly, pharmaceutical compositions containing the compounds of the present invention as the active ingredient as well as methods of preparing the instant compounds are also part of the present invention. Furthermore, some of the crystalline forms for the compounds may exist as polymorphs and as such are intended to be included in the present invention. In addition, some of the

compounds may form solvates with water (i.e., hydrates) or common organic solvents and such solvates are also intended to be encompassed within the scope of this invention.

The compounds of the present invention may also be present in the form of pharmaceutically acceptable salts. For use in medicine, the salts of the compounds of this invention refer to non-toxic"pharmaceutically acceptable salts".The pharmaceutically acceptable salt forms include pharmaceutically acceptable acidic/anionic or basic/cationic salts. The pharmaceutically acceptable acidic/anionic salt generally takes a form in which the basic nitrogen is protonated with an inorganic or organic acid. Representative organic or inorganic acids include hydrochloric, hydrobromic, hydriodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroxyethanesulfonic, benzenesulfonic, oxalic, pamoic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic, salicylic, saccharinic or trifluoroacetic. Pharmaceutically acceptable basic/cationic salts include, and are not limited to aluminum, calcium, chloroprocaine, choline, diethanolamine, ethylenediamine, lithium, magnesium, potassium, sodium and zinc.

The present invention includes within its scope the prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily converted in vivo into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to the subject. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in"Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

It is intended that the definition of any substituent or variable at a particular location in a molecule be independent of its definitions elsewhere in that molecule. It is understood that substituents and substitution patterns on the compounds of this invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques know in the art as well as those methods set forth herein.

The present invention includes compounds described can contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention

includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof.

The above Formula I is shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

When a tautomer of the compound of Formula (I) exists, the present invention includes any possible tautomers and pharmaceutically acceptable salts thereof, and mixtures thereof, except where specifically stated otherwise.

When the compound of Formula (I) and pharmaceutically acceptable salts thereof exist in the form of solvates or polymorphic forms, the present invention includes any possible solvates and polymorphic forms. A type of a solvent that forms the solvate is not particularly limited so long as the solvent is pharmacologically acceptable. For example, water, ethanol, propanol, acetone or the like can be used.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non- toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N',N'- dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine,

glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Preferred are citric, hydrobromic, formic, hydrochloric, maleic, phosphoric, sulfuric and tartaric acids. Particularly preferred are formic and hydrochloric acid. Since the compounds of Formula (I) are intended for pharmaceutical use they are preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure, especially at least 98% pure (% are on a weight for weight basis).

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I (or a pharmaceutically acceptable salt thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I, or a prodrug, or a metabolite, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a

powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion, or as a water-in- oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I, or a pharmaceutically acceptable salt thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound, or a pharmaceutically acceptable salt, of Formula I. The compounds of Formula I, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen. In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques.

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active

or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 0.05mg to about 5g of the active ingredient and each cachet or capsule preferably containing from about 0.05mg to about 5g of the active ingredient. For example, a formulation intended for the oral administration to humans may contain from about 0.5mg to about 5g of active agent, compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Unit dosage forms will generally contain between from about lmg to about 2g of the active ingredient, typically 25mg, 50mg, l00mg, 200mg, 300mg, 400mg, 500mg, 600mg, 800mg, or l000mg.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I of this invention, or a pharmaceutically acceptable salt thereof, via conventional processing methods. As an example, a cream or ointment is prepared by admixing hydrophilic material and water, together with about 5wt% to about 10wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in molds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including antioxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Generally, dosage levels on the order of from about 0.01mg/kg to about 150mg/kg of body weight per day are useful in the treatment of the above-indicated conditions, or alternatively about 0.5mg to about 7g per patient per day. For example, inflammation, cancer, psoriasis, allergy/asthma, disease and conditions of the immune system, disease and conditions of the central nervous system (CNS), may be effectively treated by the administration of from about 0.01 to 50mg of the compound per kilogram of body weight per day, or alternatively about 0.5mg to about 3.5g per patient per day.

It is understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

These and other aspects will become apparent from the following written description of the invention.

Examples

The following Examples are provided to better illustrate the present invention. All parts and percentages are by weight and all temperatures are degrees Celsius, unless explicitly stated otherwise. The following abbreviations have been used in the examples:

ATP: Adenosine triphosphate;

DIPEA: N,N-Diisopropylethylamine;

DMF: N,N-Dimethylformamide;

DMA: *N,N*-Dimethyacetamide;

DMAP: 4-*N,N*-Dimethylamiopryidine;

DMSO: Dimethyl sulfoxide;

DEAD: Diethyl azodicarboxylate;

HATU: O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate;

DIPEA: N,N-Diisopropylethylamine;

EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide;

TBAB: Tetrabutyl ammonium bromide;

TEA: Triethylamine;

EtOAc: Ethyl acetate;

GSR: Glutathione-S-Transferase;

Crk: CT10 (Chicken Tumor Retrovirus 10);

min: Minute;

h or hr: Hour;

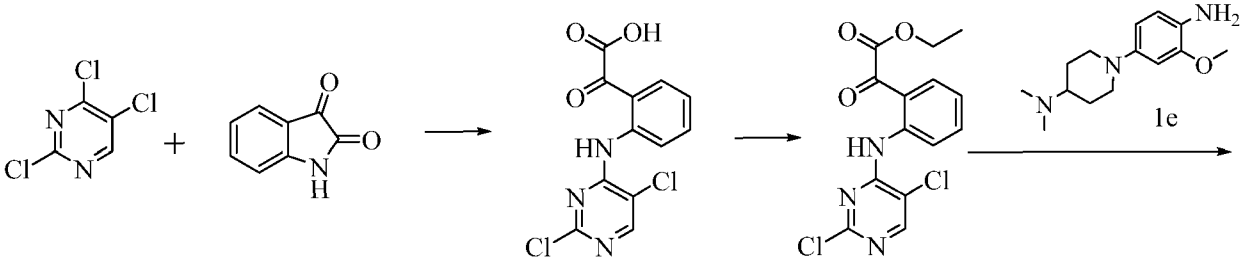
rt or RT: room temperature;

SDS, Sodium Dodecyl Sulfate;

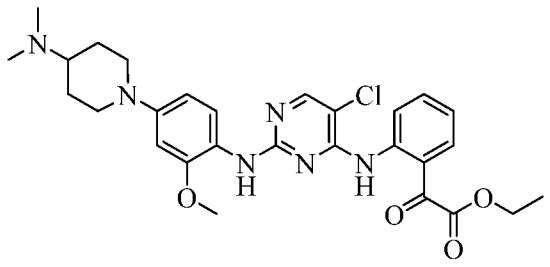
SDS-PAGE, Sodium Dodecyl Sulfate PolyAcrylamide Electrophoresis Gel;

TLC, Thin layer chromatography.

Example 1 Synthesis of compound 1



1a 1b 1c 1d



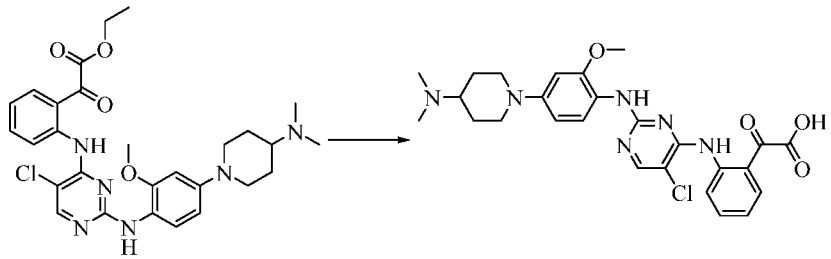
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A mixture of Compound **1a** (25g, 0.11mol), Compound **1b** (20g, 0.11mol) and K_2CO_3 (37.5g, 0.22mol) in DMF (200ml) was stirred at 70℃ for 3 hrs. Then H_2O (300ml) was added to the mixture and extracted with EA(200 ml×3), the aqueous layer was acidified with HCl (1mol/L) to pH 3-4. The precipitate was collected by filtration and washed with methanol (5ml). After dried under air for 5hrs, 23g of Compound **1c** was obtained.

$(COCl)_2$ (7.2ml in 10ml of DCM) was added to a solution of Compound **1c** (5.0 g) and 2 drops of DMF in DCM at ice bath under N_2 with stirring. After 3.5hrs, the solvent was removed. The residue was dissolved in DCM and then added 10ml of EtOH. After stirring for 1hr, the reaction mixture was quenched with water. The organic layer was separated and dried, and concentrated. The residue was purified by chromatography to give 4.7g of Compound **1d** as a yellow solid.

A mixture of Compound **1d** (200 mg) and Compound **1e** was stirred in sealed tube at 130℃ for 1hr. After the solvent was removed, the residue was purified to give Compound **1**. MS: 552.2$(M+H)^+$.

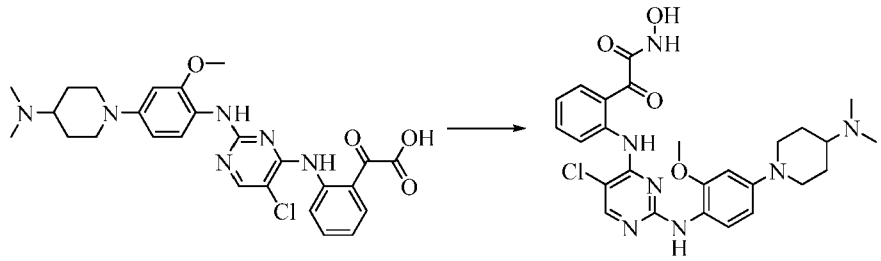
Example 2 Synthesis of compound 2



1 2

A mixture of Compound **1** and NaOH(0.5ml, 2mol/L) in MeOH was stirred at room temperature for 1hr. Then the solution was acidified with HCl to about pH 5. After filtration, the solid was dried to give the Compound **2** (37mg). MS: 524.2$(M+H)^+$.

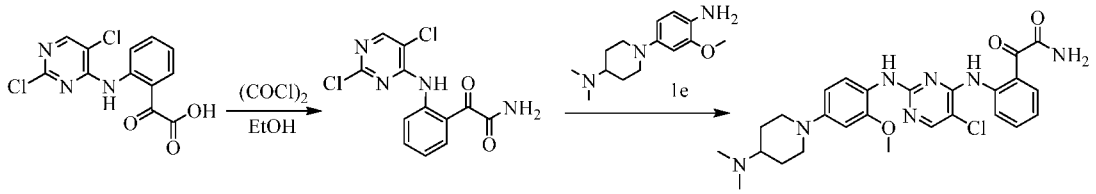
Example 3 Synthesis of compound 3



2 3

A mixture of Compound **2**(140 mg) and NH_2OH (72 mg), PyBOP(180 mg) in 10 mL of DMF was stirred at 45℃ for 3hrs. Then, the reaction solution was purified by pre-HPLC to give 30 mg of compound **3** as a solid. MS: 539.2$(M+H)^+$.

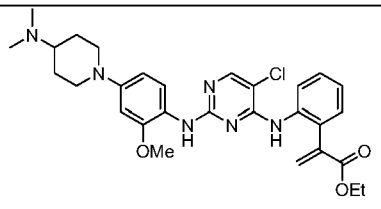
Example 4 Synthesis of compound 4

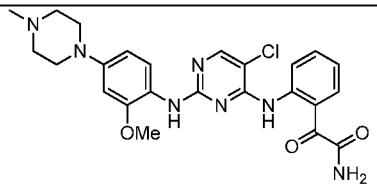
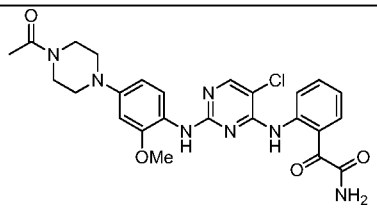
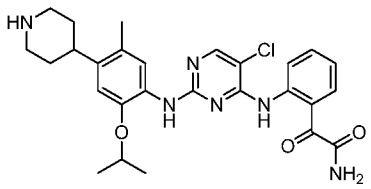
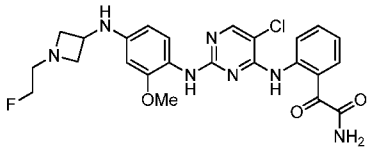
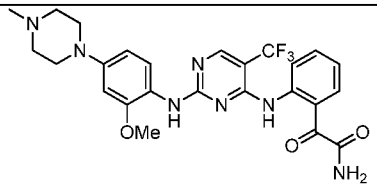
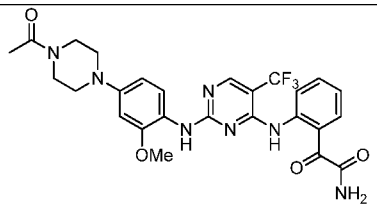
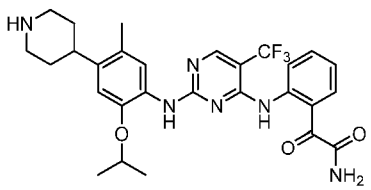


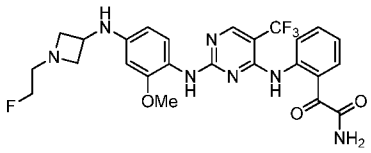
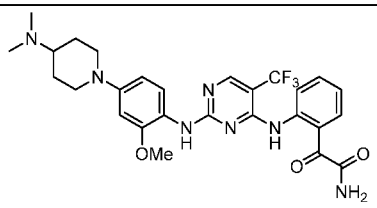
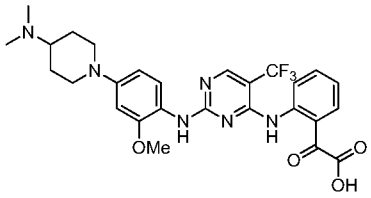
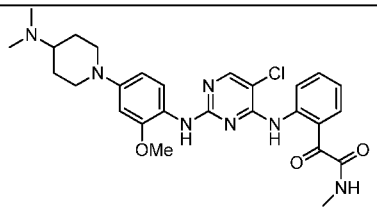
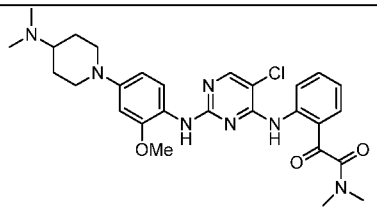
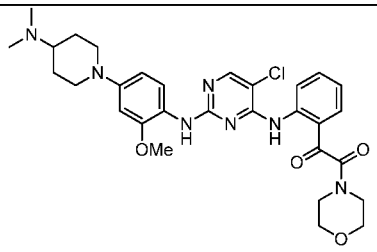
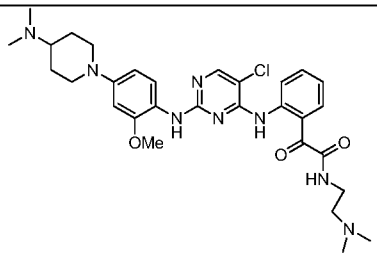
1c 1f 4

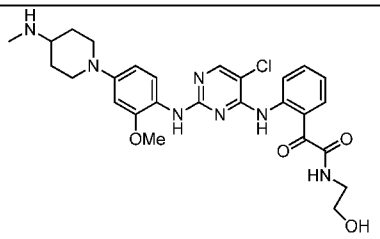
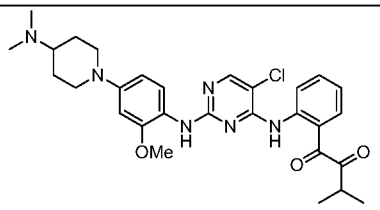
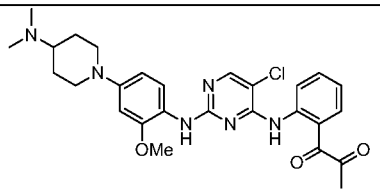
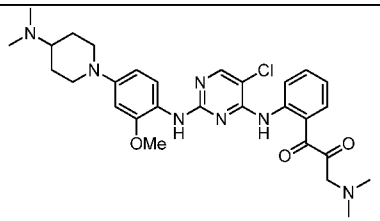
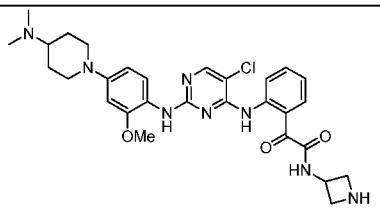
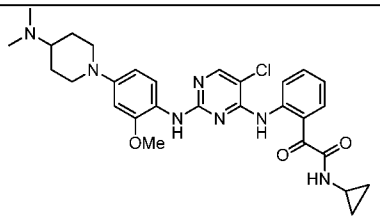
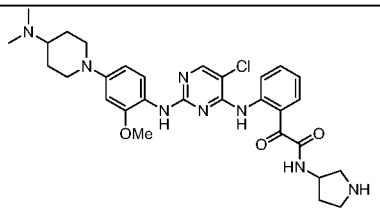
$(COCl)_2$ (7.2ml in 10ml of DCM) was added to a solution of Compound **1c** (5.0g) and 2 drops of DMF in 50 Ml of DCM at ice bath under N_2 with stirring. After 3.5 hrs, the solvent was removed. The residue was dissolved in DCM and NH_3 (aqs.) added into the solution. After stirring for 1hr, the precipitate was collected by filtration to give 6.0g of Compound **1f** as a white solid.

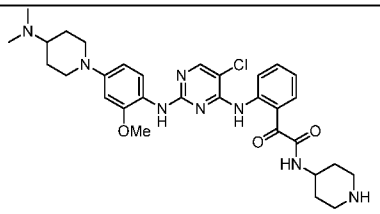
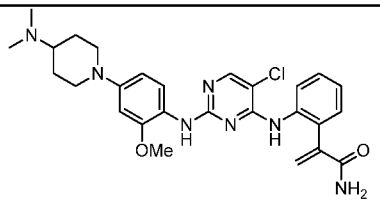
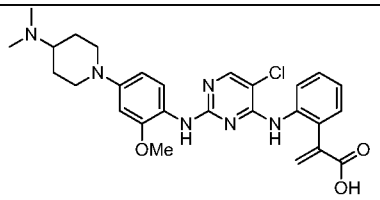
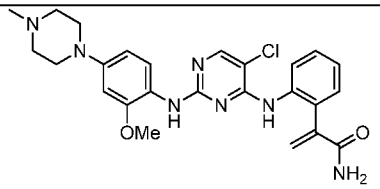
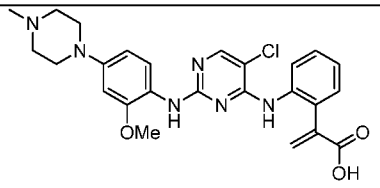
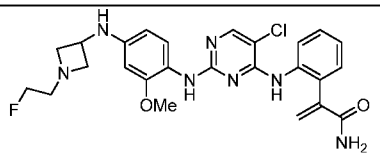
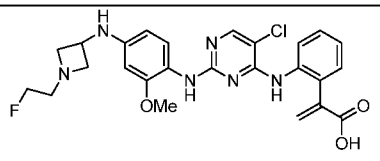
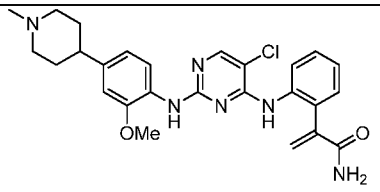
Following the same procedure as Example 1 using Compound **1f** instead of **1d** with Compound **1e** to yield Compound **4**. MS: 523.2$(M+H)^+$.

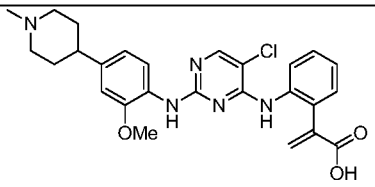
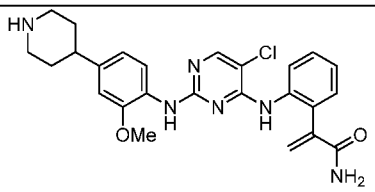
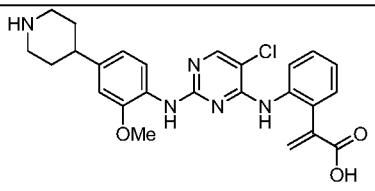
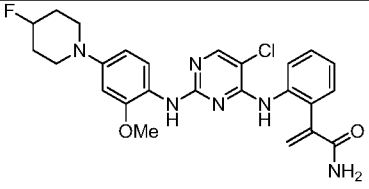
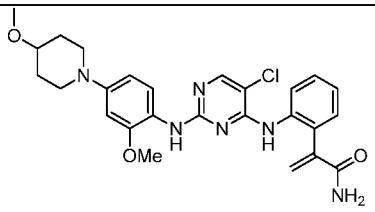
Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
5	ethyl 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)acrylate		552

Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
6	2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		496
7	2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		524
8	2-(2-((5-chloro-2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		523
9	2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		514
10	2-(2-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		530
11	2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		558
12	2-(2-((2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		557

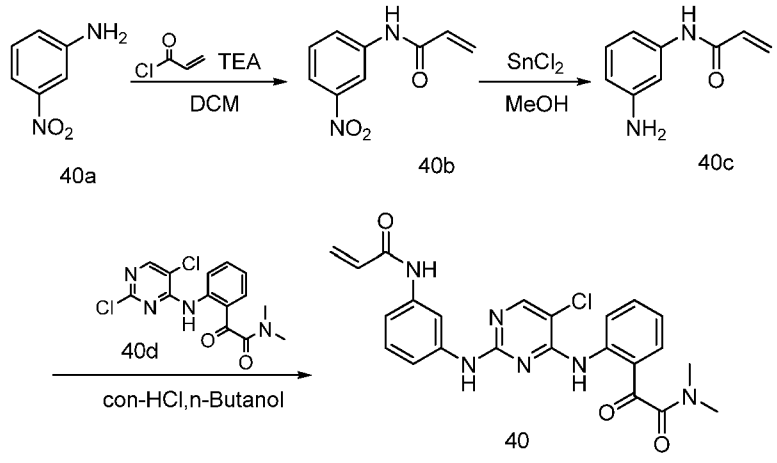
Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
13	2-(2-((2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		548
14	2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		558
15	2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetic acid		559
16	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-methyl-2-oxoacetamide		538
17	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N,N-dimethyl-2-oxoacetamide		552
18	1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-morpholinoethane-1,2-dione		594
19	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-(dimethylamino)ethyl)-2-oxoacetamide		595

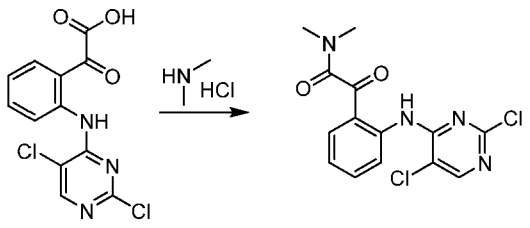
Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
20	2-(2-((5-chloro-2-((2-methoxy-4-(4-(methylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-hydroxyethyl)-2-oxoacetamide		554
21	1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-methylbutane-1,2-dione		551
22	1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)propane-1,2-dione		523
23	1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propane-1,2-dione		566
24	N-(azetidin-3-yl)-2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide		578
25	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-cyclopropyl-2-oxoacetamide		564
26	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(pyrrolidin-3-yl)acetamide		592

Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
27	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(piperidin-4-yl)acetamide		607
28	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		522
29	2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid		523
30	2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		494
31	2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid		495
32	2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		512
33	2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid		513
34	2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		493

Ex No	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
35	2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid		494
36	2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		479
37	2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid		480
38	2-(2-((5-chloro-2-((4-(4-fluoropiperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		497
39	2-(2-((5-chloro-2-((2-methoxy-4-(4-methoxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide		509

Example 40. Synthesis of compound 40





1c 40d

A three-necked round bottom flask equipped with mechanical stirrer, addition funnel and thermometer was charged with Compound **40a** (10.0g), TEA (12.0ml) and DCM (30.0ml). And then a solution of acryloyl chloride (5.9g) in DCM (20.0ml) was added dropwise (via addition funnel) after the reaction mixture was cooled to -10℃. The reaction mixture was stirred at -10℃ until the reaction was complete detected by TLC (PE:EA=3:1). Then, the reaction was quenched by water (30.0ml) and filtered to give the crude product of Compound **40b**(8.5g) used for the next reaction directly.

A three-necked round bottom flask equipped with mechanical stirrer, addition funnel and thermometer was charged with Compound **40b** (2.0g), $SnCl_2$ (14.1g) and MeOH (60.0ml). Then, the reaction mixture was stirred at 80℃until the reaction was complete detected by TLC (DCM:MeOH= 10:1). After, the reaction mixture was concentrated under reduced pressure and partitioned between ethyl acetate (50.0ml) and the aqueous solution of K_2CO_3 and filtered. The filtrate was separated and the organic phase was washed with water, dried over Na_2SO_4 and evaporated to dryness to give Compound **40c**(1.5g) as a yellow solid.

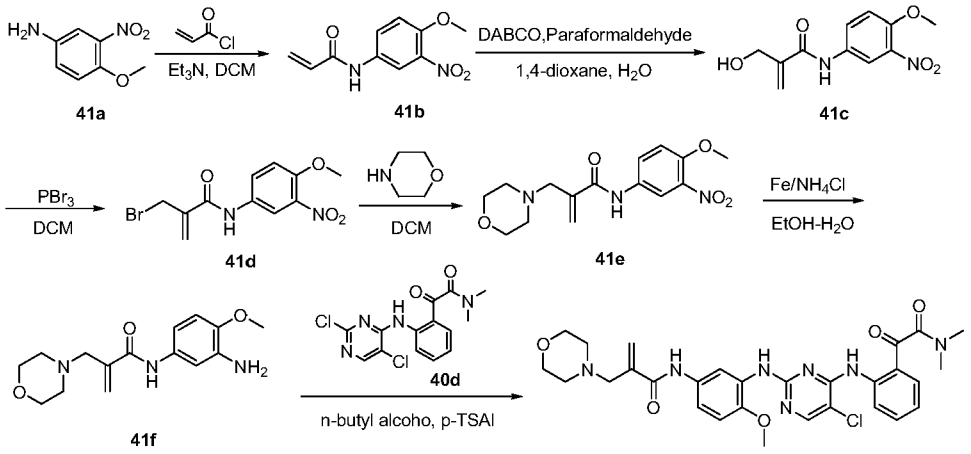
A mixture of Compound **1c** (1.03 g), dimethylamine hydrochloride (0.54 g), HATU(1.51 g), and TEA(1.00 g) in DCM(20ml) was stirred at 25℃for 6 hrs. Then, the reaction mixture was concentrated under reduced pressure and the residue was purified by chromatography to give 0.64 g Compound **40d** as a yellow solid.

Compound **40d** (200mg), Compound **40c** (96mg), con-HCl (3d) and n-BuOH(60ml) was stirred at 130℃ in sealed tube until the reaction was complete detected by TLC (DCM:MeOH=10:1). Then, the reaction mixture was washed with water and concentrated under reduced pressure. After, the residue was purified by column chromatography to give 500mg Compound **40** as a yellow solid. MS: 464.1$(M+H)^+$. H-NMR (DMSO-d6,400MHz): 10.25 (s, 1H), 9.12 (s, 1H), 8.34 (s, 1H), 7.98 (s, 1H), 7.39-7.33 (m, 2H), 7.24-7.19 (m, 2H), 6.54-6.51 (m, 2H),

6.49-6.47 (m, 1H)，6.54-6.47 (m, 1H)，6.25-6.21 (dd, 1H), 5.74-5.71 (dd, 1H), 3.00 (s, 3H), 2.90 (s, 3H).

Example 41. Synthesis of compound 41

Method 1



A mixture of 4-methoxy-3-nitroaniline (1.52g, 9.04mmol), triethylamine(1.37g, 13.54mmol) and DCM (60ml) was cooled to 0°C, acryloyl chloride (0.90g, 9.94mmol) solution in DCM (20mL) was added dropwise, the resulting mixture was stirred at 0~5°C for 20mins. The progress of the reaction was monitored by TLC. Reaction was quenched with water (50ml), the aqueous solution was extracted with DCM (30ml×2). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give 1.52g Compound **41b** as a yellow solid.

A mixture of Compound **41b** (1.50g, 6.75mmol), 1,4-Diazabicyclo[2.2.2]octane (2.27g, 20.25mmol), paraformaldehyde (1.01g, 33.75mmol), 1,4-dioxane (100ml) and water (60 ml) was heated to 80°C for 15h. Water (100 ml) was added, the resulting mixture was extracted with EA (100ml×2). The combined organic phase was washed with brine (100ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, the residue was purified by column chromatography to give 1.25g Compound **41c** as a yellow solid.

A mixture of Compound **41c** (1.20g, 4.76mmol) and DCM (130ml) was cooled to 0°C, phosphorus tribromide (1.54g, 5.71mmol) solution in DCM (20ml) was then added dropwise and quenched with water (50 ml) after 15mins, the aqueous solution was extracted with DCM (30ml×2). The combined organic phase was washed with brine (50 ml×2), dried over anhydrous

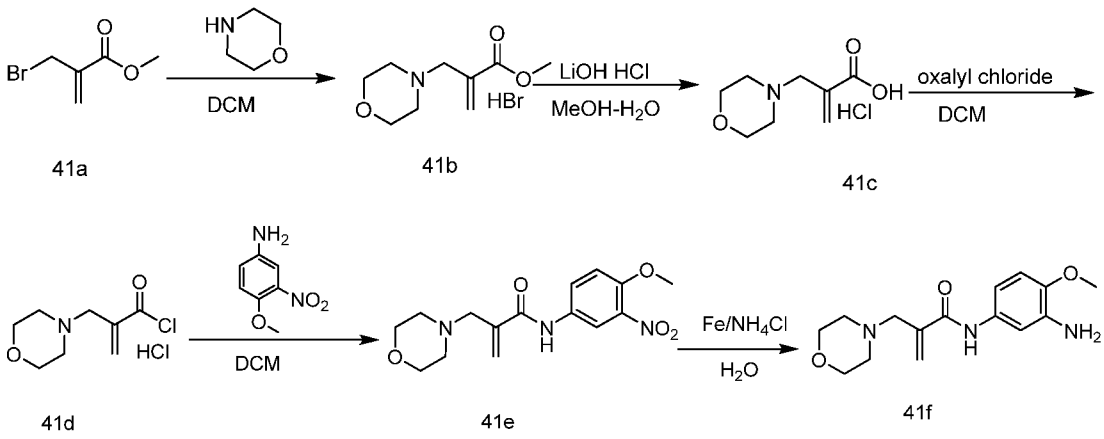
Na_2SO_4, concentrated under reduced pressure and the residue (Compound **41d**) was used for the next step without further purification.

To a solution of Compound **41d** (1.35g) in DCM (100ml) was added morpholine (1.86g, 21.40mmol). The resulting mixture was stirred at ambient for 15mins. Water (50ml) was added, the organic solution was washed with brine (30ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give 1.28g Compound **41e** as a brown solid.

A mixture of Compound **41e** (1.25g, 3.89mmol), iron power (4.34g, 77.80mmol), EtOH (50ml), saturated aqueous solution of ammonium chloride (20ml) was heated to 65°C for 30mins. After cooling the mixture was filtered, brine (20ml) was added and the product was extracted with EA (50ml×3,). The combined organic phase was washed with brine (50ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give 0.94g Compound **41f** as a brown solid.

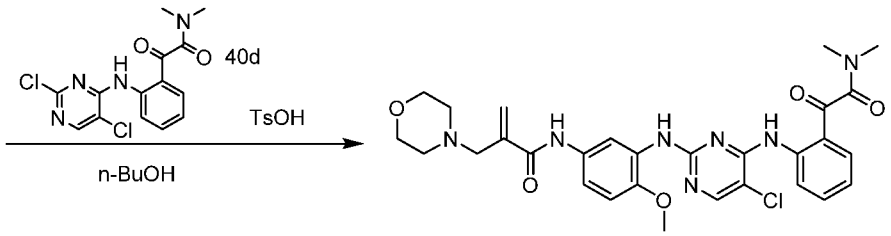
A mixture of Compound 41f (508mg, 1.74mmol), Compound 40d (705mg, 2.09mmol), p-toluenesulfonic acid (449mg, 2.61mmol) and n-butyl alcohol (100ml) was heated to 100°C for 14 hours. The mixture was cooled and concentrated under reduced pressure, the residue was basified with aqueous solution of sodium carbonate (50ml), extracted with EA (50ml, 30ml×2), the combined organic phase was washed with brine (50ml×2), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the residue was purified by column chromatography to give 198mg Compound **41** as a yellow solid.. MS: 593.2(M+H)+. HNMR (DMSO-d6, 400MHz): 11.36 (s,1H), 11.05 (s, 1H), 8.89 (d, 1H), 8.60 (s, 1H), 8.25 (s, 1H), 7.92 (s, 1H), 7.61 (d, 1H), 7.54-7.56 (m, 1H), 7.49 (t, 1H), 7.14 (t, 1H), 7.04 (d, 1H), 6.02 (s, 1H), 5.54 (s, 1H), 3.77 (s, 3H), 3.55 (s, 4H), 3.24 (s, 2H), 2.99 (s, 3H), 2.88 (s, 3H), 2.35 (s, 4H).

Method 2



41a 41b 41c

41d 41e 41f



41

To a solution of Compound **41a** (2.0g) in DCM (25ml) was added dropwise morpholine(0.6g) in DCM(5ml) at 0℃ with stirring. After that, the reaction mixture was stirred for another 3 hrs at 0-5℃. Then the reaction mixture was concentrated under reduced pressure to give 1.5g Compound **41b** as a white solid which was used for the next reaction directly.

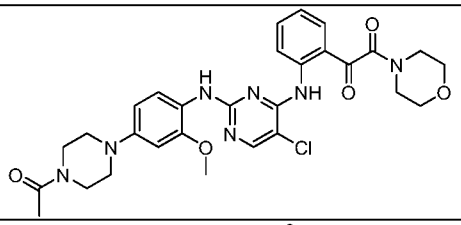
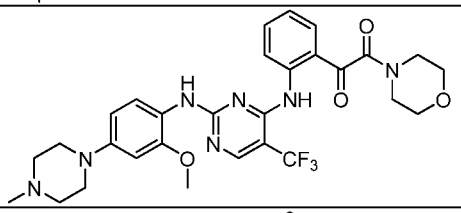
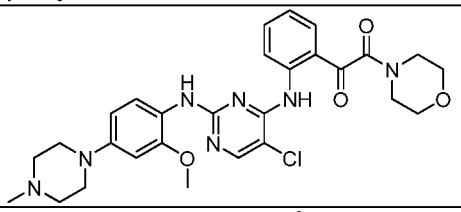
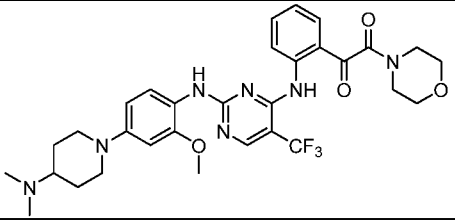
A flask was charged with Compound **41b**(1.45g), LiOH(0.46g), MeOH(10ml) and water(5ml). Then, the reaction mixture was stirred at room temperature for 1 hr. The reaction mixture was adjusted to PH=1-2 by con-HCl after most reaction solvent was removed under reduce pressure. And then, the appeared solid was filtered and the filter cake was dried to give 1.5g Compound **41c**.

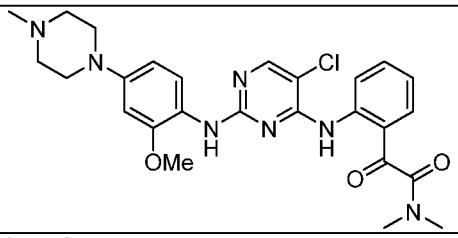
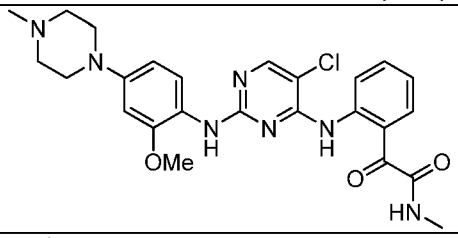
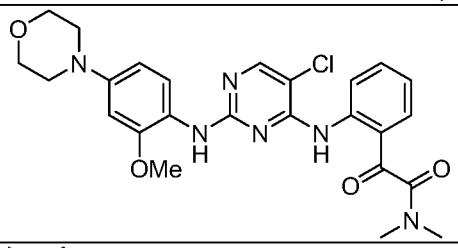
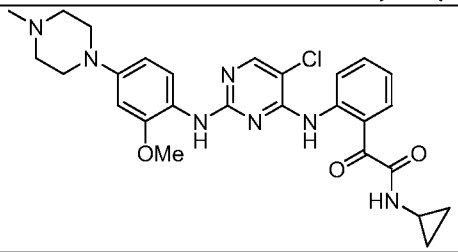
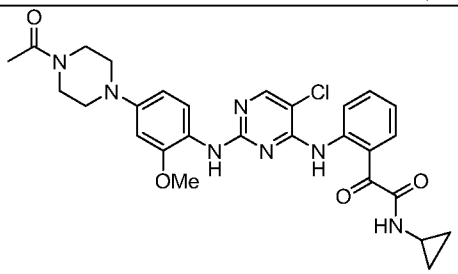
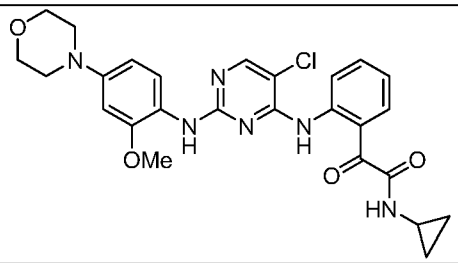
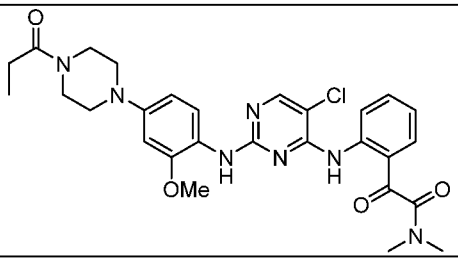
A three-necked round bottom flask equipped with mechanical stirrer, addition funnel and thermometer was charged with Compound **41c**(1.2g) and DCM(25ml). And then a solution of oxalyl chloride (1.1g) in DCM (15ml) was added dropwise (via addition funnel) at 0℃ while keeping inner temperature between 0-5℃. Then, the reaction mixture was warmed to 15℃ and then kept at 15℃ with stirring until the reaction was complete detected by TLC(DCM:MeOH=10:1). Reaction solvent was removed under reduce pressure to give 1.3g Compound **41d** used for the next reaction directly.

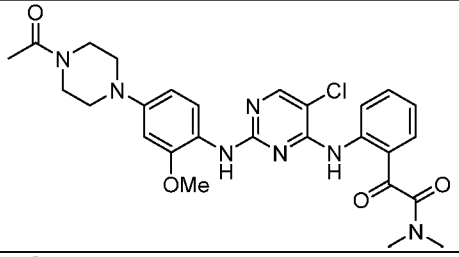
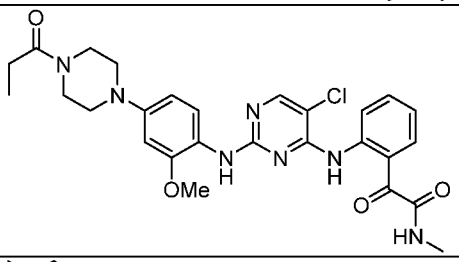
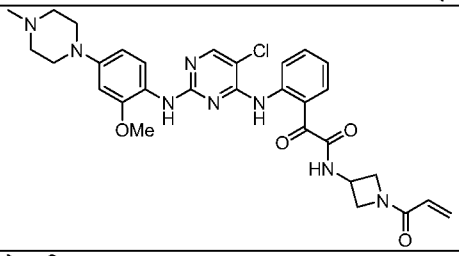
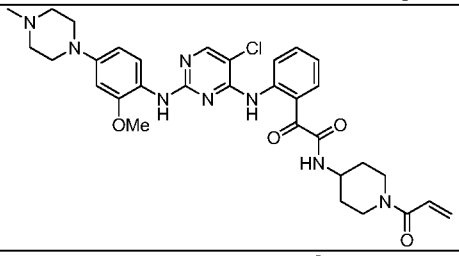
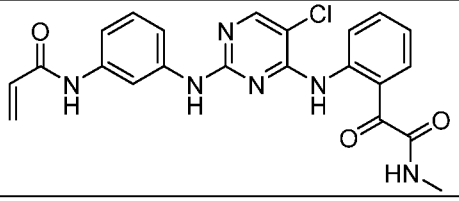
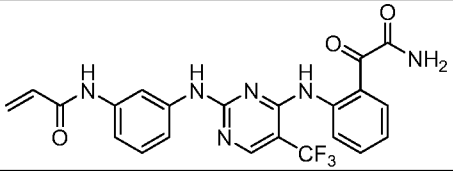
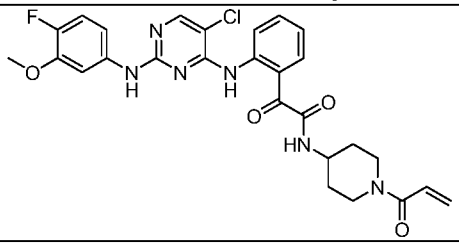
A three-necked round bottom flask equipped with mechanical stirrer, addition funnel and thermometer was charged with 4-methoxy-3-nitroaniline (0.8g) and DCM(25ml) and cooled to 0℃. After a solution of Compound **41d** (1.3g) in DCM (15ml) was added dropwise (via addition funnel) while keeping inner temperature between 0-5℃. Then, the reaction mixture was stirred with warming naturally until the reaction was complete detected by TLC(DCM:MeOH=10:1) The reaction mixture was washed with water and organic phase was concentrated under reduced pressure to a residue, and then the residue was purified by column chromatography to give 0.8g Compound **41e**.

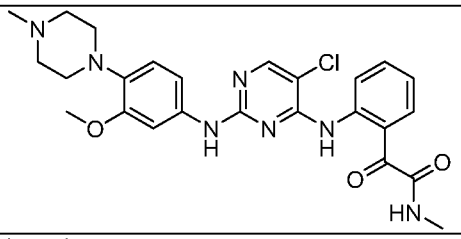
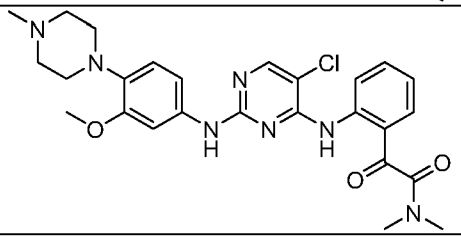
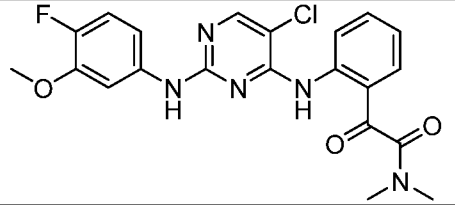
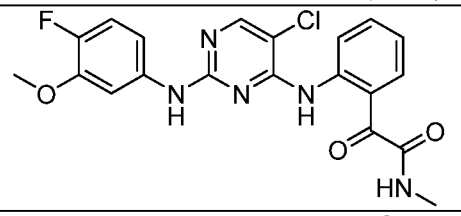
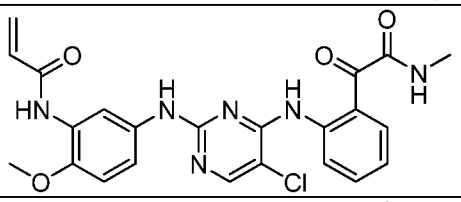
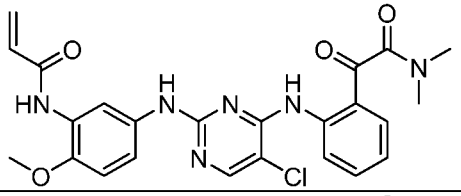
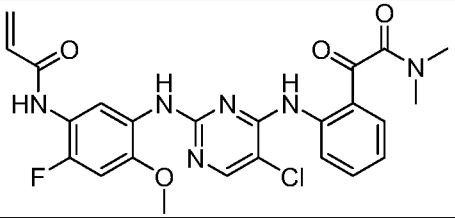
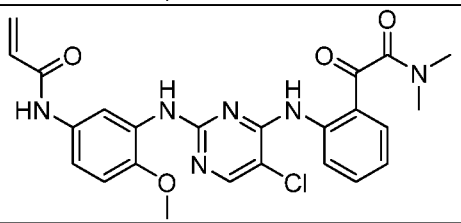
A three-necked round bottom flask equipped with mechanical stirrer and thermometer was charged with Compound **41e**(98mg), Fe(347mg), and saturated aqueous solution of NH_4Cl(15ml). Then the reaction mixture was heated to 80℃ and stirred until the reaction was complete detected by TLC(DCM:MeOH=10:1). After, most reaction solvent was removed under reduce pressure to afford a residue. Then, the residue was partitioned between ethyl acetate (20ml) and water (10ml) 3 times and the combined organic phase was washed with brine and dried over Na_2SO_4 to give 62mg Compound **41f**.

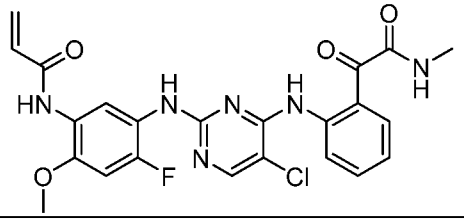
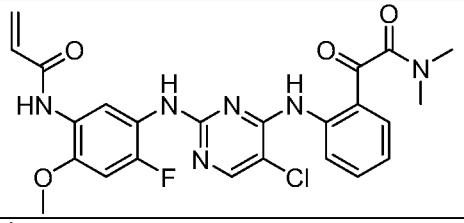
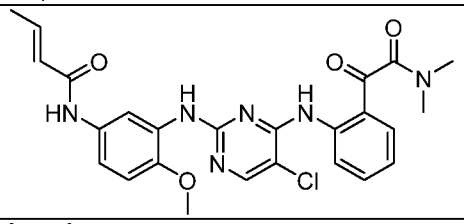
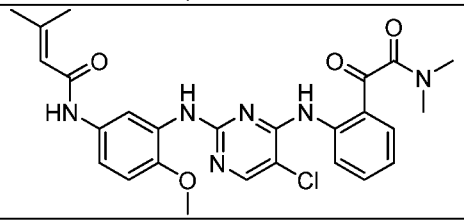
Compound **40d** (74mg), Compound **41f** (60mg), TsOH (36mg) and n-BuOH(15ml) was stirred at 90℃ in sealed tube until the reaction was complete detected by TLC (DCM:MeOH=10:1). Then, the reaction mixture was washed with water and the organic phase was concentrated under reduced pressure. After that, the residue was purified by column chromatography to give 8mg Compound **41** as a yellow solid. MS: 593.2$(M+H)^+$.

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
42	1-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione		595.0
43	1-(2-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione		600.5
44	1-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione		567.0
45	1-(2-(2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione		628.6

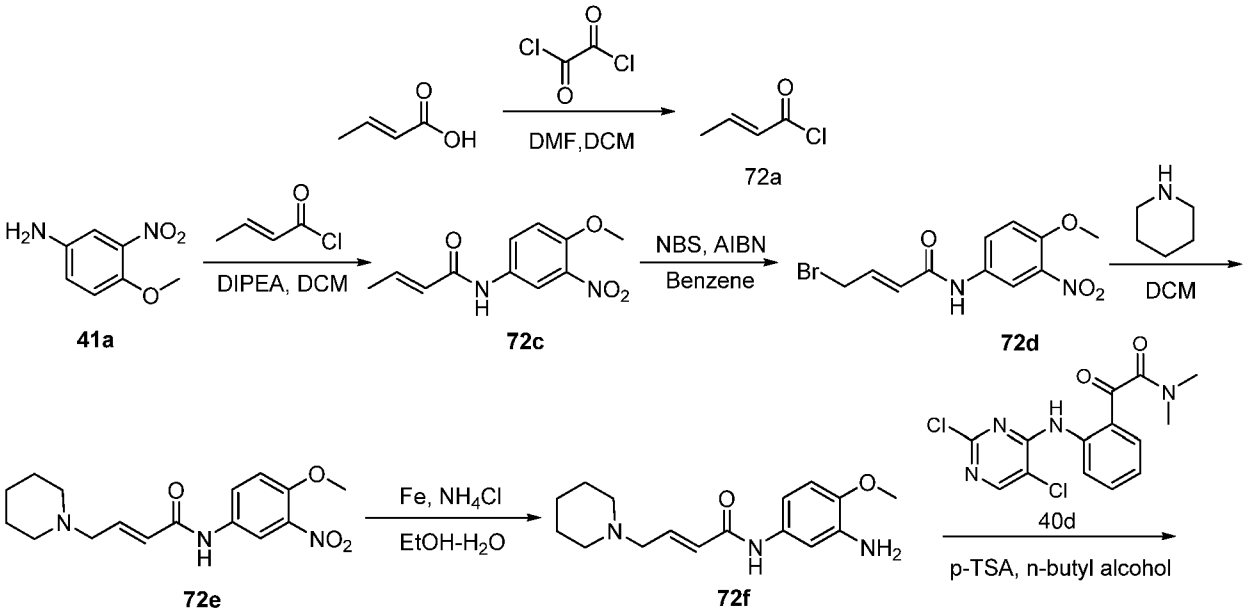
EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
46	2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		524.8
47	2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide		510.9
48	2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		511.8
49	2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide		536.9
50	2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide		564.8
51	2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide		523.7
52	2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		567

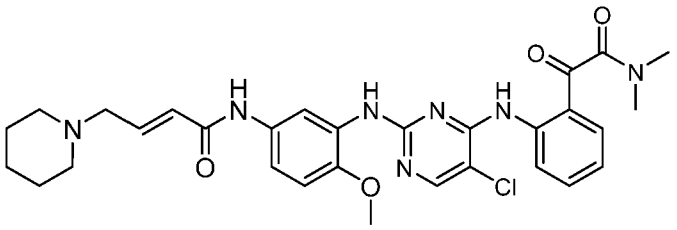
EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
53	2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		552.8
54	2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide		552.9
55	N-(1-acryloylazetidin-3-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide		606.1
56	N-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide		634
57	N-(3-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide		451.7
58	N-(3-(4-(2-(2-amino-2-oxoacetyl)phenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)acrylamide		471.3
59	N-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide		553.9

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
60	2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide		510.8
61	2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		524.9
62	2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		444.7
63	2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide		430.6
64	N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		481.7
65	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		495.8
66	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluoro-4-methoxyphenyl)acrylamide		513.9
67	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		495.7

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
68	N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide		499.8
69	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide		513.8
70	(*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)but-2-enamide		509.9
71	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-3-methylbut-2-enamide		523.8

Example 72. Synthesis of compound 72





72

To a solution of crotonic acid (5.05g, 58.65mmol) and a drop of DMF in DCM(80mL), was added oxalyl dichloride (11.12g, 87.98mmol) dropwise and the mixture was stirred at 15°C for 30min, then the solvent was concentrated under reduced pressure. The residue A (Compound 72a) was used for the next step without further purification.

To a solution of Compound **72b** (4.92g, 29.33mmol) and DIPEA(3.80g, 29.33mmol) in DCM(100mL) at 0°C, was A solution in DCM (30mL) dropwise, and the resulting mixture was stirred at 0~5°C for 30min. Reaction was quenched with water(50mL), the organic phase was concentrated under reduced pressure and the residue was purified by chromatography to give 4.21g Compound **72c** as a yellow solid.

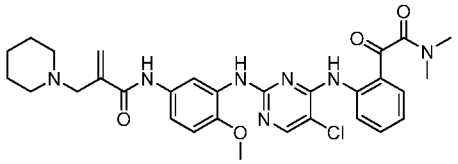
A mixture of Compound **72c** (402mg, 1.72mmol), NBS(334mg,1.88mmol), AIBN(40mg, 0.26mmol) and benzene(70mL) was heated to 80°C for 5 hours. The mixture was concentrated under reduced pressure, and the residue of Compound **72d** was used for the next step without further purification.

Compound **72d** in DCM(30mL) was added piperidine (1mL) ,the resulting mixture was stirred at ambient temperature for 2mins, evaporated to under reduced pressure, the residue was purified by chromatography to give 380mg Compound **72e** as a light yellow solid.

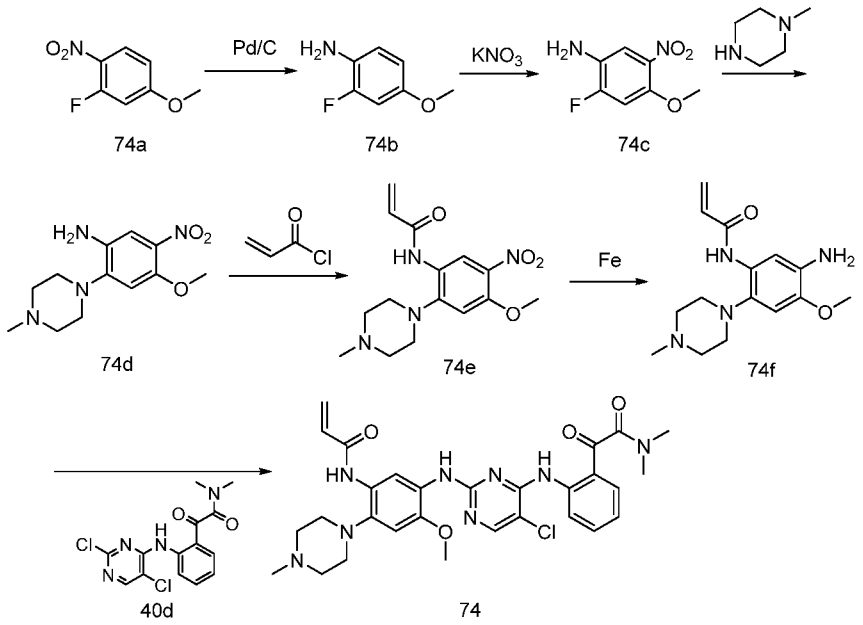
A mixture of Compound **72e** (205mg, 0.64mmol), iron power (715mg, 12.80mmol) in EtOH (20mL) and saturated aqueous solution of ammonium chloride (5mL) was heated to 65°C for 30min. After cooled, water was added to filtrate and the product was extracted with EA (50mL, 30mL), the combined organic layers was washed with brine (30mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give 108mg Compound **72f** as a brown solid.

A mixture of Compound **72f** (105mg, 0.36mmol), Compound **40d** (145mg, 0.43mmol), p-toluenesulfonic acid (93mg, 0.54mmol) in n-butyl alcohol (20mL) was heated to 100°C with stirring for 13 hours. The mixture was cooled and concentrated under reduced pressure, the residue was basified with aqueous solution of sodium carbonate (20ml), extracted with EA (50mL,30mL),

the combined organic extracts was washed with brine (30mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure, the residue was purified by chromatography to give 38mg Compound **72** as a yellow solid. MS: 591.2$(M+H)^+$.

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
73	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(piperidin-1-ylmethyl)acrylamide		592.9

Example 74 Synthesis of compound 74



A solution of Compound **74a** (50g) and Pd/C (10g) in MeOH (100ml) under H_2 was stirred at room temperature for 4hrs. After filtered, the filtrate was concentrated under reduced pressure to give 41g Compound **74b**.

To a solution of Compound **74b** (8.05g) dissolved in con.H_2SO_4 (40ml), was added KNO_3 (5.77g)with stirring for 2hrs at ice bath. The reaction mixture was poured into NaOH solution, and the appeared solid was filtered to give 8.5g Compound **74c** as a yellow solid.

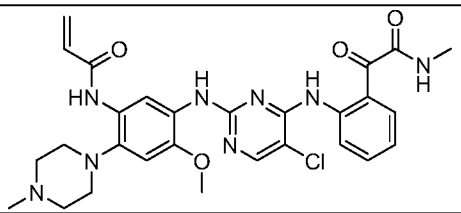
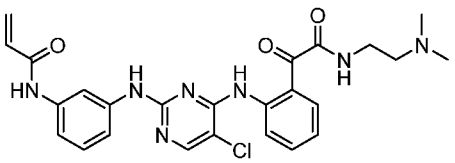
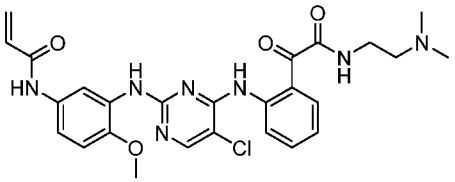
A mixture of Compound **74c** (19.7 g), 1-methylpiperazine (15.9 g), and K_2CO_3(21.94g) in DMF was stirred at 80℃ for 8 hrs. Water was added to the reaction mixture and extracted with EA, the organic layer was washed with brine, dried over Na_2SO_4, concentrated under reduced pressure

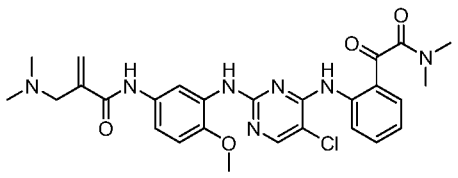
to give 10.2g Compound **74d** as a yellow solid.

To a solution of Compound **74d** (1.02g) and TEA(0.5g) in DCM (20ml), was added dropwise acryloyl chloride (0.38g) at ice bath with stirring for 1hr. The mixture was quenched with water and the organic layer was separated, after dried, it was concentrated under reduced pressure to give 0.98g Compound **74e** as a solid.

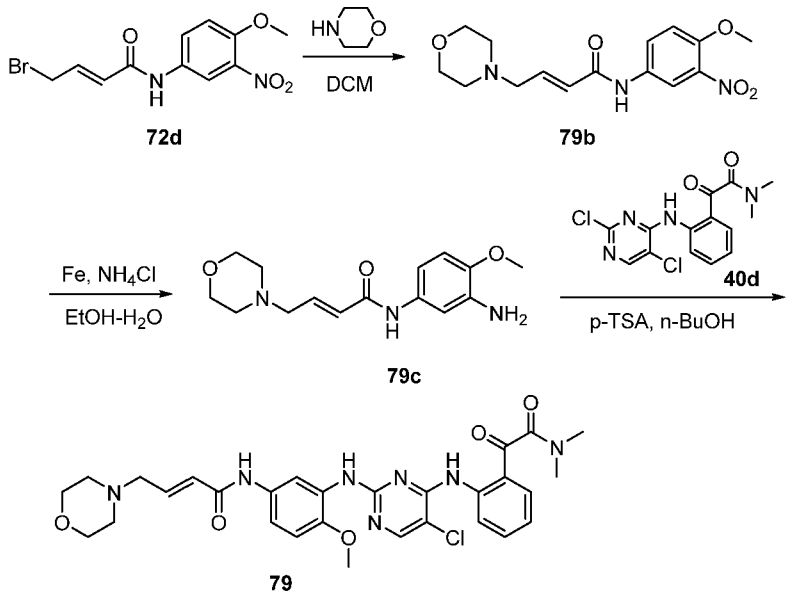
Compound 74e (0.98g), iron powder(0.85g) and NH_4Cl(0.82g) were dissolved in ethanol and water, then the mixture was stirred at 50℃ for 2 hrs. After filtered, the filtrated was extracted with EA, dried over Na_2SO_4, and concentrated under reduced pressure to give 0.58g Compound **74f** as a solid.

A mixture of Compound **74f** (16.5 g), Compound **40d** (23.2 g) and TsOH (11.75 g) in BuOH (250ml) was stirred at 70℃ for 8 hrs. After the solvent was removed, the residue was purified by chromatography to give 11.3g Compound **74** as a light yellow solid. MS: 592.2$(M+H)^+$. HNMR (DMSO-d6, 400MHz): 8.84-8.82 (d, J=7.76Hz, 1H), 8.24 (s, 1H), 8.09-8.07 (d, J= 6Hz, 1H), 7.63 −7.61 (d, J=8Hz, 1H), 7.53 (s, 1H), 7.16-7.12(t, J=7.6Hz, 1H), 6.87(s, 1H), 6.63-6.56(dd, J=10Hz, J=17.2Hz, 1H), 6.18-6.13 (d, J=16.8Hz, 1H), 5.71-5.68 (d, J=10.4Hz, 1H), 3.77 (s, 3H), 3.00 (s, 3H), 2.89 (s, 6H),2.55-2.50 (m, 5H),2.25-2.25(m, 3H).

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
75	N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide		579.8
76	N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide		508.7
77	N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		538.9

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
78	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide		552.8

Example 79. Synthesis of compound 79

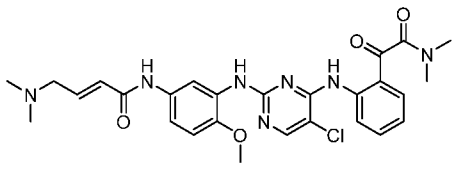
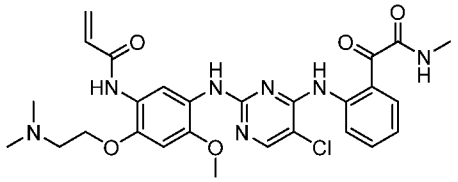
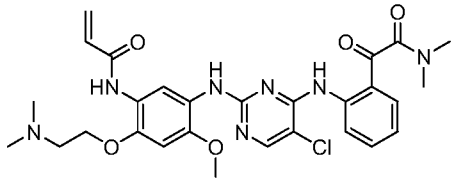
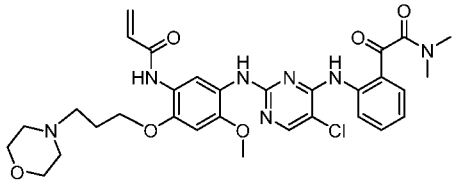
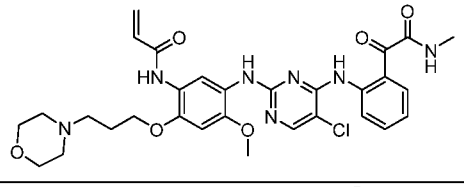
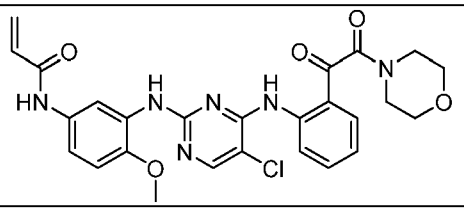


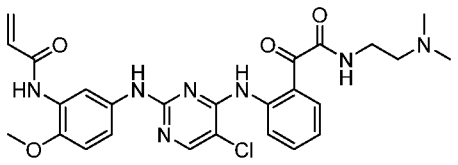
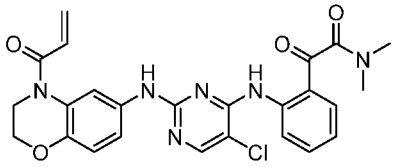
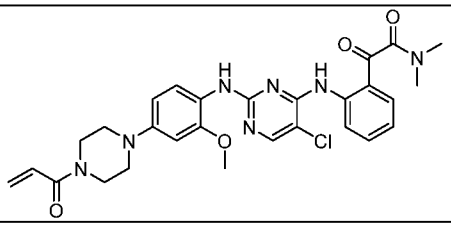
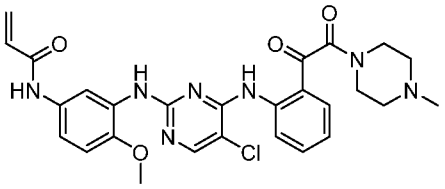
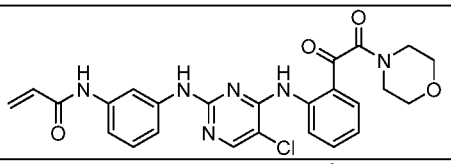
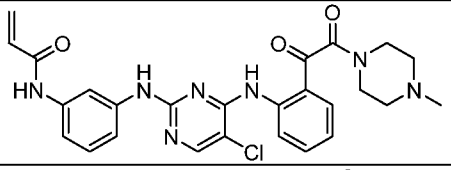
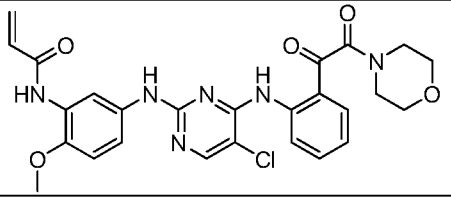
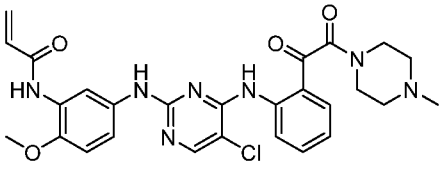
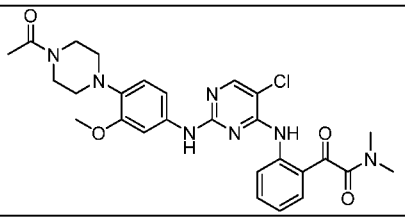
The mixture of Compound **72d** (0.5g) and DCM(50ml) was added morpholine (1ml) ,the resulting mixture was stirred at ambient temperature for 5mins, evaporated to dryness, the residue was purified by chromatography to give 350mg Compound **79b** as a light yellow solid.

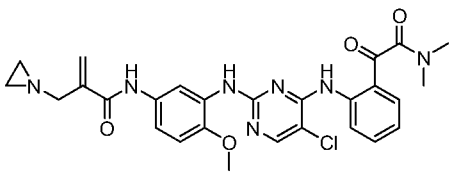
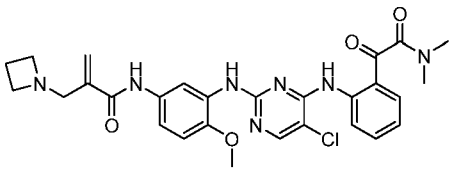
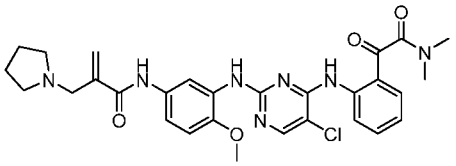
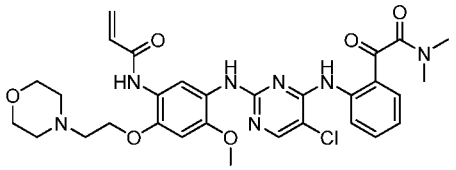
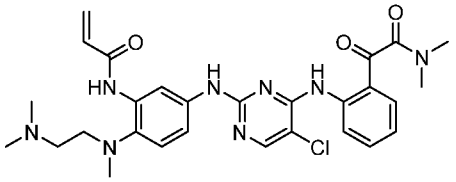
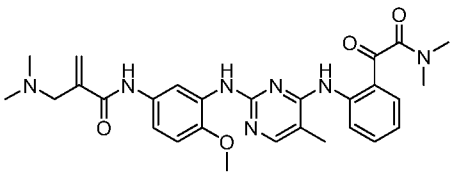
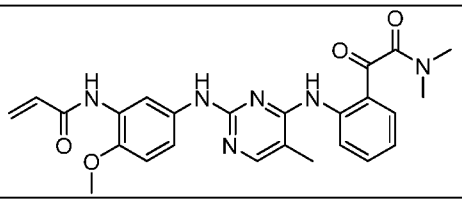
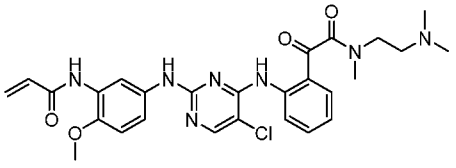
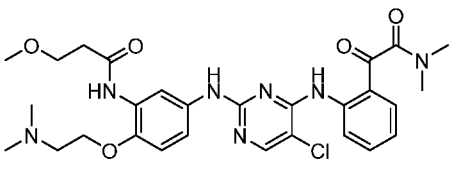
A mixture of Compound **79b** (152mg, 0.47mmol), iron power (525mg, 9.40mmol), EtOH (20ml) and saturated aqueous solution of ammonium chloride (10ml) was heated to 65°C for 15mins. After cooling the mixture was filtered, brine (30ml) was added and the product was extracted with EA (50ml ,30ml). The combined organic phase was washed with brine (30ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure to give 102mg Compound **79c** as a brown solid.

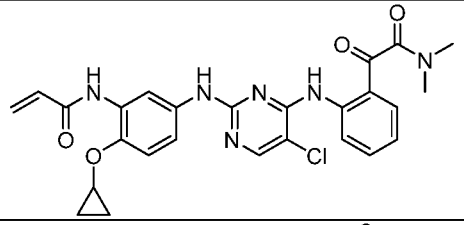
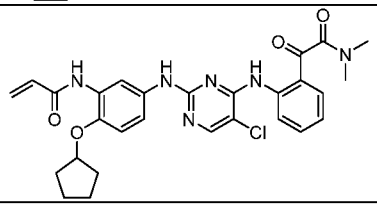
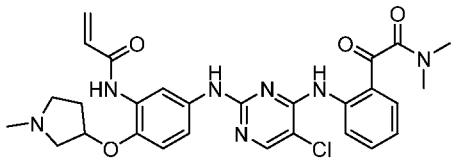
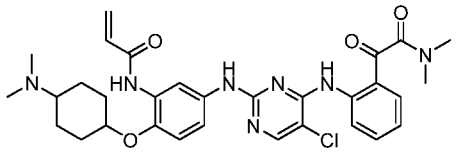
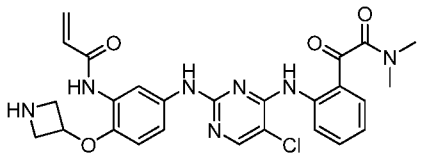
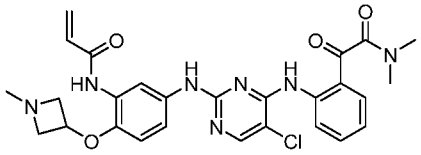
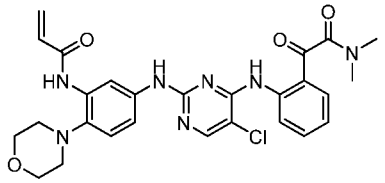
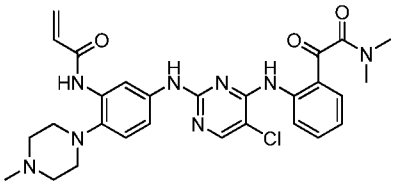
A mixture of Compound **79c** (102mg, 0.34mmol), Compound **40d** (138mg, 0.41mmol), p-toluenesulfonic acid (87mg, 0.51mmol) and n-butyl alcohol (15ml) was heated to 105°C for 7hrs. The mixture was cooled and concentrated in vacuo, the residue was basified with aqueous solution

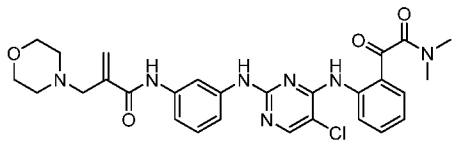
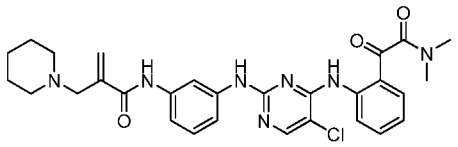
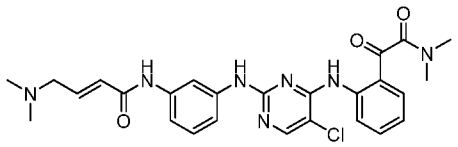
of sodium carbonate (20ml), extracted with EA (50ml, 30ml), the combined organic phase was washed with brine (30ml), dried over anhydrous Na_2SO_4 and evaporated to dryness, the residue was purified by chromatography to give 92mg Compound **79** as a yellow solid. MS: 594.9$(M+H)^+$. HNMR (DMSO-d6, 400MHz): 11.35 (s, 1H), 9.93 (s, 1H), 8.85 (d, 1H), 8.61 (s, 1H), 8.28 (s, 1H), 7.93 (s, 1H), 7.63 (d, 1H), 7.48 (m, 2H), 7.13 (t, 1H), 7.04 (d, 1H), 6.65-6.68 (m, 1H), 6.24 (d, 1H), 3.77 (s, 3H), 3.59 (s, 4H), 3.11 (s, 2H), 3.01 (s, 3H), 2.90 (s, 3H), 2.38 (s, 4H).

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
80	(*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-(dimethylamino)but-2-enamide		552.9
81	N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide		568.8
82	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide		583.1
83	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide		638.9
84	N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide		625.0
85	N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		537.9

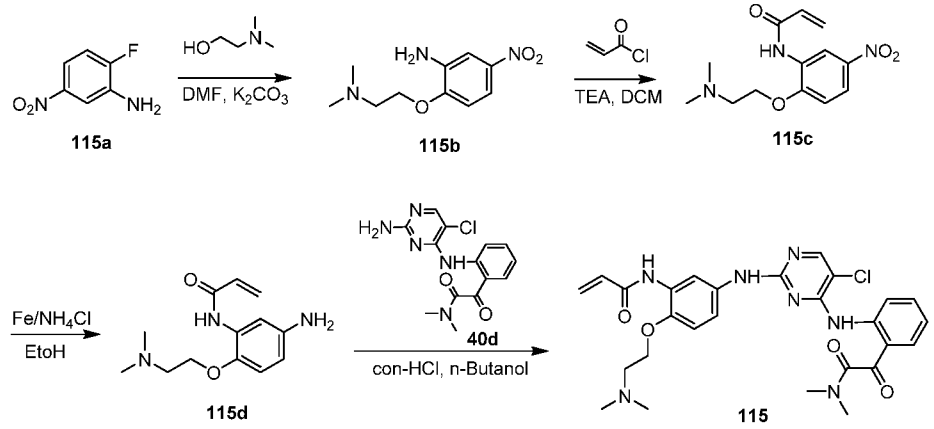
EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
86	N-(5-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		538.8
87	2-(2-(2-(4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		506.1
88	2-(2-(2-(4-(4-acryloylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		564.9
89	N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		550.8
90	N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide		507.7
91	N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide		520.9
92	N-(5-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		537.8
93	N-(5-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		550.9
94	2-(2-(2-(4-(4-acetylpiperazin-1-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		551.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
95	2-(aziridin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		549.2
96	2-(azetidin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		563.2
97	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(pyrrolidin-1-ylmethyl)acrylamide		577.2
98	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(2-morpholinoethoxy)phenyl)acrylamide		623.2
99	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide		564.2
100	N-(3-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide		531.3
101	N-(5-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		474.2
102	N-(5-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		551.2
103	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)-3-methoxypropanamide		583.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
104	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-cyclopropoxyphenyl)acrylamide		520.2
105	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(cyclopentyloxy)phenyl)acrylamide		548.2
106	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylpyrrolidin-3-yloxy)phenyl)acrylamide		563.2
107	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-(dimethylamino)cyclohexyloxy)phenyl)acrylamide		605.3
108	N-(2-(azetidin-3-yloxy)-5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide		535.2
109	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylazetidin-3-yloxy)phenyl)acrylamide		549.2
110	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide		549.2
111	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide		562.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
112	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(morpholinomethyl)acrylamide		563.2
113	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(piperidin-1-ylmethyl)acrylamide		561.2
114	(*E*)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-4-(dimethylamino)but-2-enamide		521.2

Example 115. Synthesis of compound 115

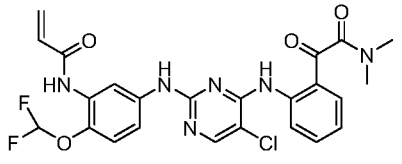
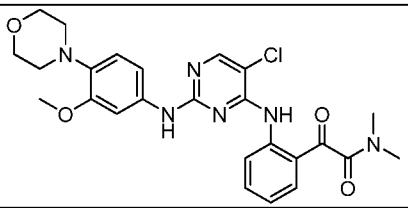


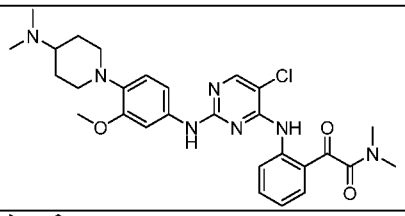
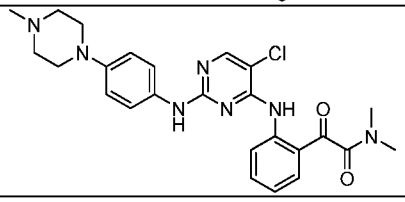
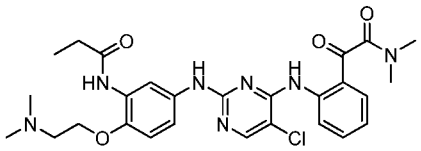
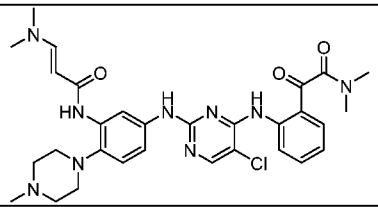
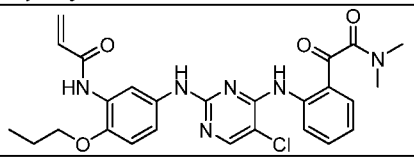
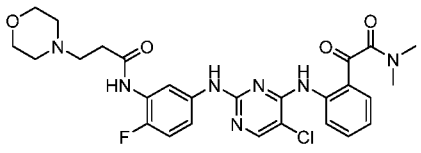
To a stirred solution of N, N-dimethylethanolamine (8.58g, 96mmol) in DMF (80 ml) at 0℃, NaH (1.54 g, 64mmol) was added slowly. After the mixture was stirred at 0-5℃ for 30 minutes, Compound **115a** (5.01 g, 32mmol) in DMF was added dropwise. Then the reaction mixture was stirred with warming naturally to the room temperature for 4 hours. The reaction was complete detected by TLC (PE:EA=1:1). Then water (80ml) was added to the solution to quench the overdose NaH. Afterwards, the mixture was extracted with ethyl acetate (80ml×2). The combined organic phase was washed with brine (80ml) and dried over sodium sulfate and concentrated under reduced pressure to give 6.49g Compound **115b**.

To a stirred solution of Compound **115b** (6.49g, 28.81mmol) and triethylamine (4.8ml, 34.58mmol) in DCM (55ml) at 0℃, a solution of acryloyl chloride (2.3ml, 31.68mmol) in DCM (10 ml) was added dropwise. The reaction mixture was stirred at 0℃ for 30 mins and then the reaction solution was washed with water (60ml) and the organic phase was concentrated under reduced pressure to give 7.32g Compound **115c**.

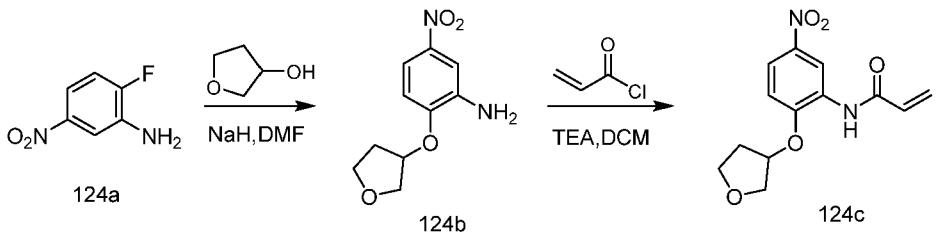
A mixture of Compound **115c** (7.32g, 25.93mmol) in ethanol (15ml), iron powder (8.84g, 155.57mmol) and ammonium chloride (2.77g, 51.86mmol) in water (70 ml) was heated to 90℃ for 30mins. Then the reaction solution was filtered and the filtrate was extracted with ethyl acetate (80ml×2) and the combined organic phase was washed with brine (80ml) and dried over sodium sulfate and concentrated under reduced pressure to give 2.31g Compound **115d**.

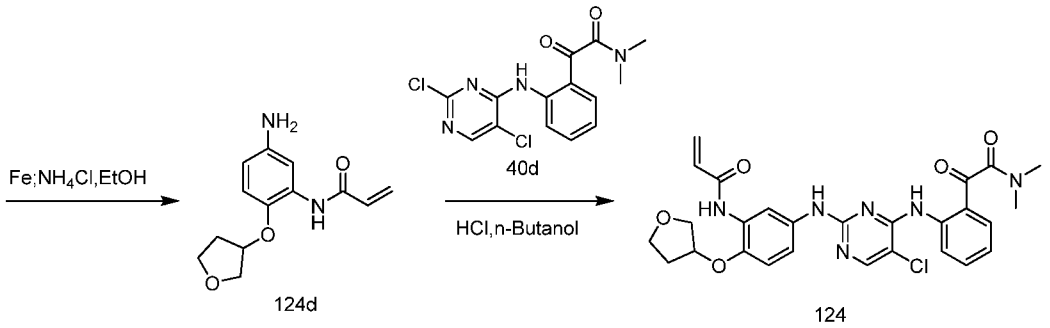
A mixture of Compound **115d** (2.30g, 9.23mmol), Compound **40d** (3.13g, 9.23mmol) and hydrochloric acid (0.3ml) in n-Butanol (30ml) was heated to 110℃ for 6 hours. The progress was monitored by TLC (DCM:MeOH=10:1). Then the reaction mixture was cooled to room temperature and concentrated under reduced pressure to afford crude compound. The crude product was purified by column chromatography to give 1.71g Compound **115** as a yellow solid. MS: 551.2$(M+H)^+$. H-NMR (DMSO-d6,400MHz): 8.35 (s, 1H), 8.29 (s, 1H), 7.88-7.82 (m, 1H), 7.47 (s, 1H), 7.32-7.15 (m, 4H), 7.05-7.02 (m, 1H), 6.25-6.21 (m, 1H), 5.70-5.67(m, 1H), 4.33-4.32 (t, 3H)，3.60-3.55 (t, 3H)， 3.00 (s, 6H), 2.90 (s, 6H).

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
116	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(difluoromethoxy)phenyl)acrylamide		530.1
117	2-(2-(5-chloro-2-(3-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		510.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
118	2-(2-(5-chloro-2-(4-(4-(dimethylamino) piperidin-1-yl)-3-methoxyphenylamino) pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		551.2
119	2-(2-(5-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		493.2
120	N-(5-(5-chloro-4-(2-(2-(dimethylamino) -2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy) phenyl)propionamide		553.2
121	(*E*)-N-(5-(5-chloro-4-(2-(2-(dimethylam ino)-2-oxoacetyl)phenylamino)pyrimidi n-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-3-(dimethylamino)acrylamide		605.3
122	N-(5-(5-chloro-4-(2-(2-(dimethylamino) -2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-propoxyphenyl)acrylamide		522.2
123	N-(5-(5-chloro-4-(2-(2-(dimethylamino) -2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluorophenyl)-3-morpholino propanamide		569.2

Example 124. Synthesis of compound 124





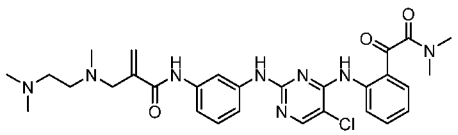
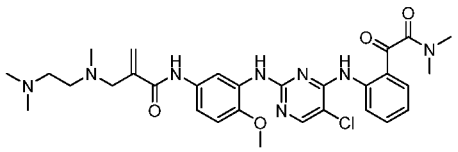
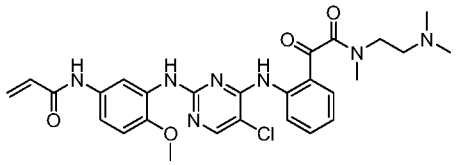
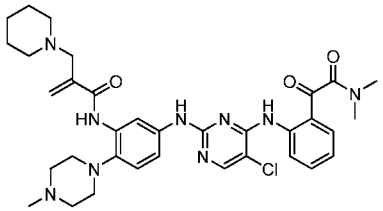
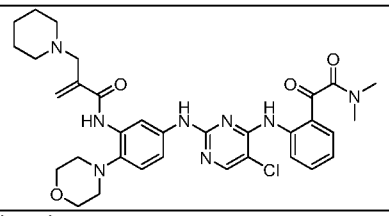
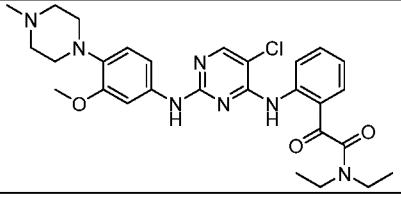
To a stirred solution of 3-hydroxy tetrahydrofuran (203mg) in DMF (10ml) at 0℃, NaH (92mg) was added slowly. After the mixture was stirred at 0-5℃ for 30 minutes, the compound **124a** (300mg) in DMF was added dropwised. Then the reaction mixture was stirred with warming naturally to the room temperature. The reaction was complete detected by TLC (PE:EA=1:1) after 4 hours. Then 15ml H_2O was added to the solution. Afterwards, the mixture was extracted by EA (15ml×2). The combined organic phase was combined and washed with aqueous solution of NaCl and dried over Na_2SO_4 and concentrated under reduced pressure to give crude Compound **124b**. The crude product was purified by column chromatography to give 226mg Compound **124b** .

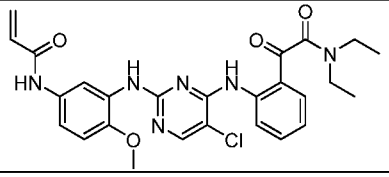
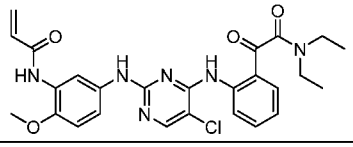
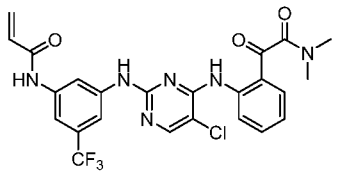
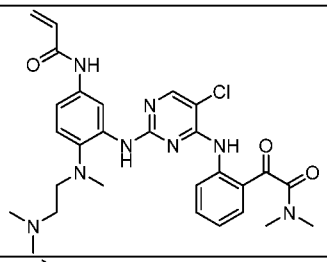
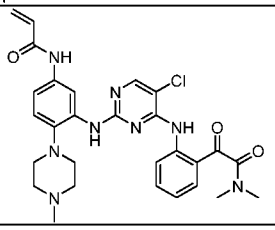
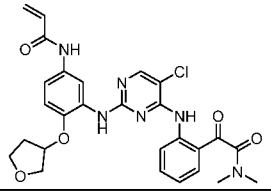
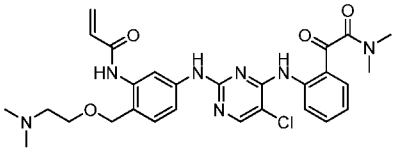
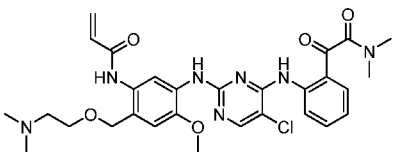
To a stirred solution of Compound **124b** (220mg) and TEA (0.2ml) in DCM (15ml) at 0℃, a solution of acryloyl chloride (0.1ml) in DCM (2.0ml) was added dropwised. The reaction mixture was stirred at 0℃ for 30 minutes. Then the reaction was complete detected by TLC (PE:EA=1:1). The reaction solution was washed by water (20ml) and the organic phase was concentrated under reduced pressure to give 220mg Compound **124c**.

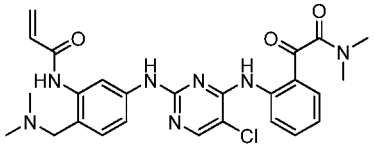
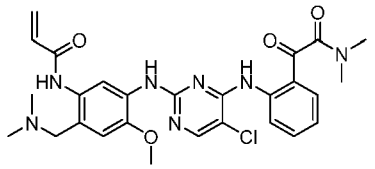
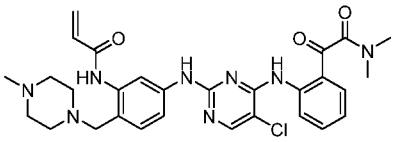
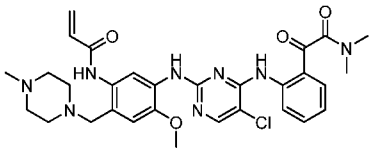
To a stirred solution of Compound **124c** (220mg) in ethanol (5ml), Fe powder (500mg) and saturated aqueous solution of NH_4Cl (15ml) was added. Then the reaction mixture was heated to 90℃ and stirred until the reaction was complete detected by TLC (DCM:MeOH=10:1). The reaction solution was filtered and the filtrate was partitioned between ethyl acetate (20ml) and water (10ml) 2 times .Then the combined organic phase was washed with aqueous solution of NaCl and dried over Na_2SO_4 and concentrated under reduced pressure to give 160mg Compound **124d**.

A mixture solution of Compound **124d** (150mg), 40d (205mg) and con-HCl(0.05ml) in n-Butanol was heated to 85℃ with stirring for 3hrs. The reaction was complete detected by TLC (DCM:MeOH=10:1). Then, after the reaction mixture was cooled to 20℃, it was filtered and the filter cake was dried to give 115mg Compound **124**. MS: 550.2$(M+H)^+$. H-NMR (DMSO-d6,

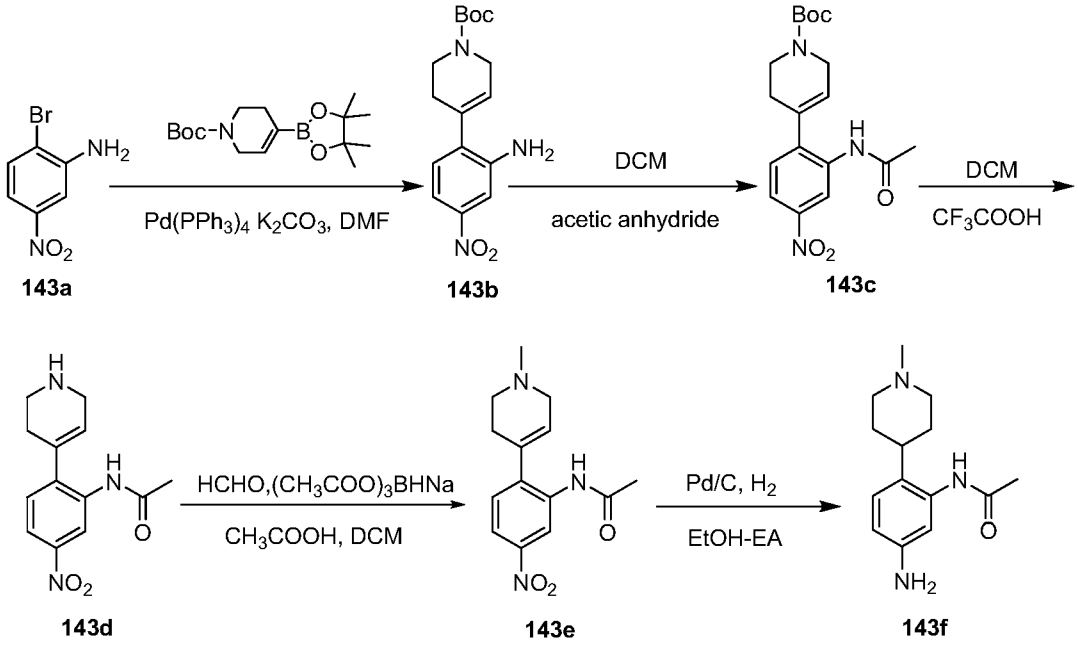
400MHz): 11.38 (s, 1H), 9.81 (s, 1H), 9.19 (s, 1H), 8.90 (s, 1H), 8.40 (s, 1H), 8.22 (s, 1H), 7.64-7.69 (m, 2H), 7.32-7.36 (m, 1H), 7.23-7.27 (t, 1H), 7.00 (d, 1H), 6.64-6.71 (dd, 1H), 6.18-6.22 (dd, 1H), 5.71-5.74 (dd, 1H), 5.02 (d, 1H), 3.87-3.94 (m, 2H), 3.73-3.78 (m, 2H), 3.00 (s, 3H), 2.90 (s, 3H), 2.19 (m, 1H), 2.05-2.10 (m, 1H).

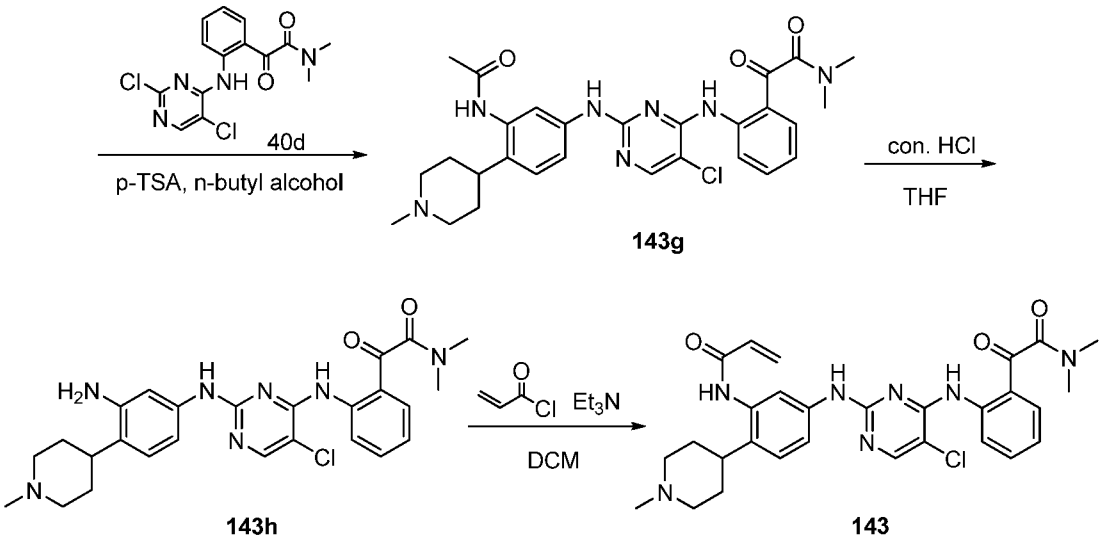
EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
125	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide		578.3
126	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide		608.3
127	N-(3-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		551.2
128	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-2-(piperidin-1-ylmethyl)acrylamide		659.3
129	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)-2-(piperidin-1-ylmethyl)acrylamide		646.3
130	2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-diethyl-2-oxoacetamide		551.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
131	N-(3-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide		522.2
132	N-(5-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide		522.2
133	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-5-(trifluoromethyl)phenyl)acrylamide		532.1
134	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide		564.2
135	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-(4-methylpiperazin-1-yl)phenyl)acrylamide		562.2
136	N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-(tetrahydrofuran-3-yloxy)phenyl)acrylamide		550.2
137	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)phenyl)acrylamide		565.2
138	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)-4-methoxyphenyl)acrylamide		595.2

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
139	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)phenyl)acrylamide		521.2
140	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)-4-methoxyphenyl)acrylamide		551.2
141	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide		576.2
142	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide		606.2

Example 143. Synthesis of compound 143





A mixture of Compound **143a** (5.12g, 23.59mmol）, tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-car-boxylate (7.30g, 23.59mmol), tetrakis (triphenylphosphine) palladium(0) (1.36g, 1.18mmol) and K_2CO_3 (8.15g, 58.98mmol) in DMF (200ml) was degassed with five vacuum/nitrogen cycles. The mixture was heated to 80°C with stirring under nitrogen for 16.5 hours. After cooled to 10°C, water (300ml) was added, and the resulting mixture was extracted with ethyl acetate (300ml, 150 ml×2). The combined organic extracts were washed with brine (200ml×2), dried over anhydrous Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by chromatography to give 4.82g Compound **143b** as a yellow solid.

A mixture of Compound **143b** (4.81g, 15.08mmol), acetic anhydride (5ml, 52.89mmol) in DCM (300ml) was stirred at 25°C for 20 hours. After concentrated in under reduced pressure, the residue was dissolved in saturated aqueous solution of sodium bicarbonate(200ml) with stirring for 12 hours at ambient temperature. The precipitated solid was collected by filtration to give 5.28g Compound **143c**.

A mixture solution of Compound **143c** (5.27g, 14.58mmol) and trifluoroacetic acid (13ml, 175mmol) in DCM was stirred at 40°C for 2 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was concentrated under reduced pressure, the residue (Compound **143d**) was used for the next step without further purification.

A mixture of Compound **143d** (3.80g, 14.54mmol), formaldehyde solution (5ml, 178.90mmol), acetic acid (1ml, 17.48mmol), sodium triacetoxyborohyride (9.25g, 43.65mmol) and DCM (150ml) was stirred at ambient temperature for 20mins. Saturated aqueous solution of

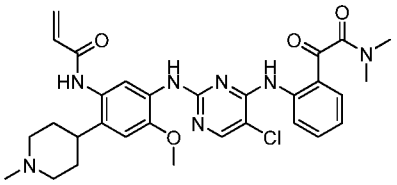
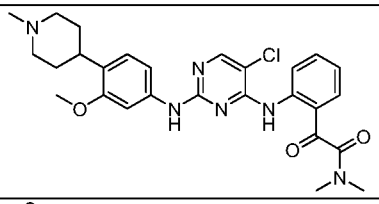
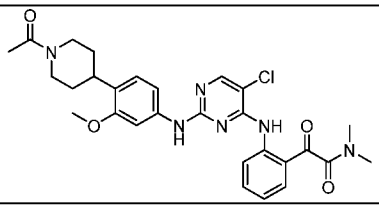
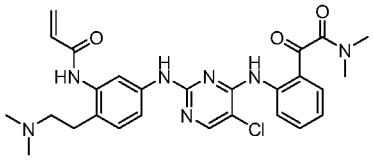
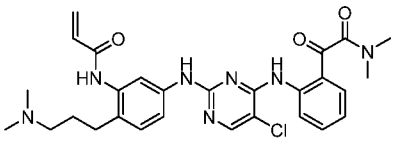
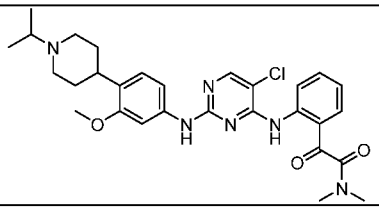
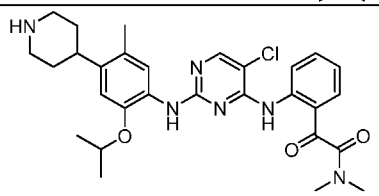
K_2CO_3 (100ml) was added, the resulting mixture was extracted with DCM (100ml×2). The combined organic layers were washed with brine (100ml), dried over anhydrous Na_2SO_4, then concentrated under reduced pressure and the residue (Compound **143e**) was used for the next step without further purification.

To a solution of Compound **143e** (3.81g,13.84mmol) in EA(100ml) and EtOH(100ml) was added palladium 10% on carbon (1.05g).The resulting mixture was stirred at ambient under hydrogen atmosphere for 2 hours. After completion of the reaction, the reaction mixture was filtered and the filtrate was concentrated to give 3.21g Compound **143f**.

A mixture of Compound **143f** (3.21g, 12.99mmol), Compound **40d** (4.40g,12.99mmol), p-toluenesulfonic acid (2.68g,15.59mmol) and n-butyl alcohol (150ml) was heated to 100°C with stirring for 7 hours. The mixture was cooled and concentrated under reduced pressure, the residue was purified by chromatography to give 5.02g Compound **143g** as a light yellow solid.

To a stirred solution of Compound **143g** (1.98g, 3.60mmol) in THF (50ml) was added con.hydrochloric acid (15ml), the resulting mixture was stirred at 65°C for 17 hours. Reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to 0-5°C and saturated aqueous solution of K_2CO_3 was added to adjust pH value to 9-10, then extracted with DCM (100ml×2), the combined organic extracts was washed with brine (100ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Crude product was purified by chromatography to give 0.28g Compound **143h** as a yellow solid.

To a solution of Compound **143h** (255mg,0.5mmol), triethylamine (100mg, 1.0mmol) in DCM(100ml) was added acryloyl chloride (69mg, 0.75mmol) dropwise and the mixture was stirred at 0-5°C. Reaction was quenched with saturated aqueous solution of potassium carbonate (200ml), extracted with DCM (100ml×3), the combined organic extracts was washed with brine (100ml×2), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the residue was purified by Pre-TLC to give 138mg Compound **143** as a yellow solid. MS: 561.2$(M+H)^+$. HNMR (DMSO-d6, 400MHz): 11.32 (s, 1H), 9.61 (s, 1H), 9.02 (d, 1H), 8.33 (s, 1H), 7.63-7.80 (m, 3H), 7.50 (d, 1H), 7.20-7.23 (m, 2H), 6.46-6.53 (m, 1H), 6.19-6.23 (dd, 1H), 5.72-5.75 (dd, 1H), 3.01 (s, 3H), 2.91 (s, 3H), 2.87 (s, 2H), 2.61-2.67 (m, 1H), 2.21 (s, 3H), 1.98 (m, 2H), 1.63-1.65 (m, 4H).

EX No.	Chemical Name	Structure	Physical Data (MS) $(M+H)^+$
144	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(1-methylpiperidin-4-yl)phenyl)acrylamide		591.2
145	2-(2-(5-chloro-2-(3-methoxy-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		522.2
146	2-(2-(2-(4-(1-acetylpiperidin-4-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		550.2
147	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethyl)phenyl)acrylamide		535.2
148	N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(3-(dimethylamino)propyl)phenyl)acrylamide		549.2
149	2-(2-(5-chloro-2-(4-(1-isopropylpiperidin-4-yl)-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		550.3
150	2-(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide		550.3

PHARMACOLOGICAL TESTING

Example A. <u>Kinase Assays (single dose inhibition)</u>

Assays were conducted for an in vitro kinase panel having EGFR WT, L858R, T790M, L858R/T790M and ALK. Assay conditions included 10μM ATP and 100 nM test compounds.

Assay Protocol:

All reactions are initiated by the addition of the MgATP mix. After incubation for 40 minutes at room temperature, the reaction is stopped by the addition of 3% phosphoric acid solution. 10μL of the reaction is then spotted onto a P30 filtermat and washed three times for 5 minutes in 75mM phosphoric acid and once in methanol prior to drying and scintillation counting. This assay is performed by Millipore. The experiment is carried out in duplicate. The value for the control sample (DMSO) was set to 100%, and the values for the compound-treated samples were expressed as activity relative to the control sample.

Kinase-Specific Assay Conditions

Alk (h) is incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 250μM KKKSPGEYVNIEFG, 10mM MgAcetate, [γ-^{33}P-ATP] (specific activity approx. 500cpm/pmol, concentration as required) and 0.1μM test compound.

EGFR (h) and EGFR (L858R) (h) are incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 10mM $MnCl_2$, 0.1mg/mL poly(Glu, Tyr)4:1, 10 mM MgAcetate, [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required) and 0.1μM test compound.

EGFR (T790M) (h) and EGFR (T790M, L858R) (h) are incubated with 8mM MOPS pH7.0, 0.2mM EDTA, 250μM GGMEDIYFEFMGGKKK, 10 mM MgAcetate, [γ-^{33}P-ATP] (specific activity approx. 500 cpm/pmol, concentration as required) and 0.1μM test compound.

Table 1

Example	Activity (control) %				
	ALK(h)	EGFR(h)	EGFR (L858R)(h)	EGFR (T790M)(h)	EGFR (T790M,L858R)(h)
CO-1686 @0.1μM	49	92	97	21	7
4 @0.1μM	8	65	8	4	2
40 @0.1μM	28	106	103	79	24
53 @0.1μM	5	109	60	21	4
61 @0.1μM	5	101	70	54	13
64 @0.1μM	47	106	100	79	39
65 @0.1μM	19	118	102	80	25
66 @0.1μM	35	107	104	66	24
67 @0.1μM	13	105	85	50	9

Example	Activity (control) %				
	ALK(h)	EGFR(h)	EGFR (L858R)(h)	EGFR (T790M)(h)	EGFR (T790M,L858R)(h)
41 @0.1μM	21	76	39	2	3
72 @0.1μM	14	102	28	54	9
73 @0.1μM	17	67	37	3	3
74 @0.1μM	9	110	73	62	12
78 @0.1μM	36	68	37	2	3
79 @0.1μM	7	92	25	16	2
80 @0.1μM	10	101	43	42	7
102 @0.1μM	5	98	57	40	5
87 @0.1μM	5	88	44	8	1
89 @0.1μM	8	67	10	5	1
94 @0.1μM	6	100	84	45	9
97 @0.1μM	23	74	46	2	6
101 @0.1μM	35	110	94	83	41
123 @0.1μM	17	115	94	84	31
111 @0.1μM	8	109	76	59	11
112 @0.1μM	21	85	66	14	1
113 @0.1μM	19	88	78	16	3
114 @0.1μM	10	91	52	47	8
115 @0.1μM	6	73	45	12	3
117 @0.1μM	8	113	88	65	14
118 @0.1μM	3	82	29	18	2
120 @0.1μM	8	115	76	62	14
124 @0.1μM	16	109	100	78	20
125 @0.1μM	20	106	54	18	2
126 @0.1μM	19	93	47	5	2
129 @0.1μM	8	104	75	24	3
130 @0.1μM	13	113	98	84	22
131 @0.1μM	9	104	104	82	27

Example	Activity (control) %				
	ALK(h)	EGFR(h)	EGFR (L858R)(h)	EGFR (T790M)(h)	EGFR (T790M,L858R)(h)
132 @0.1μM	16	103	114	77	30
135 @0.1μM	80	106	103	96	95
136 @0.1μM	29	99	104	92	54

Example B. Kinase assays (IC_{50}).

Assays were conducted for an in vitro kinase panel having EGFR WT, L858R, T790M , L858R/T790M and ALK. Assay conditions included 10pt curves with 1μM(EGFR L858R, T790M, L858R/T790M and ALK) or 10μM(EGFR WT) top concentration (duplicates) and Km ATP.

Kinase Assay Protocol:

Bar-coded Corning, low volume NBS, black 384-well plate (Corning Cat. #4514)

1. 2.5 μL – 4X Test Compound or 100 nL 100X plus 2.4 μL kinase buffer;
2. 5 μL – 2X Peptide/Kinase Mixture;
3. 2.5 μL – 4X ATP Solution;
4. 30-second plate shake;
5. 60-minute Kinase Reaction incubation at room temperature;
6. 5 μL – Development Reagent Solution;
7. 30-second plate shake;
8. 60-minute Development Reaction incubation at room temperature;
9. Read on fluorescence plate reader and analyze the data。

Kinase-Specific Assay Conditions:

ALK

The 2X ALK / Tyr 01 mixture is prepared in 50mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 1mM EGTA. The final 10μL Kinase Reaction consists of 4.25 - 96ng ALK and 2μM Tyr 01 in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 1 mM EGTA. After the 1 hour Kinase Reaction incubation, 5μL of a 1:256 dilution of Development Reagent B is added.

EGFR (ErbB1)

The 2X EGFR (ErbB1) / Tyr 04 mixture is prepared in 50mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 4mM $MnCl_2$, 1mM EGTA, 2mM DTT. The final 10μL Kinase Reaction consists of 1.1 - 8ng EGFR (ErbB1) and 2μM Tyr 04 in 50mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM MgCl2, 2mM $MnCl_2$, 1mM EGTA, 1mM DTT. After the 1 hour Kinase Reaction incubation, 5μL of a 1:64 dilution of Development Reagent B is added.

EGFR (ErbB1) L858R

The 2X EGFR (ErbB1) L858R / Tyr 04 mixture is prepared in 50mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 4mM $MnCl_2$, 1mM EGTA, 2mM DTT. The final 10μL Kinase Reaction consists of 0.2-3.36ng EGFR (ErbB1) L858R and 2μM Tyr 04 in 50mM HEPES pH 7.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 2mM $MnCl_2$, 1mM EGTA, 1mM DTT. After the 1 hour Kinase Reaction incubation, 5μL of a 1:64 dilution of Development Reagent B is added.

EGFR (ErbB1) T790M

The 2X EGFR (ErbB1) T790M / Tyr 04 mixture is prepared in 50mM HEPES pH 6.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 1 mM EGTA, 0.02% NaN_3. The final 10μL Kinase Reaction consists of 3.9-34.8ng EGFR (ErbB1) T790M and 2μM Tyr 04 in 50mM HEPES pH 7.0, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1mM EGTA, 0.01% NaN_3. After the 1 hour Kinase Reaction incubation, 5μL of a 1:64 dilution of Development Reagent B is added.

EGFR (ErbB1) T790M L858R

The 2X EGFR (ErbB1) T790M L858R / Tyr 04 mixture is prepared in 50mM HEPES pH 6.5, 0.01% BRIJ-35, 10mM $MgCl_2$, 1mM EGTA, 0.02% NaN_3. The final 10μL Kinase Reaction consists of 0.36-2.96ng EGFR (ErbB1) T790M L858R and 2μM Tyr 04 in 50mM HEPES pH 7.0, 0.01% BRIJ-35, 10mM $MgCl_2$, 1mM EGTA, 0.01% NaN_3. After the 1 hour Kinase Reaction incubation, 5μL of a 1:64 dilution of Development Reagent B is added.

Compounds formula (I) included potent inhibitors of EGFR mutants in kinase assays. For example, for the resistant mutant EGFR L858R/T790M, previously known inhibitors gefitinib, icotinib, and CO-1686 had IC_{50} values between 16.6nM to >1μM, while many compounds of formula (I) exhibited IC_{50} values in the range of 4.08 to 22.8 nM. Thus, compounds of formula (I) could provide the necessary inhibitors for EGFR-driven cancers.

Table 2

Example	IC_{50}/nm				
	ALK	EGFR (ErbB1) L858R	EGFR (ErbB1) T790M L858R	EGFR (ErbB1) T790M	EGFR (ErbB1)
Icotinib		2.02	>1000	>1000	1.23
Gefitinib		0.458	412	179	<0.508
CO-1686	145	108	16.6	13.7	101
4	27.9	44.3	4.08	7.52	45.1
61	12.2	>1000	22.8	38.2	756
67	17.3	500	15.4	18.9	273
74	9.33	422	15.5	15.8	513
87	15.1	225	14.7	21.3	354
115	8.62	547	11.7	18.7	397
118	10.8	158	5.13	4.92	77.6

Example C. Cell Proliferation Assay

NSCLC cell lines were used to examine the activity of compounds of formula (I) against 3 general forms of EGFR: wild type EGFR (the naturally occurring form, WT), EGFR with an activating mutation (delE746_A750 [Del]; this form is sensitive to first generation EGFR inhibitors), and EGFR with both an activating mutation and a T790M resistance mutation (L858R/T790M; the addition of the T790M mutation makes this form resistant to first generation EGFR inhibitors).

Effects of test compounds on in vitro proliferation were measured by MTS cell viability assay.

Cell culture

H1975 (EGFR L858R/T790M), HCC827 (EGFR Del), A549 (EGFR WT) and A431(EGFR WT) NSCLC cells were all obtained from ATCC.

H1975 and HCC827 cells were maintained in RPMI 1640 (Gibco) supplemented with 10% FBS, 100units/mL penicillin, 100 units/mL streptomycin, and 2mM glutamine.

A549 cells were maintained in Ham's F12K medium (Gibco) supplemented with 10% FBS, 100units/mL penicillin, 100units/mL streptomycin, and 2mM glutamine.

A431 cells were maintained in DMEM (Gibco) supplemented with 10% FBS, 100 units/mL penicillin, 100units/mL streptomycin, and 2mM glutamine.

MTS cell viability assay:

1. Seed cells at density of 2×103 cells per well of 96-wells plates, grow for 24 hours ;
2. Prepare test compounds in each well with a final medium volume of 200μl;
3. Incubate for 3 days of exposure;
4. Prepare reagents following the instructions in the Cell Proliferation Assay kit (Promega);
5. Change to serum-free medium with a final volume of 100μl/well. Prepare a set of wells with medium only for background subtraction;
6. Add 20μl MTS solution containing PMS to each well (final concentration of MTS will be 0.33 mg/ml);
7. Incubate 1 to 4 hours at 37°C in a humidified, 5% CO_2 atmosphere.
8. Record absorbance at 490nm using VICTOR^{TM}X5 plate reader (PerkinElmer).

All experimental points were set up in three wells and all experiments were repeated at least three times.

The Compound of Example 40, 65, 66, 67, 74, 112 and 118 demonstrated potent activity against both activated and resistant T790M forms of EGFR in vitro cellular assays. For example, in one set of studies, proliferation of HCC827 cells expressing EGFR Del were inhibited with GI_{50}s of 20nM by Example 67 and 118 ; and proliferation of H1975 cells expressing EGFR-L858R/T790M were inhibited with GI_{50}s (20nM and 10nM) similar to that of HCC827 cells.

In contrast, Example 67 and 118 were essentially inactive against EGFR WT in cellular assays, i.e., inhibited proliferation with GI_{50}s >1500 nM in A549 cells (EGFR WT), showing a great selectivity between EGFR WT and mutants. However the second generation EGFR TKI afatinib induced similar inhibition of proliferation on HCC827 cells (EGFR Del) and A431 cells (EGFR WT).

Table 3

Example	IC_{50}（H1975）/μM	IC_{50}（HCC827）/μM	IC_{50}（A549）/μM	IC_{50}（A431）/μM
CO-1686	0.08	0.09	2.00	0.45
WZ4002	0.15	0.03	>3	NA
24	>3	>3	NA	NA
18	2.86	>3	NA	NA
3	0.84	0.94	>3	NA
17	0.86	1.23	>3	0.26
16	1.13	0.90	>3	NA
1	>3	>3	NA	NA
2	>3	>3	NA	NA
4	>3	2.63	>3	NA
15	>3	>3	NA	NA
10	>3	>3	NA	NA
42	>3	>3	>3	NA
43	>3	>3	>3	NA
44	1.23	2.36	>3	NA
45	>3	>3	>3	NA
46	0.81	1.63	>3	NA
47	>3	>3	>3	NA
48	1.95	1.94	NA	NA
25	>3	>3	NA	NA
49	>3	>3	NA	NA
53	0.21	0.54	>3	0.05
40	0.01	0.07	0.64	NA
54	>3	>3	NA	NA
55	>3	>3	NA	NA
56	>3	>3	NA	NA
57	0.10	0.27	>3	NA

Example	IC_{50}（H1975）/μM	IC_{50}（HCC827）/μM	IC_{50}（A549）/μM	IC_{50}（A431）/μM
58	0.98	0.53	0.37	NA
59	0.19	>3	>3	NA
60	0.15	0.87	2.08	NA
61	0.01	0.17	0.74	0.01
62	>3	2.33	>3	NA
63	0.64	>3	>3	NA
64	0.09	0.45	>3	NA
65	0.02	0.12	>3	NA
66	0.05	0.12	>3	NA
67	0.02	0.02	1.58	0.11
68	0.65	1.20	>3	NA
69	0.31	1.20	>3	NA
70	0.31	1.05	1.37	NA
71	0.99	0.78	1.19	NA
74	0.05	0.03	0.62	0.05
87	0.01	0.02	0.05	0.06
118	0.01	0.02	1.89	0.01
112	0.01	0.03	0.04	0.10
126	0.01	0.02	NA	0.21
131	0.01	0.05	NA	0.75

The compounds of the present invention are preferably formulated as pharmaceutical compositions administered by a variety of routes. Most preferably, such compositions are for oral administration. Such pharmaceutical compositions and processes for preparing the same are well known in the art. See, e.g., REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (A. Gennaro, et al, eds., 19th ed., Mack Publishing Co., 1995). The compounds of Formula I are generally effective over a wide dosage range.

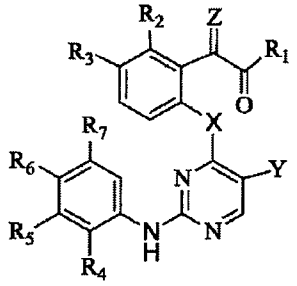
For example, dosages per day normally fall within the range of about 1 mg to about 200 mg total daily dose, preferably 1 mg to 150 mg total daily dose, more preferably 1 mg to 50 mg total

daily dose. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed. The above dosage range is not intended to limit the scope of the invention in any way. It will be understood that the amount of the compound actually administered will be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound or compounds administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms.

THE CLAIMS

What is claimed is:

1. A compound of Formula I or a pharmaceutically acceptable salt:



I

wherein,

X is absent, O, S, or NR_{16}; R_{16} is H or C_{1-6} alkyl;

Y is halogen, OH, NH_2, CN, N_3, NO_2, or C_{1-6} alkyl;

Z is O, S, NR_{20}, or $CR_{20}R_{21}$; and each R_{20} or R_{21} is independently H, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

R_1 is hydroxy, $N(R_8)(R_9)$, $N(R_8)(CH_2)N(R_8)(R_9)$, $N(R_8)(R_9)CO(R_9)$, $N(R_8)CO(R_9)$, $C(O)R_8$, $C(O)OR_8$, $C(O)NH_2$, $C(O)NH(R_8)$, $C(O)N(R_8)(R_9)$, alkyl, haloalkyl, aryl, arylalkyl, alkoxy, heteroaryl, heterocyclic, or carbocyclic; each R_8 and R_9 is independently H, hydroxy, alkyl, alkenyl, heterocyclic, cycloalkyl, or carbocyclic;

R_2 is H, halogen, or C_{1-4} alkyl; or

R_2 and R_1 together with the atoms to which they are attached form a 5- to 7-member heterocyclic ring comprising 1 - 3 hetero atoms independently selected from P, N, O or S;

R_3 is H, halogen, or a 5 or 6 member heterocyclic ring comprising 1 or 2 N atoms; or

R_2 and R_3 together form 5- to 12-membered heterocyclic ring comprising 1, 2, 3 or 4 hetero atoms independently selected from N, or O;

R_4 is H, C_{1-6}alkoxy, C_{3-6}alkenyloxy, C_{3-6}cycloalkyloxy, halogen, -O-heterocyclic, heterocyclic, or $-NR_{24}(CH_2)_PNR_{24}R_{25}$; and P is 0, 1, 2, or 3, and each R_{24} or R_{25} is independently H, halogen, C_{1-6} alkyl, or C_{1-6} alkoxy;

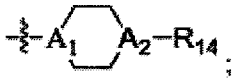
R_5 is H, F, C_{1-6}alkyl, haloalkyl which may be optionally substituted with C_{1-6}alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, C_{1-6}alkyl, halogen, or a bond, C_{1-6}alkoxy which may be optionally substituted with C_{1-6}alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, C_{1-6}alkyl, halogen, or a bond,

cycloalkyloxy, -$NR_{15}C(O)(CH_2)_nCR_{17}=CR_{18}R_{19}$ which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond, -$NR_{15}C(O)(CH_2)_nOCHR_{17}R_{18}$ which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond, -$NR_{15}C(O)(CH_2)_nCR_{17}(CH_2)_mCHR_{18}R_{19}$, -$NR_{15}C(O)(CH_2)_nCR_{17}=CH(CH_2)_mNR_{18}R_{19}$ which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond, -$NR_{15}C(O)CR_{17}(CH_2)_mNR_{18}(CH_2)_nNR_{18}R_{19}$ which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond, -$NR_{15}C(O)(CH_2)_nCHR_{17}R_{18}$ which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond, -$NR_{15}C(O)(CH_2)_nCR_{17}(CH_2)_mCHR_{18}R_{19}$, or -$NR_{15}C(O)(CH_2)_n\overset{R_{17}}{\overset{\|}{C}}(CH_2)_mCHR_{18}R_{19}$; or R_5 is a 5 or 6 member heterocyclic ring containing 1, 2 or 3 hetero atoms independently selected from N or O; and each R_{15}, R_{17}, R_{18} or R_{19} is independently absent, -H, -OH, $-NH_2$, halogen, alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic, a bond, or heteroaryl; and each m or n is independently 0, 1, 2, or 3;

R_7 is H, halogen, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$alkenyloxy, $C_{3\text{-}6}$cycloalkyloxy, $-OC(O)N(R_{10})(R_{11})$, $-NR_{10}C(O)OR_{11}$, $-NR_{22}C(O)CR_{23}=CR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sCHR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}\overset{R_{23}}{\overset{\|}{C}}(CH_2)_mCHR_{18}R_{19}$, $-NR_{22}C(O)CR_{23}=CR_{10}(CH_2)_sR_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sNR_{10}(CH_2)_tNR_{10}R_{11}$, or $-NR_{22}C(O)(CH_2)_sCR_{23}=CH(CH_2)_tNR_{10}R_{11}$; or R_7 is a 5 or 6 member heterocyclic ring comprising 1, 2 or 3 hetero atoms independently selected from N or O; and each R_{10}, R_{11}, R_{22} or R_{23} is independently H, alkyl, alkenyl, alkynyl, and heteroalkyl, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond, each of which may be optionally substituted with $C_{1\text{-}6}$alkyl, alkoxy, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond; or R_{10} and R_{11}, together with the atoms to which they are attached, combine to form a 3-, 4-, 5- or 6-membered heterocyclic ring; and each s or t is independently 0, 1, 2, or 3;

R_6 combines with R_7 to form a 6 member heterocyclic ring optionally substituted with hydroxy, alkyl, alkenyl, heterocyclic, cycloalkyl, $-OR_{13}$, $-C(O)R_{12}$, $-NR_{12}R_{13}$, or carbocyclic, or R_6 is H, halogen, -CN, $-NO_2$, cycloalkyl, heteroalkyl, heterocyclic, heterocyclic-CO-alkyl, heterocyclic-CO-alkenyl, heteroaryl , $-R_{12}$, $-OR_{13}$, $-O\text{-}NR_{12}R_{13}$, $-NR_{12}R_{13}$, $-NR_{12}\text{-}NR_{12}R_{13}$,

$-NR_{12}-OR_{13}$, $-C(O)GR_{13}$, $-OC(O)GR_{13}$, $-NR_{12}C(O)GR_{13}$, $-SC(O)GR_{13}$, $-NR_{12}C(=S)GR_{13}$, $-OC(=S)GR_{13}$, $-C(=S)GR_{13}$, $-YC(=NR_{12})GR_{13}$, $-GC(=N-OR_{12})GR_{13}$, $-GC(=N-NR_{12}R_{13})GR_{13}$, $-GP(=O)(GR_{12})(GR_{13})$, $-NR_{12}SO_2R_{13}$, $-S(O)_rR_{13}$, $-SO_2NR_{12}R_{13}$, $-NR^1SO_2NR_{12}R_{13}$, $-O(CH_2)_rR_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$, $-O(CH_2)_rNR_{12}R_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$, $-NR_{12}(CH_2)_rNR_{12}R_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$, $-NR_{12}(CH_2)_rR_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$, $-(CH_2)_rNR_{12}R_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$, or $-CH_2O(CH_2)_rNR_{12}R_{13}$ which may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$; or



each G is, independently, a bond, -O-, -S-, or $-NR_{15}$; and each R_{12}, R_{13}, or R_{15} is independently H, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroary;

r is 0, 1, 2, or 3;

each A_1 or A_2 is, independently, CH or N; and R_{14} is alkyl, alkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroalkyl, heterocyclic or heteroaryl.

2. The compound of claim 1, wherein Y is halogen, methyl, or methyl substituted with halogen.

3. The compound of claim 1 or 2, wherein Y is Cl, or CF_3.

4. The compound of any of claims 1-3, wherein X is NR_{16}.

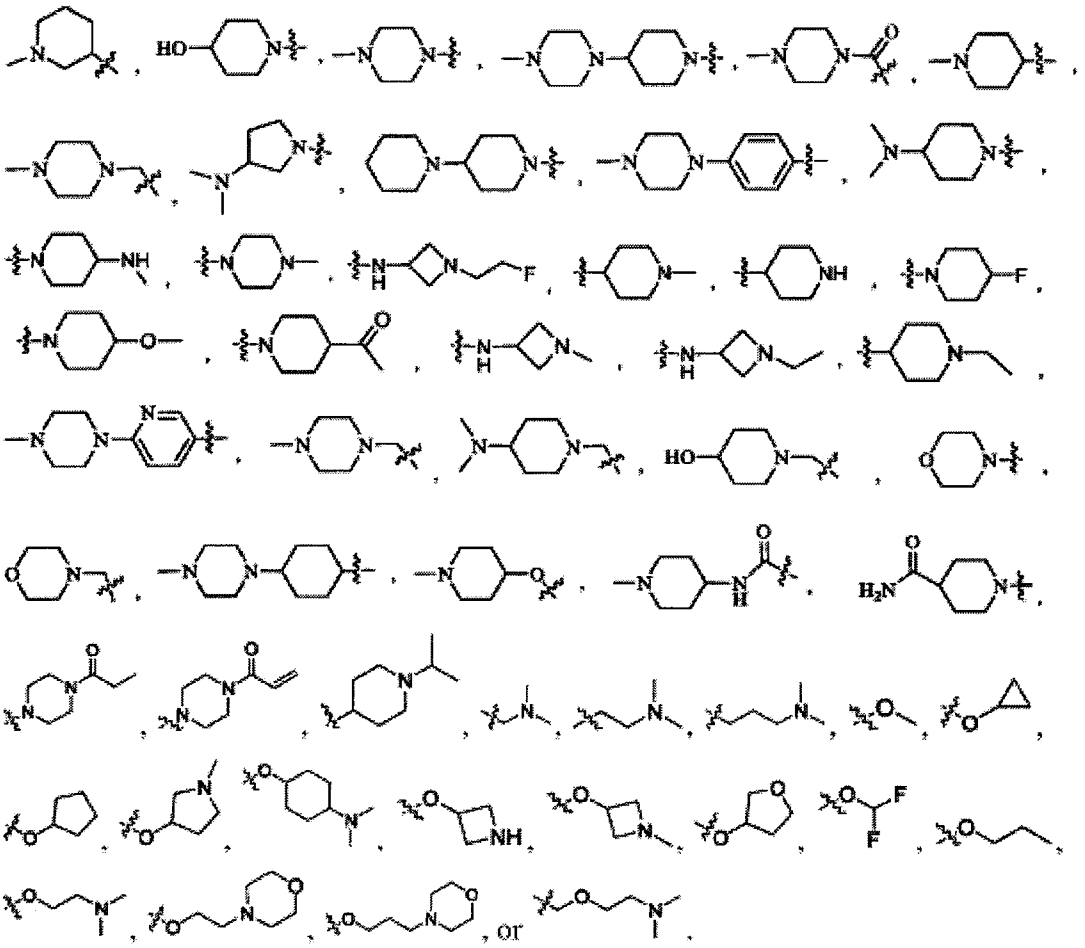
5. The compound of any of claims 1-4, wherein Z is O, or CH_2.

6. The compound of any of claims 1-5, wherein each R_6 combines with R_7 to form a 6 member heterocyclic ring optionally substituted with hydroxy, alkyl, alkenyl, heterocyclic, cycloalkyl, $-OR_{13}$, $-C(O)R_{12}$, $-NR_{12}R_{13}$, or carbocyclic; or R_6 is $-O(CH_2)_rR_{13}$, $-O(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rNR_{12}R_{13}$, $-NR_{12}(CH_2)_rR_{13}$, $-(CH_2)_rNR_{12}R_{13}$, or $-CH_2O(CH_2)_rNR_{12}R_{13}$, each of which

may be optionally substituted with C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alknyl, haloalkyl, halogen, alkoxy, $-NH_2$, $-NCH_3CH_3$, or $-NHCH_3$.

7. The compound of any of claims 1-6, wherein each R_{12}, R_{13}, or R_{15} is independently H, (C_{1-6})alkyl, (C_{2-6})alkenyl, (C_{3-6})cycloalkyl, (C_{3-6})heteroalkyl, or (C_{3-6})heterocyclic.

8. The compound of any of claims 1-7, wherein each R_6 is independently -OH, -OEt, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -H, -F,



9. The compound of any of claims 1-8, wherein R_2 and R_3 are both hydrogen.

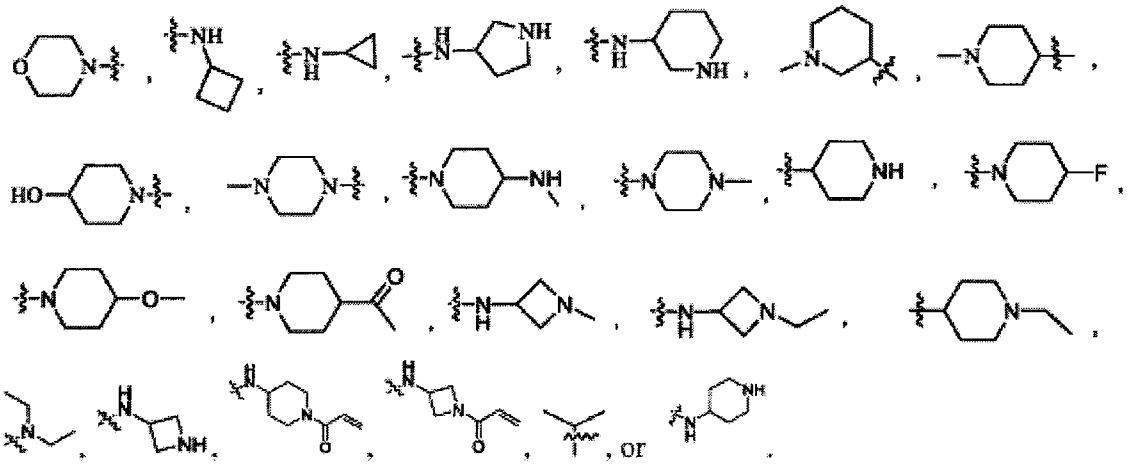
10. The compound of any of claims 1-9, wherein R_1 is hydroxy, $N(R_8)(R_9)$, alkyl, alkoxy, or haloalkyl.

11. The compound of any of claims 1-10, wherein each R_8 and R_9 is independently H, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl.

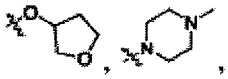
12. The compound of any of claims 1-11, wherein each R_8 or R_9 is independently methyl, or vinyl.

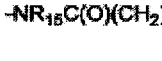
13. The compound of any of claims 1-10, wherein each R_8 and R_9 is independently heterocyclic, cycloalkyl, or carbocyclic.

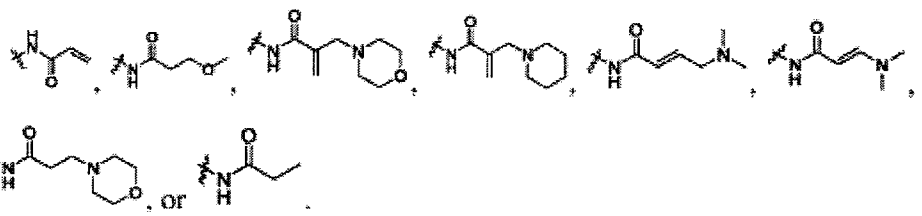
14. The compound of any of claims 1-13, wherein each R_1 is independently -OH, -OEt, -NHOH, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, $-NHCH_2CH_2NCH_3CH_3$, $-NHCH_2CH_2OH$, $-CH_2CH_3$,



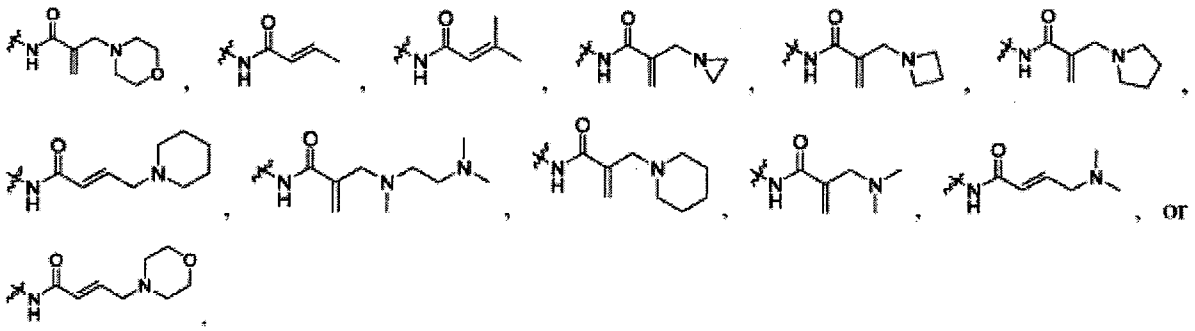
15. The compound of any one of claims 1-14, wherein R_4 is hydrogen, $C_{1\text{-}6}$alkoxy, $C_{3\text{-}6}$ alkenyloxy, $C_{3\text{-}6}$ cycloalkyloxy, halogen, -O-heterocyclic, heterocyclic, or $-NR_{24}(CH_2)_pNR_{24}R_{25}$; and P is 1, or 2, each R_{24} or R_{25} is independently $C_{1\text{-}6}$ alkyl, $C_{1\text{-}6}$alkoxy, -NHOH, $-NH_2$, $NHCH_3$, NCH_3CH_3, or halogen.

16. The compound of any one of claims 1-15, wherein R_4 is hydrogen, F, $-OCH_3$, , , or .

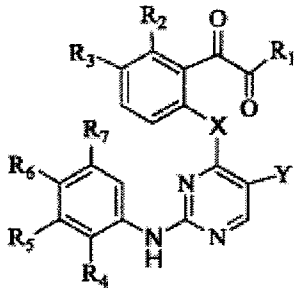
17. The compound of any of claims 1-16, wherein, R_5 is H, haloalkyl, $C_{1\text{-}6}$alkoxy, $-NR_{15}C(O)(CH_2)_nCR_{17}=CR_{18}R_{19}$, $-NR_{15}C(O)(CH_2)_nOCHR_{17}R_{18}$, , $-NR_{15}C(O)(CH_2)_nCR_{17}=CH(CH_2)_mNR_{18}R_{19}$, $-NR_{15}C(O)CR_{17}(CH_2)_mNR_{18}(CH_2)_nNR_{18}R_{19}$, or $-NR_{15}C(O)(CH_2)_nCHR_{17}R_{18}$, each of which may be optionally substituted with $C_{1\text{-}6}$alkoxy, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, -NHOH, $C_{1\text{-}6}$alkyl, halogen, or a bond; and each R_{15}, R_{17}, R_{18} or R_{19} is independently absent, -H, $C_{1\text{-}6}$alkyl, alkenyl, $C_{1\text{-}6}$alkoxy, -NHOH, $-NH_2$, $-NHCH_3$, $-NCH_3CH_3$, a bond, or $C_{3\text{-}6}$heterocyclic; and each m or n is independently 0, 1, or 2.

18. The compound of any of claims 1-17, wherein, R_5 is H, methyl, methyl substituted by halogen, methoxy, 

19. The compound of any of claims 1-18, wherein, R_7 is H, C_{1-6}alkyl, $-NR_{22}C(O)CR_{23}=CR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sCHR_{10}R_{11}$, $-NR_{22}C(O)CR_{23}=CR_{10}(CH_2)_sR_{11}$, $-NR_{22}C(O)CR_{23}(CH_2)_sNR_{10}(CH_2)_tNR_{10}R_{11}$, or $-NR_{22}C(O)(CH_2)_sCR_{23}=CH(CH_2)_tNR_{10}R_{11}$; and each R_{10}, R_{11}, R_{22} or R_{23} is independently H, alkyl, alkenyl, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond, each of which may be optionally substituted with C_{1-6}alkyl, alkoxy, heterocyclic, cycloalkyl, cycloalkyloxy, heteroalkyl or a bond; and each s or t is independently 0, 1, or 2.

20. The compound of any of claims 1-19, wherein, R_7 is H, C_{1-6}alkyl, , 

21. The compound of any one of claims 1-20, wherein the compound is of Formula II:



Formula II

22. The compound of claim 21, wherein X is NH.

23. The compound of claim 21 or 22, wherein Y is Cl, CH_3 or CF_3.

24. The compound of claim 1, wherein the compound is

ethyl 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino) pyrimidin-4-ylamino)phenyl)-2-oxoacetate;

2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyrimidi n-4-ylamino)phenyl)-2-oxoacetic acid;

2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyrimidi n-4-ylamino)phenyl)-N-hydroxy-2-oxoacetamide;

2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)pyrimidi n-4-ylamino)phenyl)-2-oxoacetamide;

ethyl 2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino) pyrimidin-4-ylamino)phenyl)acrylate;

2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)a mino)phenyl)-2-oxoacetamide;

2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-chloropyrimidin-4-yl)a mino)phenyl)-2-oxoacetamide;

2-(2-((5-chloro-2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)p yrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrim idin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((4-(4-acetylpiperazin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromethyl)pyrimi din-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)py rimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)-5-(trifluor omethyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromet hyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)-5-(trifluoromet

hyl)pyrimidin-4-yl)amino)phenyl)-2-oxoacetic acid;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-methyl-2-oxoacetamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N,N-dimethyl-2-oxoacetamide;

1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-morpholinoethane-1,2-dione;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-(dimethylamino)ethyl)-2-oxoacetamide;

2-(2-((5-chloro-2-((2-methoxy-4-(4-(methylamino)piperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-(2-hydroxyethyl)-2-oxoacetamide;

1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-methylbutane-1,2-dione;

1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)propane-1,2-dione;

1-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-3-(dimethylamino)propane-1,2-dione;

N-(azetidin-3-yl)-2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxoacetamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-N-cyclopropyl-2-oxoacetamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(pyrrolidin-3-yl)acetamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)-2-oxo-N-(piperidin-4-yl)acetamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

2-(2-((5-chloro-2-((4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)a

mino)phenyl)acrylamide;

2-(2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

2-(2-((5-chloro-2-((4-((1-(2-fluoroethyl)azetidin-3-yl)amino)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

2-(2-((5-chloro-2-((2-methoxy-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

2-(2-((5-chloro-2-((2-methoxy-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylic acid;

2-(2-((5-chloro-2-((4-(4-fluoropiperidin-1-yl)-2-methoxyphenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

2-(2-((5-chloro-2-((2-methoxy-4-(4-methoxypiperidin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(morpholinomethyl)acrylamide;

1-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

1-(2-(2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)-5-(trifluoromethyl)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

1-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

1-(2-(2-(4-(4-(dimethylamino)piperidin-1-yl)-2-methoxyphenylamino)-5-(trifluoromethyl

)pyrimidin-4-ylamino)phenyl)-2-morpholinoethane-1,2-dione;

2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N-cyclopropyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(2-(4-(4-acetylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-methoxy-4-(4-propionylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

N-(1-acryloylazetidin-3-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

N-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(2-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

N-(3-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(3-(4-(2-(2-amino-2-oxoacetyl)phenylamino)-5-(trifluoromethyl)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(1-acryloylpiperidin-4-yl)-2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-2-oxoacetamide;

2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylami

no)phenyl)-N-methyl-2-oxoacetamide;

2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(4-fluoro-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N-methyl-2-oxoacetamide;

N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluoro-4-methoxyphenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-fluoro-2-methoxyphenyl)acrylamide;

(E)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)but-2-enamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-3-methylbut-2-enamide;

(E)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-(piperidin-1-yl)but-2-enamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(piperidin-1-ylmethyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4

-methoxy-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide;

(E)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-morpholinobut-2-enamide;

(E)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-4-(dimethylamino)but-2-enamide;

N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(methylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(3-morpholinopropoxy)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(2-(dimethylamino)ethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

2-(2-(2-(4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazin-6-ylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(2-(4-(4-acryloylpiperazin-1-yl)-2-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phen

yl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-morpholino-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(4-methylpiperazin-1-yl)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

2-(2-(2-(4-(4-acetylpiperazin-1-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(aziridin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

2-(azetidin-1-ylmethyl)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(pyrrolidin-1-ylmethyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(2-morpholinoethoxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide;

N-(3-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-4-methoxyphenyl)-2-((dimethylamino)methyl)acrylamide;

N-(5-(4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)-5-methylpyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)-3-methoxypropanamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-cyclopropoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)

-2-(cyclopentyloxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylpyrrolidin-3-yloxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-(dimethylamino)cyclohexyloxy)phenyl)acrylamide;

N-(2-(azetidin-3-yloxy)-5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylazetidin-3-yloxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(morpholinomethyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(piperidin-1-ylmethyl)acrylamide;

(E)-N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-4-(dimethylamino)but-2-enamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(difluoromethoxy)phenyl)acrylamide;

2-(2-(5-chloro-2-(3-methoxy-4-morpholinophenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(4-(4-(dimethylamino)piperidin-1-yl)-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)

-2-(2-(dimethylamino)ethoxy)phenyl)propionamide;

(E)-N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-3-(dimethylamino)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-propoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-fluorophenyl)-3-morpholinopropanamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(tetrahydrofuran-3-yloxy)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)phenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)-2-(((2-(dimethylamino)ethyl)(methyl)amino)methyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-((2-(dimethylamino)ethyl)(methyl)amino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(4-methylpiperazin-1-yl)phenyl)-2-(piperidin-1-ylmethyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-morpholinophenyl)-2-(piperidin-1-ylmethyl)acrylamide;

2-(2-(5-chloro-2-(3-methoxy-4-(4-methylpiperazin-1-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-diethyl-2-oxoacetamide;

N-(3-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(diethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-methoxyphenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-5-(trifluoromethyl)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)

-4-(4-methylpiperazin-1-yl)phenyl)acrylamide;

N-(3-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-(tetrahydrofuran-3-yloxy)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((2-(dimethylamino)ethoxy)methyl)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((dimethylamino)methyl)-4-methoxyphenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-((4-methylpiperazin-1-yl)methyl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(1-methylpiperidin-4-yl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-4-methoxy-2-(1-methylpiperidin-4-yl)phenyl)acrylamide;

2-(2-(5-chloro-2-(3-methoxy-4-(1-methylpiperidin-4-yl)phenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(2-(4-(1-acetylpiperidin-4-yl)-3-methoxyphenylamino)-5-chloropyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(2-(dimethylamino)ethyl)phenyl)acrylamide;

N-(5-(5-chloro-4-(2-(2-(dimethylamino)-2-oxoacetyl)phenylamino)pyrimidin-2-ylamino)-2-(3-(dimethylamino)propyl)phenyl)acrylamide;

2-(2-(5-chloro-2-(4-(1-isopropylpiperidin-4-yl)-3-methoxyphenylamino)pyrimidin-4-ylamino)phenyl)-N,N-dimethyl-2-oxoacetamide;

2-(2-(5-chloro-2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenylamino)pyrimidin-4-yla

mino)phenyl)-N,N-dimethyl-2-oxoacetamide.

25. A pharmaceutical composition comprising a compound of any of claims 1-24 and a pharmaceutically acceptable excipient.

26. The pharmaceutical composition according to claim 25, wherein, the said compound is in a weight ratio to the said excipient within the range from about 0.0001 to about 10.

27. Use of a pharmaceutical composition of claim 25 or 26 or a compound of any of claims 1-24 for the preparation of a medicament for the treatment or prevention of, or for delaying or preventing onset or progression in, cancer or cancer metastasis by inhibiting a kinase selected from one or more of EGFR, ALK or ALK fusion proteins.

28. The use of claim 27, wherein the EGFR is a mutant EGFR; the cancer is EGFR-driven cancer, and the EGFR-driven cancer is characterized by the presence of one or more mutations selected from: (i) L858R, (ii) T790M, (iii) both L858R and T790M, (iv) delE746_A750, or (v) both delE746_A750 and T790M.

29. The use of claim 28, wherein the EGFR-driven cancer is a non-small cell lung cancer, glioblastoma, pancreatic cancer, head and neck cancer, breast cancer, colorectal cancer, epithelial cancer, ovarian cancer, prostate cancer, or an adenocarcinoma.

30. The use of claim 29, wherein the head and neck cancer is head and neck squamous cell carcinoma.

31. The use of any of claims 27-30 for treatment of a human.